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Distal Esophageal Spasm in High-Resolution Esophageal Pressure Topography: Defining Clinical Phenotypes

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Abstract

BACKGROUND—The manometric diagnosis of distal esophageal spasm (DES) uses “simultaneous contractions” as a defining criterion, ignoring the concept of short latency distal contractions as an important feature. Our aim was to apply standardized metrics of contraction velocity and latency to high-resolution esophageal pressure topography (EPT) studies to refine the diagnosis of DES.

METHODS—Two thousand consecutive EPT studies were analyzed for contractile front velocity (CFV) and distal latency to identify patients potentially having DES. Normal limits for CFV and distal latency were established from 75 control subjects. Clinical data of patients with reduced distal latency and/or rapid CFV were reviewed.

RESULTS—Of 1070 evaluable patients, 91 (8.5%) had a high CFV and/or low distal latency. Patients with only rapid contractions ($n = 186$ [17.4%] using conventional manometry criteria; $n = 85$ [7.9%] using EPT criteria) were heterogeneous in diagnosis and symptoms, with the majority ultimately categorized as weak peristalsis or normal. In contrast, 96% of patients with premature contraction had dysphagia, and all ($n = 24$; 2.2% overall) were ultimately managed as spastic achalasia or DES.

CONCLUSIONS—The current DES diagnostic paradigm focused on “simultaneous contractions” identifies a large heterogeneous set of patients, most of whom do not have a clinical syndrome suggestive of esophageal spasm. Incorporating distal latency into the diagnostic algorithm of EPT studies improves upon this by isolating disorders of homogeneous pathophysiology: DES with short latency and spastic achalasia. We hypothesize that prioritizing measurement of distal latency will refine the management of these disorders, recognizing that outcomes trials are necessary.

Keywords

Esophageal Pressure Topography; High-Resolution Manometry; Distal Esophageal Spasm; Dysphagia

Although most undiagnosed chest pain is not caused by esophageal spasm, esophageal manometry is often done in the course of its evaluation and rapidly propagated esophageal

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Conflicts of interest

The authors disclose the following: Dr Pandolfino is a consultant and educator for Given Imaging. The remaining authors disclose no conflicts.

contractions are often reported as indicative of spasm.¹ However, these rapid contractions rarely cause chest pain and most experts agree that use of this criterion leads to overdiagnosis of distal esophageal spasm (DES).¹ Arguing for a more restrictive use of the diagnosis, Spechler and Castell proposed modifying the manometric criteria for DES to require: (1) simultaneous (rapid) contractions in >10% of wet swallows and (2) contraction amplitude >30 mm Hg.² The inclusion of a minimum contractile amplitude in the definition was intended to exclude low-amplitude pressure waves from inclusion in the diagnosis, but the defining feature of “simultaneous contractions” was retained.

A lot has changed since the last reassessment of criteria for defining spasm.^{3–5} Within the realm of diagnoses, it is now recognized that reflux rather than spasm is the dominant cause of esophageal chest pain.⁶ With respect to motility testing, clinical studies are now commonly done with high-resolution systems and esophageal contractile patterns are displayed and analyzed in terms of esophageal pressure topography (EPT), rather than as line tracings. An outgrowth of this is that it has become clear that the conventional criteria for defining spasm are not easily applied to EPT. Normal regional variability in contraction velocity and regional boundaries demarcating functional esophageal segments are much more evident in EPT, requiring, at the very least, that diagnostic criteria based on propagation velocity be re-examined.^{7–9}

Conceptually, esophageal spasm is a motility disturbance in the esophageal body characterized by uncoordinated contraction. Two recently described tools in EPT analysis that may improve the recognition of spasm are the contractile deceleration point (CDP) and distal contractile latency (DL). CDP is the distal esophageal locus characterized by an abrupt slowing of the deglutitive contraction as peristalsis terminates and ampullary emptying begins.¹⁰ Consequently, identification of the CDP provides a reliable landmark for measuring peristaltic velocity. The distance latency is a related measure in that it times the occurrence of distal peristalsis relative to deglutitive upper sphincter relaxation. Together, these EPT measures facilitate objective measurement of peristaltic velocity and a means for quantifying the latency of the distal contraction as a surrogate for inhibitory ganglionic integrity¹¹ (Figure 1). Although latency can be measured with conventional manometry, it is difficult to standardize because of gaps in pressure sensor spacing and poor identification of the segmental boundaries of the contraction.

We hypothesized that the classification of DES will be improved in EPT based on localization of the CDP and measurement of distal latency. Hence, the aims of this study were to perform a systematic analysis of a large series of clinical EPT studies to distinguish EPT phenotypes characterized by rapid contractile velocity and/or reduced DL and correlate clinical features. In addition, we sought to compare conventional manometric criteria for DES with proposed EPT classifications.

Methods

Patients

Two thousand consecutive EPT studies done between January 1, 2007, and May 31, 2010, in the Northwestern Memorial Hospital manometry laboratory were analyzed. Studies were included only if there were >6 interpretable swallows and were excluded if they were found to be duplicates, associated with a large hiatus hernia (>5 cm), or done after surgery involving the esophagus or stomach. These restrictions left 1070 unique patient studies for analysis. These patients presented with a diverse set of complaints to a tertiary care practice specializing in the management of esophageal disease. Patients were characterized by dominant symptom (ie, dysphagia, chest pain, reflux) by review of their medical records and their completed symptom evaluation form in the manometry laboratory that utilized visual

analogue scales for scoring dysphagia, heartburn, chest pain, and regurgitation. In standardizing EPT metrics, findings from 75 asymptomatic control subjects were used for comparison. The study protocol was approved by the Northwestern University Institutional Review Board.

High Resolution Esophageal Pressure Topography

A solid-state high resolution manometry assembly with 36 solid-state sensors spaced at 1-cm intervals (OD = 4.2 mm) was used (Sierra Scientific Instruments Inc, Los Angeles, CA). The response characteristics of this device, calibration procedure, and poststudy thermal correction algorithm have been described previously.¹² Patients were instructed to fast for at least 6 hours before the study. The manometric catheter was passed transnasally, positioned to record from the hypopharynx to the stomach with about 5 intragastric sensors, and fixed in place by taping it to the nose. The study protocol included a 5-minute baseline period and ten 5-mL water swallows obtained in a supine posture.

Measurements of Contractile Front Velocity

EPT studies were analyzed using ManoView analysis software (Sierra Scientific Instruments Inc). Owing to its historical significance in defining DES, considerable emphasis was placed on identifying swallows with “simultaneous” contractions based on the measurement of contractile velocity. This is more complex in EPT studies than with conventional manometry because the segmental architecture of the distal esophageal contraction stands out, making regional variation in conduction velocity among segments obvious. Contractile front velocity (CFV) was measured from the transition zone^{13,14} to the CDP, defined as the point where the most abrupt deceleration in velocity occurs within the S3 segment.¹⁰ This landmark defines a transition from esophageal peristaltic clearance to emptying of the phrenic ampulla, where the mechanism was dominated by re-elongation of the distal esophagus and recoil of the phrenoesophageal ligament rather than peristaltic propagation.¹⁰ The CDP location is determined by defining the intersection point between 2 tangent lines of the 30 mm Hg isobaric contour: one extending distally from the transition zone and the other extending proximal from the esophagogastric junction (EGJ) when it re-establishes its normal postdeglutitive position. CFV is calculated by taking the best-fit tangent between the transition zone and CDP (Figure 2). Also note that in instances of increased intrabolus pressure trapped between the distal esophageal contraction and the EGJ, the CFV was determined at an isobaric contour pressure exceeding EGJ, pressure so as not to mistake esophageal pressurization for a simultaneous contraction.⁷ The upper limit of normal for the CFV was taken to be >9 cm/s based on 95th percentile values of our previous data in 75 normal subjects.¹⁰

Peristaltic velocity was also measured using the conventional manometric parameters detailed by Spechler and Castell.² Velocity was measured between 2 points, 3 and 8 cm above the proximal margin of the EGJ. The upper limit of normal for this measurement was considered to be 8 cm/s.

Measurement of Distal Latency

We used a computer simulation and normalized measurements of esophageal length to establish that the median distal latency measured from the start of upper esophageal sphincter (UES) relaxation to the CDP was 6.0s (95% confidence interval [CI]: 4.8–7.6s).¹⁵ Subsequent manual analysis of the same data without normalization found that the median time for propagation from the start of UES relaxation to the CDP was 6.2 s, with a minimal value observed of 4.6 s in the control group. Given these findings, we established a cut-off of 4.5 s from the onset of the UES relaxation to the CDP as the lower limit of normal for the distal latency (Figure 2). This threshold is also similar to the values described by Behar and

Biancani¹¹ previously, with a small shift to account for the difference in landmarks for the beginning of the swallow.

Metrics of EGJ Relaxation and Contractile Activity

Key metrics developed previously for analysis of clinical EPT studies include the integrated relaxation pressure¹⁶ and the distal contractile integral.⁷ The integrated relaxation pressure quantifies lower esophageal sphincter relaxation both in completeness and persistence. It reports the lowest mean EGJ pressure for 4 contiguous or noncontiguous seconds in the 10-s period after deglutitive UES relaxation. The normal range of the integrated relaxation pressure with this instrumentation is <15 mm Hg.¹⁷ The distal contractile integral reflects the magnitude of the distal esophageal contraction exclusive of the lower esophageal sphincter. Conceptually, the distal contractile integral is the volume of the contraction >20 mm Hg base between P and D in Figure 2 (when plotted in 3-dimensions) expressed as (mm Hg-s-cm). The upper limit of normal for the distal contractile integral with this instrumentation is 5000 mm Hg-s-cm.⁷ The integrity of the peristaltic contraction was also characterized by the presence or absence and size of breaks in the 20 mm Hg isobaric contour.¹⁸

Clinical Data

Patients with abnormal EPT studies on the basis of contraction velocity or latency were grouped according to the scheme summarized in Table 1 and illustrated in Figure 3. Each EPT study was reviewed independently by 3 investigators and the final interpretation was agreed on by 2 blinded investigators (S.R. and J.E.P.). Clinical data were then explored on these subsets of patients to look for similarities within groups and differences among groups in presenting symptoms.

Statistical Analysis

EPT metrics were summarized using median values and 95% CI. Nonparametric analysis of variance was used to compare the median values among patient groups. The relationship between velocity measures was assessed in 200 random studies using Pearson correlation. Kappa analysis was utilized to assess agreement of diagnosis in all 1070 studies. For the Kappa analysis, patients were categorized as potentially having DES using conventional measures if at least 2 swallows had a velocity >8 cm/s or using EPT measures if 2 swallows had a CFV >9 cm/s.

Results

Rapid Contractions

Table 2 summarizes the findings with respect to the detection of rapid contraction velocity measured in conventional and EPT metrics. Evident in the Table, the agreement between measures was only fair ($\kappa = 0.267$; 95% CI: 0.168–0.366) and there were a substantial number of discordant patients using the prespecified limits of normal. Similarly, although there was a significant correlation between the conventional metric and CFV for peristaltic velocity, the strength of the relationship was weak ($r = 0.38$, $P < .01$) and the absolute difference between the 2 measurements in 200 random studies was significant (mean, 0.5 cm/s; standard deviation, 6.4 cm/s; $P < .01$).

Examining first the discordant patients, there were 38 categorized as rapid only in EPT and 139 only by conventional metrics. Of the 38 patients with an abnormal CFV and normal conventional measurement of peristaltic velocity, 4 were ultimately diagnosed and managed as DES. Of the remaining 34 patients, 8 were judged to be normal, 20 had weak peristalsis (large breaks in the 20 mm Hg isobaric contour), 3 had evidence of hypertensive peristalsis

and 3 had EGJ outflow obstruction. These last 3 patients may have had a syndrome evolving into achalasia. Conversely, among the 139 patients classified as having “simultaneous contractions” using the conventional metric, when evaluated in EPT terms, 62 had weak peristalsis, 54 were normal, 5 had hypertensive peristalsis, and 16 had EGJ outflow obstruction. Only 2 (1.4%) patients were ultimately diagnosed and managed as DES.

Forty-seven patients had rapid contractions measured both in conventional and EPT terms. Although the criteria of having both measurements of velocity being abnormal identified more patients with spasm and achalasia, the group was still quite heterogeneous. In terms of the final clinical diagnosis, the breakdown was 2 patients with DES, 14 with spastic achalasia, 4 with EGJ outflow obstruction, 19 with weak peristalsis, 2 with hypertensive peristalsis, and 6 normal. Although the majority of patients had a dominant symptom of dysphagia (70%), slightly more than one-quarter (26%) had dominant reflux symptoms and 4% had globus as their dominant symptom.

Premature Contractions

Among 1070 studies, only 24 patients (2.2%) exhibited premature contractions (distal latency <4.5 s). Eighteen of these patients had concomitant rapid contraction (CFV >9 cm/s), and 6 had reduced distal latency without an elevated CFV. In the 6 patients without an elevated CFV, 3 had borderline velocities marginally <9 cm/s and 3 others had a somewhat unusual EPT pattern with a CDP location that nearly intersected the EGJ. All 24 of these patients’ dominant symptom was dysphagia or chest pain, suggesting this finding to be uniformly of clinical significance. Six of the 24 patients were diagnosed and managed as DES and 18 as spastic achalasia. Interestingly, although the diagnostic criteria utilized for premature contractions were based on the 2 most abnormal swallows, 96% (23 of 24) of these patients had no normal peristalsis. The 1 patient with evidence of normal peristalsis had 4 borderline normal swallows (distal latency 4.5–5.0 s), was classified as premature contraction, and managed as spasm.

Rapid or Premature Contractions

Comparing the findings derived from the EPT analyses of contraction velocity and latency, 3 potential phenotypes of spasm emerge because of the overlap between the 2: rapid contractions, premature contractions, and premature rapid contractions. Of the 91 patients with at least 1 abnormal metric, 67 (73.6%) had only rapid contractions. Table 3 and Figure 4 summarize the blinded manometric diagnoses of the EPT studies from all 3 groups. Evident in Table 3, most of these patients were ultimately judged to fit criteria for an alternative diagnosis or judged normal. Additionally, the only 2 patients potentially defined as spasm, based only on rapid contractions, had short segments of contraction and could potentially be described as weak peristalsis (Figure 3B). In contrast, patients with premature contractions or premature rapid contractions were all diagnosed with achalasia or DES and 96% of these patients had dysphagia as a dominant symptom. On the other hand, the dominant symptom was more heterogeneous in the rapid contraction group: dysphagia 56%, gastroesophageal reflux disease 34%, and other 10%.

Discussion

Although well-ensconced in the literature, the manometric diagnosis of DES based on the detection of “simultaneous contractions” has always been somewhat enigmatic, identifying a mixture of patients with and without relevant contractile anomalies. Attempts at clarifying this by revising conventional manometric criteria have not solved the riddle. The aim of this study was to carefully apply standardized metrics for contractile velocity and contractile latency to a large series of clinical high-resolution EPT studies in an attempt to refine the

diagnosis of DES. The major finding of the study was that rapid contractile velocity was a very nonspecific finding, rarely the defining feature of a clinically significant disorder unless accompanied by reduced contractile latency. Tutuian et al¹⁹ similarly concluded that conventionally defined DES identified a very heterogeneous population based on an assessment of bolus transit in 71 such patients with combined manometry and impedance. Reduced distal latency, however, measured from the time of deglutitive UES relaxation to the onset of contraction in the distal esophagus, was better, both in terms of being a much less common entity and a much more homogeneous clinical entity. Affected patients almost uniformly had severe dysphagia. However, threequarters of these individuals were ultimately managed as an achalasia subtype (spastic achalasia), raising the question of whether or not spastic achalasia and “DES with short latency” are not actually minor variations on the same theme of impaired inhibitory neuronal function in the distal esophagus.

The concept of reduced contractile latency in spasm was initially proposed by Behar and Biancani¹¹ in elegant studies utilizing conventional manometry to describe the time interval between the onset of contraction in the proximal and distal esophagus (Figure 1). They used a station pull-through technique at 2-cm increments and plotted the latency of the distal contraction from the onset of the swallow. Their findings suggested that patients with simultaneous contractions had a marked reduction in the DL. Utilizing paired swallows at 5-s intervals, they also illustrated the absence of deglutitive inhibition in simultaneous contractions characterized by reduced distal latency, leading them to conclude that reduced DL was indicative of a defect in distal neuromuscular inhibition. Although the patients described in that study match the physiology of the “DES with reduced latency” patients described in the present study, they were insufficiently characterized to ascertain whether or not any of them may have had spastic achalasia using current EPT criteria.

Although quantifying DL is not unique to high-resolution EPT,^{20,21} the technique certainly simplifies and potentially standardizes this measurement. EPT provides the detail required to define the segmental architecture of peristalsis necessary to differentiate regional variations in contraction velocity from more global changes. Key to this methodology was identification of the CDP, a landmark demarcating the transition from peristaltic contraction in the tubular esophagus to the initiation of ampullary contraction in the sphincteric segment.¹⁰ Consequently, the CDP represents a logical end point for measurement of both contraction velocity and latency of the distal contraction. However, to accurately measure velocity, there must also be a reliable starting point, and this is not always the case, as illustrated in Figure 3B, with a large break in the 20 mm Hg isobaric contour. Attempting to measure the CFV in such circumstances is unreliable, whereas the validity of measuring the distal latency is unaffected. Together, these observations argue for prioritizing the measurement of distal latency over CFV in defining peristaltic disorders with rapid contractile propagation.

A limitation of this study was the retrospective nature of the analysis, making it difficult to ascertain the significance of the novel manometric diagnoses proposed in Table 3 (DES with short latency and rapid contraction with normal latency). However, the dominant clinical relevance of restricting the diagnosis of DES to disorders characterized by uniform pathophysiology lies in reducing a large heterogeneous group of patients to a small homogeneous one, thereby making it much more reasonable to test a physiologically targeted intervention. For instance, evident in Tables 2 and 3, large numbers of patients with “simultaneous contractions” identified by either conventional or EPT metrics were ultimately classified as having weak peristalsis, a condition that is very unlikely to benefit from therapies targeted at reducing contractile vigor. In fact, the heterogeneity of DES diagnosed by conventional criteria may largely explain the extreme inconsistency in

therapeutic outcomes evident in the clinical trials.^{22–25} In addition, it is likely that patients with rapid contraction velocity in the context of weak peristalsis may be more likely to have symptoms related to bolus escape and impaired transit. These patients may benefit from therapies targeting transition zone defects,²⁶ visceral hypersensitivity,²⁷ or reflux if associated with gastroesophageal reflux disease.²⁸ On the other hand, we hypothesize that therapy intended to compensate for the loss of deglutitive inhibition (smooth muscle relaxants, nitric oxide donors, etc) may benefit conditions dominated by that pathophysiology (eg, DES with short latency and spastic achalasia). These patients are likely those with poor esophageal transit evidenced by a “corkscrew” or “rosary bead” pattern on fluoroscopy.

Conclusions

We performed a systematic analysis of a large series of clinical EPT studies to refine the diagnostic criteria for DES. Our findings suggest that the current paradigm focused on “simultaneous contractions” (evident by rapid contraction velocity measured between 2 points 3 and 8 cm above the EGJ) identifies a large heterogeneous population, most of which do not have a clinical syndrome suggestive of esophageal spasm. Incorporating the measurement of DL into the diagnostic algorithm improves upon this by isolating disorders of distinct pathophysiology, characterized by functionally impaired inhibition in the distal esophagus (eg, DES with short latency and spastic achalasia). We hypothesize that prioritizing the measurement of distal latency over measures of contractile velocity will help refine the management of these disorders by isolating the relevant therapeutic target. This hypothesis will need to be tested in long-term natural history studies and tailored outcomes trials based on these phenotypes.

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Abbreviations used in this paper

CDP	contractile deceleration point
CFV	contractile front velocity
DES	distal esophageal spasm
DL	distal contractile latency
EGJ	esophagogastric junction
EPT	esophageal pressure topography
UES	upper esophageal sphincter

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Figure 1.

The concept of reduced distal latency in spasm as described by Behar and Biancani.¹¹ (A) The latency of propagation for normal controls (*blue circles*) and a patient with spasm (*white circles*) adapted from Behar and Biancani. The latency interval was measured using conventional manometry as time from onset of contraction at sensor 21 to onset of contraction at sensor 1. The latency interval was determined to be a marker of the inhibitory ganglionic integrity, suggesting that patients with spasm had evidence of reduced latency and premature contraction. In the *right panels*, the latency interval plots from the conventional manometry study are superimposed on EPT tracings of a swallow with normal latency (*top*) and short latency (*bottom*). In each case, the time and sensor position scales are adjusted to approximate those of the conventional manometry tracing.

Figure 2.

Measurement of DL and CFV in an EPT plot of a normal swallow. The *black line* is the 30-mm Hg isobaric contour circumscribing areas on the plot with intraluminal pressure >30 mm Hg. The peristaltic esophageal contraction has 2 pressure troughs, 1 centered proximally at P and 1 distally at D. The CDP represents the inflexion point in the contractile front propagation. It is localized by fitting 2 tangential lines to the initial and terminal portions of the 30-mm Hg isobaric contours and noting intersection of the lines (*white dot*). The CFV is calculated by taking the best-fit tangent of the 30-mm Hg isobaric contour between P and CDP. The distal latency is measured from UES relaxation to the CDP.

Figure 3.

EPT phenotypes of abnormal propagation based on DL and CFV measurements. The most common phenotypes were A and B with normal latency and a large defect in the 30-mm Hg isobaric contour. The swallow in (A) with a rapid contraction and a large proximal break fulfills criteria for both weak peristalsis and rapid contraction. (B) Illustrates the problem with measuring CFV with weak peristalsis and a nonpropagating segmental contraction. Although the CDP provides a reasonable temporal end point for measuring velocity, the large break eliminates any appropriate proximal landmark resulting in what would be a negative CFV. However, the DL is normal suggesting this to be an artifact of weak peristalsis. The swallow in (C) is also associated with a large break (7.5 cm); however, it is also associated with short latency (3.0 s) and rapid CFV (45 cm/s), thereby representing a distinct phenotype compared to (A) and (B). The swallow in (D) is premature (DL = 4.4 s) with a normal CFV (6 cm/s). This swallow is associated with impaired EGJ relaxation and bolus pressurization consistent with functional EGJ obstruction or an achalasia variant.

Figure 4.

Blinded diagnoses of 91 EPT studies with rapid propagation subdivided into studies with short distal latency (<4.5 s) or rapid CFV. Patients with premature contractions defined by a distal latency <4.5 seconds were uniformly diagnosed with a spastic disorder of the distal esophagus. In contrast, patients with only a rapid CFV were likely to have a non-spastic disorder, especially weak peristalsis.

Table 1

Characteristics of EPT Patient Groups With Abnormal Contraction Velocity or Latency

EPT designation	Rapid contractions (CFV >9 cm/s)	Reduced latency (distal latency <4.5 s)	Breaks in peristalsis
Premature rapid	Yes	Yes	No criteria
Premature	No	Yes	No criteria
Rapid	Yes	No	None or <5 cm
Weak	Yes ^a	No	5 cm

NOTE. Designations of either rapid contractions or reduced latency were based on at least 20% (20%–100%) of test swallows meeting criteria.

^aMay be unable to calculate CFV with a large break in the 30-mm Hg isobaric contour.

Table 2

Comparison Between Findings Using the Conventional Manometric Criteria and EPT Criteria for Rapid Contraction Velocity in 1070 Consecutive Patients

	<u>Abnormal CFV (>9 cm/s), n = 85</u>		<u>Normal CFV, n = 985</u>	
	n	%	n	%
Abnormal conventional (>8 cm/s), n = 186	47	4.4	139	13
Normal conventional, n = 884	38	3.6	846	79

Table 3

Phenotypes of Rapid Propagation

EPT classification	Rapid contraction (CFV >9 cm/s), n = 67	Premature contractions (distal latency <4.5 s), n = 6	Premature rapid contractions, n = 18
DES with short latency ^a		2	4
Rapid contraction with normal latency ^a	2 ^b		
Spastic achalasia	—	4	14
EGJ outflow obstruction ^c	7	—	—
Weak peristalsis	39	—	—
Hypertensive	5	—	—
Otherwise normal	14	—	—

^aProposed on the basis of these findings.

^bCould be classified as weak peristalsis based on concomitant large breaks in 20-mm Hg isobaric contour.

^cMay be an achalasia variant.