Terminating motor events for TLESR are influenced by the presence and distribution of refluxate

Shiko Kuribayashi,1 Benson T. Massey,1 Muhammad Hafeezullah,1 Lilani Perera,1 Syed Q. Hussaini,1 Linda Tatro,1 Ronald J. Darling,2 Rose Franco,3 and Reza Shaker1

1Dysphagia Institute, Division of Gastroenterology and Hepatology and Departments of 2Otolaryngology and 3Sleep Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

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NEUROALLY MEDIATED RELAXATION of the lower esophageal sphincter (LES) occurs during three prototypical motor events including 1) deglutitive LES relaxation, where pharyngeal stimulation may be the sensory trigger (11, 17, 26); 2) LES relaxation as a component of secondary peristalsis, where esophageal distension provides the sensory trigger (17); and 3) transient LES relaxations (TLESRs), which are primarily triggered by gastric distension (6, 10). TLESRs differ from the other two forms of LES relaxation by having 1) activation of the sensory trigger site distal to the LES, 2) concurrent inhibition of diaphragmatic crural activity (9, 12), 3) larger and more variable duration of LES inhibition (2, 7), and 4) an unpredictable pattern of terminating motor event in the esophagus, which can either be primary peristalsis (PP) or spontaneous contractions (2).

TLESRs are the major mechanism for the occurrence of gastroesophageal reflux (GER) (2, 3, 15). Therefore, the terminating esophageal motor events of a TLESR potentially are important for the clearance of refluxate from the esophagus. Earlier studies indicated that swallow-induced peristalsis (PP) was the most common esophageal motor event after GER episodes in healthy subjects (2, 15, 20, 23), whereas other studies found that secondary peristalsis was the most common termination event following a TLESR (16, 18). A potential limitation for all of these previous studies is the use of pH monitoring or common cavity pressure phenomena as methods for identifying reflux events. These studies also did not attempt to assess whether features of the reflux event itself might determine the pattern of motor activity terminating TLESR. Therefore, the goals of this study were to address the limitations of previous studies by assessing TLESR-termination events and their relationship to acid and nonacid reflux events using concurrent high-resolution manometry and esophageal pH/impedance recordings.

MATERIALS AND METHODS

Subjects. Fifteen healthy subjects (7 men, age range 18–56 yr) without reflux-related symptoms were studied. None of the subjects had previous gastrointestinal surgery or were taking medications that affect gastrointestinal motor function or acid secretion. The study protocol was approved by the Medical College of Wisconsin Institutional Review Board, and informed consent was obtained from each subject.

Transnasal endoscopy. Transnasal endoscopy (21) was performed without sedation using a 6-mm diameter endoscope (Pentax, Tokyo, Japan) in the sitting position after at least a 6-h fast. Transnasal endoscopy was conducted to confirm absence of erosive esophagitis, Barrett’s esophagus, and hiatal hernia.

Manometry. A solid-state manometric assembly with 36 circumferential sensors spaced in 1-cm intervals (outer diameter, 4.2 mm) was used (Sierra Scientific Instruments, Los Angeles, CA). Before the recording, the transducers were calibrated, and a thermal compensation program was applied using external pressure.

Impedance/pH recordings. Either single-catheter or bifurcated-catheter 1.5-mm diameter Comfortec multiluminal impedance (MII)-pH probes (Sandhill Scientific, Highlands Ranch, CO) were used. These probes have six-channel impedance sites and two-channel pH sensors. The pH sensors were calibrated before the study using standard pH 4 and 7 buffers. Impedance/pH recordings were used to detect the features of refluxate such as liquids or gas, or acid or nonacid.

Polysomnogram. Alice 5 (Respirronics, Murrysville, PA) or Sandman Elite (Nellcor Puritan Bennett, Kanata, ON, Canada) were used to conduct the polysomnogram (PSG). PSG was performed in
all subjects and included electroencephalogram, electrocardiogram, electro-ophthalmogram, electromyogram (chin and legs), respiratory measurements (chest and abdomen), pulse oximetry, and snoring measurement. A baseline PSG was performed without manometry and impedance/pH recordings in all subjects before the study to exclude sleep disorders.

**Study protocol.** For the Awake Study, study subjects reported to the laboratory during daytime hours after a 6-h fast. The nasal passage was anesthetized with 2% lidocaine jelly. The manometric assembly was passed transnasally and positioned to record from the hypopharynx to the stomach. After the position of the upper esophageal sphincter (UES) and LES was confirmed, an impedance/pH catheter was placed via the same or the other nare. The proximal pH sensor was placed 2 cm above the proximal end of the UES high-pressure zone, and the distal pH sensor was positioned 5 cm above the proximal end of the LES high-pressure zone. The two proximal impedance sites were positioned in the hypopharynx, and the two distal impedance sites were positioned in the distal esophagus. The remaining two middle impedance sites were positioned in the proximal mid-esophagus.

After catheters were positioned, subjects ate a 1,000-calorie meal (cheeseburger) with 350 ml of carbonated soda. After completion of the meal, recording was continued for 2 h in supine position.

For the Sleep Study, the study was performed on a separate day from the Awake Study. The protocol was similar to the Awake Study protocol except that subjects reported to the sleep laboratory in the evening. Subjects additionally had the PSG sensors placed. Recordings in the Sleep Study started ~1 h after the meal and continued for 6–8 h.

**Synchronizing devices.** At the beginning of the Awake Study, for the manometric recordings and the impedance/pH recordings, an event mark was entered simultaneously in both records to allow synchronized reading of the two studies. To synchronize analysis of data from both the high-resolution manometry recording and the impedance/pH-metry recordings, event buttons were pressed simultaneously on both devices at several different times over the course of the study. To determine the extent of the variability in times of event-marker activation on the two recording systems, we examined the absolute difference between time measurements between the same two marked events for both devices. This analysis indicated that the average absolute difference between the event markings was 0.15 s, with the maximum value observed being 0.86 s. The Sleep Study used two additional synchronization methods. The first method involved input of a timing signal produced by a synchronization signal generator (Sandhill Scientific) to both impedance/pH recordings and the PSG. The second method involved video recording an image that showed the manometric device time in the PSG monitor.

**Data analysis.** Manometric data and impedance/pH recordings were analyzed with ManoView (Sierra Scientific Instrument) and BioView (Sandhill Scientific) manually by one study investigator and were confirmed by a second investigator. TLESR events were defined in accordance with previously published criteria (7, 13). TLESR-termination esophageal motor events were classified as 1) PP, defined as a full propagating wave form UES to LES after swallow-related UES relaxation/pharyngeal contraction (Fig. 1); 2) primary peristalsis (PSC), defined as a full propagating wave from UES to LES without UES relaxation/pharyngeal contraction sequence, followed by a peristaltic pressure wave that terminates the TLESR.

Changes in baseline esophageal body pressure after TLESR events were measured in the manometric tracings when the impedance recording indicated that a GER event had occurred. End-expiratory esophageal pressures, showing stable pressures in the esophagus during at least three end-expiratory phases before events, were measured as baseline esophageal pressures. Pressure differences between baseline esophageal pressure and esophageal pressure during reflux events were calculated. The average of calculated pressure differences from three separate sites in esophagus was taken as a common cavity pressure. If the pressure difference was not able to be calculated because of large vascular effects at one site in the esophagus, the common cavity pressure was averaged from the remaining two sites in the esophagus.

Sleep stages and respiratory events recorded during PSG were scored by registered PSG technologists. The sleep stages, arousal events, and respiratory events were all scored using standardized criteria (1, 8, 19). Analysis was performed separately for periods of sleeping (any stage) and awakening (interval between first observed sleep stage and end of study).

**Statistical analysis.** The incidence of TLESR, GER, or EPR events was analyzed by the Chi-square test between three groups (PP, PSC, and PSC). TLESR duration, common cavity pressure, and time duration between the end of a meal and the onset of events were analyzed by ANOVA for the same groups. Data in the text are given as means ± SD unless stated otherwise.

**RESULTS**

**Awake Study.** For the 15 subjects, a total of 152 TLESR events were available for analysis. Of these, 120 were accompanied by GER events. Only one TLESR event was terminated.
by an unclear esophageal motor event, which may have represented a spastic esophageal contraction. The remaining events were terminated by PP, FSC, or PSC. Thirty-five out of 152 events were terminated by PP (23%), 24 events by FSC (16%), and 92 events by PSC (61%) (Table 1).

TLESRs terminated by PP were accompanied by significantly fewer reflux events than with FSC or PSC ($P < 0.05$) (Table 1). This trend of fewer TLESR terminations by PP when refluxate was present did not depend on the acidity of the refluxate. Although infrequent, EPR events were significantly more common when TLESR events were terminated by FSP than by PP or PSC ($P < 0.05$) (Table 1). Common cavity pressure in the esophagus during GER events was similar among three groups. When GER was present, as determined by impedance, the duration of TLESR was significantly longer (18 ± 6 vs. 15 ± 4 s, respectively) ($P = 0.01$). Duration of TLESR terminated by FSC was significantly longer than the others ($P < 0.05$) (Table 1).

Sleep Study. Total sleep time was 305 ± 43 min (range 244–377 min), and awakening time after the sleep onset was 84 ± 45 min (range 13–173 min). A total of 130 TLESR events during the night were found. Forty-one out of 130 TLESR events (32%) occurred during sleep. The number of TLESR events/hour while awake was significantly greater than the number/hour during sleep (5 ± 4 vs. 1 ± 1, respectively) ($P < 0.01$). The remaining events were terminated by PP, FSC, or PSC. The distribution of TLESR-terminating esophageal motor events was similar during both nighttime awakening and sleep time (Table 2). However, careful inspection of the Sleep Study tracings showed that, when the TLESR was terminated by PP, the swallow always started during an interval of arousal from sleep. The trend for fewer TLESRs to be terminated by PP seen in the Awake Study was also observed in the nighttime study (Table 2). The finding of longer TLESR duration with termination by FSC seen in the Awake Study was also observed during both sleep and awake periods of the nighttime study ($P < 0.05$) (Table 2).

When all study periods were combined, four subjects (27%) had PP, one subject (7%) had FSC, and nine subjects (60%) had PSC as the main type of TLESR-terminating event, with one subject (7%) having equal numbers of PP and PSC terminating events.

**DISCUSSION**

In the present study, the most common TLESR-terminating esophageal motor event in the recumbent position in postprandial healthy subjects was a SC, rather than PP resulting from a swallow. The vast majority of these SCs involved only the distal esophageal segment, rather than a full peristaltic sequence extending along the entire length of the esophagus. The distribution of terminating events was similar in both awake and sleeping states.

TLESR events usually, but not always, are associated with GER. In this study for the awake state, the presence of GER as detected by impedance was a significant predictor of the type of terminating event because termination by a SC was more likely to be associated with GER. This trend seemed apparent with TLESR occurring during sleep as well although the number of events did not provide adequate power for statistical testing. Whether the GER contained acid did not affect this pattern.

In this study, we grouped all terminating contractions not resulting from a swallow into either PSC or FSC, the latter being instances where high-resolution manometry clearly showed the contraction originating at the level of the UES and continuing to termination at the level of the LES. This distinction appears to be of some physiological relevance in that FSC were more likely to have evidence of proximal reflux, as assessed by impedance, as well as EPR. Moreover, a FSC was never seen when the TLESR was not accompanied by reflux. The TLESR duration was also longer with FSC, but this may simply reflect the longer time needed for the contraction wave to traverse the entire length of the esophagus.

Although PSC were the most common terminating event observed, careful inspection of these events did not identify...
any with features of high amplitude, prolonged duration, and repetitive contractions, which have previously been reported to be associated with exaggerated esophageal shortening (16). There are several differences between this prior study and our study, including study position (upright vs. recumbent), possible esophageal irritation by attached devices (clip vs. none), and study population (symptomatic patients vs. healthy volunteers).

The findings of this study suggest that termination of TLESRs by SC may be a motor response to esophageal distension by refluxate from the stomach. This does raise the question as to why any TLESRs are terminated by PP. Termination by PP may be in response to some other stimulus than those assessed in this study. Alternatively, termination by PP may be a chance event attributable to random timing between the occurrence of spontaneous swallows and TLESRs.

The studies to date in which TLESR termination events have been assessed have found varying results. Earlier studies in the recumbent position found the most common terminating event to be PP (2, 15, 20, 23), whereas more recent studies found SC to be the most common (16, 18). One ambulatory study found that body position had an effect on the terminating event, showing (similar to our study) that SC was the most common terminating event while recumbent but that PP was the most common while upright (20). Several aspects of study design could contribute to these varied findings, including small numbers of widely spaced point sensors (most with poor frequency response), varying definitions of a TLESR, reliance of pH change or common cavity events to detect reflux, stimulation by a distended balloon or attached clip, study position, and type of subjects studied. Major strengths of our study include the use of high-resolution manometry, which allows reliable detection of swallows and origins of contraction waves, use of impedance for more reliable detection of reflux events, use of PSG to reliably distinguish sleep from awake events, and an unambiguously normal study population lacking both esophageal symptoms and silent (but endoscopically detectable) esophageal abnormalities. The major limitation of our study is that subjects were only studied in the recumbent position.

TLESR events are infrequent during sleep (5). The small number of TLESR events with onset during sleep in our study precludes meaningful statistical comparison with TLESR events in the awake state. Nevertheless, the overall trends in sleep-related TLESRs appear similar to what is seen in the awake state, which is that most continue to be terminated by SCs.

The findings regarding TLESR-terminating events seen in the healthy volunteers in this study may be different from what occurs in patients with GER disease (GERD). First, our study was performed in the recumbent position, whereas most patients with GERD, when studied on 24-h ambulatory pH or impedance testing, tend to have reflux while in an upright, postprandial state. Second, when supine reflux does happen in GERD patients, this is often in the setting of patients with severe esophagitis, hiatal hernia, low LES pressure, and/or ineffective esophageal motility. In these cases, reflux is more likely to occur outside of TLESR events. Clearance of refluxate in such patients may be impaired by poor esophageal motility and re-reflux of an initially cleared bolus (14). Third, healthy subjects and GERD patients appear to differ in the initial esophageal motor event following acid reflux events, with secondary peristalsis being more common in healthy subjects and primary peristalsis in GERD patients (4). This prior study did not specifically examine TLESR-terminating events. Whether the distribution of TLESR-terminating esophageal motor events is different in GERD patients and whether this has relevance for clearance of acidic and nonacidic refluxate will require additional investigation in this patient group.

### Table 1. Awake Study

<table>
<thead>
<tr>
<th>TLESR Termination Event</th>
<th>Number of TLESR Events</th>
<th>With Any Reflux</th>
<th>With Acid Reflux</th>
<th>With Mixed Liquid Reflux</th>
<th>With EPR Events</th>
<th>TLESR Duration, s</th>
<th>Mean Time After Taking Meal, min</th>
<th>Common Cavity Pressure in Esophagus During Reflux Events</th>
<th>With Reflux That Extended Above Distal Esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>35 (23%)</td>
<td>18 (51%)*</td>
<td>14 (40%)**</td>
<td>15 (43%)*</td>
<td>1 (3%)*</td>
<td>17.5</td>
<td>46±34</td>
<td>7±2</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>FSC</td>
<td>24 (16%)</td>
<td>24 (100%)</td>
<td>12 (50%)</td>
<td>18 (75%)</td>
<td>6 (25%)*</td>
<td>24±6**</td>
<td>57±38</td>
<td>6±3</td>
<td>24 (100%)*</td>
</tr>
<tr>
<td>PSC</td>
<td>93 (61%)</td>
<td>78 (84%)</td>
<td>63 (68%)</td>
<td>77 (83%)</td>
<td>3 (3%)</td>
<td>16±2</td>
<td>65±31</td>
<td>5±3</td>
<td>62 (79%)*</td>
</tr>
</tbody>
</table>

Applicable values are means ± SD. TLESR, transient lower esophageal sphincter relaxation; EPR, esophagopharyngeal reflux; PP, primary peristalsis; FSC, full secondary contraction; PSC, partial secondary contraction. *P < 0.05 against FSC or PSC, **P < 0.05 against PP or PSC, ***P < 0.05 against PSC.

### Table 2. Sleep Study

<table>
<thead>
<tr>
<th>TLESR Termination Event</th>
<th>Number of TLESR Events</th>
<th>With Any Reflux</th>
<th>With Acid Reflux</th>
<th>With Mixed Liquid Reflux</th>
<th>With EPR Events</th>
<th>TLESR Duration, s</th>
<th>Mean Time After Taking Meal, min</th>
<th>Common Cavity Pressure in Esophagus During Reflux Events</th>
<th>With Reflux That Extended Above Distal Esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Awake state after sleep onset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>21 (24%)</td>
<td>10 (48%)</td>
<td>6 (29%)</td>
<td>10 (48%)</td>
<td>0 (0%)</td>
<td>16±3</td>
<td>283±116</td>
<td>6±3</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>FSC</td>
<td>7 (8%)</td>
<td>7 (100%)*</td>
<td>3 (43%)</td>
<td>5 (71%)</td>
<td>2 (29%)*</td>
<td>23±6*</td>
<td>179±94</td>
<td>5±3</td>
<td>7 (100%)*</td>
</tr>
<tr>
<td>PSC</td>
<td>61 (69%)</td>
<td>37 (61%)</td>
<td>11 (18%)</td>
<td>35 (57%)</td>
<td>0 (0%)</td>
<td>16±3</td>
<td>294±114</td>
<td>4±3</td>
<td>23 (62%)*</td>
</tr>
<tr>
<td><strong>Sleep state</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>8 (20%)</td>
<td>2 (25%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>0 (0%)</td>
<td>15±3</td>
<td>218±114</td>
<td>7±4</td>
<td>1 (50%)*</td>
</tr>
<tr>
<td>FSC</td>
<td>3 (7%)</td>
<td>3 (100%)</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>21±3</td>
<td>243±136</td>
<td>4±1</td>
<td>3 (100%)*</td>
</tr>
<tr>
<td>PSC</td>
<td>30 (73%)</td>
<td>17 (57%)</td>
<td>5 (17%)</td>
<td>14 (47%)</td>
<td>0 (0%)</td>
<td>16±3</td>
<td>292±103</td>
<td>4±3</td>
<td>9 (53%)*</td>
</tr>
</tbody>
</table>

Applicable values are means ± SD. *P < 0.05 against PP or PSC, **P < 0.05 against PSC.
In conclusion, in healthy recumbent subjects, the most common TLESR termination event is a SC, rather than PP. Presence and distribution of the refluxate is a major influence on the type of terminating contraction.

REFERENCES