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chapter 6

Distension of the esophagogastric junction
augments triggering of transient lower
esophageal sphincter relaxation

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ABSTRACT

Background: Patients with gastroesophageal reflux disease show an increase in esophago-gastric junction (EGJ) distensibility and in frequency of transient lower esophageal sphincter (LES) relaxations (TLESR) induced by gastric distension.

Aim: Study the effect of localized EGJ distension on triggering of TLESR in healthy volunteers.

Methods: An esophageal manometric catheter incorporating an 8 cm internal balloon adjacent to a sleeve sensor was developed to enable continuous recording of EGJ pressure during distension of the EGJ. Inflation of the balloon doubled the cross-section of the trans-sphincteric portion of the catheter from 5 mm OD (round) to 5x11 mm (oval). After catheter placement and a 30 min adaptation period, the EGJ was randomly distended or not, followed by a 45 min baseline recording. Ten healthy subjects consumed a 'refluxogenic meal' and recordings were made for 3 hours post prandially. A repeat study was performed on another day with EGJ distension status reversed.

Results: Number of TLESR increased during periods of EGJ distension with the effect being greater after a meal (baseline: 2.0 (0.0-4.0) vs 4.0 (1.0-11.0), $p=0.04$; post prandial: 15.5 (10.0-33.0) vs. 22.0 (17.0-58.0), $p=0.007$ for undistended and distended respectively).

Conclusion: EGJ distension augments meal-induced triggering of TLESR in healthy volunteers. It is unlikely that a 'classic' gastric mechanoreceptor mediated mechanism can explain this for two reasons. One, no accommodation of the effect was seen during prolonged distension. Second, MRI imaging of the catheter, shows the diameter of the proximal stomach largely exceeding the intragastric part of the sleeve/balloon. Our data suggest the existence of a population of vagal afferents located at sites in/around the EGJ that may influence triggering of TLESR.

INTRODUCTION

Up to 40% of gastroesophageal reflux (GER) disease patients respond incompletely to proton pump inhibitor (PPI) therapy.¹ An alternative therapeutic approach is to inhibit transient lower esophageal sphincter relaxations (TLESR) that underlie the majority of gastroesophageal reflux (GER) events. During a TLESR, the esophago-gastric junction (EGJ) opens due to simultaneous relaxation of the lower esophageal sphincter and the crural diaphragm without a swallow preceding it. Physiologically, TLESRs are thought to be present to vent swallowed air. However, they also allow liquid GER to occur. It has been shown that TLESRs account for up to 90% of GER episodes in non-hiatus hernia GER disease patients as well as in healthy volunteers.²⁻⁵

TLESRs are triggered by gastric distension and can be initiated by a meal, gas infusion or intragastric balloon distension.⁶⁻⁸

Current data indicate that TLESRs are mediated via a vago-vagal pathway initiated by tension receptors located in the proximal stomach musculature.⁹ The vagal tension receptors have central terminals in the brain stem (nucleus tractus solitarius) which synapse with neurons of a central program generator that is sensitive to a number of other inputs relating to consciousness and body position.^{10,11} There are several simultaneous outputs from the program: first is a brief and powerful activation of inhibitory vagal motor neurons (in the adjacent dorsal vagal nucleus) leading to LES relaxation. Second is a suppression of excitatory vagal output to the esophageal body leading to inhibition of peristalsis. Third is a suppression of motor output from the phrenic nucleus to the crural diaphragm leading to laxity of the external striated muscle sphincter, even during inspiration.¹²

Although this pathway itself is now well described, the mechanisms initiating it, as well as the determination of the nature of refluxate (gas, liquid or mixed), appear to be more complex than is explained by a single gastric mechanoreceptor reflex alone. Compared to GER disease patients, healthy volunteers more selectively trigger gas GER episodes during TLESRs. Although this is likely to be at least partly due to normal EGJ anatomy, such selectivity still suggests the presence of sensing capacities of the proximal stomach and/or EGJ.^{4,13-15} The mechanisms underlying this selectivity remain largely unknown. Also, the rate of gastric emptying, which should affect the degree and duration of gastric distension does not correlate with triggering of TLESRs.¹⁶ Indeed, recent studies of the effect of left/right positioning in neonates on gastric emptying and TLESRs showed that right positioning accelerated gastric emptying and paradoxically increased triggering of TLESRs.^{17,18} These observations suggest that other mechanisms can also modulate triggering of TLESRs.

Nasogastric tubes have been shown to exacerbate reflux in a number of studies.¹⁹⁻²¹ However, rather than increasing reflux by causing 'leakage' of gastric contents across the esophago-gastric junction, the existing data indicate an increase in the number of discrete GER episodes as well as a further increase in the number of GER episodes with increasing

size of the nasogastric tube.¹⁹⁻²¹ As the majority of GER episodes are caused by TLESRs, it seems most likely the presence of a nasogastric tube increases the number of TLESRs or makes it more likely that GER occurs in association with a TLESR.²² In addition, patients with gastroesophageal reflux disease, especially those with a hiatus hernia, show an increase in EGJ distensibility and in the frequency of transient lower esophageal sphincter relaxations (TLESR) induced by gastric distension.^{23,24} A mechanism by which increased distensibility of the EGJ may increase stimulation of TLESR via vagal afferents localized to EGJ has not been previously considered.

In this study we explore the possibility of the existence of neural mechanisms that are localized to the EGJ and sensitive to distension which can influence the TLESR pathway and therefore modulate the threshold for triggering of TLESRs and GER.

MATERIALS AND METHODS

Subjects

Healthy adult volunteers were enrolled at two study sites. Approval for the studies was obtained from the Research Ethics Committee of the Children, Youth and Women's Health Service as well as from the Medical Ethical Committee of the Academic Medical Centre and written informed consent was obtained from each subject. All subjects filled out a validated Reflux Disease Questionnaire (RDQ) to confirm the absence of gastroesophageal reflux symptoms. Subjects with a score of >1 on the specific GER disease dimension were excluded from the study.^{25,26}

Recording technique

A distilled water perfused manometric catheter was specifically designed and built for this study. It incorporated a 6 cm long LES sleeve sensor and 6 manometric side holes located -3.0, +3.0, +8.0, +13.0, +18.0 and +29.0 cm, relative to the sleeve midpoint (*figure 1*). The pharyngeal channel was perfused at 0.15 ml/min and all other sideholes and sleeve were perfused at 0.3 ml/min. The catheter also incorporated an 8 cm long balloon that was located in the center of the catheter shaft adjacent to the sleeve sensor. The diameter of the sleeve sensor with the balloon uninflated was 5.0 mm (round) and inflation of the balloon ovalised the cross section and doubled the cross-sectional area to 5.0 x 11.0 mm (*figure 2*). This design allowed continuous recording of EGJ tone and relaxation during periods when the balloon was deflated as well as inflated. The balloon was inflated with air and maintained at a constant pressure of 120 mmHg using a purpose built low pressure blow-off valve. Bench testing was performed to confirm that inflation and deflation of the balloon did not deform the sleeve membrane or alter sleeve performance. MRI imaging in one of the volunteers confirmed the diameter of the inflated balloon to be 11 mm in

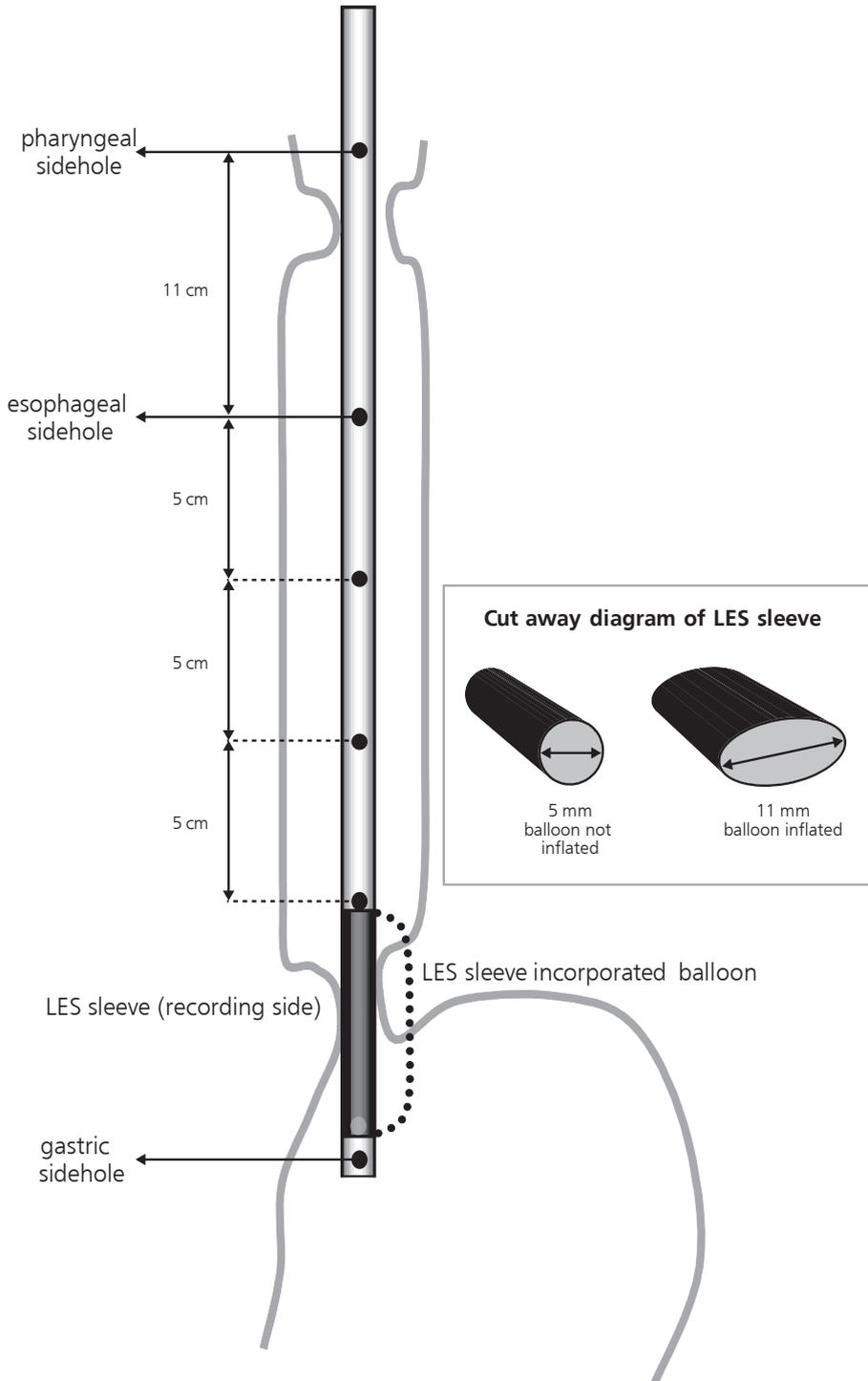


Figure 1. Catheter design. LES: Lower esophageal sphincter.

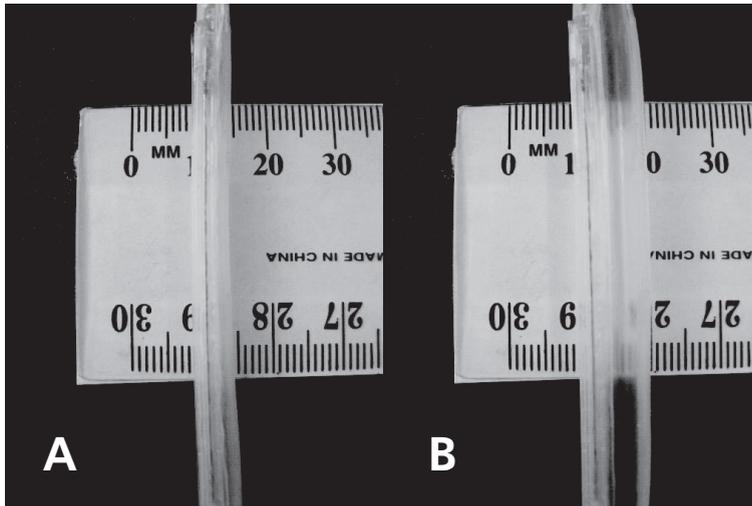


Figure 2. Catheter with balloon deflated (panel A) and inflated (panel B).

coronal view at the EGJ. Data acquisition and analysis were performed with the use of the BioView GER monitoring and manometry system (Sandhill Scientific, Denver, Colorado, USA) or the Stationary Solar Gastro System (MMS Inc., Enschede, The Netherlands).

Study protocol

The study protocol used was designed to test the effect of EGJ distension on the triggering of TLESRs and GER following a refluxogenic meal to induce TLESRs and gas reflux.

Subjects fasted for at least six hours prior to each study. Before the first study they were randomized to have the balloon inflated during either the first or the second study. The catheter was passed trans-nasally into the esophagus with the tip in the proximal stomach and the sleeve straddling the EGJ high pressure zone. Thirty minutes after positioning the catheter, the balloon was inflated or left deflated, depending on how the patient was randomized. After 45 minutes of baseline recordings, subjects were given a refluxogenic meal (Mac Donalds® Quarter Pounder® with 250 ml orange juice and 75 g French fries) and asked to complete it within 15 minutes. During the entire study, subjects were asked to report any belching episodes which were marked on the tracing. Subjects were studied in upright position, were not informed of balloon status and were not permitted to see the tracing during acquisition. To account for possible order effects, subjects were studied twice on two separate days with the order of distension reversed. Half of the patients were studied with the balloon inflated during the first study and the other half with the balloon inflated during the second study.

Additionally, in one subject MRI was performed to establish the exact position of the balloon in the inflated state.

Analysis of manometric tracings

The acquired data were divided over 3 periods (baseline, meal and post prandial). The post prandial period was further divided in the 1st, 2nd and 3^d post prandial hour.

Analyses were performed blinded to the status of the balloon. All pressures given are relative to gastric pressure. Mean basal end-expiratory EGJ pressure was determined at 2 minute intervals. All tracings were analyzed for TLESRs. These were defined using well established criteria: 1) absence of swallowing for 4 s before to 2 s after the onset of EGJ relaxation; 2) relaxation rate of > 1 mmHg/s; 3) time from the onset of relaxation to complete relaxation of < 10 s; and 4) nadir pressure of < 2 mmHg. Excluding EGJ relaxations associated with multiple swallows, EGJ pressure falls that fulfill the last three criteria but have a duration of > 10 s were also judged to be TLESRs, irrespective of the timing of the onset of the EGJ pressure fall to swallowing.²⁷ Also, nadir pressure during TLESRs was evaluated. Swallows were recognizable as brief spikes in pharyngeal pressure and their presence was recorded. Nadir of spontaneous swallow related EGJ relaxation was determined every 10 minutes.

Statistical analysis

Parameters with a distribution that was assumed to be normal were described using mean +/- SD. All other parameters are described using median (range). Primary outcome measure was defined as the number of TLESRs in the post prandial period. Secondary outcome measures were (1) the number of TLESRs during baseline recordings and (2) the number of belches during all periods in both protocols. Since no normal distribution could be assumed for the primary and secondary outcome measures (the number of TLESRs and belches), the paired data were compared using Wilcoxon's paired signed rank sum test. For repeated measures of non parametric data, the Friedman test was used.

Nadir pressure values were also compared using non-parametric tests, while baseline EGJ pressure values were assumed to be normally distributed and therefore tested using paired T-tests.

RESULTS

Subjects

All healthy subjects that enrolled (n=10, 7 male, median age: 29.5 (24-39) years) completed both studies. All subjects had RDQ-scores of ≤ 1 (median score: 0 (0-1)). None had difficulty consuming the meals. Subjects did not react to or report any symptoms or sensations at the time of balloon inflation / deflation. All subjects reported they could only guess during which study the balloon was inflated, both when asked for general sensation, but also with respect to meal perception.

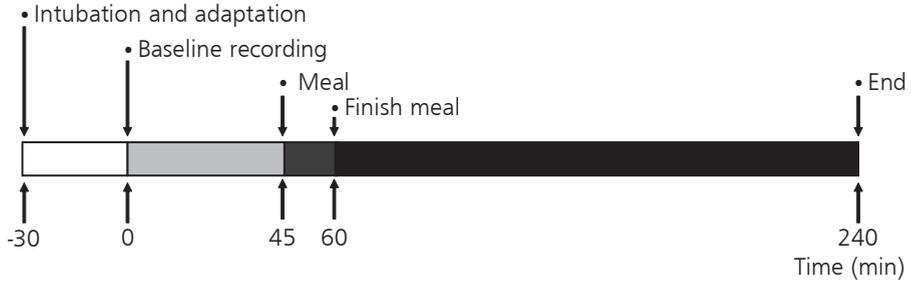


Figure 3. Study protocol. All patients underwent two studies on two separate occasions. At the start of the baseline recording, the balloon was randomly inflated or left deflated and kept in that state for the remainder of the study. The study was repeated with the balloon in reversed status.

EGJ pressure

Median EGJ pressure during the adaptation period was 13 (10-26) mmHg. Inflation of the balloon caused an immediate and significant rise in EGJ pressure which was sustained for the entire baseline period. Median EGJ pressure was 14 (10-26) mmHg 0 – 30 min before and 21 (15-34) mmHg 0 – 30 min after inflation, $p=0.005$). EGJ baseline pressure dropped significantly during and following consumption of the test meal from 18.5 (10-35) mmHg before the start of the meal to a nadir of 11 (6-18) mmHg after the meal ($p<0.001$), and recovered slowly over an average of 57.8 ± 9.4 minutes. When the balloon was uninflated a $39.1 \pm 10.8\%$ decrease was seen with recovery in 56.9 ± 9.3 minutes while during balloon inflation this decrease was $40.4 \pm 13.5\%$ (mean difference 1.3% (95% CI: -9.2 – 6.6%) $p=0.72$) and recovery was seen in 58.6 ± 9.9 min (mean difference: 1.7 min (95% CI: -7.0 – 3.6 min), $p=0.48$).

TLESRs, belching and swallowing

Figure 4 shows the effect of balloon distension on the primary outcome measure: the number of post prandial TLESRs. The numbers of TLESRs and reported belches are given in table 1. The post prandial distribution of TLESRs over the first, second and third post prandial hour, both with the balloon un-inflated and inflated, is also shown in figure 4. Whilst the number of TLESRs triggered post-prandially decreased over time, the degree of augmentation of TLESR triggering induced by inflation of the balloon increased over time with the inflated state being associated with 24%, 58% and 67% more TLESRs during the first, second and third post prandial hour respectively ($p=0.045$).

Median nadir pressures during TLESRs were comparable during baseline recordings (not inflated vs. inflated: 1 (0-5) vs. 1 (0-3) mmHg, $p=0.62$) as well as during the post prandial period (1 (0-3) vs. 1 (0-2) mmHg, $p=0.21$). Median nadir pressure during swallow related EGJ relaxations did not differ between periods where the balloon was inflated and not inflated (baseline: 2 (0-6) vs 2 (1-8), $p=0.81$; post prandial: 3 (1-9) vs 2 (1-7), $p=0.36$).

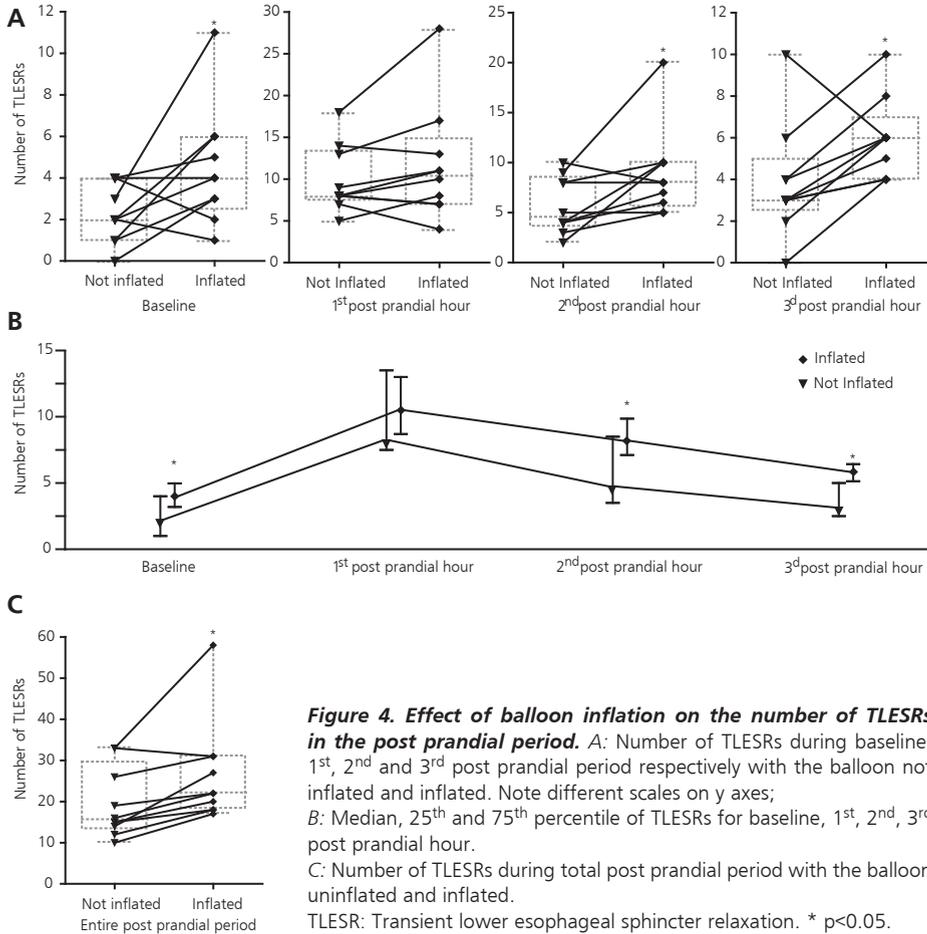


Figure 4. Effect of balloon inflation on the number of TLESRs in the post prandial period. A: Number of TLESRs during baseline, 1st, 2nd and 3rd post prandial period respectively with the balloon not inflated and inflated. Note different scales on y axes; B: Median, 25th and 75th percentile of TLESRs for baseline, 1st, 2nd, 3rd post prandial hour. C: Number of TLESRs during total post prandial period with the balloon uninflated and inflated. TLESR: Transient lower esophageal sphincter relaxation. * p<0.05.

Period	Measure	Balloon not inflated	Balloon inflated	p-value
Baseline	TLESR	2.0(0.0-4.0)	4.0(1.0-11.0)	0.043
	Belches	0.0(0.0-4.0)	2.5(0.0-8.0)	0.033
Meal	TLESR	1.0(0.0-4.0)	2.0(0.0-6.0)	0.337
	Belches	1.5(0.0-2.0)	1.5(0.0-8.0)	0.114
Post prandial	TLESR	15.5(10.0-33.0)	22.0(17.0-58.0)	0.007
	Belches	7.5(1.0-32.0)	8.5(0.0-51.0)	0.515
Total	TLESR	22.0(14.0-40.0)	28.5(21.0-71.0)	0.005
	Belches	8.5 (1.0-30.0)	15.5(0.0-60.0)	0.214

Table 1. Effect of balloon inflation on primary and secondary outcome measures. Data for transient lower esophageal sphincter relaxations (TLESR) and the number of reported belches are given. Data are compared using Wilcoxon’s paired signed rank sum test. p-values below the cut off value of 0.05 are bold.

DISCUSSION

This is the first study investigating the possibility that localized stimulation of EGJ mechanoreceptors can influence triggering of the vagal pathway triggering TLESRs. Our data clearly show that distension of the EGJ, increases the number of TLESRs triggered during baseline and in response to a test meal. The novel purpose-built manometric assembly enabled continuous sleeve recording of EGJ pressure during balloon distension of the EGJ. This approach allowed the changes in EGJ resting pressure and EGJ relaxation pressures to be continuously monitored during application of the distending stimulus to the EGJ. The typical changes in EGJ pressures and TLESR triggering induced by a meal have been described in detail^{2,3,6,28-31} and our general observations with this current experimental protocol are not qualitatively different to these. Application of the distending stimulus did however produce a significant increase in resting EGJ pressure without altering minimum pressures recorded during (transient or swallow related) EGJ relaxation or the characteristics of the post-prandial EGJ pressure drop. We can infer therefore that the increase of catheter diameter produced by inflation of the balloon was large enough to induce an increase in wall tension at the level of the EGJ whilst at the same time not so large as to produce non-physiological residual EGJ pressures that would impede bolus flow across the EGJ.

Consumption of the test meal caused an increase in the triggering of TLESRs and reported belches compared to baseline. This phenomenon is well described and believed due to stimulation of gastric tension receptors. Prolonged application of the EGJ distending stimulus augmented the triggering of TLESRs when compared to the un-distended state. This effect was apparent irrespective of the order of inflation/deflation of the balloon. During the baseline period prior to administration of the test meal, an augmentation in triggering of TLESRs and belches was seen as well. The degree of augmentation produced by EGJ distension seen during the baseline period was however much smaller than that recorded during the post-prandial period suggesting that EGJ distension, by itself, may not directly trigger the TLESR reflex.

The effect of EGJ distension revealed in this experiment cannot be adequately explained based upon current understanding of the vago-vagal TLESR reflex pathway. Although the catheter passes into the proximal stomach, we do not believe that a distension stimulus is being applied to the stomach itself as evidenced by MR imaging showing that the diameter of the most proximal part of the stomach exceeds that of the inflated catheter. The distension stimulus is instead applied directly to the most dependent part of the EGJ i.e. the LES/crural diaphragm complex. It could be argued that mechanoreceptors involved in triggering TLESRs may be localized at the most proximal margin of the proximal stomach. However, our experiments show that the application of the distending stimulus to the EGJ does not in itself produce a large increase in triggering of TLESRs, which is the case when a balloon is positioned in the proximal stomach and inflated.⁸ The effect we

describe appears to be more subtle but at the same time longer lasting, as evidenced by the fact that the degree of augmentation relative to the non distended state appears to increase over time and does not display accommodation to the stimulus as is typical for triggering of TLESRs via direct gastric distension.³²

The neural mechanism underlying the effect of EGJ distension that we describe is unknown. In applying a physiological tension stimulus directly to the EGJ it is likely that vagal afferent receptors within and around the EGJ complex are being stimulated. Such receptors have already been described and localized to the squamo-columnar junction of the ferret³³ and mouse.³⁴ Furthermore, a vagal afferent innervation of the crural diaphragm and phreno-esophageal ligament has also been recently described in the ferret.³⁵ In this study, Young et al show that these crural diaphragm vagal afferents show mechanosensitivity to distortion of the EGJ.

We would hypothesize that vagal mechanoreceptors localised to the EGJ which respond to local anatomical changes to the EGJ, may play a role in the neuro-modulation of the TLESR reflex pathway by attenuating or potentiating the threshold for stimulation of the TLESR central pattern generator in response to gastric distension. It is important to recognize that a tension-receptor initiated mechanism may be but one of several similar sensory pathways by which the intraluminal environment at the level of the EGJ may be sampled. Vagal mucosal tactile receptors have been characterized in several species (see³⁴), which terminate centrally in regions of the brainstem nuclei likely to form the central pattern generator for TLESR. Here they may be discrete or overlap with central endings of tension receptors.³⁶ Mucosal receptors are almost certain to exist in the human, where they may facilitate 'sampling' luminal contents and modulate TLESR triggering accordingly.

The findings of this study may have relevance to the pathophysiology of GER disease. Recent evidence suggests that the EGJ of GER disease patients is more compliant to distension than healthy controls,^{23,24,37} especially so in hiatus hernia patients.^{23,24} In the latter group, it has been shown that TLESRs are triggered at a lower threshold of gastric distension.³⁸ However, it is currently unclear how this alteration of EGJ compliance influences the severity of GER. Interestingly, anti-reflux surgery (fundoplication) decreases the compliance of the EGJ.^{39,40} It is generally assumed that the efficacy of anti-reflux surgery relates to an effective increase in basal nadir pressure resulting from the tightness of fundoplication wrap, however the reduced distensibility may also play a role via the attenuation of mechanism demonstrated in the current study. In light of these observations, the effect of EGJ distension on triggering of TLESRs in patients with GER disease as well as subpopulation of patients before and after fundoplication surgery may provide important insights in the pathophysiology of GER disease.

In conclusion, we have shown that distension of the EGJ can augment gastric distension induced triggering of TLESRs after a refluxogenic meal. We propose a role for tension receptors within the EGJ region (mucosa or smooth muscle of the LES, within the crural

diaphragm, or phreno-esophageal ligament) in regulating the threshold for triggering TLESRs in response to gastric distension. Further studies are needed to establish the exact receptors involved and to understand the neural architecture as well as the physiological and patho-physiological importance of this putative pathway.

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