Upper esophageal sphincter function during gastroesophageal reflux events revisited

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Upper esophageal sphincter function during gastroesophageal reflux events revisited. Am J Physiol Gastrointest Liver Physiol 279: G262–G267, 2000.—Upper esophageal sphincter (UES) function during gastroesophageal reflux events is not completely elucidated because previous studies addressing this issue yielded conflicting results. We reexamined the UES pressure response to intraluminal esophageal pressure and pH changes induced by reflux events. We studied 14 healthy, asymptomatic volunteers (age 49 ± 6 yr) and 7 gastroesophageal reflux disease patients (age 48 ± 5 yr). UES pressure, intraesophageal pressure, and pH were monitored at the distal, middle, and proximal esophagus concurrently in the supine position 1 h before and 2 h after a 1,000-calorie meal. A total of 321 reflux events were identified by the development of abrupt reflux-induced intraesophageal pressure increase (IPI); 285 events occurred in patients and 36 in control subjects. In control subjects 33 of 36 and in patients 252 of 285 IPI events were associated with a pH drop. Among patients and control subjects, 99% and 100%, respectively, of all IPI events irrespective of pH drop were associated with abrupt increase in UES pressure (34 ± 2 and 27 ± 6 mmHg, respectively). The average percentage of maximum UES pressure increase over prereflux values ranged between 66% and 96% (control subjects) and 34% and 122% (patients). IPIs induced by both acidic and nonacidic reflux events evoked strong UES contractile responses.

METHODS

We studied 14 healthy, asymptomatic volunteers (age 49 ± 6 yr) and 7 patients (age 48 ± 5 yr) with subjective reports and objective findings of gastroesophageal reflux diseases ranging from single erosion to ulcerative esophagitis. All normal volunteers, with one exception, underwent unsedated transnasal esophagogastroduodenoscopy (7, 20) and did not show any abnormalities of the esophagus, stomach, or duodenum, and none had heartburn or regurgitation. All patients complained of daily heartburn and similarly underwent either unsedated transnasal or conventional esophagogastroduodenoscopy (EGD) and exhibited erosion (1 patient), ulceration (2 patients), distal narrowing (1 patient), Barrett’s esophagus (2 patients), and erythema (1 patient). The study was approved by the Human Research Review Committee of the Medical College of Wisconsin, and normal volunteers and patient volunteers gave informed written consent before the studies.

Studies were done in the supine position after an overnight fast. UES and intraesophageal pressures were monitored using a manometric assembly that incorporated a 6-cm UES sleeve device (60 × 7 × 4 mm, Dentsleeve) and recording

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sites at both ends of the sleeve, 7 and 14 cm distally. The sleeve sensor as well as other manometric ports were perfused at the rate of 0.5 ml/min. This assembly was passed transnasally and positioned across the UES so that the sleeve sensor straddled the UES high-pressure zone. In this position, the recording site at the lower end of the sleeve was located 1–2 cm distal to the UES and the other two recording sites were located 7 and 14 cm more distal. These sites were perfused and were used to monitor the development of and subsequently to measure the reflux-induced IPIs frequently referred to as common cavity. Intraesophageal pH was monitored at the distal, middle, and proximal esophagus corresponding to the pressure recording sites using three pH electrodes (Medtronic Synectics, Shoreview, MN) with a 1.2-mm outer diameter tied together by Parafilm wrap. After instrumentation, subjects were monitored for 60 min. They then ate a 1,000-calorie meal and subsequently were monitored for 2 h again in the supine position. Subjects signaled swallowing and belching using a hand-held marker. Swallowing was also monitored by submental surface electromyography using bipolar electrodes taped beneath the chin over the mylohyoid-geniohyoid muscle complex. Respiration was monitored using a pneumobelt.

Because entry of gastric content (fluid or gas) into the esophagus is associated with an increase in intraesophageal pressure and, depending on the pH of the refluxate, this event may or may not be associated with an intraesophageal pH change, the occurrence of a sudden IPI as well as pH decrease, individually and in combination, was used to document the reflux events.

To distinguish an event as gastroesophageal reflux the following criteria were set before the studies: 1) a minimum of 3-mmHg abrupt IPI with or without a pH drop; 2) an intraesophageal pH drop of at least 0.5 pH unit. When the intraluminal pH at a given site was under 4.0 and a further 0.5-unit drop could not be ascertained, the event was not included in the pH analysis portion of the UES response to the reflux event. Tracings of each subject were analyzed by two independent observers. Using these techniques we determined 1) UES pressure before and after development of a reflux-induced IPI and/or a pH drop, 2) interval between the onset of IPI and UES pressure change, 3) duration of UES pressure increase, if any, after reflux events, and 4) development or lack thereof of secondary peristalsis after a reflux event.

Statistical analyses were done using analysis of variance, Mann-Whitney rank-sum test, and regression analysis as appropriate. Data are presented as means ± SE unless otherwise stated.

RESULTS

Reflex events. A total of 321 reflux events were identified by the development of abrupt reflux-induced IPIs. Of these, 285 occurred in patients (range 2–91/}

<table>
<thead>
<tr>
<th>IPI Type</th>
<th>D</th>
<th>D + M</th>
<th>D + M + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>6% (2/36)</td>
<td>6% (2/36)</td>
<td>88% (32/36)</td>
</tr>
<tr>
<td>Patients</td>
<td>2% (7/285)</td>
<td>50% (142/285)</td>
<td>48% (136/285)</td>
</tr>
</tbody>
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Numbers in parenthesis are numbers of events. IPI, intraesophageal pressure increase; D, distal; M, middle; P, proximal esophagus.

Fig. 1. Average magnitude of intraesophageal pressure increases (IPI) caused by gastroesophageal reflux events limited to distal (D), distal and middle (D + M), and encompassing distal, middle, and proximal esophagus (D + M + P) among control subjects and patients (n = no. of events). As seen, very few events produced IPI limited to D and D + M among control subjects. Among gastroesophageal reflux disease patients, except for 7 events, all IPI either encompassed the whole esophagus or distal and middle sites. The upper esophageal sphincter (UES) response to reflux events was not dependent on either magnitude or distribution of IPI.

In control subjects, 89% of the IPI events encompassed all three esophageal recording sites, distal, middle and proximal, whereas in patients, 48% of IPI events encompassed all three sites and 50% only the distal and middle sites (Table 1). The magnitudes of IPI events in healthy control subjects and patients are shown in Fig. 1. In general, the magnitudes of IPI events were similar among groups and averaged 13 ± 3 and 12 ± 0.4 mmHg in patients and control subjects, respectively.

Association of IPI events and intraesophageal pH drops. In control subjects, 33 of 36 IPI events were associated with a pH drop. One common cavity event was without a pH drop, and in two events the pH was below 4 when IPI occurred and a further change in pH was not discernible. Of the 285 IPI events in patients, 33 were not accompanied by any pH drop and 37 events occurred when the pH was already below 4 and a discernible drop of 0.5 pH units could not be ascertained. The remaining 215 were associated with a discernible pH drop.

UES response to reflux events. Among patients and control subjects, 99% and 100%, respectively, of the total IPI events were associated with an abrupt increase of >5 mmHg in UES resting pressure (Fig. 2). Three IPI events were not associated with an abrupt UES pressure increase. The average maximum UES pressure increase after all reflux events regardless of IPI distribution was 34 ± 2 and 27 ± 6 mmHg in patients and control subjects, respectively (Fig. 3). The average percentage of maximum UES pressure increase over the prereflux values ranged between 66%
and 96% and between 34% and 122% in control subjects and patients, respectively.

In 22% and 25% of reflux events in control subjects and patients, respectively, the onset of IPI coincided with the onset of UES pressure increase. In 50% and 55% of events the UES pressure increase occurred 2.0 ± 0.2 and 1.5 ± 0.7 s, respectively, after onset of the IPI. In the remaining events, the UES pressure increase developed 1.2 ± 0.1 (control subjects) and 1.4 ± 0.1 (patients) s before onset of IPI. The frequency of UES pressure response to reflux events in healthy control subjects was similar to that in patients. There was no correlation between the magnitude of reflux-induced IPI and the magnitude of UES pressure increase in either group. Duration of UES pressure increase in control subjects (25 ± 3 s) was significantly longer than that in esophagitis patients (15.0 ± 0.4 s) (P < 0.01). The magnitude of UES pressure increase in response to reflux events in control subjects (27 ± 6 mmHg) and patients (34 ± 2 mmHg) was significantly larger than that of the IPI (13 ± 3 and 12.0 ± 0.4 mmHg, respectively) (P < 0.05).

In patients, 95% of UES pressure increases during reflux events were followed by development of a secondary peristaltic pressure wave. In control subjects this was true in 50% of the UES pressure increases. The frequency of these reflux-induced secondary peristaltic pressure waves in control subjects was significantly less than that in patients (P < 0.05). The interval between the onset of reflux-related UES pressure increases and the development of a secondary peristaltic pressure wave in control subjects (8.0 ± 1.0 s) was significantly longer than that of esophagitis patients (5.0 ± 0.3 s) (P < 0.05).

A total of 34 IPI events were not associated with a pH drop while the intraesophageal pH was above 4.0. Thirty-three of these events occurred in three patients and one in a normal volunteer. All of these events were associated with a significant pressure increase over the UES prereflux pressure values (P < 0.05) (Fig. 4).

The UES pressure increases caused by acidic (213) and nonacidic (33) reflux events were compared in the same three patients. On average, there were no differences in the magnitude of reflux-induced IPI events between acidic and nonacidic reflux events. Analysis of variance showed that the average UES nonacidic reflux-induced pressure increase for all IPI events (65 ± 10%) was significantly lower than UES pressure in-

Fig. 2. Examples of abrupt UES pressure increase in response to gastroesophageal reflux events accompanied by a clear secondary peristaltic pressure wave (SP; A) and absence of a recognizable SP (B). In both instances the IPI encompasses the entire esophageal length, whereas a pH drop spares the proximal esophagus in B and does not reach 4.0 in A. The UES pressure increase lasts for 22 and 25 s, respectively. Note that although in the instance shown in A there is no change in respiration, in B there seems to be a shallow respiration at the onset of UES pressure increase and IPI. PE, proximal esophagus; ME, middle esophagus; DE, distal esophagus; EMG, electromyograph.
crease associated with acidic reflux events (95 ± 5%) (P < 0.05).

In addition to the analyzed reflux events, there were 22 reflux episodes that were immediately followed by a spontaneous dry swallow. Because of an inherent pre-deglutitive UES pressure rise and because of the difficulty in differentiating between this phenomenon and UES response to reflux events, these events were not analyzed further. However, during all of these events UES pressure increased precipitously before the swallow occurred.

**DISCUSSION**

In this study we reevaluated the UES pressure response to gastroesophageal reflux events. Study findings indicate that there is a dynamic relationship between reflux-induced intraluminal esophageal pressure increases and UES resting tone, wherein each reflux event is associated with an abrupt and short-duration increase in UES pressure. The magnitude of this reflux-induced UES pressure increase is significantly higher than that of the reflux-induced intraluminal pressure increase, and the increase seems to be an all-or-none phenomenon.

UES pressure response to simulated and actual reflux events has been the subject of many previous studies. Earlier reports generally used the station pull-through technique for recording the UES pressure (1, 6, 9, 13, 25, 28), whereas more recent studies have used a modified sleeve device for this purpose (15, 27, 30).

Creamer and Schlegel (6) described the contractile response of the UES to balloon distension and water infusion in 1957. This contractile response was found by Car and Roman (4) to involve the cricopharyngeus muscle (4). Freiman et al. (10) showed that bilateral cold block of the cervical vagus completely abolished the UES response to HCl infusion and partially blocked its response to balloon distension in dogs.

Wallin et al. (28) reported an increase in UES pressure after 1 min of intraesophageal acid infusion in humans using the pull-through technique. However, this increase was not maintained 4 min later. Gerhardt et al. (13), using the pull-through technique, demonstrated that the UES pressure augmentation occurs in response to volume distension and that this response is further enhanced by HCl and is not dependent on osmolarity of the infusate.

Vakil et al. (27), using a sleeve sensor, monitored UES pressure continuously during acid reflux events and compared the mean UES pressure between periods of 135 s before and after reflux events and did not find a significant reflux-induced UES pressure augmentation. This study corroborated an earlier report by Kahrilas et al. (15), who also did not find a UES pressure increase in response to gastroesophageal reflux during sleep. In the latter study, UES pressure during 28 reflux events, defined as intraluminal esophageal pH below 4.0 for a minimum of 15 s, was compared between similar periods before and after these events. Average durations of acid exposure time during these reflux events were reported as 152 ± 137 s. Although sustained long-duration UES response was not found in these studies, it is possible that averaging the UES pressure over a long period in these two studies had obscured the immediate, relatively short-duration UES pressure increase after reflux events.
Conversely, in a study of a pediatric population with supraesophageal complications of reflux disease, Willing et al. (30) reported a significant increase in mean basal UES pressure after reflux events, recognizable as esophageal common cavity episodes irrespective of esophageal luminal acidification. Fifty-four percent of common cavity events in this study were accompanied by abrupt relaxation of the UES. A pathogenetic role was suggested for this high percentage of reflux-induced UES relaxation in regard to aerodigestive tract complications. It is likely that this relaxation may have been induced by activation of an esophageal belch reflex caused by generalized distension of the esophagus by the refluxate or may simply reflect regurgitation or gastric belch. Except for a few instances identified by the subjects as belching, the above-mentioned UES relaxation was not observed in the present study of the adult population.

The period immediately after reflux episodes constitutes the most critical time with regard to airway safety, because during this period the intraesophageal pressure associated with refluxate may overcome the UES resting pressure, causing pharyngeal reflux. However, in the postimmediate period development of secondary esophageal peristalsis could help clear the esophagus and prevent pharyngeal reflux. Therefore, the abrupt response of the UES to a reflux event plays a critical role in airway safety. The findings of the present study confirm the existence of such an abrupt UES pressure response to reflux events in the immediate postreflux period.

Intraluminal esophageal and UES pressure can be evaluated in end expiration or end inspiration. In the inspiratory phase of respiration the intraluminal esophageal pressure decreases, whereas the UES pressure increases (2, 15). In the expiratory phase, the UES pressure is less than that of the inspiratory phase and more reliably reflects UES basal tone. However, in the expiratory phase of respiration the intraluminal esophageal pressure is higher compared with that of the inspiratory phase. In the present study, after reflux events, the magnitude of the UES pressure increase was found to be significantly larger than the associated reflux-induced intraesophageal pressure increases in both phases of respiration, suggesting that the UES pressure increase in response to reflux would have prevented pharyngeal entry of the refluxate even if the prereflux UES tone had been negligible.

Our finding of abrupt UES pressure increase in response to reflux events irrespective of the development of a pH drop corroborates earlier studies (13, 30) and indicates that this phenomenon is primarily triggered by distension of the esophagus and is mediated primarily through tension-sensitive esophageal receptors and not by the intraluminal pH drop and acid-sensitive receptors. However, the finding of a significantly larger pressure increase in UES pressure associated with acidic compared with nonacidic refluxate suggests the possibility of an augmenting or facilitating role for acid in reflux-induced UES pressure increase. This possibility is in concordance with previous studies that have shown an augmenting effect of acidic fluid on UES pressure increase induced by esophageal volume distension (30) as well as a facilitating effect of hydrochloric acid in stimulation of secondary peristalsis in an opossum model (17).

The majority of UES pressure increases in response to reflux events that were documented in this study were accompanied by development of a secondary peristalsis. The interval between the onset of these two responses, however, was variable. The fact that in 5% and 50% of reflux events in patients and control subjects, respectively, the UES pressure increase was not accompanied by a secondary peristaltic wave suggests that, although the UES pressure increase during reflux events may be governed by the same mechanism that mediates development of secondary peristalsis, it may develop independent of secondary peristalsis. Differences in intensity of stimulation or involvement of different groups of receptors may be responsible for this phenomenon.

The higher frequency of secondary peristalsis in the patient group compared with the control subjects, as documented in the present study, may reflect increased sensitivity of the stretch receptors mediating secondary peristalsis in the patient group. This finding is different from experimentally induced secondary peristalsis using intraesophageal balloon, air, or water distension reported previously (19). These discrepancies may be caused by differences in the experimental condition, subject’s age, or modes of esophageal distension.

Despite the fact that gastroesophageal reflux events are common among both asymptomatic individuals and patients with reflux disease, relatively few of these patients present with aerodigestive complications of gastroesophageal reflux (8), suggesting the existence of competent defense mechanisms guarding against pharyngeal entry of gastric refluxate. The findings of the present study confirm the physiological stimulation of one of these mechanisms, namely, the esophago-UES contractile reflex, described originally by Creamer and Schlegel (6).

In summary, a strong positive relationship exists between UES tone and intraesophageal pressure increases induced by gastroesophageal reflux events. Although both acidic and nonacidic reflux events induce UES contraction, intraluminal pH drops below 4 seem to augment this contractile response. This functional relationship has significant implications in airway protection during gastroesophageal reflux episodes.

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REFERENCES