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Assessing the pre- and post-peak phases in a swallow using esophageal pressure topography

Yinglian Xiao¹, Dustin A. Carlson², Zhiyue Lin², Nicolas Rinella², Daniel Sifrim³, and John E. Pandolfino²

¹Department of Gastroenterology and Hepatology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

²Department of Medicine, the Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

³Department of Gastroenterology, Barts and the London School of Medicine and Dentistry, Wingate Institute of Neurogastroenterology, Queen Mary University of London, UK

Abstract

Background and aim—The current paradigm of measuring esophageal contractile vigor assesses the entirety of a pressure wave using a single measurement, the distal contractile integral (DCI). We hypothesize that an assessment identifying separate phases of the contractile pressure wave before and after the pressure peak may help distinguish abnormalities in patients presenting with chest pain and dysphagia. The aim of the present study was to develop a technique to assess the individual phases and report on the values in healthy controls.

Method—71 Healthy controls were enrolled. High resolution manometry studies of five intact liquid swallows in both supine and upright positions were analyzed using a customized MATLAB program to divide swallows into a pre-peak phase and post-peak phase, and compute the contractile integral of both phases. The contractile integrals were also controlled by duration over each phase.

Result—The composite DCI measurement in healthy controls appears to be weighted towards slightly higher contractile activity during post-peak phase based on post-peak to pre-peak ratios in both the supine and upright position (1.50 and 1.49 respectively). The contribution of post-peak phase on the composite DCI was weakened when controlled by time (0.92 and 0.96 in both supine and upright position respectively).

Conclusion—We developed a novel measurement focused on separating the pre-peak and post-peak components of the peristaltic contractile activity during swallowing. Using this technique, it

Correspondence: Yinglian Xiao, MD & Ph.D, Department of Gastroenterology and Hepatology, The First Affiliated Hospital, Sun Yat-sen University, 58 Zhongshan Road 2, Guangzhou, China, 510080, Fax: 86-20-87332916, yinglian.xiao@gmail.com.

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appears that overall contractile activity is higher during post-peak phase and this is related to the longer time component during this phase.

Keywords

Esophagus; Swallow; Physiology; High Resolution Manometry

Background

Peristaltic function is classically described by the contractile vigor of the propagating wave and is phenotyped into categories based on hypo- and hyper-contraction in conventional line tracing manometry based on the pressure wave amplitude of the tracing [1]. With the advent of high-resolution manometry (HRM), a composite measure was developed to assess contractile vigor that incorporated contraction duration and length with pressure amplitude of the contractile segment: the distal contractile integral (DCI) [2]. Although this approach was a more comprehensive measure of contractile activity, it largely ignored the nuance and detail of contractile activity that is made up of an isometric contraction during the pre-peak phase and isometric relaxation that is occurring during the post-peak phase.

Chest pain and dysphagia are two major symptoms in patients with hypercontractile esophagus or jackhammer esophagus. These symptoms are believed to be derived from over-contraction in the distal esophagus. However, using the current paradigms of esophageal motility interpretation, there is a poor correlation between contractile activity and symptoms noted on both conventional manometry and HRM [3–5]. We theorize that the added detail provided by HRM could be leveraged to further delineate *phases* of the esophageal contractile wave. The up-slope of the peristaltic pressure wave (“pre-peak”) can be separately assessed to describe the contractile (active) phase of esophageal peristalsis, while assessment of the down-slope of the contractile pressure wave (“post-peak”) would reflect the relaxing phase. Novel characterization of the quantitative and qualitative aspects of these phases of the esophageal peristaltic pressure wave may address the discrepancy between symptoms and contractile activity as presently evaluated.

Thus, the goal of the present study was to develop a technique to assess the individual pre-peak and post-peak phases of peristalsis and determine normative values.

METHODS

Subjects

Volunteers were recruited by advertisement or word of mouth and had no history of esophageal symptoms (heartburn, regurgitation, dysphagia), previous gastrointestinal surgery, or significant medical conditions. These subjects have been previously described [2]. A total of 75 healthy controls were recruited (age range 19–48 yrs, 35 females); 4 subjects were excluded due to an insufficient number of analyzable swallows. The study protocols were approved by the Northwestern University Institutional Review Board and informed consent was obtained from each subject.

Study protocol

HRM studies were done after at least a 6-hr fast. The HRM catheter was 4.2 mm outer diameter solid-state assemblies with 36 circumferential sensors at 1-cm intervals (Medtronic Inc, Shoreview, MN). Transducers were calibrated at 0 and 300 mmHg using externally applied pressure. The manometry assembly was placed transnasally and positioned to record from the hypopharynx to the stomach with about 3 intra-gastric sensors. The study protocol included at least 30-s baseline recording and ten, 5-ml water swallows in both the supine and upright positions.

Esophageal pressure topography (EPT) analysis

EPT data were analyzed using ManoView™ analysis software (Given Imaging, Los Angeles, CA), as well as a customized MATLAB (The Math Works, Natick, MA) program. The first 5 intact swallows in both supine and upright positions were analyzed. For each swallow, the distal contractile integral (DCI) was measured in the traditional method [6]. Then, components of the DCI were measured using a novel analysis paradigm using the MATLAB program [7]: the DCI of each swallow was divided into a pre-peak phase and post-peak phase by plotting the trajectory of the pressure wave peaks at 1 cm intervals from the transition zone to the proximal aspect of the EGJ (Figure 1). The contractile integral, i.e. pressure amplitude $\times$ duration $\times$ axial length (mmHg $\bullet$ s $\bullet$ cm), was then computed for both phases: the pre-peak contractile integral (PREP-CI) and post-peak contractile integral (POSP-CI) (Figure 2). Thus, the sum of the PREP-CI and POSP-CI equaled the traditional DCI of a single swallow.

To account for the contribution of contraction-phase durations to the contractile integrals, time-controlled (tc) metrics, i.e. pressure amplitude $\times$ axial length, were also obtained. To generate the tc metrics, the duration in seconds of each phase was measured for each 1-cm axial segment; the 1-cm segment contractile integral was then divided by the segment duration to generate the tc-measure in mmHg $\bullet$ cm. The PREP-CI-tc and POSP-CI-tc were then calculated as the sum of all the time-controlled axial segments for the PREP and POSP phases, respectively. The DCI-tc was calculated similarly for the total pressure-wave durations, and therefore equaled the sum of the PREP-CI-tc and POSP-CI-tc.

The component measurements of distal peristalsis were also applied to the second (S2) and third (S3) contractile segments, as defined by Clouse and Staiano [8].

Finally, the directionality and propagation velocity of the pressure wave peaks was assessed. To assess the directionality, the time between pressure wave peaks was calculated for each 2-cm axial interval: positive time-value would reflect antegrade propagation while negative time-values would reflect uncoordinated and/or retrograde propagation. The peak propagation velocity (PPV) was defined as the slope from the peak pressure point in the transition zone to the corresponding point in the EGJ (Figure 3).

Statistical analysis

To maintain statistical independence of variables, the median values of the five analyzed swallows by position and the single swallow with the greatest DCI for each position from

each subject were utilized for statistical analysis. All the data including the PREP-CI, POSP-CI, POSP-CI/PREP-CI ratio, DCI, PREP-CI-tc, POSP-CI-tc, POSP-CI-tc/PREP-CI-tc ratio, DCI-tc were presented as median (inter-quartile range, IQR). Statistical comparisons were performed using the Wilcoxon-signed rank test. A p-value <0.05 was considered significant. The statistical analysis was done by using the IBM SPSS 20.0 (IBM, Chicago, USA).

RESULTS

Novel contractile EPT metrics, median values

The median values of PREP-CI, POSP-CI, POSP-CI/PREP-CI, DCI, PREP-CI-tc, POSP-CI-tc, DCI-tc and POSP-CI-tc/PREP-CI-tc for supine and upright positions are presented in Table 1. The composite DCI measurement in healthy controls appears to be weighted towards a slightly higher contractile integral during post-peak phase based on POSP-CI/PREP-CI ratios in both the supine and upright position at both S2 and S3 section (Table 1). However, when the integral was controlled by time, the influence of POSP-CI was weakened.

Novel contractile EPT metrics for both supine swallows and upright swallows with maximal DCI

The metrics of this novel measurement in the swallows with the maximal DCI in both supine and upright positions are presented in Table 2. Again the composite DCI measurement in healthy controls appears to be weighted towards a slightly higher contractile integral during relaxation based on POSP-CI/PREP-CI ratios in both the supine and upright position. And the influence of POSP-CI was once again reduced when controlled by time.

Normative data for the time distance from the first pressure propagating peak towards the EGJ

The normative data for the time distance from the first pressure propagating peak towards the EGJ in the first 5 eligible swallows in both supine and upright position are presented in Table 3. There is no negative data among these indicating only antegrade peristalsis in the healthy controls.

Discussion

The concept of dividing the peristaltic wave into a pre-peak and post-peak phase is derived from the hypothesis that patients with hypercontractile disorders may have variable phenotypes related to abnormalities in both the excitatory and inhibitory components of the contractile wave. Abnormalities of the contractile vigor in the pre-peak and post-peak phase of a peristaltic contraction might indicate different mechanisms of dysfunction as these phases are dependent on different neuromyogenic mechanisms. The smooth muscle of esophagus is phasic in nature and is innervated by intramural inhibitory (nitric oxide releasing) and excitatory (acetylcholine releasing) neurons that receive inputs from separate sets of preganglionic neurons [9]. Additionally, muscle contraction is also governed neurogenically by depolarization and a return to resting membrane potential and it is also possible that impaired relaxation may be related to abnormalities in hyperpolarization or a

prolonged depolarized state. Therefore, development of a methodology that can assess both the pre-peak and post-peak component of the contractile wavefront could help better define subtle defects in peristalsis related to these factors.

Our results suggest that the relaxation, i.e. post-peak, phase has a more significant contribution to the contractile effort than the contractile, i.e. pre-peak, phase in asymptomatic controls. Further, this appears to be a manifestation of duration of activity, as opposed to overall contractile effort. When we controlled for the duration of time when the esophageal body was in a state of contraction versus relaxation, we found that the pre-peak phase was consistent with higher density of contraction, whereas the post-peak phase is consistent with a more diffuse and prolonged activity. Given these findings, we speculate that patients with a hypercontractile esophageal motor disorder could be separated into different phenotypes based on the relative contribution of each phase to overall contractile state (Figure 4). For instance, the contractile pattern in patients with higher contractile effort during the pre-peak phase may be influenced by higher cholinergic tone or a heightened sensitivity to acetylcholine. In contrast, the motor dysfunction in patients with prolonged post-peak phase may be related to preferential defects in ion channels that impede return to resting membrane potential or resistance to the inhibitory influence of neurotransmitters, such as nitric oxide. These findings could have clinical implications as therapies could target the imbalance of these neurogenic influences.

Previous data suggests that the hypercontractile esophagus pattern can be induced by distal obstruction [10] and it would be interesting to see whether differences in the ratio of isometric relaxation and contraction could help discriminate this pathogenic condition from a primary motor abnormality. The St. Louis group has determined that obstruction is associated with a more pronounced S2 contractile effort [11] and we theorize that obstruction at the EGJ could also be associated with differences in the ratio of POSP-CI/ PREP-CI. This hypothesis may have some truth as the current study showed a significant difference in POSP-CI/PREP-CI ratio between S2 and S3 segment in controls. This finding may be related to the varying mechanisms which innervate the peristalsis in both segments [12].

In the current study, another novel measurement of time distance was described. In the previous version of Chicago classification, the contractile front velocity was measured to indicate the velocity of bolus transit or smooth muscle contraction [13]. This metric was abandoned in the current version due to the finding that incorporating distal latency into the diagnostic algorithm of EPT studies better discriminated disorders of inhibition and latency [6]. However, using the distal latency alone, it is impossible to tell the time sequence of the propagating pressure peak and this may be another important variable that could alter bolus transport and perception. The time distance serves to measure both the time duration and the direction of peristaltic activity and we suspect that levels below the 5th percentile of normal would suggest that propagation of the peak contraction is disorganized and not appropriately sequenced through the myenteric plexus.

There are some limitations in the current study. There is no data on symptomatic patients, which could help to demonstrate the phenotypes based on the abnormality in either pre-peak

or post-peak phase. However, this work was primarily focused on describing new measurement approaches and future work will apply these paradigms to patients with chest pain and dysphagia. The ultimate goal of developing this novel measurement is to understand the contribution of the contraction and relaxation phase as it pertains to symptom genesis, and these measurements will be incorporated into translational and animal models to better explore the hypercontractile disease states.

In conclusion, we developed a novel measurement focused on separating the pre-peak and post-peak components of the peristaltic contraction during swallowing. Using this technique, it appears that contractile activity is higher during the post-peak phase, however, this is related to the longer time component during this phase. We theorize that disorders of contractile vigor may be better phenotyped based on increased values during each phase of peristaltic activity.

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Key message

1. The current paradigm of measuring esophageal contractile vigor assesses the entirety of a pressure wave using a single measurement, the distal contractile integral.
2. We hypothesize that an assessment identifying separate phases of the contractile pressure wave before and after the pressure peak may help distinguish abnormalities in patients presenting with chest pain and dysphagia.
3. We developed a novel measurement in the study focused on separating the pre-peak and post-peak components of the peristaltic contractile activity during swallowing. Using this technique, it appears that overall contractile activity is higher during post-peak phase and this is related to the longer time component during this phase.

Figure 1.
A schematic diagram of the separation of pre-peak phase and post-peak phase in the peristalsis wave.

Figure 2. The methodology of the novel measurement in the esophageal pressure topography (EPT)

A single swallow was divided into a pre-peak contractile integral (PREP-CI) and a post-peak contractile integral (POSP-CI) phase by plotting the trajectory of the pressure wave peaks at 1-cm intervals. The contractile integral (mmHg●cm●s) at each 1 cm interval before (PREP-CI) and after (POSP-CI) the peak were measured from the transition zone to the proximal aspect of the EGJ. In the swallow displayed, the PREP-CI was 894 mmHg●cm●s and the POSP-CI was 1285 mmHg●cm●s, which made the composite DCI into 2179 mmHg●cm●s.

Figure 3. The measurement of the time distance

The directionality and propagation velocity of the pressure wave peaks was assessed. To obtain this, the time between pressure wave peaks was calculated for each 2-cm axial interval: positive time-value would reflect antegrade propagation while negative time-values would reflect uncoordinated and/or retrograde propagation. The peak propagation velocity (PPV) was defined as the slope from the peak pressure point in the transition zone to the corresponding point in the EGJ.

Figure 4. The two phenotypes of jackhammer swallows based on the novel measurement
 A) A jackhammer swallow with normalized POSP-CI (composite DCI=15237 mmHg●cm●s), the POSP-CI/PREP-CI ratio was 1.56. The POSP-CI-tc/PREP-CI-tc was 0.85 after controlled by the phase duration. B) A jackhammer swallow with prolonged POSP-CI (composite DCI=16502 mmHg●cm●s), the POSP-CI/PREP-CI ratio was 2.93. The POSP-CI-tc/PREP-CI-tc was 1.11 after controlled by the phase duration.

Table 1

Novel contractile metrics, median values

Values reflect the median values of five swallows by position per subject and are displayed as median (interquartile range).

Position Segment	Supine swallows			Upright swallows		
	S2	S3	Total	S2	S3	Total
DCI (mmHg●cm●s)	583 (370–845)	825 (627–1345) [^]	1526 (1026–2120)	254 (160–400)	637 (435–1020) [*]	968 (649–1452)
PREP-CI (mmHg●cm●s)	246 (153–336)	335 (249–501) [^]	596 (439–813)	101 (67–149)	254 (171–409) [*]	382 (250–560)
POSP-CI (mmHg●cm●s)	338 (215–496)	500 (374–876) [^]	904 (626–1308)	156 (101–242)	367 (252–665) [*]	566 (385–858)
POSP-CI/ PREP-CI	1.46 (1.37–1.56)	1.50 (1.41–1.61) [^]	1.50 (1.42–1.64)	1.54 (1.40–1.66)	1.48 (1.40–1.60) [*]	1.49 (1.40–1.59)
DCI-4c (mmHg●cm)	223 (147–271)	281 (238–396) [^]	515 (407–615)	142 (101–197)	295 (214–393) [*]	428 (330–560)
PREP-CI-4c (mmHg●cm)	227 (155–302)	304 (251–438) [^]	557 (428–757)	138(104–197)	282 (215–379) [*]	431 (328–588)
POSP-CI-4c (mmHg●cm)	221 (144–253)	278 (227–380) [^]	496 (399–650)	138 (104–196)	279 (215–364) [*]	421 (333–545)
POSP-CI/ PREP-CI-4c	0.92 (0.86–0.98)	0.92 (0.85–0.97)	0.92 (0.86–0.97)	1.0 (0.94–1.0)	0.96 (0.92–1.0) [*]	0.96 (0.91–1.0)

S2: Segment 2 of the contractile wave; S3: Segment 3 of the contractile wave

DCI: Distal Contractile Integral; PREP-CI: Pre-peak contractile integral; POSP-CI: Post-peak contractile integral; POSP-CI/ PREP-CI: the ratio of POSP-CI to PREP-CI;

DCI-4c: the DCI controlled by time; PREP-CI-4c: the PREP-CI controlled by time; POSP-CI-4c: the POSP-CI controlled by time

[^]: p<0.05 when compared with S2 in the supine position

^{*}: p<0.05 when compared with S2 in the upright position

Table 2***Novel contractile metrics, maximal DCI swallow***

Values reflect the swallow with greatest DCI by position from each subject and are displayed as median (interquartile range).

Position Segment	Supine		Upright		Total
	S2	S3	S2	S3	
DCI (mmHg●cm●s)	661 (474–946)	1074 [^] (802–1596)	400 (247–557)	881 [*] (566–1506)	1239 (916–2031)
PREP-CI (mmHg●cm●s)	283 (189–378)	450 [^] (305–610)	164 (100–234)	351 [*] (239–546)	494 (376–721)
POSP-CI (mmHg●cm●s)	378 (267–600)	625 [^] (489–966)	225 (148–337)	530 [*] (337–890)	757 (537–1273)
POSP-CI/ PREP-CI	1.41 (1.30–1.62)	1.55 [^] (1.42–1.70)	1.51 (1.39–1.63)	1.48 (1.31–1.40)	1.48 (1.32–1.62)
DCI-4c (mmHg●cm)	251 (186–318)	339 [^] (267–449)	186 (136–265)	347 [*] (264–468)	519 (432–699)
PREP-CI-4c (mmHg●cm)	261 (195–338)	368 [^] (287–495)	186 (131–278)	370 [*] (275–515)	544 (451–725)
POSP-CI-4c (mmHg●cm)	233 (179–292)	326 [^] (262–424)	186 (137–260)	336 [*] (257–471)	518 (424–675)
POSP-CI/ PREP-CI-4c	0.89 (0.84–0.97)	0.90 (0.84–0.96)	0.97 (0.91–1.01)	0.94 [*] (0.88–0.97)	0.95 (0.90–0.98)

S2: Segment 2 of the contractile wave; S3: Segment 3 of the contractile wave

DCI: Distal Contractile Integral; PREP-CI: Pre-peak contractile integral; POSP-CI: Post-peak contractile integral; POSP-CI/ PREP-CI: the ration of POSP-CI to PREP-CI;

DCI-4c: the DCI controlled by time; PREP-CI-4c: the PREP-CI controlled by time; POSP-CI-4c: the POSP-CI controlled by time

[^]: p<0.05 when compared with S2 in the supine position

^{*}: p<0.05 when compared with S2 in the upright position

Table 3

Time distance from the first pressure propagating peak in the transition zone to the esophagogastric junction in the healthy subjects (median(IQR))

Position	Supine	Upright
Time distance(seconds)	2.99(2.45–3.34)	2.64(2.29–3.06)
Propagation peak velocity (cm/s)	1.83(1.57–2.22)	2.25(1.79–2.49)
Position	Supine swallows with greatest DCI	Upright swallows with greatest DCI
Time distance(seconds)	2.97(2.45–3.80)	2.09(1.86–2.60)
Propagation peak velocity (cm/s)	1.46(1.12–1.80)	1.91(1.58–2.30)