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Characteristics of the Esophageal Low-Pressure Zone in Healthy Volunteers and Patients With Esophageal Symptoms: Assessment by High-Resolution Manometry

Daniel Pohl, M.D.,[1] Mentore Ribolsi, M.D.,[2] Edoardo Savarino, M.D.,[3] Heiko Frühauf, M.D.,[1] Michael Fried, M.D.,[1] Donald O. Castell, M.D.,[4] and Radu Tutuian, M.D.[1]

[1]*Division of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland;* [2]*Department of Digestive Diseases, University Campus Bio Medico, Rome, Italy;* [3]*Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy; and* [4]*Division of Gastroenterology and Hepatology, Medical University of South Carolina, Charleston, South Carolina*

BACKGROUND: Esophageal motility studies in humans have documented a low-pressure zone (LPZ) in the area of transition from striated to smooth muscle. While preliminary studies indicate that a bolus might be retained in this area, the clinical relevance of the LPZ remains unclear.

AIM: To investigate a possible relationship between esophageal symptoms and the size of the esophageal LPZ.

METHODS: We reviewed high-resolution manometry (HRM) data from patients with esophageal symptoms (dysphagia, chest pain, and heartburn/regurgitation) and asymptomatic volunteers. The proximal border of the LPZ was defined as the point where the amplitude of the proximal contraction wave declined below 30 mmHg, and the distal border as the point where the distal contraction wave first increased above 30 mmHg.

RESULTS: The average ($\pm$ standard error of mean [SEM]) length of the LPZ in 44 asymptomatic individuals was 5.4 $\pm$ 0.6 cm and did not differ ($P = 0.222$) from the LPZ in 64 patients with dysphagia (6.8 $\pm$ 0.4 cm), 34 patients with chest pain (6.4 $\pm$ 0.6 cm), and 42 patients with gastroesophageal reflux disease (GERD) symptoms (7.0 $\pm$ 0.6 cm). These results did not change when the length of the LPZ was corrected for total esophageal length. The time width of the LPZ in asymptomatic individuals (1.6 $\pm$ 0.2 s) was shorter than in patients with dysphagia and GERD symptoms (dysphagia 2.4 $\pm$ 0.2 s, GERD symptoms 2.8 $\pm$ 0.3 s).

CONCLUSION: A time delay between the proximal and distal esophageal contraction waves might be a meaningful variable in GERD and dysphagia.

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INTRODUCTION

The primary function of the esophagus is the transport of food and liquids from the oral cavity to the stomach by propulsive muscle contractions. Esophageal manometry provides information on the amplitude and velocity of esophageal peristalsis and the location and pressure profile of the upper and lower esophageal sphincter (LES). Over the past 50 yr, esophageal manometry has become the primary clinical tool to evaluate esophageal motility abnormalities (1). Conventional esophageal manometry is performed in the supine position and evaluates esophageal peristalsis during the swallowing of water (2). Taking advantage of the technologic advances and an increasing computing power, newer systems are able to simultaneously integrate data from 32–36 manometric channels into high-resolution manometry (HRM) to evaluate esophageal motility. HRM allows a more detailed evaluation of the relaxation of the upper and lower esophageal sphincter and esophageal peristalsis. Recent studies indicate that it might be superior to conventional manometry in predicting bolus transit (3, 4).

Histologic studies have shown that the proximal one-third of the human esophagus is composed of mainly striated muscle, while the distal two-thirds is composed of smooth muscle. Manometric studies have documented a low-pressure zone (LPZ) at this junction between the upper striated muscle part of the esophagus and the lower smooth muscle part (5–7). Anatomically, this transition zone (TZ) is situated adjacent to the aortic arch and carina (4, 8). In fluoroscopic barium swallows, the LPZ corresponds to an area of contrast retention

in the mid-esophagus, a phenomenon considered physiologic by some radiologists (9). The relevance of the LPZ has been a subject of controversy. While for some, bolus retention in this zone might be accepted as physiologic, others consider bolus stasis in this zone as pathologic (10, 11). A study in 6 healthy volunteers using HRM and video fluoroscopy found a wider LPZ, possibly to be more likely associated with bolus stasis (11). However, the possible clinical impact of the occurrence and characteristics of the LPZ in symptomatic patients have not been investigated. The aim of our study was to assess the characteristics of the esophageal LPZ in patients and healthy volunteers.

PATIENTS AND METHODS

We reviewed HRM studies from patients referred to our tertiary care center for the evaluation of esophageal symptoms or as part of the research protocols between April 2003 and December 2005. The ethics committee of the University of Zurich approved the analysis of these data. The study complies with the Declaration of Helsinki (last general assembly, Tokyo, 2004).

Symptom Data

The patients were asked to fast at least 4 h prior to the examination. Symptom data were collected for typical esophageal symptoms (dysphagia, chest pain, and heartburn/regurgitation). For heartburn and chest pain, the patients were asked to rate the frequency on a 5-point scale (never, less than once/wk, once every 3 days, once every 2 days, and daily), number of episodes on a 6-point scale (never, once a day, twice a day, three times a day, four times a day, and more than 4 times a day), duration of the episode on a 7-point scale (none, 1 min, 1–5 min, 5–10 min, 10–30 min, 30–60 min, and more than 60 min), and intensity of episodes on a 6-point scale (none, very mild, mild, medium, strong, and very strong). For regurgitation, the patients were asked to rate the frequency, number of episodes, and intensity of the complaints on the scales as described above. For dysphagia, the patients were asked to rate the frequency and intensity as described above. For each symptom, composite scores were computed according to the Eraflux questionnaire (12). In patients with multiple symptoms, the symptom with the highest score was considered the primary symptom.

An HRM silicone micrometric catheter (4-mm external diameter) with 32 channels (Dentsleeve, Wayville, South Australia, Australia) spaced helically along it was used for esophageal manometry. The distance between the two most distally inserted channels was 5 cm. The channels 2–10 and 25–32 were 1 cm apart, while the channels 11–24 were 1.3 cm apart. The manometry catheter was preflushed with CO_2 to remove air, and perfusion offsets were removed at the beginning of every study. The catheter was perfused with distilled water using a pneumatically activated manometric pump designed and built by G. Hebbard, Royal Melbourne Hospital, Melbourne, Australia. Each channel was connected to an external transducer (Abbott Transpac IV; Abbott Laboratories, Mississauga, Ontario, Canada). Manometric data were acquired at an acquisition frequency of 25 Hz using the HAD software system (G. Hebbard, Royal Melbourne Hospital).

Data Acquisition

Prior to the insertion of the HRM catheter, one nostril was anesthetized using a Lidocaine gel 2%. The manometry catheter was inserted transnasally through the esophagus and positioned so that the most distal channel was located in the stomach and the distal closely spaced channels spanned the LES. The contraction amplitude of the esophageal contractions was referenced to the gastric baseline. The patients were given 10 water swallows (10 mL each) in a recumbent position 20–30 s apart (2).

Data Analysis

Manometric data from the 32 channels were stored and analyzed by the TRACE! version 1.2 software system (Trace! v1.2 videomanometry system; G. Hebbard, Royal Melbourne Hospital) using a spatiotemporal plot representation. Data from patients with less than six analyzable swallows (see below) were not included in the analysis.

We analyzed the 32-channel HRM data obtained during the water swallows in the left lateral decubitus position recorded in patients with esophageal symptoms and asymptomatic volunteers. At the time of reading, the investigator was blinded to the diagnosis and symptoms. Double swallows and swallows containing cough-induced pressure artifacts were excluded from the analysis. Only datasets with six or more water swallows (10 mL each) free of artifacts and spaced at least 20 s apart were included in the analysis (13). Using a two-dimensional spatiotemporal color plot, we identified the distal border of the upper esophageal sphincter, the proximal border of the LES, and the LPZ. The LPZ was measured extending from (1) the point where the amplitude of the proximal contraction wave below the upper esophageal sphincter declined below 30 mmHg to (2) the point where the amplitude of the distal contraction wave first increased above 30 mmHg for at least 3 cm (Fig. 1). Length (in mm) defining a spatial separation and width (in seconds time) defining a temporal separation were assessed by these cutoff values above. The proximal contraction wave was measured from the lower border of the upper esophageal sphincter to the beginning of the LPZ, and the distal contraction wave from the end of the LPZ to the upper border of the LES. Total esophageal length was measured extending from the lower border of the upper esophageal sphincter to the upper border of the LES. In order to evaluate the clinical impact of the LPZ, we did not exclude ineffective or simultaneous swallows. Due to the nature of simultaneous recordings from multiple pressure sites with the HRM equipment, mapping of the esophageal TZ was possible also in these swallows. In addition, we reviewed tracings for the presence of hiatal hernias (14). When present, the size of the hiatal hernia was estimated by measuring the distance

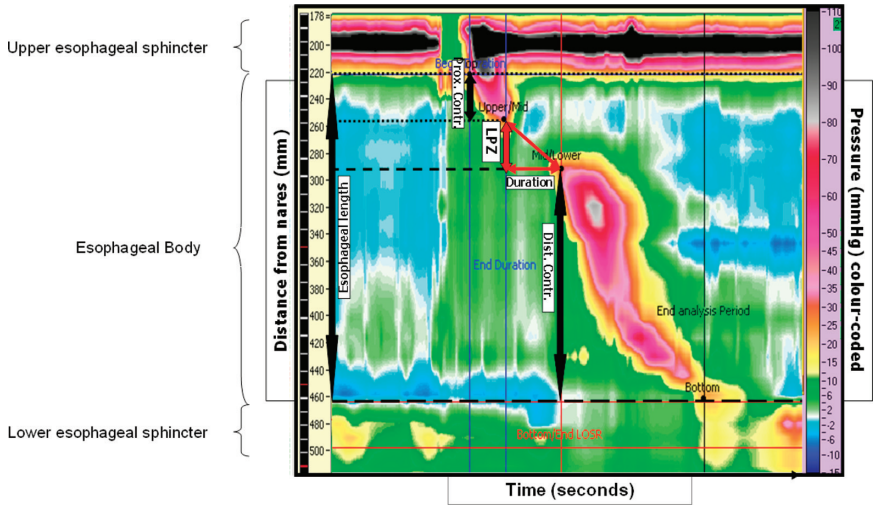

Figure 1. Pressure zones of an esophageal peristalsis measured during a 32-channel high-resolution manometry (HRM). The proximal contraction extends from the lower end of the upper esophageal sphincter (UES) to the point where pressure declines below 30 mmHg. The low-pressure zone (LPZ) is measured between the drop below and rise above 30 mmHg along the contractile front horizontally (duration in seconds) and vertically (length in mm). The distal contraction extends from the end of the LPZ to the upper margin of the lower esophageal sphincter (LES).

between the point of maximal LES resting pressure and point of maximal diaphragmatic pressure during normal breathing at least 30 s after a swallow in recumbent position (15). Patients with achalasia were excluded from the analysis.

Statistical Analysis

Data are presented as mean ± standard error of mean (SEM) unless otherwise specified. All manometric parameters were analyzed on a subject-by-subject basis by calculating the mean values of each parameter. Continuous parameters were analyzed using an analysis of variance (ANOVA) with a Bonferroni *post hoc* correction for comparisons between individual groups. The correlations were evaluated using the Spearman coefficient rho (2-tailed). Given the previously published data in normal volunteers (16), we estimated that 32 patients in each group would provide an 80% power to identify a 30% difference between the groups. A P value of ≤ 0.05 was considered statistically significant in all analyses.

RESULTS

Data from 187 individuals (99 women, 88 men, mean age 46 yr, range 16–88 yr) were included for the analysis. This included data from 65 patients with dysphagia, 34 patients with chest pain, and 43 patients with gastroesophageal reflux disease (GERD) symptoms (heartburn/regurgitation). Data from 45 asymptomatic individuals served as the control group. Asymptomatic individuals were ($P < 0.001$) younger (34 ± 2 yr) than patients with chest pain (53 ± 3 yr), dysphagia (52 ± 2 yr), and GERD (44 ± 2 yr). In addition, GERD patients were younger ($P < 0.05$) than patients with dysphagia and chest pain.

Total Esophageal Length

The tubular esophagus was longer ($P < 0.01$) in men (22.0 ± 2.2 cm) compared with women (21.1 ± 2.1 cm). In asymptomatic individuals, the total esophageal length (22.5 ± 2.8 cm) was greater than in patients with chest pain (21.0 ± 4.1 cm, $P = 0.011$) and GERD (20.8 ± 3.5 cm, $P = 0.001$) but not dysphagia (21.7 ± 2.3 cm, $P = 0.31$).

Low-Pressure Zone

We identified distinct pressure zones in 184 (98%) subjects (44 asymptomatic patients, 42 GERD patients, 34 chest pain patients, and 64 dysphagia patients). The average (± SEM) length of the LPZ measured was 5.4 ± 0.6 cm in asymptomatic individuals and did not differ ($P > 0.05$) from the LPZ measured in patients with dysphagia (6.8 ± 0.5 cm), chest pain (6.4 ± 0.6 cm), and GERD symptoms (7.0 ± 0.6 cm; Table 1). These results did not change when the length of the LPZ was calculated as percentage of the total esophageal length in order to correct for the differences in the esophageal length (Table 1).

The time gap between the proximal and distal contraction waves (*i.e.*, "time width" of the LPZ) in asymptomatic individuals (1.6 ± 0.2 s) was shorter than in symptomatic patients ($P = 0.004$). Pair-wise comparisons using Bonferroni's correction for multiple testing found the time gap in asymptomatic individuals shorter than that measured in patients with GERD symptoms (2.8 ± 0.3, $P < 0.01$) and dysphagia (2.4 ± 0.2 s, $P < 0.05$) but not in patients with chest pain (2.4 ± 0.2 s, $P = 0.115$).

Proximal and Distal Contraction

The average (± SEM) length of the proximal contraction (4.7 ± 0.2 cm) in asymptomatic individuals was greater than in symptomatic patients (Table 1). When correcting for

Table 1. The Absolute and Relative Length of Esophageal Peristaltic Segments and Duration of the Low-Pressure Zone (LPZ) Stratified According to Main Symptom

		Asymptomatic (N = 44)	Dysphagia (N = 64)	Chest Pain (N = 34)	GERD (N = 42)	*P* Value
Proximal contraction length	mm	47.1 ± 2.4	39.9 ± 2.1	35.4 ± 2.7	37.4 ± 2.4	0.007
	%	21.2 ± 1.1	18.5 ± 0.9	17.1 ± 1.3	18 ± 1.2	0.088
LPZ length	mm	54.2 ± 6.2	68.5 ± 5.2	63.6 ± 6.0	70.3 ± 6.3	0.222
	%	24.0 ± 2.6	30.4 ± 2.4	30.7 ± 2.9	33.0 ± 3.5	0.155
	duration in seconds	1.6 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	2.8 ± 0.3	0.004
Distal contraction length	mm	129.4 ± 4.7	111.7 ± 4.5	111.7 ± 5.9	102.4 ± 6.7	0.007
	%	57.8 ± 2.0	49.3 ± 2.1	51.8 ± 2.8	44.4 ± 3.5	0.005

total esophageal length, this difference became nonsignificant, with no difference between individual patient groups.

GERD but not dysphagia or chest pain patients displayed a shorter distal contraction wave (10.2 ± 0.7 cm) compared with asymptomatic individuals (12.9 ± 0.5 cm, $P = 0.004$; Table 1). This difference remained significant when correcting for total esophageal length (GERD 44.4 ± 3.5% *vs* asymptomatic 57.8 ± 2%, $P = 0.003$). To assess the possible role of hiatal hernia in changing the length of the distal segment, we compared the size of the hiatal hernia in patients with GERD symptoms and asymptomatic individuals: patients with GERD symptoms had larger ($P < 0.001$) hiatal hernias (1.8 ± 0.2 cm) compared with asymptomatic individuals (0.7 ± 0.2 cm).

Correlation Between Symptom Intensity, Length, and Width of the LPZ

Of all 140 patients with an identifiable esophageal LPZ, 68 patients reported a dysphagia symptom score >0, 65 patients reported a chest pain score >0, and 84 patients reported a GERD score >0. No correlation was found between the intensity of dysphagia (rho = 0.167, $P = 0.172$), chest pain (rho = 0.189, $P = 0.132$), or symptoms of GERD (rho = –0.074, $P = 0.505$) and length of the esophageal LPZ. No correlation could be determined between the individual symptom strength in patients with chest pain (rho = 0.004, $P = 0.973$) and GERD (rho = 0089, $P = 0.421$) and width of the esophageal LPZ (Fig. 2). A significant but poor correlation was found between the symptoms of dysphagia and width of the esophageal LPZ (rho = 0.299, $P = 0.013$; Fig. 2).

DISCUSSION

Evaluating the characteristics of the esophageal LPZ in asymptomatic individuals compared with patients with chest pain, dysphagia, and GERD symptoms, we found differences in the time gap between the proximal and distal esophageal contraction waves but not in the length of the esophageal LPZ. There was no meaningful correlation between the severity of individual symptoms and size of the LPZ. In addition, we noted that the distal esophageal peristaltic segment was shorter in GERD patients than in asymptomatic individuals. These differences in the characteristics of the esophageal LPZ suggest that these parameters might play a role in the development of different esophageal symptoms, even though they cannot explain the intensity of individual symptoms.

The esophageal LPZ corresponds anatomically to the TZ in the proximal esophagus from striated to smooth muscle. In an autopsy study, Meyer *et al.* documented that the TZ from striated to smooth muscle occurs gradually through a mixed muscle-type TZ and extends an average of 7.6 cm (34% of esophageal length) (7). This is similar to the length of the esophageal LPZ as measured by HRM in our subjects with a mean length of 24% of total esophageal length in asymptomatic individuals and 31% in symptomatic patients.

Prior to the availability of HRM, the esophageal LPZ was measured during conventional manometry by performing distinct sets of swallows at one level and then withdrawing catheters at 1 cm intervals as described by Humphries and Castell (8). Evaluating the presence of distinct pressure zones in the esophagus, Peghini *et al.* reported an LPZ in 26% of patients with esophageal symptoms and 18% of healthy volunteers (17). The difference between these and our findings (*i.e.*, esophageal LPZ present in 98% of patients) is likely to be due to the different measuring techniques and definitions of the esophageal LPZ. Using conventional manometry, Peghini *et al.* defined the pressure trough as a decrease in pressure below one third of the mean distal esophageal amplitude. Narawane *et al*. evaluated the length of the TZ in a small set of young, predominantly male patients from India using a pull-through manometry (18). The TZ (40 ± 17 mm) appears shorter compared to that found in our asymptomatic individuals (54 ± 6 mm). However, this is likely to be due to the different methodology and population characteristics as Narawane *et al.* used the typical waveform of striated *versus* smooth muscle proposed by Richter *et al.* (19) to define the TZ and applied a 40-mmHg cutoff or a change in pressure over time (dp/dt) of <50 mmHg/s in swallows with amplitudes between 40 and 50 mmHg to locate the proximal and distal borders of the TZ. The advantage of HRM to measure pressure changes at closely spaced intervals in the esophagus at the same time offers the opportunity of more accurate measurements of the proximal and distal components of the esophageal peristalsis during the same swallow.

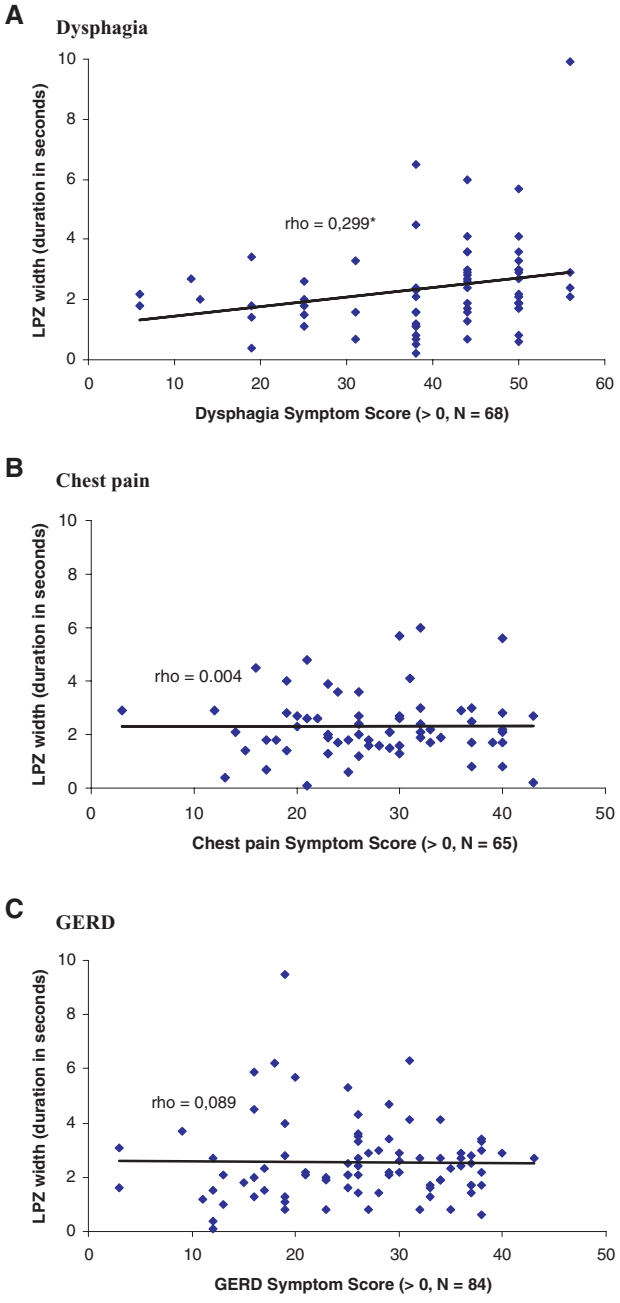

Figure 2. Correlation between symptom intensity as calculated with the Eraflux Score for all patients with an individual symptom score >0 in (*A*) dysphagia (*$P = 0.013$), (*B*) chest pain, and (*C*) GERD (x-axis) and the width (duration in seconds) of the esophageal low-pressure zone (LPZ; y-axis).

Using solid-state HRM, Ghosh *et al.* reported on the size of the esophageal LPZ in 75 healthy volunteers. Data from this study were used to set cutoff values to define the LPZ and determine sample size for comparisons between healthy volunteers and patients. As suspected, the size of the esophageal LPZ is in direct relationship to the pressure cutoff values used to define low pressure (16). Since Ghosh *et al*. noticed esophageal LPZ in the majority of volunteers when using cutoff values of 30 mmHg to define the borders of the LPZ, we decided to use this single cutoff in our study. We are aware that lower peristaltic pressures may be sufficient to promote bolus transport through the proximal esophagus compared with the distal esophagus. However, a single cutoff is practical in the clinical setting, and the 30-mmHg value has been used over the years to separate normal from ineffective contractions (20).

Prior studies suggested that the time delay between the end of the proximal and the onset of the distal esophageal peristaltic segment (width), and not solely a spatial mismatch of the LPZ, could be responsible for bolus stasis (21). Ghosh *et al.* evaluated the dynamics of the upper and lower esophageal contraction waves and the LPZ using a combined HRM and video fluoroscopy in 6 healthy subjects (11). Observing two separate contraction waves above and below the esophageal LPZ, they hypothesized that the TZ may cause bolus retention, resulting from poor coordination of the upper and lower contraction waves. If true, the translation of this phenomenon into symptoms of esophageal dysfunction have to be assessed. In our patients, the only but poor correlation between the individual symptom strength and width of the esophageal pressure zone was found in the dysphagia group. However, using HRM to determine the esophageal LPZ, our study provides no valid information on bolus transit in this zone. The concomitant use of video fluoroscopy or multichannel intraluminal impedance to assess bolus transit might have allowed us to interpret more accurately the relationship between the LPZ and bolus stasis causing esophageal symptoms.

One might argue on the effect of aging on the LPZ in light of the different mean ages of the patient and volunteer groups. Currently, there is no published evidence that specifically addresses a temporal or spatial extension of the esophageal LPZ with age. Animal studies documented an age-dependent neurodegeneration in the esophageal plexus of Auerbach with possibly decreased contractional power (22). As we based the length of the LPZ on a contraction amplitude cutoff (30 mmHg), it is possible that the loss in the contractional power would explain a longer LPZ in elderly individuals. This, however, does not explain the longer duration of the LPZ, especially in GERD patients, who were younger than other symptomatic patients. Possibly, a wider LPZ as suggested before (21) leads to impaired esophageal clearance, ultimately causing symptoms of GERD and dysphagia. As our data allow only establishing an association, further studies are warranted to investigate the cause–effect relationship.

In conclusion, our data suggest that measuring the duration of the esophageal LPZ, as defined by the time delay between the upper and lower contraction waves, may be of greater importance when characterizing the LPZ than the spatial separation between the contraction waves. Further clinical studies, ideally incorporating interventions that change the characteristics of the esophageal LPZ, will help understand the clinical utility of measuring the esophageal LPZ.

STUDY HIGHLIGHTS

What Is Current Knowledge

- An esophageal low-pressure zone (LPZ) has been described by manometric and radiographic studies.
- Bolus stasis is suggested to be associated with a larger esophageal LPZ.
- The differences between patients and asymptomatic individuals are not established.
- The clinical relevance in patients with esophageal symptoms is unclear.

What Is New Here

- The width of the esophageal LPZ is longer in patients with esophageal symptoms compared with asymptomatic individuals.
- The length of the LPZ is not different in patients with esophageal symptoms.
- The size of the LPZ is not correlated with the intensity of esophageal symptoms.
- Contractile coordination in the transition zone between the upper and lower esophagus might be relevant for a diagnostic workup.

Reprint requests and correspondence: Daniel Pohl, M.D., Division of Gastroenterology and Hepatology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.
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CONFLICT OF INTEREST

Guarantor of the article: Daniel Pohl, M.D., and Radu Tutuian, M.D.
Specific author contributions: Daniel Pohl and Radu Tutuian: design of the study, data collection and analysis, writing of the manuscript, and approving of the final version; Mentore Ribolsi and Edoardo Savarino: data analysis, writing of the manuscript, and approving of the final version; Heiko Fruehauf: data collection and analysis and approving of the final version; and Michael Fried and Donald O Castell: writing of the manuscript and approving of the final version.
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