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Functional aspects of distal oesophageal spasm: the role of onset velocity and contraction amplitude on bolus transit

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Abstract

Background—Distal oesophageal spasm (DES) is a rare and under-investigated motility abnormality. Recent studies indicate effective bolus transit in varying percentages of DES patients.

Aim—Explore functional aspects including contraction onset velocity and contraction amplitude cut-off values for simultaneous contractions to predict complete bolus transit

Methods—We re-examined data from 107 impedance-manometry recordings with a diagnosis of DES. Receiver operating characteristic (ROC) analysis was conducted, regarding effects of onset velocity on bolus transit taking into account distal oesophageal amplitude (DEA) and correcting for intra-individual repeated measures.

Results—Mean area under the ROC curve for saline and viscous swallows were 0.84 ± 0.05 and 0.84 ± 0.04 , respectively. Velocity criteria of $>30\text{cm/s}$ when $\text{DEA} > 100\text{mmHg}$ and 8cm/s when $\text{DEA} < 100\text{mmHg}$ for saline and 32cm/s when $\text{DEA} > 100\text{mmHg}$ and $>7\text{cm/s}$ when $\text{DEA} < 100\text{mmHg}$ for viscous had a sensitivity of 75% and specificity of 80% to identify complete bolus transit. Using these criteria, final diagnosis changed in 44.9% of patients. Abnormal bolus transit was observed in 50.9% of newly diagnosed DES patients versus 7.5% of patients classified as normal. DES patients with $\text{DEA} > 100\text{mmHg}$ suffered twice as often from chest pain than those with $\text{DEA} < 100\text{mmHg}$.

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Conclusion—The proposed velocity cut-offs for diagnosing distal oesophageal spasm improve the ability to identify patients with spasm and abnormal bolus transit.

Keywords

DES; diffuse oesophageal spasm; distal oesophageal spasm; bolus transit; Impedance Manometry; MII-EM; dysphagia; chest pain; GERD

Introduction

Distal oesophageal spasm is an uncommon oesophageal motility abnormality with an estimated prevalence between 3-5% in patients undergoing oesophageal manometry testing [1, 2]. The clinical relevance, diagnostic and therapeutic implications as well as underlying pathophysiology have been a subject of controversy since 1889, when a case series of patients with symptoms of chest pain and dysphagia attributed to oesophageal motility abnormality were described in the surgical literature [3].

Before the advent of manometry, spasm was a clinical and radiologic diagnosis. However due to limited sensitivity and specificity, radiologic exams were later shown to be primarily complimentary [4, 5]. Manometry was first used to define spasm as a motor disorder incorporating simultaneous contractions and intermittent regular peristalsis in the 1960's [6, 7]. Since then the definition of spasm has changed over the years with variable cut-off values used for amplitude, frequency and propagation velocity. Currently, spastic swallows are defined by a distal oesophageal propagation velocity faster than 8cm/second with an amplitude of >30mmHg in the distal oesophagus. If more than 20% of contractions meet these criteria a patient is diagnosed with oesophageal spasm [8, 9]. A review of the current American Gastroenterology Association (AGA) guidelines for oesophageal manometry and the available published literature on oesophageal spasm did not allow us to clearly retrace the origin of the widely accepted 8cm/s discriminatory value for peristaltic front wave velocity [8, 9] in separating simultaneous from peristaltic swallows. It was most likely based on a study discerning bolus transit dependent on propagation velocity in a small number of patients with a variety of oesophageal motility disorders. The authors reported an excellent sensitivity and positive-predictive value in determining abnormal abnormal bolus transit as validated by video-fluoroscopy for an onset velocity of > 6.25cm/s [4]. However later studies from our group reported normal bolus transit in 33-67% of simultaneous swallows in contrast to 100% incomplete bolus transit data from the fluoroscopically viewed swallows [4, 11, 12]. We were therefore interested in further exploring the diagnosis of oesophageal spasm on the basis of both propagation velocity and patient symptoms in regard to both manometric and bolus transit properties.

Objectives

This study evaluates the physiologic properties of patients with DES focussing on the effects of propagation velocity related to bolus transit properties and patient symptoms. As the currently accepted speed cut-offs have been based on bolus transit as per barium radiography, the aim of our study was to characterize bolus transit, manometric findings and symptoms with respect to oesophageal propagation velocity using combined oesophageal multichannel impedance-manometry during saline and viscous swallows.

Methods

We identified patients with a diagnosis of distal oesophageal spasm from patient files analyzed between June 2004 and March 2009. Clinical and demographic patient information used was age of patient and primary presenting symptoms during a standardized interview

prior to each impedance-manometry study. Ethical approval was granted for the retrospective patient data analysis of our patient database by the local institutional review board.

Each patient underwent oesophageal function testing using combined MII-EM with a Koenigsberg 9-channel probe (EFT-catheter; Sandhill Scientific Inc., Highlands Ranch, CO, USA). The 4.5-mm-diameter catheter generates pressure data from 5 solid-state pressure sensors placed 5cm apart. Impedance measuring segments consisting of two metal rings placed 2cm apart are centred at 10, 15, 20, and 25cm from the tip. The EFT catheter was inserted transnasally into the oesophagus up to a depth of 60cm, and collection of impedance and manometric data (30Hz) was initiated. The lower oesophageal sphincter (LES) was identified using a station pull-through technique and the most distal sensor was placed in the high-pressure zone of the LES. Intraesophageal pressure sensors and impedance measuring segments were thus located at 5, 10, 15, and 20cm above the LES.

Patients were given 10 swallows of 5 ml normal saline and 10 swallows of 5 ml viscous (Sandhill Scientific Inc., Highlands Ranch, CO, USA) test substance 20–30 seconds apart. Manometric parameters used to characterize swallows included (1) contraction amplitude at 5 and 10cm above the LES, (2) distal oesophageal amplitude (DEA) as an average of contraction amplitude at 5 and 10cm above the LES, (3) onset velocity of oesophageal contractions in the distal part of the oesophagus (i.e., contraction velocity between 10 and 5cm above the LES, Figure 1). The LES residual pressure was measured as the lowest pressure during swallow-induced LES relaxation. Manometric landmarks were identified incorporating impedance information for bolus entry to avoid misinterpreting intra-bolus pressure as peristaltic front (Figure 1). Bolus entry at a specific level was identified by the 50% point between 3-s pre-swallow impedance baseline and impedance nadir during bolus presence. Bolus exit was determined as return to this 50% point on the impedance recovery curve as discussed in previous studies (Figure 1) [13]. Total bolus transit time was calculated as the time elapsed from bolus entry in the proximal channel 20cm above the LES to bolus exit in the distal channel 5cm above the LES when bolus exit was present. For each patient, we calculated mean DEA for liquid and viscous swallows, mean LES residual pressure and mean bolus transit time. Swallows were classified using previously published manometric criteria [9]. All patients diagnosed as DES based on criteria mentioned above had their individual swallows grouped and classified according to receiver operating characteristic (ROC) analyses results. Complete bolus transit was defined when bolus entry occurred at the most proximal site (20cm above LES) and bolus exit points were recorded in all three distal impedance-measuring sites (i.e., 15, 10, and 5cm above the LES). Incomplete bolus transit was diagnosed when bolus exit was not identified at any one of the three distal impedance-measuring sites. For the 10 grouped swallows oesophageal transit abnormalities overall incomplete liquid transit was defined by at least 30% of swallows showing incomplete bolus transit and incomplete viscous transit if at least 40% of swallows had incomplete bolus transit [13].

Statistics

Descriptive statistics (number and percentages) were used to describe manometric and impedance findings in this group of patients. Continuous data are presented as mean ($\pm$ standard deviation) unless specified otherwise.

A series of generalized linear mixed models were fit to the data in order to determine a final predictive model for incomplete bolus transit as determined by MII with fixed effects of bolus transit velocity (cm/sec) and DEA. Receiver operating characteristic (ROC) analyses were conducted for saline and viscous swallows, separately, to determine ideal velocity cut-off values for predicting incomplete bolus transit for a given DEA value.

The ROC analyses consisted of a bootstrap sampling method in which a computer algorithm randomly sampled one swallow from each subject's record, generating a sampled dataset of independent observations. A simple logistic regression model involving the DEA category variable and velocity was fit to each sampled dataset. A ROC curve was constructed based on this model for each iteration, and parameter estimates and areas under the ROC curve were captured. ROC results and parameter estimates were averaged across all iterations in order to estimate final model parameters and an overall ROC curve.

Generalized linear mixed models (GLMM) for repeated measures were constructed for outcomes of MII diagnosis (complete vs. incomplete), bolus transit time, and LES residual pressure. Average DEA, LES pressure and BTT were calculated for each subject, and analysis of variance (ANOVA) was used to calculate the differences in these values among the groups of patients with chest pain, dysphagia, and GERD symptoms. Bonferroni corrections for simultaneous comparisons were used for all post-hoc analyses comparing means across groups. Statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA). Statistical significance level was set at 0.05.

Results

Patient demographics

From June 2002 to March 2009 a total of 2726 oesophageal motility exams involving combined MII-EM were performed at our laboratory, and 125 (4.5%) patients were diagnosed with distal oesophageal spasm in this time period. Data from 107 patients were available for analysis. Sixty-three patients were female (mean age 56, range 18-87) and 44 male (mean age 62, range 19-86, $p=0.1$)

Swallow Characteristics dependent on propagation velocity – per swallow analysis

A total of 1070 liquid and 1065 viscous swallows were available for analysis. Of the saline swallows 46.2% were classified as simultaneous, 47.5% as normal and 6.3% as ineffective. Of the viscous swallows 37.9% were simultaneous, 51.4% normal and 10.7% were ineffective. After exclusion of all ineffective swallows (maximum contraction amplitude <30mmHg at 5 and/or 10cm above LES), the remaining liquid (1003) and viscous (950) swallows were reclassified manometrically based on propagation velocity between measuring points 5 and 10cm above the upper border of the LES and ROC results.

The mean area ($\pm$ standard deviation) under the ROC curve across all simulations for saline swallows was 0.84($\pm$ 0.05) with 95% bootstrapped confidence limits (0.73,0.93). Similarly, the mean area under the ROC curve for viscous swallows 0.84($\pm$ 0.04), with 95% bootstrapped confidence limits (0.76,0.92) indicating a good model fit (Figure 2). During data interpretation it became evident that both velocity and contraction amplitude strongly predict bolus transit. The ROC analysis therefore incorporated both velocity and contraction amplitude.

Due to the relevance of rising contraction amplitude regarding bolus transit we had to divide our data set. In order to generate a clinically feasible tool we decided to use a simple dichotomous split in swallows generating more and less than 100mmHg. This split could have been performed using a continuous data model or with smaller differentiation fields (i.e. 10 or 20mmHg difference), yet we found using a discriminatory cut-off of 100mmHg yielded consistent results in predicting bolus transit. Individual swallows with a peristaltic front velocity greater than 30cm/s for DEA 100mmHg had between 70% and 75% average sensitivity and an average false positive rate between 15% and 21% in predicting incomplete swallows. For low DEA values (<100mmHg), a cut-off of 8cm/s had essentially the same

average sensitivity and specificity in predicting incomplete bolus transit (Table 1). Similarly, the viscous cut-off values based on ROC analyses were 32cm/s and 7cm/s for high and low DEA values, respectively (illustrates the average ROC curves observed across all simulations for saline and viscous swallows).

Saline swallows reclassified as simultaneous were significantly more likely to have incomplete (n=138/261, 52.9%) bolus transit than those classified as normal (n=53/739, 7.2%, $p<0.0001$). In the low DEA group, the odds of incomplete bolus transit for simultaneous swallows were 8.8 times the odds of incomplete bolus transit for normal swallows (95% confidence limits (4.6,17.2)), and in the high DEA group, the odds of incomplete bolus transit for simultaneous swallows were 14.1 times the odds of incomplete bolus transit for normal swallows (95% confidence limits (6.4,30.8)). The same could be seen in viscous swallows ($p<0.0001$, OR for low DEA=5.5 with 95% confidence limits (3.2,9.2), OR for high DEA=14.8 with 95% confidence limits (7.3,29.8)). Overall percentages are depicted in Figure 3.

For liquid and viscous swallows with successful bolus transit, mean $\pm$ SEM bolus transit time (BTT) for liquids was not different for simultaneous swallows (6.6 $\pm$ 0.2s) compared to normal ones (6.3 $\pm$ 0.1s, $p=0.56$). Similarly, BTT for viscous swallows were similar ($p>0.05$) for simultaneous 6.8 $\pm$ 0.2s and normal 6.9 $\pm$ 0.1 sec contractions. Furthermore no difference in lower oesophageal sphincter residual pressure (LES-RP) during liquid and viscous peristaltic and simultaneous swallows was found (6.2 $\pm$ 0.2mmHg liquid versus 6.5 $\pm$ 0.3mmHg viscous and 7.5 $\pm$ 0.4mmHg liquid versus 7.1 $\pm$ 0.4mmHg viscous swallows ($p=0.73$ liquid, $p=0.06$ viscous)).

Swallow characteristics dependent on symptoms– per patient analysis

The patients' most common presenting chief complaint was dysphagia (n=47, 44%), 25 (23%) complained of chest pain, and 35 (33%) indicated primarily GERD symptoms.

Mean $\pm$ SEM distal oesophageal amplitude (DEA) was higher in the chest pain group (178 $\pm$ 24mmHg) compared to patients presenting with dysphagia (118 $\pm$ 7mmHg) or GERD (119 $\pm$ 10mmHg) symptoms both for liquid ($p=0.0029$ and $p=0.0059$, respectively) swallows and viscous swallows (DEA chest pain 163 $\pm$ 24mmHg versus dysphagia 111 $\pm$ 7mmHg and GERD 118 $\pm$ 13mmHg, $p=0.02$ and $p=0.09$, respectively).

Saline BTT was overall fastest in the chest pain group, however in the post hoc analysis this was significant only when compared to dysphagia patients ($p=0.03$). For viscous swallows, there were no significant differences in BTT based on patient symptoms. Residual lower sphincter pressure was also not statistically different when compared across symptom groups. Mean $\pm$ standard deviation (to provide a measure of the variability of data) manometric and bolus transit data grouped according to main presenting symptom are displayed in Table 2.

Patient re-classification based on ROC analysis results

If 20% or more (2/10) of a patient's liquid swallows exceeded the velocity cutoff determined by the ROC analysis (8cm/s for low DEA and 30cm/s for high DEA), that patient was classified as DES. This resulted in a change of final diagnosis in 48 (44.9%) patients. Due to average DEA 220mmHg, 8 of these 48 patients now qualified for diagnosis of nutcracker oesophagus [14]. Fifty-nine (55.1%) patients remained classified with the diagnosis of DES, and all patients in the low DEA group remained classified as DES. Twenty-seven of the newly classified DES patients (45.8%) complained of dysphagia, 10 from chest pain (16.9%) and 22 from GERD symptoms (37.3%). The symptom breakdown for the newly classified patients is displayed in Figure 4.

The newly classified DES patients showed a larger percentage of swallows with incomplete bolus transit than newly classified normal and nutcracker oesophagus for liquid (29.4% for DES versus 7.7% normal and 5.0% nutcracker, respectively, $p<0.0001$) and viscous (38.6% DES versus 13.9% normal and 1.2% nutcracker, $p<0.0001$).

Of 107 patients originally diagnosed with DES, bolus transit was abnormal in 33 (30.8%) based on liquid swallow diagnosis. After implementation of the new diagnostic criteria, 37/40 (92.5%) patients classified as normal and 8/8 (100%) of those with nutcracker oesophagus showed overall normal bolus transit based on saline swallows compared to only 29/59 (49.2%) of patients with a diagnosis of DES ($p<0.0001$).

Discussion

In the present study we propose a new definition for distal oesophageal spasm based on bolus transit information assessed by multichannel intraluminal impedance measurements. Current data advocate for different velocity criteria tailored to the amplitude of contractions and consistency of swallowed material. The new criteria better identify better manometric simultaneous contractions associated with abnormal bolus transit compared to the conventional.

A major review in 1984 concluded that oesophageal spasm was a poorly understood entity, and future developments in oesophageal manometry should yield additional information [15]. However little advances have been made since: The original criterion for the number of simultaneous contractions to be considered indicative of oesophageal spasm resulted from an analysis of 95 normal healthy volunteers of whom none had more than 10% simultaneous contractions. Oesophageal spasm was considered a rare entity, even when the cut-off for definition of oesophageal spasm was set as low as 20% liquid swallow simultaneous contractions [16]. It led authors to suggest that a minimum amplitude for the diagnosis of spasm should not be considered as this would make spasm a very rare diagnosis [15]. Initially 4.5% of our 2726 patients studied with combined impedance-manometry were diagnosed with distal oesophageal spasm. Using the new criteria only half (2.5% total) of those patients would still be given a diagnosis of spasm. This is in accordance to the most recent technical review of the American Gastroenterological Association (AGA) commenting on the rare occurrence of oesophageal spasm [8].

Current velocity criteria are based on a study in 16 patients with oesophageal spasm, nutcracker oesophagus, and non-specific oesophageal motility disorder: The authors reported 98% sensitivity and positive-predictive value for incomplete bolus transit with a propagation front velocity $> 6.25\text{cm/s}$ during oesophageal manometry when using video-fluoroscopy as reference method [4]. Contraction amplitude was not taken into account, and onset velocity was determined manually off paper print manometry records. Other authors employed 10cm/s [17] or 20cm/s [18] contraction velocity discriminating between normal peristalsis and spasm, and still others descriptively separated on basis of “progressiveness of peristalsis at adjacent manometry ports” [19] or even included assessment of peak peristalsis [20]. Earlier reports describing oesophageal spasm patients with low amplitude simultaneous contractions were most likely misdiagnosing achalasia for spasm and are therefore difficult to put into context with our data [21]. Although we changed the criteria for propagation wave velocity cut-off, we still used the 20% minimum number of simultaneous swallows required for a diagnosis of spasm. We believe that a reduction to a single simultaneous swallow would lead to a great decrease in specificity, as even normal subjects occasionally exhibit a singular aperistaltic or fast antegrade swallow [16].

Contraction amplitude proved an important determinant in patient symptomatology: Chest pain patients exhibited the highest DEA and newly classified nutcracker oesophagus patients exhibited chest pain in 62% of cases versus only 17% of DES patients. In agreement with data from Allen and DiMarino, DES patients with a mean DEA >100mmHg complained more often from chest pain than those below that threshold [17]. Vice versa one case series reported that only 3% of patients with dysphagia and chest pain show a manometric presentation of spasm [22]. This underlines that these symptoms itself are non-specific and cannot be used to predict oesophageal spasm. Other studies underlining the association of spasm with chest pain described patients that really would be termed nutcracker oesophagus or possibly “spastic nutcracker” by our criteria [23, 24]. These patients may suffer from chest pain due to muscular ischemia [25] rather benefitting from amplitude reduction versus patients with bolus transit defects and lower contraction amplitudes, who might even experience worsening of their condition with such treatment. Spasm was an incidental finding in the majority of our patients classified as DES that were being tested in the evaluation for GERD related symptoms. Oesophageal spasm has been shown to be elicited by intra-oesophageal acid infusion both by manometry and more recently using endoscopic ultrasound [26, 27]. Pehlivanov et al. documented sustained oesophageal contractions after oesophageal acid exposure, showing that heartburn could result from abnormality at the muscle level of the oesophagus [27]. Other authors have been able to document acid-induced oesophageal spasm with concurrent chest pain [26].

Increased LES pressure has been described in patients with distal oesophageal spasm; other studies have failed to demonstrate consistent effects. We found numerically higher LES residual pressures in simultaneous swallows, however changes were not significant compared to normal swallows. Our findings are consistent with Campo and Traube reporting both higher and lower LES pressures in patients with DES, making either finding unspecific [20]. Incomplete LES relaxation is one feature of achalasia. In older case series describing the progression of DES to achalasia [28, 29] in conjunction with higher LES sphincter basal or residual pressure, patients may have been misclassified as DES initially as often seen in our referral practice.

The reclassification of DES patients may have important implications toward treatment of symptoms based on underlying pathophysiology. We hypothesize that patients with higher mean DEA, especially those associated with chest pain, might profit from therapies decreasing oesophageal body and LES residual pressure such as nitrate-donors and calcium channel inhibitors in addition to aggressive antacid treatment. In contrast, patients with dysphagia, especially associated with low contraction amplitudes and impaired bolus transit as underlying pathology, might respond better to prokinetic therapy with procholinergic agents such as pyridostigmin to facilitate better bolus transport.

In conclusion, based on our analysis of the largest reported DES cohort to date in conjunction with assessment of bolus transit, we propose a new classification for the diagnosis of distal oesophageal spasm. We suggest using the term spasm for saline swallows with an onset velocity >30cm/s when DEA ≥ 100mmHg and faster than 8cm/s when DEA <100mmHg. These criteria will make the diagnosis of oesophageal spasm rarer but more specific with regards to functional defect.

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Figure 1.

Example of a liquid swallow with fast antegrade peristalsis (18.5 cm/s) as determined between 5 and 10 cm above the lower oesophageal sphincter (LES). The yellow lower part portrays the manometric channels (EM) including the LES, with amplitude given in mmHg on the y-axis and time on the x-axis. The upper part shows four impedance segments (MII) with a bolus that fully clears. The lines on the y-axis are measured in ohms over time on the x-axis, the purple colour allows better visualization of bolus present.

Figure 2.

Panel A: The red arrows correspond to values in Table 1 for **saline swallows**.

(1) corresponds to sensitivity of 70% and false positive rate of 15%. The velocities associated with this point are 31.4 cm/sec for high DEA (≥ 100 mmHg) and 10.1 cm/sec for low distal oesophageal amplitude (DEA <100 mmHg).

(2) Corresponds to 75% sensitivity, 21% false positive rate, and 28.8 cm/sec and 7.5 cm/sec for high and low DEA, respectively.

(3) Corresponds to 80% sensitivity, 28% false positive rate, and 26.2 cm/sec and 4.9 cm/sec for high and low DEA, respectively.

Panel B: The red arrows correspond to values in Table 1 for **viscous swallows**.

- (1) Corresponds to sensitivity of 70% and false positive rate of 17%. The velocities associated with this point are 32.6 cm/sec for high DEA (≥ 100 mmHg) and 8.1 cm/sec for low distal oesophageal amplitude (DEA <100 mmHg).
- (2) Corresponds to 75% sensitivity, 21% false positive rate, and 31.0 cm/sec and 6.4 cm/sec for high and low DEA, respectively.
- (3) Corresponds to 80% sensitivity, 27% false positive rate, and 29.2 cm/sec and 4.7 cm/sec for high and low DEA, respectively.

Figure 3. Percentages of Complete and Incomplete Swallows for New Classification Criteria

Figure 4. Patient Reclassification based on new criteria and their symptom and manometric properties

Table 1
Receiver Operated Curve Results

Substance	Mean False Positive Rate *	Mean Sensitivity	Velocity Cutoff High DEA (100)	Velocity Cutoff Low DEA (<100)
Saline	15%	70%	31.4 cm/sec	10.1 cm/sec
	21%	75%	28.8 cm/sec	7.5 cm/sec
	28%	80%	26.2 cm/sec	4.9 cm/sec
Viscous	17%	70%	32.6 cm/sec	8.1 cm/sec
	21%	75%	31.0 cm/sec	6.4 cm/sec
	27%	80%	29.2 cm/sec	4.7 cm/sec

* False positive rate is equivalent to 1-specificity

DEA, distal oesophageal amplitude

Table 2
Saline and Viscous (mean±standard deviation) manometric and bolus transit property values grouped according to main presenting symptom

Saline			
Symptom Comparison	Mean DEA	Mean BTT	Mean LES-RP
(1) GERD	118.52±57.58	6.40±1.59	6.28±3.95
(2) Dysphagia	117.83±45.17	6.89±2.00	6.60±4.39
(3) Chest Pain	178.44±117.94	5.72±1.65	6.23±8.05
Overall Comparison of Means ^{††}	p=0.0018	p=0.0329	p=0.9465
(1) GERD-(2) Dysphagia	0.69 (-38.47,39.85)	-0.49 (-1.47,0.49)	-0.33 (-3.23,2.58)
(1) GERD-(3) Chest Pain	-59.92 (-105.85,-13.99) ^{**}	0.68 (-0.46,1.83)	0.05 (-3.36,3.45)
(2) Dysphagia-(3) Chest Pain	-60.61 ±17.84 (-104.03,-17.19) ^{**}	1.18 (0.09,2.26) [*]	0.37 (-2.85, 3.59)
Viscous			
Symptom Comparison	Mean DEA	Mean BTT	Mean LES-RP
(1) GERD	117.99±74.33	7.25±2.28	5.07±5.76
(2) Dysphagia	110.64±48.23	7.15±2.27	7.09±5.47
(3) Chest Pain	162.78±118.01	6.55±1.85	7.54±6.49
Overall Comparison of Means ^{††}	p=0.0234	p=0.4312	p=0.1887
(1) GERD-(2) Dysphagia	7.35 (-34.90,49.60)	0.10 (-1.10,1.30)	-2.02 (-5.18,1.14)
(1) GERD-(3) Chest Pain	-44.79 (-94.35,-4.77) [‡]	0.70 (-0.70, 2.09)	-2.46 (-6.17,1.24)
(2) Dysphagia-(3) Chest Pain	-52.14 (-98.99,-5.29) [*]	0.60 (-0.72, 1.92)	-0.44 (-3.94,3.06)

p<0.05,

^{**}

p<0.01,

^{***}

p<0.001,

[‡]

p<0.10,

^{††}

95% adjusted confidence intervals are given in parenthesis where appropriate

DEA, distal oesophageal amplitude; BTT, bolus transit time; LES-RP, lower oesophageal sphincter residual Pressure; GERD, gastro-oesophageal reflux disease