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High-resolution manometry assessment of the lower esophageal sphincter after-contraction: normative values and clinical correlation

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Abstract

Background—The Chicago Classification v3.0 proposed extending the distal contractile integral (DCI) measurement domain to include the lower esophageal sphincter (LES) to enhance the detection of esophageal hypercontractility. However, normative and clinical data for this approach are unreported. We aimed to describe the application of an extended DCI measurement in asymptomatic controls and patients.

Methods—High-resolution manometry (HRM) of 65 asymptomatic controls and 72 patients with normal motility were evaluated retrospectively. Dysphagia and chest pain symptoms were assessed using the brief esophageal dysphagia questionnaire (BEDQ); 10 was considered abnormal. HRM studies of 10 supine swallows were evaluated via the standard DCI and an extended DCI measurement domain (DCI+) to include the lower esophageal sphincter (LES) during and after the peristaltic wave. The DCI-increment was calculated as the DCI+ minus DCI.

Key Results—Among controls, the median (5–95th percentile) DCI+ was 1915 (1359 – 6921) mmHg•cm•s and DCI-increment was 534 (126 – 1488) mmHg•cm•s. Two patients (3%) had 2 swallows with DCI+ > 8,000 mmHg•cm•s and seven (10%) patients had at least one swallow with DCI+ > 8,000 mmHg•cm•s, i.e. had potential motility reclassification by application of DCI+.

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Seven of these nine patients (78%) were evaluated for dysphagia or chest pain, but only 3/9 (33%) had an abnormal BEDQ.

Conclusions & Inferences—Extension of the DCI measurement domain may aid quantifying hypercontractility that involves the LES. However, adjusting management strategies based on reclassification of patients with otherwise normal motility should be cautiously considered.

Keywords

high-resolution manometry; lower esophageal sphincter; dysphagia; esophageal motility

Introduction

The topographic analysis of peristalsis first proposed by Clouse et al described four contractile segments; S1 proximal to the transition zone, S2 and S3 distal to the transition zone but proximal to the lower esophageal sphincter (LES) and S4, the LES.(1) Excessive contraction in S2 and/or S3 is the defining feature of the hypertensive esophageal motility disorders, formerly classified as nutcracker esophagus, and more recently as jackhammer esophagus.(1–4) Symptomatically, these can be associated with dysphagia and/or chest pain.(5) Hypercontractility of the LES (S4) is also observed, albeit rarely, and also may be associated with dysphagia and/or chest pain.(3, 6) However, contractility involving the LES following the peristaltic wave (i.e. the LES after-contraction) is not typically evaluated with the standard metrics applied during high-resolution manometry (HRM) interpretation.(4, 7)

Assessment of the vigor of a potentially *hypercontracting* LES by extending the distal contractile integral (DCI) measurement domain to include the LES was proposed by the International Esophageal HRM Working Group.(4) Though clinical data to support this approach was not available, it was assumed that the ‘normal’ increase created from an extended DCI metric was likely to be minimal and thus maintaining a DCI threshold of 8,000 mmHg•cm•s could be utilized to identify patients with hypercontractility that would not be detected using the conventional DCI measurement domain. Consequently, the aim of this study was to evaluate an extended DCI measurement (DCI+) in asymptomatic controls to determine the expected addition to the DCI resulting from including the LES after-contraction. Further, we hypothesized that detection of otherwise overlooked abnormal hypercontractility using the DCI+ might improve motility classification of patients. Thus, we also aimed to examine the clinical significance of applying this measurement to patients otherwise classified as having normal motility on evaluation with HRM using Chicago Classification v3.0 criteria.

Methods

Subjects

High-resolution manometry studies from 72 previously described, healthy, asymptomatic volunteers were reviewed according to the Chicago Classification v3.0.(4, 5) Those meeting criteria for normal motility were included for further analysis involving an extended DCI; patients with an HRM classification of ineffective esophageal motility were excluded to make the control group otherwise comparable to the patient group.

The patient group was retrospectively identified using a query of the Esophageal Center at Northwestern (ECN) Motility Laboratory Registry, which includes English-speaking patients aged 18–85 that were evaluated at the ECN for esophageal symptoms with HRM. 72 consecutive patients evaluated between August, 2013 and December, 2015 were included if they had 1) an HRM motility diagnosis of normal motility,(4) 2) and completed the Brief Esophageal Dysphagia Questionnaire (BEDQ)(8). Other exclusions were: 1) previous foregut surgery, 2) hiatal hernia > 3 cm, or 3) a mechanical obstruction, including esophageal eosinophilia (i.e. esophageal biopsies with > 15 eosinophils/hpf), which is routinely evaluated for in patients with dysphagia. A waiver of informed consent was obtained. The study protocol was approved by the Northwestern University Institutional Review Board.

Symptom assessment

Symptoms of chest pain and dysphagia were evaluated using a validated questionnaire, the BEDQ, which was completed at the time of HRM.(8) The questionnaire consists of eight 6-point Likert scale questions (scored 0–5) that assess frequency and severity of symptoms and two open-ended questions regarding frequency of food impaction and related emergency room visits (each scored 0 – 5 for ‘never’ to ‘>4 times’). Scores were calculated as the sum of all 10 items and ranged from 0 (asymptomatic) – 50. A BEDQ score > 10 was considered abnormal as this threshold was determined to be the optimal cut point to distinguish patients with major esophageal motor dysfunction.(8)

HRM study protocol

Manometry studies were completed using a 4.2-mm outer diameter solid-state assembly with 36 circumferential pressure sensors at 1-cm intervals (Medtronic Inc, Shoreview, MN). After a minimum 6-hour fast, the HRM assembly was placed transnasally and positioned to record from the hypopharynx to the stomach with approximately three intragastric pressure sensors. The HRM protocol included a 5-minute baseline recording and ten 5-ml swallows in a supine position at 20–30 second intervals.

Data analysis

Manometry studies were analyzed using ManoView version 3.0 analysis software to measure basal esophagogastric junction (EGJ) pressure at end-expiration during the baseline recording; the integrated relaxation pressure (IRP), DCI, and distal latency were measured for each swallow, as described for the Chicago Classification.(4, 7)

The DCI and DCI+ were measured above an isobaric contour of 20 mmHg. The DCI was measured in the conventional fashion with the measurement domain extending in axial length from the transition zone to the proximal border of the esophagogastric junction (EGJ), and in duration from the onset of the second contractile segment to the end of peristalsis, Figure 1. The duration of peristalsis was also measured (seconds). To measure the DCI+, the DCI measurement domain was extended distally to include the EGJ and to a duration of 15-seconds from the onset of the S2 contraction (Figure 1). A fixed duration was utilized to standardize the metric; 15 seconds was chosen to include sufficient time to detect hypercontractility localized to the LES after-contraction, while also reliably avoiding an

effect of deglutitive inhibition from the subsequent swallow. The *DCI-increment* was the added contractile integral resulting from extending the DCI domain and was calculated as the DCI+ minus DCI. As an internal evaluation of inter-rater agreement for the various metrics, the first swallow from the first 20 asymptomatic controls and the first 20 patients were analyzed by three separate raters (MT, ZL, KR).

Statistical analysis

To maintain statistical independence, measures from the single swallow with the greatest DCI were primarily included for analysis. Descriptive statistics are reported as median (interquartile range) unless otherwise stated. Inter-rater agreement was assessed with a two-way mixed intra-class correlation coefficient and degree of agreement was interpreted as excellent for intra-class correlation of 0.75–1.0, good for 0.6 – 0.74, fair for 0.4 – 0.59, and poor for < 0.4. Correlations were assessed using Spearman's rho. Groups were compared using the Kruskal-Wallis or Mann-Whitney U test for continuous variables and χ^2 or Fischer's Exact tests for dichotomous and categorical variables. For multiple comparisons, post-hoc tests were applied with a Bonferroni correction. Analyses otherwise assumed a 5% level of statistical significance.

Results

Subjects

Six of the 72 asymptomatic controls met criteria for ineffective esophageal motility and were excluded from further analysis, providing 66 controls (ages 19 – 47 years) for inclusion (Table 1). Among the 72 patients (ages 21 – 72), dysphagia was the most common primary indication for HRM, followed by reflux symptoms then chest pain for the remainder (Table 1). Twelve patients were referred for evaluation of more than one symptom. The controls did not complete the BEDQ. The median (IQR) BEDQ scores were 7 (3 – 16) among the patients; 23 (32%) patients had a BEDQ score ≥ 10 . Endoscopy reports were available for review in 63 patients: 9 (14%) had LA class A esophagitis and 12 (19%) had a small (i.e. < 3 cm) hiatal hernia. The remainder of the endoscopies were normal.

LES after-contraction metrics: normative values and comparison with patients

The median (IQR) basal EGJ pressure was 15 (8 – 21) mmHg in controls and 16 (11 – 23) mmHg in patients ($p = 0.380$). The median IRP (across 10 swallows) was 8 (6 – 11) mmHg in controls and 9 (6 – 12) mmHg among patients ($p = 0.971$).

The intra-class correlation coefficient (5–95% confidence interval) of metrics among the raters was 0.979 (0.965 – 0.988) for DCI, 0.998 (0.996 – 0.999) for DCI+, 0.833 (0.719 – 0.906) for peristaltic duration, 0.891 (0.833 – 0.931) for IRP, 0.949 (0.914 – 0.971) for distal latency. Thus excellent inter-rater agreement was observed across all HRM metrics.

Data reflecting the single swallow with the greatest DCI are included in Figure 2. The median (5 – 95th percentile) observed among the greatest DCI swallows for the asymptomatic controls was 1915 mmHg•cm•s (1071 – 5835) for DCI, 2492 mmHg•cm•s (1359 – 6921) for DCI+, and 534 (126 – 1488) for the DCI-increment. The greatest single

swallow values observed among the controls were a DCI of 6573 mmHg•cm•s, DCI+ of 7485 mmHg•cm•s, and DCI-increment of 1770 mmHg•cm•s.

The swallow with greatest DCI among patients had a greater DCI ($p < 0.001$), greater DCI+ ($p < 0.001$), and greater DCI-increment ($p < 0.001$) than the controls (Figure 2). Patients had similar IRP (9.2 mmHg (6.1 – 12.9) vs 7.6 (5.7 – 11) and distal latency (8.3 (7.1 – 9.1) vs 8.1 (7.3 – 8.9)). The greatest DCI observed from a single swallow among the patients was 7381 mmHg•cm•s. The greatest DCI+ observed from a single swallow among the patients was 11789 mmHg•cm•s and the greatest DCI-increment was 5758 mmHg•cm•s.

Symptom association with LES after-contraction metrics

Correlation (Spearman's rho) of HRM metrics from the swallow with greatest DCI with BEDQ was 0.202 for DCI, 0.244 for DCI+, 0.131 for DCI-increment: 0.131, 0.074 for distal latency: 0.074, and 0.066 for IRP. Correlation was also weak between BEDQ and basal EGJ pressure (0.054) and median IRP (0.014).

When comparing metrics from the swallow with greatest DCI between controls, patients with BEDQ < 10, and patients with BEDQ ≥ 10, group differences were detected with DCI ($p < 0.001$), DCI+ ($p < 0.001$), and DCI-increment ($p < 0.001$), but not distal latency ($p = 0.288$) or IRP ($p = 0.183$); Figure 2. Basal EGJ pressure and median IRP did not differ among the three groups. Post-hoc testing (which assumed statistical significance at a p-value of 0.017 based on a Bonferroni adjustment for multiple comparisons) demonstrated differences in DCI, DCI+, and DCI-increment between controls and both patients with BEDQ < 10 and BEDQ ≥ 10 (all p-values < 0.008). However, no differences were detected in DCI, DCI+, or DCI-increment, between patients with BEDQ < 10 and BEDQ ≥ 10.

Clinical correlations with LES after-contraction metrics

There were nine patients (13% of 72) with at least one swallow with a DCI+ of > 8000 mmHg•cm•s. Two (3%) of these had ≥ 2 swallows with DCI+ > 8000 mmHg•cm•s and would thus have their diagnosis altered to jackhammer esophagus if applying the DCI+.(4) One of these patients was evaluated for frequent chest pain with dysphagia and had a BEDQ of 19, Figure 3A. Endoscopy, esophagram, and 24-hour esophageal pH-impedance testing (on proton-pump inhibitor) were normal. This patient was taking opioids for chronic pain. The management plan for this patient was escalation of therapy for poorly controlled anxiety and depression as well as referral for cognitive behavioral therapy for functional chest pain. The other patient with ≥ 2 swallows with DCI+ > 8000 mmHg•cm•s was evaluated for infrequent dysphagia, had a BEDQ score of 5, and was noted to have a small sliding hiatal hernia on endoscopy and barium esophagram (which were otherwise normal); Figure 3B. The management plan was for reassurance and observation. The remaining seven patients (10% of the patient cohort) had only a single swallow with DCI+ > 8000 mmHg•cm•s, and thus could have had their motility diagnosis altered to jackhammer esophagus if applying the extended DCI metric and using a previous version of the Chicago Classification in which the criterion for jackhammer was a single hypercontractile swallow.(7) Three of these patients were evaluated for dysphagia (**including** Figure 3C), two for chest pain, and two for reflux symptoms. Two of these seven patients (28%) had an abnormal BEDQ score. Therefore, in

total 7/9 (78%) of patients with at least one swallow with $\text{DCI}^+ > 8000 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$ were evaluated for dysphagia or chest pain, but only 3/9 (33%) had an abnormal BEDQ.

Additionally, there were 13 patients (18% of 72) with at least one swallow with a DCI -increment greater than the upper limit of normal observed in controls (i.e. $1770 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$); Figure 3D. Six of these patients also had at least one swallow with $\text{DCI}^+ > 8000 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$ (including both of the patients with 2 swallows with $\text{DCI}^+ > 8000 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$). Among the 13 patients with a swallow with a DCI -increment $> 1770 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$, the indication for manometry was dysphagia for seven (54%), chest pain for five (38%), and reflux symptoms for one (8%); 8 patients (62%) had a $\text{BEDQ} < 10$, while the remaining 5 (38%) had a $\text{BEDQ} > 10$.

None of the potentially reclassified patients underwent subsequent endoscopic or surgical therapies (i.e. dilation, botulinum toxin injection, nor myotomy) at our center.

Discussion

We evaluated the LES after-contraction by extending the measurement domain of the DCI and found that the phenomenon of hypercontractility previously described for S2 and S3 can also affect the LES. Among control subjects, including the LES after-contraction within the DCI measurement domain (DCI^+) resulted in an increase in the DCI (DCI -increment) of up to $1770 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$, but $300 - 900 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$ was the typical range. Use of the DCI^+ reclassified two patients (3% in this series) as hypercontractile that were previously considered as having normal motility. Among our evaluated cohort of patients, the majority of reclassified patients were evaluated for dysphagia or chest pain, but inconsistently reported a validated symptom score in the expected range for major esophageal motility disorders (i.e. $\text{BEDQ} > 10$).

Hypercontractility of the LES after-contraction has been previously reported. A “hypercontracting sphincter”, defined as an unusually prolonged post-glutitive LES contraction with or without excessive pressure amplitudes, was observed in 11 (3%) of 381 consecutive patients evaluated with esophageal manometry.(6) Among these patient, 7/11 (64%) were evaluated for chest pain and 2/11 (18%) were evaluated for dysphagia. The first version of the Chicago Classification included a motility classification titled “nutcracker LES” that was defined by a mean $\text{DCI} > 5000 \text{ mmHg}\cdot\text{cm}\cdot\text{s}$ with a hypertensive contraction (amplitude $> 180 \text{ mmHg}$) limited to the LES after-contraction.(3, 9) This sub-classification of esophageal hypercontractility was observed in only 3 (0.8%) of 400 patients. The subsequent consensus update of the Chicago Classification omitted an assessment of the LES after-contraction,(7) until the concept of assessing the LES after-contraction was again raised in the most recent Chicago Classification update.(4)

Incorporating the DCI^+ into the HRM classification scheme may simplify the measurement of contractile vigor and was proposed as a method to improve characterization of esophageal hypercontractility. While the majority of our potentially reclassified patients were evaluated for symptoms typically associated with esophageal hypercontractility (i.e. dysphagia or chest pain), a strength of our study was use of a validated dysphagia-chest pain scale, the

BEDQ, to quantify patient symptoms beyond simply using manometry-referral indication as the method to characterize symptoms.(8) Among the patients reclassified by DCI+ or DCI-increment, only a portion (33 – 50%, depending on criteria to define *hypercontractile*) of patients reported a BEDQ score above the threshold consistent with major esophageal motility disorders.(8) Thus, although successful treatment of hypercontractility located within the esophageal body with botulinum toxin injection or esophageal myotomy has been reported,(10, 11) our results suggest that pursuing invasive therapy (e.g. botulinum toxin injection or esophageal myotomy) to treat a hypercontractile LES after-contraction (as assessed with extended DCI metrics) may not be necessary and was not pursued for any of the potentially reclassified patients within this cohort (who were instead generally managed via observation or as functional disorders).

While the use of the DCI+ appears to infrequently impact the motility diagnosis among patients categorized as normal motility with Chicago Classification v3.0, extended DCI metrics could also aid in the characterization of other esophageal motility disorders. A recent study applied an extended DCI measure among patients with Jackhammer esophagus (with and without EGJ outflow obstruction) and found that hypercontractility localized to the LES, i.e. a measure assessed analogous to our DCI –increment, of > 2000 mmHg•cm•s, was associated with a referral indication of dysphagia.(12) Evaluation of the LES after-contraction could also aid characterization in patients with an HRM motility diagnosis of EGJ outflow obstruction, although this application remains uninvestigated.

This study carries significance by providing normative values and offering a systematic evaluation for a previously untested method proposed within the most recent version of the Chicago Classification.(4) However, the study is limited by its retrospective nature. Additionally, a relatively small sample size of patients with a potential hypercontracting LES were identified, which somewhat limits the clinical description related with this finding. However, the study demonstrated that application of this measure to a modest number of patients detected multiple patients that had their diagnostic impression altered by extension of the DCI domain.

In conclusion, this study demonstrates that hypercontractility can involve the LES after-contraction, albeit infrequently. Extending the DCI measurement domain to include the LES after-contraction can increase the DCI by up to 1770 mmHg•cm•s, as demonstrated in the control subjects. Although extended DCI metrics may be related to symptoms of dysphagia and chest pain, their application among patients with otherwise normal motility did not appear to consistently identify patients with a degree of symptom severity typically associated with major esophageal motility disorders. While global application of the extended DCI measures may lead to *over-diagnosis* of esophageal hypercontractility among patients with otherwise normal motility, it may aid characterization of esophageal hypercontractility when applied in the appropriate clinical context with supportive complementary testing. Future studies remain necessary to demonstrate the impact of use of extended DCI metrics or assessment of the LES after-contraction on patient management strategies and outcomes.

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Abbreviations

BEDQ	Brief Esophageal Dysphagia Questionnaire
DCI	distal contractile integral
EGJ	esophagogastric junction
HRM	high resolution manometry
IRP	integrated relaxation pressure
LES	lower esophageal sphincter

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Key Points

- The Chicago Classification v3.0 proposed extending the distal contractile integral (DCI) to include the lower esophageal sphincter (LES) and potentially improve detection of esophageal hypercontractility, however normative data and the clinical impact of this approach were unknown.
- Utilization of an extended DCI metric (DCI+) led to reclassification as hypercontractile in a small portion of patients that were otherwise classified as normal on high-resolution manometry.
- Identification of hypercontractility involving the LES could aid characterization of esophageal motility, however, reclassification of patients with otherwise normal motility should be cautiously performed.

Figure 1. High-resolution manometry metrics of contractile vigor and the lower esophageal sphincter after-contraction

The measurement domains of the distal contractile integral (DCI – pink-dashed box), DCI+ (white box), and DCI-increment (black-dashed box) are displayed on a swallow from an asymptomatic control.

Figure 2. Group comparisons among metrics of contractile vigor

A Brief Esophageal Dysphagia Questionnaire (BEDQ) score of 10 was considered the ideal threshold to distinguish between patients with and without major esophageal motility disorders.(8) ○= outlier; *=extreme outlier. Distal contractile integral – DCI.

Figure 3. Modified classification of esophageal hypercontractility

Swallows from patients that could have reclassification of their esophageal motility diagnosis (i.e. from normal motility to hypercontractile) based on utilization of extended distal contractile integral (DCI) metrics are displayed. Patients in **A** (evaluated for chest pain) and **B** (evaluated for dysphagia) both had > 2 swallows with DCI+ > 8000 mmHg•cm•s. The patient in **C** was evaluated for dysphagia, had a brief esophageal dysphagia questionnaire (BEDQ) score of 3, and had a single swallow with DCI+ > 8000 mmHg•cm•s. The patient in **D** was evaluated for dysphagia, had a BEDQ score of 2, and had a greater-than-normal DCI-increment in 2 swallows, but DCI and DCI+ < 8000 mmHg•cm•s among all swallows.

Table 1

Subject characteristics.

	Controls	Patients
n	66	72
Age, years, mean +/- SD	27 +/- 5	47 +/- 14 ^I
Gender (% female)	44	69 ^I
Indication for manometry, n (%)		
Dysphagia	--	33 (46%)
Chest pain	--	11 (15%)
Reflux symptoms	--	28 (39%)

^I p-value < 0.05 compared with controls.