Published in final edited form as:

Neurogastroenterol Motil. 2008 December ; 20(12): 1283–1290. doi:10.1111/j.1365-2982.2008.01169.x.

Oesophageal peristaltic transition zone defects: real but few and far between

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Abstract

This study analysed the association between oesophageal transition zone (TZ) defects [characterized by a delay and/or spatial gap between the terminus of the proximal oesophageal (striated muscle) contraction and the initiation of the distal oesophageal (smooth muscle) contraction] and dysphagia in a large patient cohort. Four hundred consecutive patients (178 with dysphagia) and 75 controls were studied with 36-channel high-resolution manometry (HRM). The resultant pressure topography plots were first analysed for impaired oesophagogastric junction (OGJ) relaxation, distal segment contractile abnormalities, and proximal contractile abnormalities using normal values from the 75 controls. If these aspects of oesophageal motility were deemed normal, the TZ was characterized by length and duration between the proximal and distal contractions using a 20 mmHg isobaric contour to establish the segment boundaries. Patients were then classified according to whether or not they exhibited TZ defects (spatial separation or delay) and the occurrence of unexplained dysphagia. Of the 400 patients, 267 were suitable for TZ analysis and of these 55 had a spatial or temporal TZ measurement exceeding the 95th percentile of the controls (2 cm, 1 s). Exactly 34.6% of the patients ($n = 19$) with spatial and/or temporal TZ defects had unexplained dysphagia, which was significantly more than seen with normal TZ dimensions (19.8%). Although far less common than distal peristaltic or OGJ abnormalities, TZ defects may be related to dysphagia in a minority of patients (<4% in this series) and should be considered a distinct oesophageal motility disorder.

Keywords

oesophageal transition zone; oesophageal motility; oesophagus; high-resolution manometry; striated muscle

INTRODUCTION

Two recent technological advances in clinical oesophageal manometry were the introduction of practical high-resolution manometry (HRM) systems and the development of computerized algorithms to display and quantify oesophageal function using pressure topography plots. In the context of oesophageal peristalsis, the resultant highly resolved pressure topography plots facilitate imaging peristaltic contractions in terms of segmental constituents. This contrasts with the conventional approach of localizing measures at arbitrary distances relative to the upper sphincter or oesophagogastric junction (OGJ) that can unpredictably localize within one or another contractile segment.^{1,2} Pressure topography plots are also particularly useful in

localizing and characterizing the transition zone (TZ) that exists between the proximal and distal contractile segments. In fact, recent HRM studies have shown that oesophageal peristalsis actually comprises two distinct contractile waves, corresponding to the distinct muscle types and neural control mechanisms of the proximal and distal oesophagus.^{3–6} The TZ represents the region of spatiotemporal merger between these two contractile waves. In order to effect uninterrupted bolus transport across the TZ, the proximal and distal contractile waves normally exhibit smooth spatiotemporal coordination.^{4,7}

Despite the theoretical potential noted here, HRM with pressure topography analysis has yet to be broadly applied to study TZ characteristics. As a preliminary step in that pursuit, we recently reported on TZ characteristics in 75 normal subjects as part of a detailed HRM pressure topography analysis of oesophageal peristalsis.⁷ Two case reports have also emerged of instances in which TZ defects identified with HRM pressure topography were associated with impaired bolus transit across the TZ.^{8,9} The aim of the present study was to broadly apply the TZ analysis methodology developed in the work on normal subjects to a series of 400 consecutive patients to determine how common such defects are and whether or not they are uniformly associated with dysphagia. In doing so, we hope to continue with the systematic, quantitative definition of oesophageal motility disorders in terms of pressure topography that has thus far encompassed the OGJ¹⁰ and the distal oesophageal segment.¹¹

METHODS

Patients

HRM studies performed between February 2003 and July 2005 on 400 consecutive patients (248 males, aged 18–87) referred to the Northwestern Memorial Hospital manometry laboratory were analysed. These patients presented with a diverse set of conditions to a tertiary care practice specializing in the management of oesophageal disease. One hundred and seventy-eight patients were undergoing evaluation for dysphagia, 146 for predominantly gastro-oesophageal reflux disease (GORD) symptoms (heartburn, regurgitation), 54 for chest pain, and 22 for miscellaneous complaints or follow-up. Thereafter, the patient's medical records were analysed along with their manometry tracing to establish the most likely pertinent diagnosis. Typical of a referral practice, some patients had already undergone treatment for their condition: 34 patients had prior fundoplication and 38 patients had undergone treatment for achalasia (BotoxTM injection, pneumatic dilation, Heller myotomy, or some combination of the three).

Manometric findings from the patient group were compared with those of the 75 asymptomatic control subjects. HRM paradigms developed and reported for the normal subjects were directly applied to the patient groups.⁷

High-resolution manometry

A solid-state HRM 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 post-study thermal correction algorithm have been described in detail elsewhere.¹² To summarize, each sensor is circumferentially sensitive, accurate to within 1 mmHg, capable of recording transient pressure changes in excess of 6000 mmHg s⁻¹, and zeroed to atmospheric pressure. Studies were performed in a supine position after at least a 6-h fast. The HRM assembly was passed transnasally and positioned to record from the hypopharynx to the stomach with about five intragastric sensors. The catheter was fixed in place by taping it to the nose. The manometric protocol included a 5-min period to assess basal sphincter pressure and ten 5-mL water swallows. All pressure measurements were referenced to atmospheric pressure.

Data were analysed using both ManoView™ analysis software (Sierra Scientific Instruments Inc.) and MATLAB™ (The MathWorks Inc., Natick, MA, USA). Although pressure topography plots can be generated using ManoView™, MATLAB™ was preferentially used because of greater flexibility in customizing isobaric contour plots and as it also provides a tool for devising and refining computer programs to explore novel HRM paradigms. Once written, these programs could systematically analyse each relevant swallow within the manometric dataset for the parameter under analysis.

Characterization of the TZ motility using pressure topography parameters

Fig. 1 depicts a typical pressure topography plot of an intact peristaltic sequence in a normal individual. The centre of the TZ is easily localized between the proximal and distal oesophageal contractile segments as the locus of the nadir pressure amplitude during peristalsis. This is illustrated by the spatial pressure variation plot in Panel B of Fig. 1 depicting the greatest contractile pressure occurring at each locus along the oesophagus during the peristaltic contraction. However, once the TZ nadir is defined, quantifying a spatial length and temporal duration to the TZ depends upon the threshold pressure that is specified. This is illustrated in Fig. 1 by the two blackened isobaric contours, 20 and 40 mmHg. Clearly, the spatial (x) and temporal (t) dimensions of the TZ increase as the specified threshold pressure increases. Conversely, if the specified threshold pressure is less than the TZ nadir, the dimensions of the TZ are 0 s and 0 cm. The other consideration in selecting a threshold pressure for defining the TZ limits is that it should be greater than typical intrabolus pressure to insure that one indeed defines the limits of lumen obliterating contractions. Both our own work in normal subjects⁷ and physiological observations of the relationship between contractile amplitude and bolus clearance using multichannel intraluminal impedance¹³ led us to conclude that a threshold pressure of 20 mmHg was appropriate.

Although the problem did not arise in the analysis of normal subjects, another challenge in identifying TZ defects in a patient population is in differentiating them from defects of the distal or proximal segment contractions. Clearly, a grossly hypotensive proximal or distal contractile segment could alternatively be described as a lengthened and prolonged TZ. In order to avoid this confounding factor, we restricted our TZ analysis to patients with normal proximal and distal contractile segments. The metrics used to define a normal distal contraction were that there be normal OGJ relaxation (4-s integrated relaxation pressure ≤ 15 mmHg) and normal distal pressurization front velocity (< 8 cm s⁻¹). This excluded individuals with achalasia, distal oesophageal spasm, and hypotensive peristalsis.¹¹ Individuals with abnormalities of the proximal oesophageal contraction were identified using the normal values for proximal contractile velocity (1.8–4.2 cm s⁻¹) and proximal contractile integral (250–1500 mmHg cm s) derived from the normal controls and identifying patients whose values were outside those of the 95th percentile confidence intervals.⁷

All high-resolution manometric parameters described before were summarized using mean $\pm$ SE. The proportion of patients presenting with dysphagia was compared between patients with normal and abnormal TZ function using the z -ratio for the significance between two independent proportions.

RESULTS

Distal contractile abnormalities

Of the 400 patients, two had oesophageal cancer and were excluded from the analysis. Of the remaining 398, 35 patients had technically inadequate studies due to a broken sensor in the proximal oesophagus or across the TZ and were excluded. Thus, 363 patients were evaluated for OGJ abnormalities. Among these, 54 subjects had achalasia with panoesophageal

pressurization and were excluded from the analysis of the proximal oesophagus. Thus, 309 patients were appropriate for evaluation of abnormalities of the proximal oesophageal segment. Of these patients, 42 had either absent or weak distal peristalsis that could potentially confound the TZ assessment. Thus, 274 patients were evaluated for TZ defects. This patient segregation is summarized in Fig. 2.

Proximal contractile abnormalities

The integrity of the proximal contractile segment was first assessed by the proximal contractile integral (PCI), defined as the product of length, time, and amplitude of the proximal contraction. Fig. 3 illustrates the distribution of PCI values encountered in the 309 patients analysed. Forty-one patients were identified with abnormally low PCI (≤ 250 mmHg cm s) and seven with an abnormally high value (≥ 1450 mmHg cm s). Examples of each of these are illustrated in Panels B and C of Fig. 3. Of the 41 patients with a weak proximal contraction, 27 also had abnormalities of the distal segment (11 peristaltic dysfunction, 2 scleroderma pattern, 5 nutcracker, 2 distal spasm, 7 functional OGJ obstruction). Of the remaining 14 patients, now characterized with a normal distal contractile segment but weak proximal segment, six were undergoing evaluation for dysphagia, six for reflux symptoms, and two for chest pain. The finding of a weak proximal segment was of clear clinical significance in only two of these with clear evidence of neuromuscular disease and oropharyngeal dysphagia.

Of the seven patients identified with an abnormally high PCI (≥ 1500 mmHg cm s), two had a nutcracker pattern in the distal oesophagus, one had aperistalsis in the distal segment, and four had normal distal segment function. In no case was the finding of a hypercontractile proximal segment of clear clinical significance.

TZ abnormalities

Fig. 4 illustrates the nadir TZ pressure of the 267 patients in whom this could be analysed. Note that in only 28% of these patients ($n = 74$) was the nadir TZ pressure less than 20 mmHg, the minimal value necessary for it to be characterized as having spatial and temporal dimensions greater than zero.

Theoretically, temporal prolongation of the TZ could be alternatively attributed to an abnormally fast proximal contractile velocity (PCV). Fig. 5 illustrates this relationship. Panel A shows the distribution of PCV values among the 309 patients analysed while panel B illustrates an example of a subject with an abnormally low PCV and Panel C an individual with a rapid PCV. In Panel B, this has the effect of shrinking what might otherwise have been a prolonged TZ while in Panel C the rapid PCV has the effect of exaggerating the duration of the TZ. In all, five patients were identified with a low proximal segment PFV: one with dysphagia, one with chest pain, and three with GORD, all with normal distal oesophageal motility. Thirty-four patients were identified with a high PCV: 18 dysphagia, 7 chest pain, 7 GORD, and 2 globus. However, the rapid PCV was associated with a prolonged TZ (1.9 s) and dysphagia in only one patient making this an unusual explanation for clinically significant TZ prolongation.

Fig. 6 illustrates the spatial and temporal TZ dimensions of the 267 patients in whom it could be characterized. Among these, the values of 55 patients (20.5%) exceeded the spatial and/or temporal limits seen in the normal controls (2.0 cm, 1.0 s using 20 mmHg isobaric contour threshold). As illustrated in Fig. 6, the proportion of patients presenting with dysphagia was significantly higher in patients with abnormal TZ function compared with the patients with normal TZ characteristics ($P = 0.02$; z -ratio for independent proportions). The likelihood of an individual having dysphagia was greater with increased spatial and/or temporal dimensions of the TZ (34.6%) than with only temporal prolongation (16.6%) or normal dimensions (19.8%).

Fig. 7 illustrates the pressure topography pattern of a peristaltic contraction in the individual with the largest TZ defect encountered in this patient series.

DISCUSSION

While significant interest has appropriately been focused on the distal oesophagus and OGJ in the genesis of oesophageal dysphagia, the functional role of the proximal oesophagus and the TZ has received sparse attention. Historically, this was primarily due to the lack of an appropriate technology to facilitate a detailed segmental analysis of oesophageal peristalsis. The highly resolved pressure topography plots used in this analysis fill that void. The major findings of the analysis were that, although rare, clinically relevant abnormalities of the proximal oesophagus and TZ do occur in about 6% of the patients and potentially account for unexplained dysphagia in about half of them. In particular, the combination of both temporal prolongation (>1 s) and spatial elongation (>2 cm) of the TZ was strongly associated with dysphagia.

Bolus transit through the oesophagus depends on the smooth integration between the proximal and distal oesophageal segments. Histologically, these segments are thought of as representing the transition from striated to smooth muscle, with the caveat that only the most proximal 5% of the human oesophagus is entirely striated muscle with the subsequent 45% typically exhibiting a progressive transition to smooth muscle that eventually becomes the exclusive type.⁵ From a neurophysiological perspective, the segmental architecture represents a shift in control mechanism. The proximal oesophagus is directly innervated by motor neurons residing in nucleus ambiguus with the aboral sequencing of contraction being a property of medullary circuitry.⁶ The distal oesophageal segment, on the other hand, is indirectly controlled by the dorsal motor nucleus of the vagus with the timing of contraction determined by intramural myenteric plexus ganglion neurons.¹⁴ In fact, subsegments within the distal oesophagus can be defined in pressure topography plots² characterized physiologically by the dominance of excitatory cholinergic myenteric plexus neurons in the proximal subsegment and inhibitory (predominantly nitric oxide) myenteric plexus neurons in the distal segment.^{3,14} Thus, multiple mechanisms exist wherein exaggerated spatial or temporal dimensions of the TZ might occur: rapid proximal segment propagation, delayed onset of distal segment contraction, a spatial gap between the terminus of the medullary control, and the onset of the myenteric plexus control.

While the current work did not establish the precise correlation between spatiotemporal dimensions of the TZ and impaired bolus transit, prior case reports using concomitant fluoroscopy⁸ have demonstrated the occurrence of impaired transit though the TZ and dysphagia in individuals with TZ zone dimensions on the order of 2 s duration and 1 cm length had they been measured using the criteria set forth in the current analysis. Similarly, although not conducted in such a way as to permit localization or measurement of the TZ, impedance studies suggest that peristaltic amplitudes of less than 20 mmHg in this region (the threshold pressure we used to establish the spatiotemporal dimensions of the TZ) are likely to be associated with impaired bolus transit. It also stands to reason that impaired transit in this region would be most profound for solid food given the greater dependency on peristalsis, especially in a recumbent posture.^{15,16} Furthermore, TZ pathophysiology in combination with other oesophageal motility defects may be more likely to cause symptoms.¹⁷ Although scant data are available on the topic, there is also the possibility that defects in TZ bolus transit may be amenable to specific pharmacological intervention given that tegaserod,¹⁶ cisapride,¹⁸ and bethanechol¹⁹ have been shown to improve smooth muscle peristalsis and diminish TZ dimensions, with a trend towards improved bolus transit in the case of tegaserod and bethanechol.

In conclusion, we utilized highly resolved pressure topography plots of oesophageal peristalsis to develop a standardized method for quantifying the spatiotemporal dimensions of the TZ that exists between the proximal and distal oesophagus. Applying this analysis to a 400 patient series suggested that TZ defects greater than 2 cm in length and 1 s in duration were strongly associated with otherwise unexplained dysphagia, occurring in 57% of the 25 patients so identified. These findings suggest that, although not nearly as common as abnormalities of the OGJ or distal oesophagus, TZ defects represent a distinct oesophageal motility disorder that should be considered in the evaluation of unexplained dysphagia.

Acknowledgments

This work was supported by RO1 DC00646 (P. J. Kahrilas) from the Public Health Service.

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Figure 1.

Method for oesophageal transition zone (TZ) measurement. Panel A is a pressure topography plot during a normal peristaltic contraction. Time is on the horizontal axis and length along the oesophagus on the vertical axis. Pressure magnitude is encoded in colour corresponding to the scale shown at the bottom. Two isobaric contour lines at 20 and 40 mmHg are blackened. The spatial (x) and temporal (t) dimensions of the TZ at each pressure are shown. Panel B shows the methodology for determining the position of the TZ nadir. A spatial pressure variation plot of maximal contractile amplitude locus along the oesophagus is made and the nadir pressure is designated the TZ nadir. The corresponding TZ nadir location is shown in Panel A with a black dot.

Patient dropout in proximal esophagus and TZ analysis

Figure 2.

Dominant symptom profile and manometric abnormalities in the study population. Because severely abnormal proximal or distal contractile segments as well as high-grade oesophagogastric junction obstruction prevent transition zone analysis, patients with these abnormalities needed to be excluded.

Figure 3.

Distribution of proximal contractile integral (PCI) values among 309 patients in which it was not confounded by distal segment abnormalities (Panel A). Forty-one patients had an abnormally low PCI (<250 mmHg cm s) and seven had an abnormally high PCI (>1450 mmHg cm s). Panel B illustrates a swallow from a dysphagia patient with a weak proximal oesophageal contraction (PCI = 31.3 mmHg cm s) and neuropathy of the proximal oesophagus. Panel C illustrates a swallow of a patient with a hypercontractile proximal oesophagus (PCI = 1798.8 mmHg cm s).

Figure 4.

The distribution of the nadir transition zone (TZ) pressure values in the 267 patients in whom it could be measured. Seventy-four patients (28%) had a nadir TZ pressure <20 mmHg, the minimal value necessary for it to be characterized as having spatial and temporal dimensions greater than zero.

Figure 5.

Distribution of proximal contractile velocity (PCV) values among 309 patients in which it was not confounded by distal segment abnormalities (Panel A). Five patients had an abnormally low PCV ($<1.8 \text{ cm s}^{-1}$) and 34 patients had an abnormally high PCV ($>4.2 \text{ cm s}^{-1}$). Panel B illustrates a swallow from a patient with a low PCV (1.5 cm s^{-1}) resulting in a seamless melding between the proximal and distal contraction waves. Panel C shows a swallow of a patient with a rapid PCV (7.4 cm s^{-1}) with a normal distal velocity resulting in a temporal mismatch (1.9 s) between the two contraction waves.

Figure 6.

Transition zone (TZ) dimensions for 267 patients in whom it could be measured using a 20 mmHg isobaric contour to define the limits of the proximal and distal contractions. The black circles represent patients presenting with a primary symptom of dysphagia and the open circles represent patients without dysphagia. The horizontal and vertical lines depict the 95th percentile values determined from the 75 normal controls ($x < 2$ cm; $t < 1$ s). Significantly more patients with increased length and duration of the TZ had dysphagia (57%) compared with those without TZ defects (19.7%) or with only a temporal defect (16.8%).

Figure 7.

Example of a large transition zone defect from a patient with unexplained dysphagia. The patient had a normal proximal contractile integral, distal contractile velocity, and oesophagogastric junction relaxation.