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In Ineffective Esophageal Motility, failed swallows are more functionally relevant than weak swallows.

Short title: Relevance of Peristaltic Vigor in IEM

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ABSTRACT

Background:

Esophageal pressure topography (EPT) diagnosis of Ineffective Esophageal Motility (IEM) can be nonspecific with unclear clinical significance.

Aims:

To determine whether peristaltic vigor or lower esophageal sphincter (LES) integrity is associated with poor clearance and acid reflux in IEM.

Methods:

Bolus clearance on High-resolution impedance manometry (HRIM) and available reflux studies in patients with IEM were retrospectively reviewed. Bolus clearance was assessed using both line tracing and colored contour methods on HRIM. EPT parameters, bolus clearance, and acid reflux variables were explored.

Key Results:

Eighty-eight patients with IEM were included. Bolus clearance occurred in 71% of all swallows, and 55.7% of patients had complete bolus transit (CBT, bolus clearance in ≥80% of swallows). Bolus clearance was impaired in swallows with Distal Contractile Integral (DCI) <100mmHg-s-cm compared to DCI 100-450 (0.43 vs 0.79, p<0.0001). A cutoff at DCI 100mmHg-s-cm was associated with clearance with an accuracy of 76% compared to 49% at DCI 450 (p=0.0001 for both). A median DCI <100 was associated with a higher Eckardt score (9 vs 3, p=0.03), and on reflux testing available in 47 patients, with abnormal acid exposure time (p=0.002). Peristaltic reserve (PR) defined as (DCI of Multiple Rapid Swallow/ median DCI of wet swallows), Integrated Relaxation Pressure, and resting Lower Esophageal Sphincter pressure were not associated with clearance or acid exposure.

Conclusions and Inferences:

Failed peristalsis, as defined by DCI <100mmHg-s-cm, is associated with impaired bolus clearance and more severe dysphagia in IEM, and likely abnormal acid exposure.

Abbreviations: AET: Acid-exposure Time, AUC: Area-under-the-curve, BFT: Bolus Flow Time, CBT: Complete Bolus Transit, DCI: Distal Contractile Integral, EGJOO: Esophagogastric Junction Outflow Obstruction, EII: Esophageal Impedance Integral, EPT: Esophageal Pressure Topography, FC: Functional Clearance, HRM: High-resolution Manometry, HRIM: High-resolution Impedance Manometry, IRB: Institutional review board, IRP: Integrated Relaxation Pressure, LES: Lower Esophageal Sphincter, PFA: Pressure-flow-analysis, PPI: Proton-pump inhibitor, PR: Peristaltic reserve, ROC: Receiver Operating Characteristic

KEY POINTS

- Ineffective esophageal motility (IEM) is an esophageal motility disorder with unclear clinical implications. We aim to determine whether strength of peristalsis, peristaltic reserve or lower esophageal sphincter integrity predicts symptoms or clinical outcomes.
- We found that a Distal Contractile Integral (DCI) of <100 mmHg-s-cm is associated with impaired bolus clearance and a higher degree of dysphagia in IEM.
- Treatment of IEM should be conservative when DCI is >100 mmHg-s-cm. More aggressive treatment of present reflux disease and prokinetic agents may be indicated when DCI is <100.

INTRODUCTION

Ineffective esophageal motility (IEM), a nonspecific or minor motility disorder characterized by a combination of weak and failed peristalsis, is a frequent esophageal manometric finding oftentimes with unclear clinical significance. With the implication of poor esophageal emptying, IEM has been associated with prolonged acid exposure and peptic complications [1, 2], as well as symptomatic nonobstructive dysphagia [3]. The definition of IEM has evolved over time. In the conventional line tracing (CLT) era, IEM was defined as low-amplitude (<30 mmHg) distal esophageal contractions in 50% or more wet swallows. Using this definition, studies have found impaired liquid bolus transit in up to ~70% of patients with IEM [4-6], and the association of IEM with gastroesophageal reflux disease had been assessed [7, 8]. Since the introduction of high-resolution manometry (HRM), the CLT definition of IEM was initially translated in esophageal pressure topography (EPT) as weak peristalsis with small and large peristaltic defects or frequently (>30%) failed peristalsis, then more recently as 50% or more swallows with a Distal Contractile Integral (DCI) less than 450 mmHg-s-cm [9]. An evaluation of bolus transit in the current EPT diagnosis of IEM has not been conducted. Furthermore, correlation of impaired bolus transit in IEM with symptoms and distal esophageal acid exposure has not been evaluated.

IEM is the most common manometric abnormality (up to 20-30%)[5]; yet a standard clinical approach for this diagnosis does not exist. Moreover, the clinical relevance and benefit of treating IEM is unclear for several reasons. Many patients with this manometric finding are asymptomatic; and those symptomatic have variable complaints including dysphagia, cough, or reflux symptoms [10]. Management of IEM is challenging as the impact of weakened peristaltic vigor on symptoms is uncertain, and prior studies have associated minor esophageal motor abnormalities with good long-term prognosis even with minimal intervention [11]. There is currently no therapeutic intervention that reliably restores smooth muscle contractility in patients with IEM. Use of bethanechol, a muscarinic receptor agonist shown to be effective in improving esophageal contraction in small case series of IEM patients, has been limited by side effects of dizziness, headaches, nausea, and vomiting, that frequently outweigh potential clinical benefits [12, 13]. In IEM patients with refractory reflux, tailored fundoplication is sometimes employed as the management strategy; however, this approach has not been shown to be beneficial [14].

The most recent iteration of the Chicago Classification v3.0 has retained its definition of IEM as a minor motility disorder [15] where the clinical significance of the condition continues to be actively debated. There has been significant interest in phenotyping IEM based on the degree of peristaltic impairment and using Multiple Rapid Swallows (MRS) to characterize Peristaltic Reserve (PR), the DCI ratio after MRS / median DCI of the 10 swallows [16-19]. The aim of our study was to determine whether the degree of impairment in peristaltic vigor, as measured by DCI and PR, or lower esophageal sphincter integrity is associated with poor clearance and acid reflux in IEM. We set out to determine the parameter and its threshold value that would help identify the subpopulation of IEM patients with poor bolus transit.

MATERIALS AND METHODS

Study design

This was a cross-sectional retrospective cohort study. Consecutive high-resolution impedance manometry (HRIM) procedures performed in adult patients (older than 18 years of age) in the Gastrointestinal Physiology Lab at the University of Michigan between February of 2015 and May of 2016 were screened for the diagnosis of weak peristalsis, frequently failed peristalsis, and IEM. HRIM tracings for included patients were reviewed again to confirm an accurate diagnosis of IEM per Chicago Classification v3.0. Study protocol was approved by the Institutional Review Board (IRB) at the University of Michigan.

Review of medical record

The electronic medical records of included subjects were reviewed. Data obtained included demographic information, medical and surgical history, medications, diagnostic testing such as endoscopy, barium esophagram, and pH testing, esophageal symptoms, and patient reported outcome (PRO) questionnaires which included Eckardt, Brief Esophageal Dysphagia Questionnaire (BEDQ) and GERDQ [20-22].

Manometry and Intraluminal Impedance measurement

Patients underwent manometry using a combined High-resolution manometry and intraluminal impedance (HRIM) system. This is a solid-state assembly with 36 levels of pressure sensors and 12 impedance-sensing segments (Medtronic, Dublin, Ireland). The response characteristics of this device, calibration procedure, and post-study thermal correction algorithm have been described in detail previously [23]. Briefly, the HRIM assembly was passed transnasally and positioned to record from the hypopharynx to the stomach with about 5 intragastric sensors. The manometric protocol included a 5-minute period for acclimatization and to assess basal sphincter pressure followed by ten 5ml liquid swallows of 0.45% saline in the supine position. In most studies an additional MRS sequence involving five 2ml swallows every 2-3 seconds was performed in the upright position. The combined pressure-impedance data were manually analyzed using the ManoView ESO v.3.0.1 software (Medtronic). After thermal compensation, the HRM studies were manually analyzed in accordance with the Chicago Classification v3.0. After confirming the diagnosis of IEM, data for individual swallows were extracted by documenting the values for each parameter: basal lower esophageal sphincter (LES) pressure, distance between LES-crural diaphragm (LES-CD), Integrated Relaxation Pressure (IRP), and Distal Contractile Integral (DCI). DCI after Multiple Rapid Swallows (MRS) was also recorded. Then the color isobaric contour plots were overlaid with impedance line tracings by selecting the "enabling impedance trace on contour" option. The display mode button was changed to impedance tracing on contour (colored contour and lines). Included studies were re-analyzed retrospectively by a single primary reader blinded to the clinical profile. Bolus transit was assessed via line-tracing and contour methods as below. A second reader blindly reviewed 22 (25%) randomly selected studies for comparison.

Bolus clearance

Complete Bolus Transit

Bolus transit was assessed for each swallow using impedance line tracings. Bolus entry was defined as a >50% drop in impedance level from baseline at the proximal recording site; and 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 the three distal recording sites following bolus entry [3]. In instances where the impedance baseline before each swallow was low indicating retained bolus pre-swallow, impedance baseline during the “landmark-ID” measurement period was used as the reference impedance level to assess bolus transit. Each of the 10 wet swallows was scored as either complete or incomplete bolus clearance. Examples of complete and incomplete bolus transit are shown in Figure 1.

Functional Clearance

Bolus clearance was also assessed via colored contour method. Impedance data were displayed as a monochrome color gradient overlaying the pressure topography by changing the contour mode. The color contrast, manually adjustable by changing the level of impedance indication in kOhm, was adjusted so that the contour showed an emptying esophagus before initiation of the 0.45% saline swallow sequence, and the liquid ingested with each swallow was just visible. Bolus clearance was defined by the absence of bolus in the distal esophagus after each swallow. Incomplete functional clearance (FC) was defined as evidence of residual fluid bolus in the distal esophagus.

24-hour Multichannel Intraluminal Impedance-pH (MII-pH) Monitoring

The combined pH-impedance assembly (Sandhill Scientific, Highlands Ranch, CO) was positioned with the proximal pH electrode 5 cm above the manometrically identified lower esophageal sphincter (LES). Impedance was measured 3, 5, 7, 9, 15, and 17 cm above the LES. Event markers recorded occurrence of symptoms, meals, and changes in posture. The recorded data was analyzed in accordance with previously published criteria [24]. Total percent time pH < 4, or the acid exposure time (AET), was chosen as the primary reflux parameter. Active proton-pump inhibitor (PPI) usage and dosing was noted. An AET of > 4.2% off PPI, and an AET of > 1.6% on PPI were considered abnormal [25]. All MII-pH studies were performed on the same day as HRIM or within 4 months afterwards.

Statistical methods

CBT and FC were determined for each of 10 supine swallows. Agreement between CBT and FC was calculated across all supine swallows. CBT frequency was calculated in swallows in distinct DCI subgroups. Receiver-operating characteristic (ROC) curve was constructed for CBT based on DCI for all swallows. ROC curves for complete bolus transit defined as CBT in 80% or more of 10 supine swallows were constructed based on % ineffective swallows and % failed swallows [(5)]. Cutoff values for ROC curves were selected using Youden's index. Logistic regression analysis was performed to evaluate associations between CBT and AET with the following variables as relevant: IRP, resting LES pressure, PR, median DCI, mean DCI. Correlation between elevated AET and DCI at our chosen cutoff was assessed. Parametric variables were compared using unpaired t-test. Non-parametric variables were compared using Mann-Whitney test. Categorical variables were analyzed using chi-square or Fisher's exact test. A p-value of 0.05 was considered statistically significant for all analyses. On ROC curves, an area under the curve (AUC) greater than 0.70 was deemed sufficient for categorical analysis.

RESULTS

Sample description

Eighty-eight adult patients with a confirmed EPT diagnosis of IEM were included in this analysis. Eighty-seven of these studies were originally diagnosed using Chicago Classification V3.0 criteria; one study was re-classified from frequent failed peristalsis on V2.0 to IEM. Seventy-five patients had available multiple rapid swallows. Ten patients with IEM had a history of prior fundoplication. Forty-seven patients had available MII-pH testing after excluding patients with prior fundoplication. Sixteen of these studies were performed on patients off PPI therapy, and the remaining 31 studies were performed in patients on PPI therapy.

Demographics and relevant clinical data are displayed in Table 1. Mean age in our IEM group was 53.1 (SD 16.5); female: male ratio was 1.6. In addition to the 10 patients with prior fundoplication, 1 patient each with prior Roux-en-Y gastric bypass

(RNYGB) and sleeve gastrectomy were included. One patient with eosinophilic esophagitis and 3 patients with scleroderma were included. The indications for manometry were dysphagia (44%), GERD (37%), nausea (6%), cough (3%), pre-lung transplant evaluation (3%), chest pain (2%), dyspnea (2%), globus (1%), and abdominal pain (1%). A breakdown of all symptoms in the IEM group is shown in Table 2. Reflux-like symptoms including heartburn and/or regurgitation were the most prevalent symptoms in 60.2% of patients, followed by dysphagia in 45.5%, abdominal pain in 26.1%, and nausea in 23.9%. Seventy-nine % of patients with heartburn and/or regurgitation were on a PPI; 82.5% of patients with dysphagia were on a PPI. Prevalence of certain medication classes prescribed to IEM patients are also shown in Table 2. Opioids were prescribed in 20.4% of patients. Esophageal testing data is shown in Table 3. Dysmotility on esophagram was seen in 61.4%, gastroesophageal reflux in 52.6%. Erosive esophagitis or Barrett's was noted in 26.2% of upper endoscopies. Hiatal hernia was noted on manometry in 29.5%.

Bolus Transit

Proportion of CBT and FC in 880 swallows in IEM patients were 0.71 and 0.73 respectively, with a kappa value of 0.83, indicating excellent agreement between the two methods to assess bolus transit on HRIM. The ROC curve for CBT according to DCI is shown in Figure 2. The Area Under the Curve (AUC) was 0.77. A DCI of less than 100 mmHg-s-cm had the best accuracy (76%) for impaired bolus transit, and a negative predictive value of 83% ($p = 0.0001$). A DCI of cutoff of 450 mmHg-s-cm had an accuracy of 49% ($p = 0.0001$). CBT and FC in DCI subgroups are shown in Figure 3. The largest step-off was noted between the DCI < 100 (CBT 0.43, FC 0.42) and DCI 100-249 groups (CBT 0.77, FC 0.78). In the DCI > 450 group, CBT was 0.91 and FC was 0.92. When CBT in each group was compared to the other 3 groups using Mann-Whitney test, all were statistically significant other than the DCI 100-249 group (p values 0.0001 – 0.10 as shown in Figure 3). Agreement with a second reader in 25% of randomly selected studies was excellent (k=0.80 for CBT, k=0.83 for FC).

Complete bolus transit in ≥80% of swallows was observed in 55.7% of patients. ROC curves for all ineffective swallows (weak and failed) and failed swallows alone in association with complete bolus transit in 80% or more swallows are in shown in Figure 4. AUC for all ineffective swallows was 0.52 whereas for failed swallows only was 0.73. Failed swallows ≥ 30% had an accuracy of 72% and a NPV of 80% ($p = 0.0001$). On logistic regression analysis, mean DCI and median DCI were associated with complete bolus transit (p-values 0.04 and 0.05 respectively); however, on individual ROC curve analysis, AUCs were low at 0.57 and 0.60 respectively. DCI after multiple rapid swallow (MRS) and the peristaltic reserve (PR = DCI MRS / wet swallows ratio) were not associated with complete bolus transit.

We performed a secondary analysis of CBT in association with DCI across all supine swallows, excluding patients with any foregut surgery history (N=76). AUC was similar at 0.76, and a DCI of <100 mmHg-s-cm was associated with impaired clearance ($p = 0.0001$) with accuracy of 77% and NPV 84%.

Acid Exposure Time

With exclusion of patients with prior fundoplasty, 23 of 47 patients (48.9%) had an elevated AET. No associations between mean DCI, median DCI, resting LES, median IRP, MRS DCI, or PR and elevated AET were found. However, on categorical analysis, all 8 patients with a median DCI < 100 mmHg-s-cm had an elevated AET (PPV 100%, accuracy 68.1%, $p = 0.002$). When median DCI was > 100 mmHg-s-cm, 25 / 40 (61.2%) of patients had a normal AET.

Separating acid exposure by PPI use – 5 of 16 patients (31.3%) off PPI; and 18 of 31 (58.1%) on PPI had an elevated AET. There were no differences in median DCI, CBT or MRS augmentation ratio in association with elevated AET using this grouping. However, there appeared to be a trend towards impaired MRS augmentation in the elevated AET group off PPI (ratio of 0.1 vs 2.2).

We performed a separate analysis of the 46 patients without any foregut surgery, excluding an additional patient with a prior sleeve gastrectomy. Median DCI <100 mmHg-s-cm remained associated with an elevated AET in all 8 patients, and 25/39 (64.1%) of patients with a median DCI >100 mmHg-s-cm had a normal AET.

Patient Reported Outcomes (PRO)

PRO questionnaires were collected from a total of 38 patients with IEM at the time of HRIM. These included 38 Eckardt, 36 BEDQ, and 36 completed GERDQ surveys. In patients with available MII-pH testing, 24 Eckardt scores, 22 BEDQ scores, and 22 GERDQ surveys were collected. Median scores for patients with complete and incomplete bolus transit, normal and elevated AET, and DCI >100 and <100 mmHg-s-cm are shown in Figure 5 and Table 4. There was a trend towards higher scores when median DCI was <100, with a statistically significant difference in Eckardt score (9 vs 3, p = 0.03). Although no statistically significant differences were noted with abnormal CBT or AET, a trend towards higher BEDQ scores was noted with abnormal CBT and elevated AET.

DISCUSSION

The latest iteration of the Chicago Classification reinstated the diagnosis of ineffective esophageal motility, which is now defined as decreased contractile vigor with DCI <450 mmHg-s-cm in 50% or more swallows. This includes a combination of weak and failed swallows. However, the clinical significance of IEM remains unclear. Attempts at subtyping IEM based on type of abnormal bolus transit (viscous, liquid, or both), and most recently, degree of peristaltic dysfunction [(17)] have been made. Since transition to EPT, no studies have attempted to phenotype IEM using impaired bolus transit on intraluminal impedance as the primary indicator of clinicalyl significant IEM.

Our study showed that a DCI of less than 100 mmHg-s-cm – the DCI threshold used for failed peristalsis – identifies a phenotypically more severe subgroup of IEM with decreased bolus clearance, more severe dysphagia, and likely abnormal acid exposure. Our results support DCI as the most functionally relevant metric in evaluation of IEM, over the IRP or the peristaltic reserve. The most clinically relevant finding is that patients with a median DCI of >100 mmHg-s-cm had a normal Eckardt score (median 3) in the setting of >80% complete bolus transit, whereas those with a DCI <100 mmHg-s-cm had a median Eckardt score of 9. Our study is the first to correlate patient reported outcomes with HRM metrics in IEM. We feel this difference provides enough evidence for conservative management of IEM with DCI >100 mmHg-s-cm. Conversely, it may be reasonable to trial procholinergic agents such as bethanechol in patients with a median

DCI <100 mmHg-s-cm and dysphagia. The clinical implication of our reflux analysis results is less certain. However, despite our low number of patients studied off PPI, the elevated AET in all of our patients with a median DCI <100 mmHg-s-cm is important. This justifies more aggressive lifestyle or medical reflux treatment, or consideration of antireflux surgery such as a partial fundoplication, in this group. Our results do not clarify the mechanism or reflux or the cause-effect relationship between IEM and GERD – our findings do not imply IEM as a cause of GERD; the reverse could be equally true.

Our study has some limitations. A major limitation of our study is the fact that we included very few (16) patients in our reflux analysis that were off PPI. A large portion of patients were only referred for manometry without pH testing. In order to assess a reflux outcome, we included patients on-PPI threshold using a threshold of 1.6% for abnormal AET based on prior literature. (25, 26) Second, we did not include a control population for comparison of bolus transit. Although the analysis has not been repeated using the EPT definition; bolus transit in IEM has been compared extensively to normal manometry and more subtle peristaltic abnormalities using CLT and impedance line tracings and was thus not an aim of our study (4-6). Third, our HRIM protocol does not include viscous swallows, which might improve the sensitivity for detecting abnormal bolus transit (27). Fourth, we included patients with prior fundoplication given the relevance of IEM in this population, although clearance could arguably be impaired. However, we found that impaired lower esophageal sphincter relaxation, possibly related to a fundoplication wrap, was not associated with poor bolus clearance. Additionally, five of our ten fundoplication patients had incomplete clearance, which is in keeping with the rest of our cohort. Finally, we currently do not have long-term clinical outcome data to address whether IEM patients with DCI <100mmHg-s-cm results in a more unfavorable clinical aftermath.

There have been multiple proposed methods of characterizing bolus clearance on impedance manometry, including in IEM. Carlson and colleagues found that the bolus flow time (BFT) and esophageal impedance integral (EII) correlated with non-obstructive dysphagia (28). Omari and colleagues found that time from nadir impedance to peak pressure (TNadImp) and impedance radio (IR) are other useful pressure-flow-analysis (PFA) metrics for analyzing bolus clearance (29). Our goal was to study a universally available method that could be utilized by clinical gastroenterologists. Our group recently showed that the conventional line tracing method of evaluating bolus transit and colored contour method were useful in measuring bolus transit in achalasia and esophagogastric junction outflow obstruction (EGJOO). [30]. We have now shown similar reliability between these two methods in IEM. There may be future utility in performing PFA for a more nuanced characterization of bolus transit abnormalities in IEM.

In summary, our study shows that 50% or more failed peristalsis in IEM is associated with poor bolus clearance and a higher degree of dysphagia. This group of severe IEM also likely has elevated acid exposure. Further outcome analysis and therapeutic trials are needed to address the longer-term clinical significance of phenotyping IEM and for development of an IEM management guideline.

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TABLES

Table 1: Clinical Data (N=88)	
Age (mean) [range]	53.1 [20-83]
Sex (%)	
Male	34 (39%)
Female	54 (61%)
Body Mass Index (mean) [SD]	28.1 [5.4]
Other UGI history (%)	
Fundoplication	10 (11.3%)
RNYGB	1 (1.1%)
Sleeve Gastrectomy	1 (1.1%)
Eosinophilic Esophagitis	1 (1.1%)
Scleroderma	3 (3.4%)

Abbreviations: SD: standard deviation, RNYGB: Roux-en-Y gastric bypass, UGI: upper gastrointestinal

Table 2: HRIM Characteristics by Age and BMI					
Age	Number	IRP	Basal LES-P	DCI	% CBT
<40	19	4.7	12.7	271.5	63.1%
41-60	31	6.2	17	279	45.1%
>60	38	6.4	19	257	60.5%
BMI					
<25	26	5.9	23.7	276	61.5%
25-30	32	4.8	15.3	255	46.8%

>30	23	7.1	16	192	60.8%

Abbreviations: BMI: Body Mass Index, CBT: Complete Bolus Transit, DCI: Distal Contractile Integral, HRIM (High-resolution Impedance Manometry, IRP: Integrated Relaxation Pressure, LES-P: Lower Esophageal Sphincter Pressure

Table 3: Symptoms and Medication Use (N=88)	
Symptom	% of patients
Heartburn and/or regurgitation	60.2%
Dysphagia	45.5%
Abdominal pain	26.1%
Nausea	23.9%
Cough	17.0%
Class of Medication	% of patients
Opioids	20.4%
Calcium channel blockers	8.0%
Muscle relaxants	6.8%
Tricyclic antidepressants	6.8%
Nitrates	3.4%

Table 4: Esophageal Diagnostic Testing	
Esophagram (N=57)	
Dysmotility	35 (61.4%)
Reflux	30 (52.6%)
Hiatal hernia	24 (42.1%)
Normal	5 (8.8%)
Upper Endoscopy (N=72)	
Erosive esophagitis	11 (15.2%)
Barrett's	8 (11.0%)
pH testing (N=47)	
Off PPI therapy (%)	16 (34%)
Elevated AET (%)	5 (31.3%)
On PPI therapy (%)	31 (66%)
Elevated AET (%)	18 (58.1%)
Elevated AET overall (%)	23 (48.9%)

HRIM (N=88)	
Complete Bolus Transit	49 (55.7%)
LES-CD ≥ 2 cm	26 (29.5%)
DCI (mmHg-s-cm)	
Mean [SD]	341 [218]
Median [range]	218 [21-1035]
IRP (mmHg)	
Mean [SD]	6.0 [3.8]
Median [range]	5.9 [0.9-13.1]
Basal LES pressure (mmHg)	
Mean [SD]	19.7 [11.6]
Median [range]	17.5 [4.8-41]

Abbreviations: AET: Acid-exposure Time, CD: Crural Diaphragm, DCI: Distal Contractile Integral, HRIM: High-resolution Impedance Manometry, IRP: Integrated Relaxation Pressure, LES: Lower Esophageal Sphincter, PPI: proton-pump inhibitor, SD: standard deviation

Table 5: Patient Reported Outcomes

	Eckardt		**BEDQ**		**GERDQ**	
	Median [IQR]	P value	Median [IQR]	P value	Median [IQR]	P value
CBT	4 [2-6]	0.36	6 [2.5-15]	0.15	6 [6-11.5]	0.98
No CBT	3 [2-5]		12 [5-25]		7 [6-11]	
AET nl	3 [2-4]	0.99	4 [0-10]	0.19	7 [6-10]	0.80
AET elev	3 [2-5]		8 [4-12]		7 6-12]	
DCI>100	3 [2-5]	0.03*	7 [3-14]	0.12	6 [6-10]	0.16
DCI<100	9 [3.5-9.5]		25 [10-26]		11 [6.5-12]	
AET nl (off PPI)	4 [2-5]	0.20	4 [0-14]	>0.99	7 [6-13]	0.33
AET elev (off PPI)	1.5 [1-2]		3.5 [0-7]		5.5 [5-6]	
AET nl (on PPI)	3 [1-5]	0.38	5 [0-10]	0.11	6.5 [6-10]	0.27
AET elev (on PPI)	4 [2-6]		12 [4-25]		8 [6-13]	

Abbreviations: AET: Acid-exposure Time, BEDQ: Brief Esophageal Dysphagia Questionnaire, CBT: Complete Bolus Transit, DCI: Distal Contractile Integral, GERDQ: Gastro-esophageal Reflux Disease Questionnaire, IQR: interquartile range

FIGURE LEGENDS:

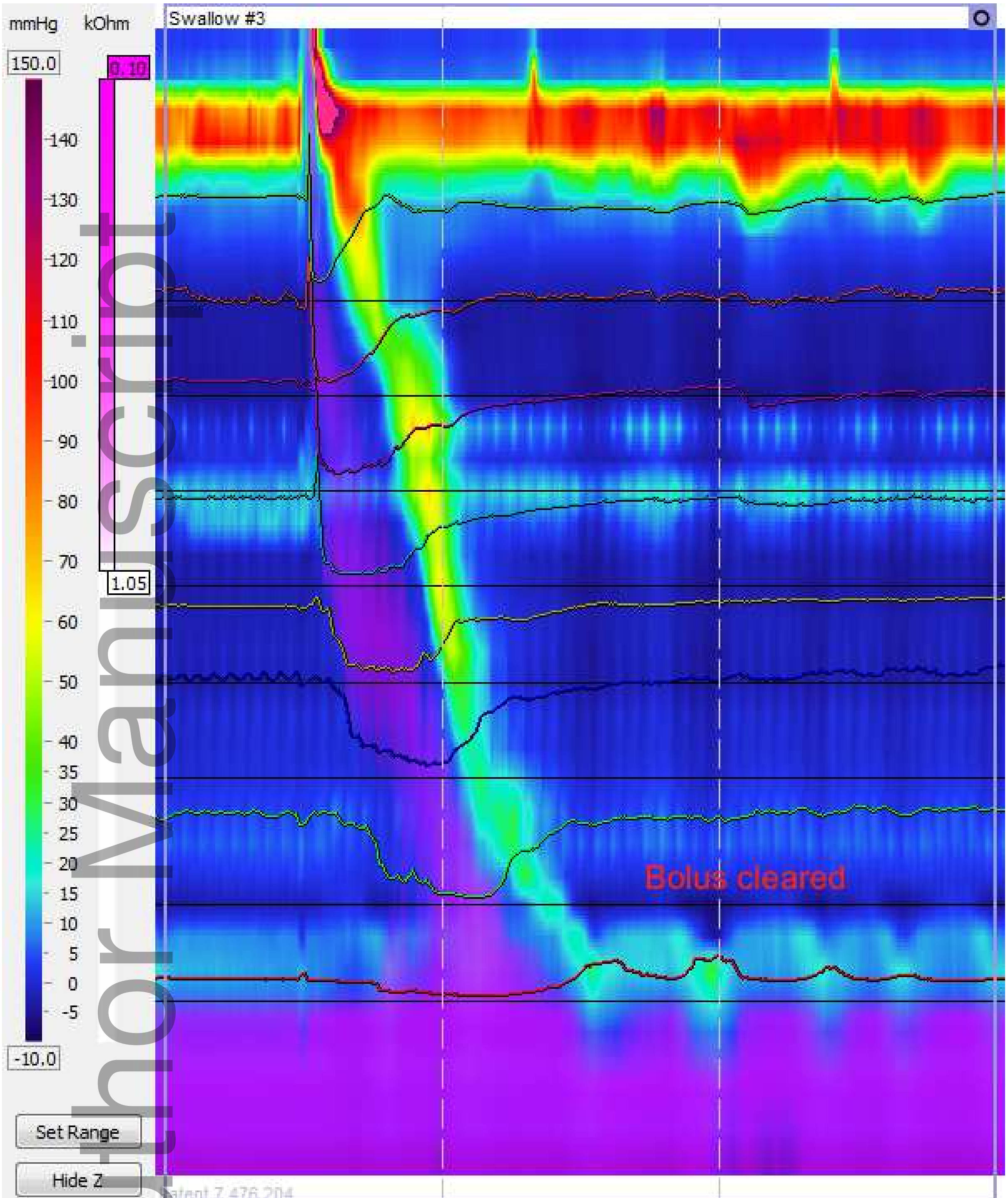
Figure 1: High-resolution Impedance Manometry (HRIM) depictions of bolus clearance in Ineffective Esophageal Motility. Conventional Impedance line tracings are superimposed on HRIM plots with colored impedance contour. Panel A shows an example of Complete bolus transit; Panel B shows an example of incomplete clearance.

Figure 2: Receiver-operating-characteristic curve of complete bolus transit (CBT) in association with Distal Contractile Integral (DCI) in all supine swallows.
AUC: Area-under-the-curve, NPV: Negative predictive value

Figure 3: Complete bolus transit compared amongst different Distal Contractile Integral (DCI) groups in Ineffective Esophageal Motility. Lines indicate comparisons to other groups. Asterisks (*) indicate presence of and magnitude of statistical significance.

Figure 4: Receiver-operating-characteristic curves showing incomplete clearance in association with ineffective swallows (Panel A) and failed swallows only (Panel B).
AUC: Area-under-the-curve, NPV: Negative predictive value

Figure 5: Box-and-whisker plots showing median scores for Eckardt, Brief Esophageal Dysphagia Questionnaire (BEDQ), and Gastroesophageal Reflux Disease Questionnaire (GERDQ) based on clearance, Acid-exposure time (AET), and median Distal Contractile Integral (DCI) per patient.
Asterisk (*) indicates statistical significance.
CBT: Complete bolus transit



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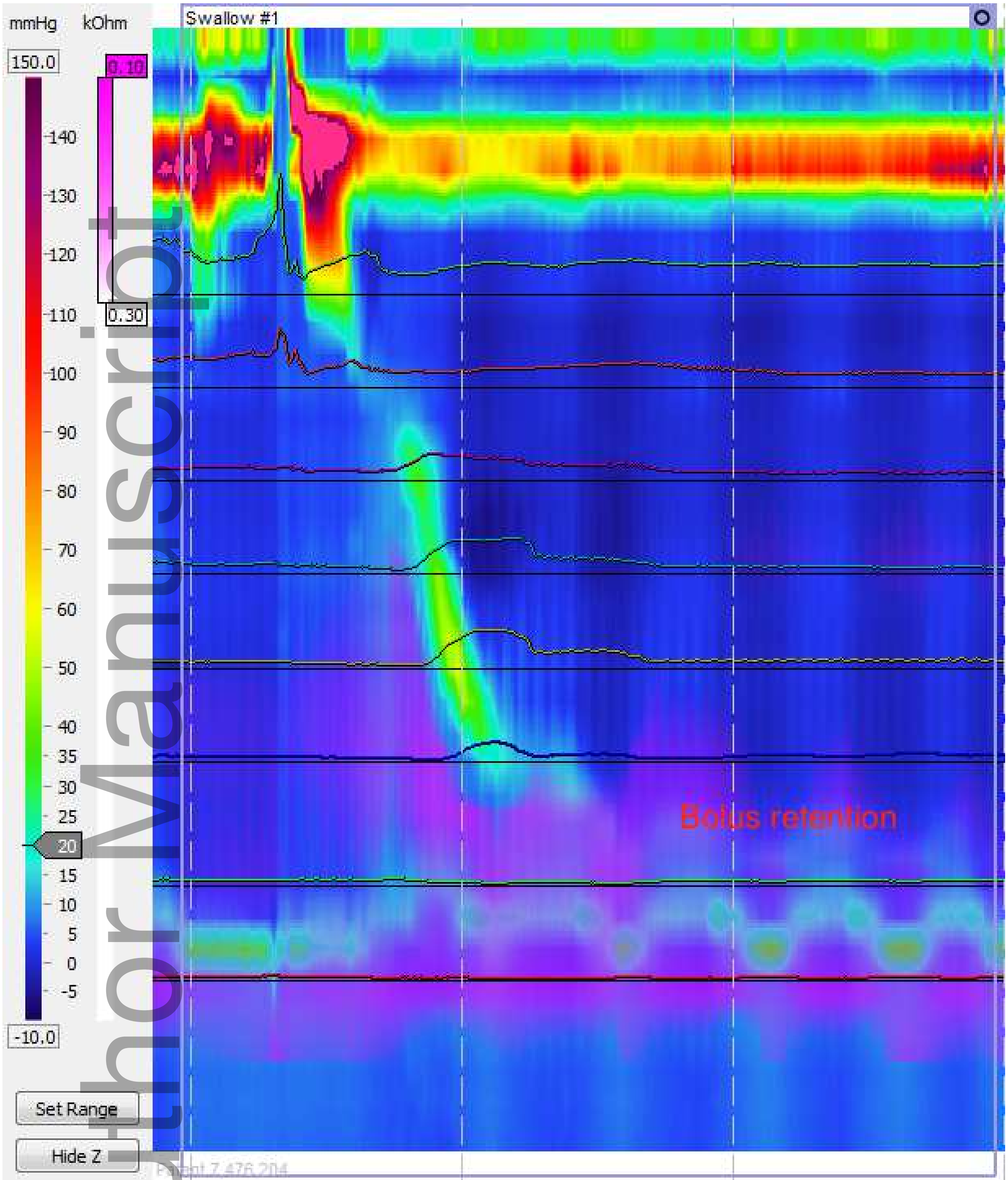

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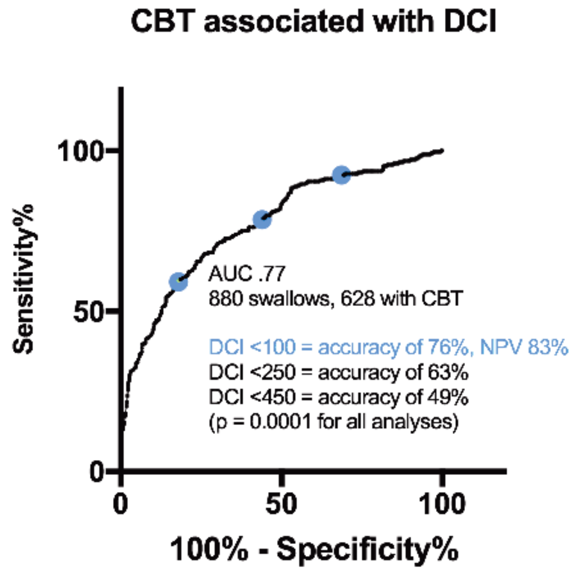

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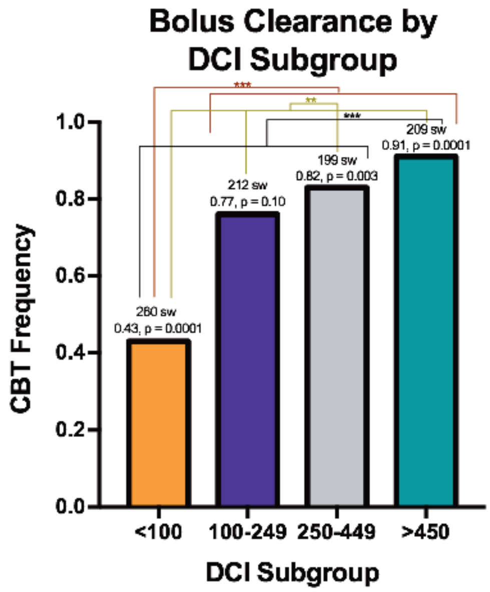

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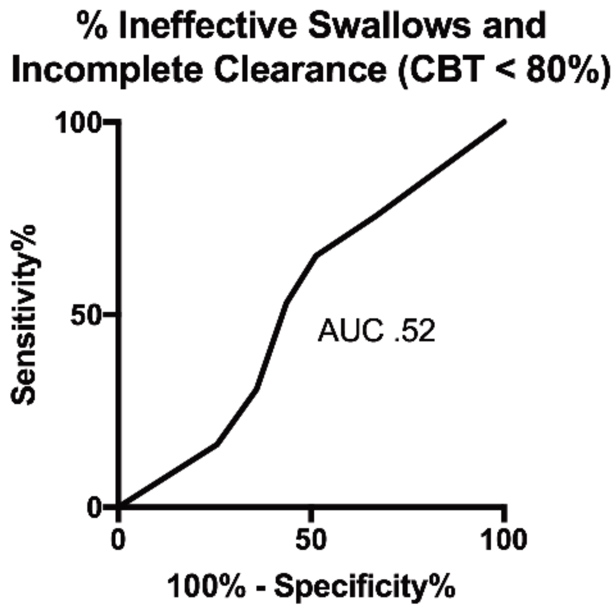

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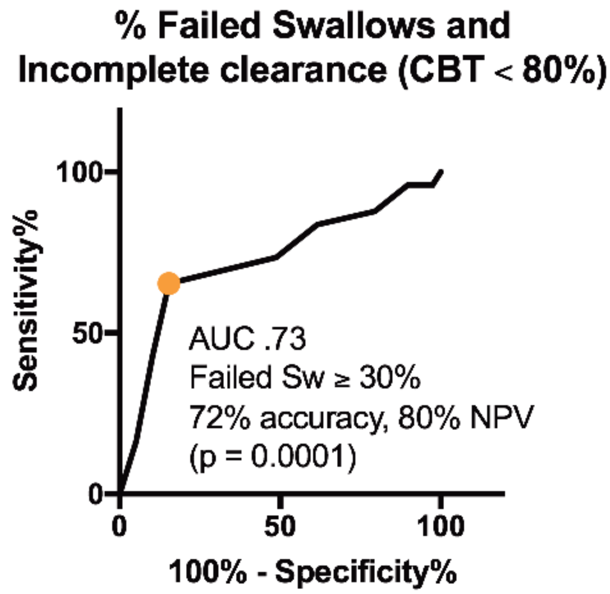

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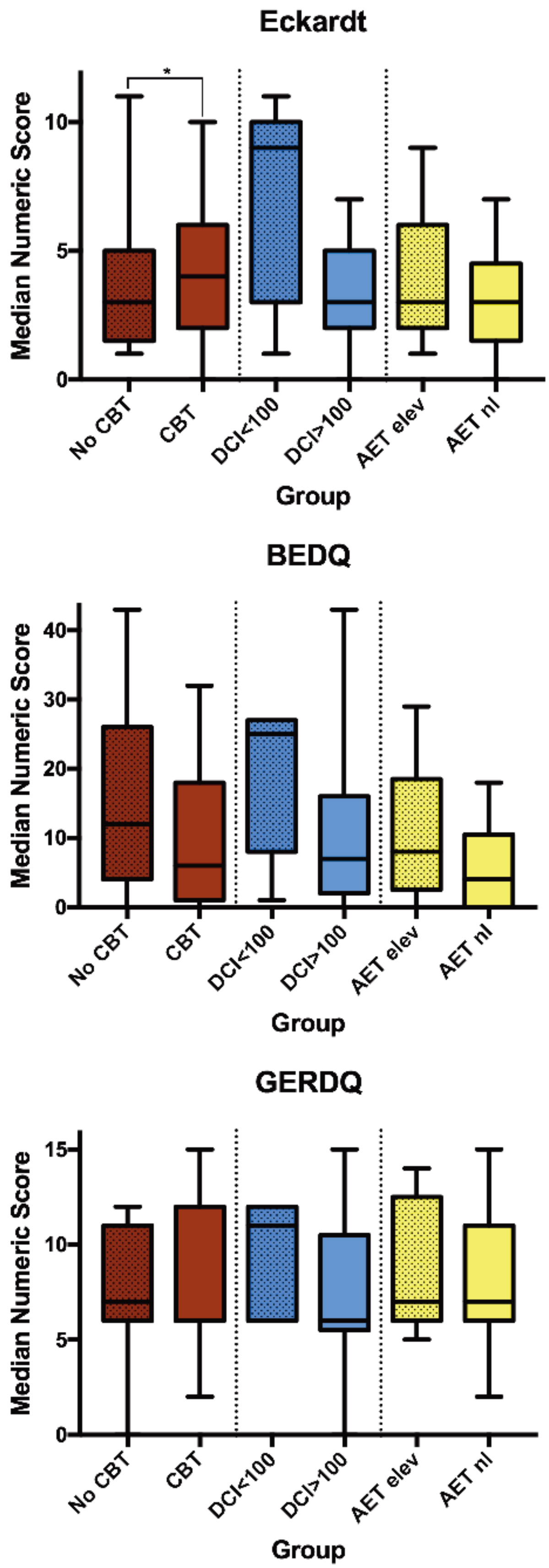

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