Sustained esophageal contraction: a motor correlate of heartburn symptom

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Received 21 March 2001; accepted in final form 10 May 2001

Pehlivanov, Nonko, Jianmin Liu, and Ravinder K. Mittal. Sustained esophageal contraction: a motor correlate of heartburn symptom. Am J Physiol Gastrointest Liver Physiol 281: G743–G751, 2001.—Heartburn occurs in the presence as well as the absence of acid reflux. We searched for a motor correlate of heartburn. Twelve subjects with heartburn were studied with 24-h synchronized pressure, pH, and high-frequency intraluminal ultrasound (HFIUS) imaging of the esophagus. The HFIUS images were analyzed every 2 s for a period of 2 min before and 30 s after the onset of heartburn during 20 acid reflux-positive and 20 acid reflux-negative heartburn episodes. The esophageal muscle thickness was measured as a marker of contraction. Esophageal pressure and HFIUS images were recorded during the Bernstein test in 15 subjects. Sustained esophageal contractions (SECs) were identified during 13 of 20 heartburn episodes associated with acid reflux and 15 of 20 heartburn episodes without acid reflux. SECs were detected during 2 of 40 matched control periods only (P < 0.05). The duration of SECs was 44.9 ± 26.9 s. The Bernstein test reproduced heartburn symptoms in 8 of 15 subjects. SECs were identified during 6 of 8 (75%) Bernstein-positive and in 1 of 7 (14.3%) Bernstein-negative tests (P = 0.04). We conclude that a SEC precedes both spontaneous and induced heartburn symptoms and may be the cause of heartburn sensation.

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MATERIALS AND METHODS

Study of spontaneous heartburn events. Study subjects with symptoms of heartburn were recruited from the outpatient clinics at the University of Virginia. Subjects were eligible for enrollment if they had chronic heartburn or heartburn and chest pain of noncardiac origin for more than 6 mo. The inclusion criterion for the study was heartburn at least once per day in the absence of a clearly definable cardiac, respiratory, or musculoskeletal cause. Heartburn was defined as a burning sensation localized to the retrosternal region, with or without radiation to the neck and other adjacent areas (4, 24, 28). In addition to heartburn, some of the patients had chest pain, which was defined as a pressure or squeezing sensation located in the retrosternal region. When chest pain was present, cardiac etiology of the pain had been excluded by the referring physician. An upper endoscopy and/or barium studies of the esophagus were performed, when necessary, to exclude any other major pathology of the esophagus. These subjects were given a standardized questionnaire detailing the chronicity, character, severity, and other precipitating factors of heartburn and chest pain.

The study protocol was approved by the Human Investigation Study Committee of the University of Virginia and by the Human Investigation Committee of the General Clinical...
Research Center. All subjects gave written informed consent before enrollment in the study protocol.

Data recording. Subjects were admitted to the Clinical Research Center after an overnight fast. All medications affecting gastrointestinal motility and gastric acid production were stopped for 5 days before the study. A catheter assembly consisting of a 6.2-F catheter equipped with a 12.5-MHz ultrasound transducer (Endosound; Boston Scientific, Watertown, MA), a solid-state pressure transducer catheter (FTC; Synectics Medical, Stockholm, Sweden), and a single crystal antimony pH probe catheter (Monocrystant; Medtronic Synectics, Stockholm, Sweden) was placed through the nose. The catheter assembly was positioned in such a fashion that the pH electrode, one of the pressure transducers, and the ultrasound transducer were located 5 cm above the lower esophageal sphincter (LES). Additional pressure transducers were located 10 and 15 cm above the LES. In addition, a submental electromyogram signal was recorded with three cutaneous electrodes placed under the chin for detection of the swallow signal. The pressure and submental electromyograph signals were recorded by a digital data recording device (MicroDigitrigger; Synectics Medical) with the additional capability of electronic marking of the heartburn events and meal periods. The ultrasound images were recorded in real time with a high-resolution ultrasound unit (Diasonic, Milpitas, CA) and a videotape recorder (Panasonic AG-1980P, Matsushita Electric, Osaka, Japan). The video recordings and digital data recordings were synchronized with a video time code signal. Five standardized 5-ml water swallows were recorded in each subject. Patients kept a diary during the study to record heartburn events, meals, and recumbent periods. The severity of heartburn events was rated on a 10-point visual analog scale (0, no complaints; 10, severe heartburn). Recordings were to last 24 h. Meals and snacks were permitted, and the subjects spent 24 h in the Clinical Research Center, remaining in a recumbent position. Patients were the criteria for acid reflux. The muscle thickness during the asymptomatic periods was compared with the asymptomatic baseline and control periods. The baseline muscle thickness was calculated for each heartburn episode during a 5-min period recorded 30 min before the onset of heartburn. If the baseline period occurred during a meal or during another symptom event or acid reflux episode, it was chosen as one of the following (in hierarchical order): 1) 60 min before the event, 2) 30 min after the event, or 3) 60 min after the event. Thus all baselines were recorded within 60 min of the heartburn event for each subject. Figure 1 sketches the analytic protocol of the study.

Asymptomatic control periods were matched to group A and group B symptomatic events. For group B symptomatic events (without acid reflux), the muscle thickness during an asymptomatic 2.5-min control period was analyzed 30 min before the heartburn event. If it coincided with acid reflux or a meal, another randomly matched period was chosen according to the hierarchical order described previously. Symptomatric heartburn events associated with acid reflux (group A) were matched with asymptomatic reflux control periods. Each control period consisted of a 2-min interval before and a 2-min interval after the onset of the pH drop. The asymptomatic reflux periods used were selected by means of a table of random numbers from the list containing all asymptomatic reflux episodes (pH < 4.0) that occurred in the record of each individual. The 2-min baseline periods for the asymptomatic episodes with acid reflux were analyzed 30 min before the reflux episode as described previously (1).

A maximum of six heartburn events, three with and three without acid reflux, were analyzed per subject so as not to

Fig. 1. A: analytic protocol for heartburn events with acid reflux. A baseline was selected 30 min before the heartburn event. Each event was then matched to a randomly selected asymptomatic reflux control period (see text) comprising 2 min before and 2 min after the pH drop (vertical line in gray box), and the baseline was analyzed 30 min before the control period. B: analytic protocol for heartburn events without acid reflux. A 2-min baseline period was analyzed 30 min before each heartburn event. A 2.5-min asymptomatic control period was analyzed 30 min before the baseline period. Arrow, onset of heartburn.
skew the results toward any one subject. The events with the highest symptom scores were analyzed preferentially.

The onset of a SEC was defined as the occurrence of a sustained increase in muscle thickness. The increase in muscle thickness was required to be >95th percentile above baseline thickness and last more than eight consecutive seconds. The SEC was defined as terminated once the muscle thickness was ≤75% of baseline thickness. In addition to the increase in muscle thickness, the total duration of SEC had to be longer than the mean (±3 SD) duration of a swallow-associated contraction, i.e., 18 s. The investigator performing the image analysis (N. Pehlivanov) was blinded to the esophageal pressures and pH changes.

**Esophageal pressure analysis.** Esophageal pressure recordings were analyzed during the same periods, i.e., 2 min before and 30 s after the heartburn events and control periods. The tracings were evaluated with regard to simultaneous, multipeaked, high-amplitude, and long-duration contractions. The pressure threshold of a valid contraction was set at a level of 15 mmHg, with the duration of the contraction peaks, in consecutive pressure ports, was ≥1 s. A high-amplitude contraction was defined to be >180 mmHg. Contractions were considered simultaneous if the maximum time interval between the contraction peaks, in consecutive pressure ports, was <0.3 s. Multipeaked contractions were defined as when the amplitude of the secondary peaks was at least 10% of the main peak, trough-to-peak duration was 0.5 s, and the trough was at least 15% of the amplitude of the main peak. Contraction duration of >7 s was defined as abnormal.

Elevations of end-expiratory esophageal baseline pressure were estimated during SEC episodes in both groups. The pressure was measured 5 cm above the LES. End-expiratory baseline before the onset of SEC served as the basis for comparison. Intrathoracic pressure was considered elevated if the end-expiratory pressure during a SEC remained >5 mmHg above the baseline for >10 s.

**Esophageal pH analysis.** Duration of acid reflux time was determined for each individual. Symptom index, i.e., the ratio between the number of symptoms associated with acid reflux and the total number of symptoms, was also calculated. The total number of acid reflux episodes with or without heartburn was also determined.

**Study of provoked heartburn events.** Patients referred to the Diagnostic Motility Laboratory for evaluation of heartburn and/or heartburn and chest pain were eligible for enrollment. An HFIUS catheter was affixed to an eight-lumen water-perfused manometry catheter and placed transnasally to record esophageal pressure and ultrasound images simultaneously. The ultrasound transducer and distal manometric side hole were positioned 7 cm above the LES. After a routine esophageal motility study, an acid perfusion test (Bernstein test) was performed by dripping either saline or 0.1 N hydrochloric acid into the esophagus for 10 min at a rate of 6 ml/min (5). The subjects reported every 60 s whether they felt heartburn or chest pain. The HFIUS images were analyzed every 2 s. The muscular thickness was assessed during a 2-min interval at the beginning of the saline perfusion; this served as a baseline for comparison of the thickness during the acid perfusion. A 5-min period during the acid perfusion, starting 2 min after the onset of the acid drip, was analyzed. The investigator performing the ultrasound image analysis was blinded to the symptoms during the Bernstein test.

**Statistical analysis.** Data are presented as means ± SD unless otherwise stated. Comparisons of data regarding the duration of SECs in different groups were made with the Mann-Whitney and Student’s t-tests. The Fisher exact test was used to compare the occurrence of SEC in symptomatic versus control episodes and in Bernstein test-positive versus Bernstein-negative groups and the occurrence of motility disorder between SEC-positive and control episodes.

**RESULTS**

**Analysis of spontaneous heartburn symptoms.** Twelve subjects (4 men and 8 women; age 47.4 ± 9.4 yr) were enrolled in the study protocol. Eleven of these twelve subjects had one or more episodes of heartburn (7 subjects) or a combination of heartburn and chest pain (4 subjects) during the investigation. The demographic features of the studied groups are shown in Table 1.

The duration of the recordings was 14.8 ± 8.45 h (range 5.1–23.5 h). Recordings were terminated in three cases after 5–6 h of monitoring because of pharyngeal discomfort and nausea. Recordings in six subjects were longer than 22 h. The pH recordings showed an acid exposure of pH < 4 for 18.5 ± 14.1% of the recorded time (range 6–56.8%). The symptom index was 48.5 ± 30.3% (range 0–91.7%). However, only a small number of acid reflux episodes (5.8 ± 5.2%, range 0–15.7%) were perceived by the subjects during the investigation. Eight of the eleven subjects experienced more than three episodes of heartburn, and the remainder had at least one episode during the recorded period (range 1–25 episodes/subject). A total of 153 symptom episodes were registered during the investigation in 11 subjects: 89 (58.2%) were heartburn, 46 (30.0%) were chest pain, and 18 (11.8%) were a combination of heartburn and chest pain. Events with chest pain alone were not analyzed in this study protocol. Twenty episodes with acid reflux (group A) in nine subjects and twenty episodes without acid reflux (group B) in eleven subjects were selected for the final analysis. Thus a total of 40 (37.4%) of 107 episodes (heartburn and a combination of heartburn and chest pain) were analyzed in this study. Heartburn was the only symptom in 31 (77.5%), and heartburn along with chest pain was the complaint in the other 9 (22.5%) instances. The mean severity of the complaints according to the symptom score in groups A and B was 5.95 (range 2–10) on a 10-point visual analog scale; this did not differ significantly from the severity of episodes (5.09 ± 2.2) not analyzed in the study (P = 0.22).

A sustained esophageal contraction was identified in 28 (70%) of the 40 spontaneous heartburn episodes (Fig. 2). Examples of two SECs are presented in Figs. 3 and 4. An example of a SEC, as seen on HFIUS images,
There were two patterns of pressure changes observed during SECs; a sustained increase in baseline pressure and brief phasic contractions of much shorter duration than SECs. The former were observed during 6 of 13 SECs (46.1%) in group A and 5 of 15 SECs (33.3%) in group B. The pressure increases in groups A and B were 7.9 ± 3.6 and 6.3 ± 2.7 mmHg ($P = 0.19$), respectively. Brief phasic increases in pressure during the SECs were associated with an additional increase in the muscle thickness (Fig. 4). Some of these phasic contractions represented abnormal motor events. The incidence of abnormal contractions, both in the presence and absence of SECs, was not different between symptomatic and control periods (Table 2).

Analysis of heartburn episodes associated with acid reflux. Thirteen (65%) of the twenty heartburn events in group A were associated with SECs (Fig. 2). The drop in esophageal pH preceded the onset of heartburn in all except one case in which the pH drop occurred 10 s after the onset of heartburn. The mean severity scores of the symptoms associated with SEC-positive and SEC-negative episodes were 6.3 and 5.3 ($P = 0.58$), respectively. The incidence of SECs during the symptomatic periods was significantly greater than that in the asymptomatic acid reflux control periods ($P = 0.0008$). SECs were observed during 2 of the 20 asymptomatic control periods. A typical SEC episode associated with symptomatic acid reflux is shown in Fig. 3. The duration of SECs in group A was 34.5 ± 11.6 s, which was significantly longer than the duration of the two SECs observed during the control periods (21.0 ± 1.4 s). The duration of SECs associated with heartburn was 30.4 ± 10.8 s ($n = 9$ episodes), and it differed significantly from the duration of SECs associated with heartburn and chest pain (43.5 ± 8.4 s; $n = 4$ episodes; $P = 0.04$).
Analysis of heartburn episodes not associated with acid reflux. SECs were detected during 15 (75%) of the 20 symptomatic episodes in group B. An example of a SEC without acid reflux is shown in Fig. 4. Thirteen (86.7%) of these fifteen episodes were heartburn, and the remaining two (13.3%) were a combination of heartburn and chest pain. None of the 20 asymptomatic control periods showed a SEC. The mean severity scores of the symptoms associated with SEC-positive and SEC-negative episodes were 5.8 and 6, respectively ($P = 0.68$).

Analysis of the provoked heartburn events. Fifteen subjects (8 men and 7 women age 40.5 ± 12.5 yr) were randomly selected from a pool of 27 patients referred for an acid perfusion (Bernstein) test for evaluation of heartburn and/or noncardiac chest pain (Table 1). Eight subjects (53.5%) had acid-induced heartburn during the test, i.e., a positive Bernstein test, and the remaining seven had a negative test. An example of a SEC occurring during the acid perfusion test is presented in Fig. 8. A SEC was identified in six of the eight patients with a positive test and in only two of the seven patients with a negative test ($P = 0.04$). The time from the onset of acid perfusion to the onset of symptoms was 3.01 ± 0.46 min. All SEC episodes preceded the onset of the complaints. The duration of SEC in Bernstein test-positive subjects was 46.0 ± 33.5 s (range 22–106 s).

The incidence of motility abnormalities detected by conventional pressure recordings during Bernstein-
positive and -negative tests as well as during saline and acid perfusion did not differ significantly.

**DISCUSSION**

Our data show that a large number of heartburn symptoms are associated with SECs. These SECs are not seen on conventional manometry records but can be observed on the ultrasound recordings of the esophageal muscle wall. A SEC preceded 28 of the 40 spontaneous heartburn or heartburn and chest pain events. The incidence of SECs did not differ between acid reflux-positive and -negative heartburn events. Furthermore, heartburn induced by acid perfusion of the esophagus was temporally associated with SEC. This unique esophageal contraction, SEC, was not usually observed in the symptom-free periods and was seen infrequently during a negative Bernstein test. Our data strongly support a strong temporal relationship between SEC and heartburn and thus raise the possibility that SEC is an important intermediary in the chain of events that produces heartburn symptoms.

Was our study group representative of an average heartburn patient? A number of our patients experienced chest pain in addition to heartburn. However, heartburn was the chief complaint in each of our subjects. We did not screen our patients for the presence or absence of esophagitis. The major goal of our study was to determine the motor correlate of garden-variety heartburn symptoms. The major inclusion criterion in our study was the presence of daily heartburn.

The results of our study raise two important questions. 1) Does SEC, a motor event, rather than acid in the esophagus cause heartburn, and 2) What is the relationship between acid reflux and SEC? Winkelstein (28) indicated that heartburn could be secondary to esophageal muscle spasm. Bernstein and Baker (5) suggested that esophageal dismotility could precipitate the symptoms of heartburn and chest pain. Siegel and Hendrix (20) observed that the heartburn in reflux patients, reproduced during an acid perfusion (Bernstein) test, was associated with three distinct types of abnormal motility patterns: 1) an increase in amplitude and duration of peristaltic contractions, 2) non-progressive esophageal contractions, and 3) an increase in esophageal tone. They concluded that the symptom of heartburn was associated more closely with the reactivity of the esophagus to perfused acid than it was with the presence of inflammation. These earlier investigators used balloons and nonperfused motility catheter techniques. Several investigators who used improved noncompliant pressure recording methods...
systems have found that acid infusion into the esophagus did not induce esophageal contraction abnormalities and that the acid-induced esophageal motor abnormalities were neither a common accompaniment nor necessary for the reproduction of heartburn symptoms (6, 9, 17).

The current accepted hypothesis is that heartburn is the result of stimulation of the acid-sensitive chemoreceptors of the esophagus (8). The nerve endings located in the mucosa and submucosa are thought to carry these chemoreceptive sensations, mostly through sympathetic nerves (18, 19). The major problem with this hypothesis is that prolonged pH recordings reveal a poor correlation between acid reflux events and heartburn (2). The symptom index, which reflects the number of heartburn episodes associated with the pH drops, has been used as a test of the cause and effect relationship between acid reflux and heartburn symptoms (11, 16, 21, 27). Our data show that only 5% of the pH drops were associated with symptoms of heartburn. Recently we constructed receiver operating characteristic curves to test the strength of the relationship between heartburn and acid reflux using various reflux parameters and found that there is indeed no correlation between acid reflux as measured by the pH probe and symptoms of heartburn (23). In the current study, we observed that the frequency of SECs was similar during acid reflux-positive and acid reflux-negative heartburn events, which argues in favor of our hypothesis that SEC rather than chemoreceptor stimulation is the pathophysiological correlate of heartburn sensation.

Acid inhibition therapy is an effective approach to treating heartburn. What, then, is the relationship between acid and SECs? Paterson (14) and Barclay et al. (3) reported that acid in the opossum esophagus induces contraction of the longitudinal muscles and that this effect is mediated through the release of a chemical substance from the mast cells. Mast cell stabilizers inhibit the acid-induced muscle contraction (14). Recently, Dunne and Paterson (7) also reported that acid induced longitudinal muscle contraction in the human esophagus. Because SECs are not recorded by intraluminal pressure measurement techniques, they may very well represent a longitudinal muscle contraction of the esophagus. However, it is more than likely that other pathways besides acid exist for the induction of SECs because the latter were observed in the presence as well as in the absence of acid reflux.

Recently, we reported (1) a strong temporal relationship between symptoms of noncardiac chest pain and SECs. Eighteen of the twenty-four spontaneous chest pain episodes (two-thirds) were preceded by a SEC in that study. In the present study, we found that two-thirds of the heartburn events correlated with SECs. How can the same motor event induce both chest pain and heartburn? Esophageal distension is known to cause heartburn as well as chest pain. Shifting of

Table 2. Mean incidence of esophageal motility abnormalities detected by conventional manometry tracings

<table>
<thead>
<tr>
<th>Type of Motility Abnormality</th>
<th>AR (+) Symptomatic</th>
<th>Controls</th>
<th>AR (-) Symptomatic</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simultaneous contractions</td>
<td>0.95</td>
<td>0.75</td>
<td>1.20</td>
<td>1.10</td>
</tr>
<tr>
<td>Multipeak contractions</td>
<td>0.05</td>
<td>0.05</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>Contractions with long duration</td>
<td>0.15</td>
<td>0.05</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>High-amplitude contractions</td>
<td>0.20</td>
<td>0.05</td>
<td>0.15</td>
<td>0</td>
</tr>
</tbody>
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Values are mean incidence of motility abnormalities per 2.5-min period during spontaneous heartburn and control episodes as detected by manometry tracings. Incidence of any specific dismotility pattern did not differ significantly in symptomatic episodes vs. matched controls in both groups, with [AR (+)] and without [AR (-)] acid reflux.
heartburn to chest pain during the Bernstein test has been reported by a number of investigators (4, 5, 12). Therefore, a number of other stimuli, depending on the stimulus intensity, may induce two different kinds of sensation. We believe that the duration of a SEC may be the discriminating feature; a shorter-duration SEC may induce heartburn and a longer-duration SEC could cause chest pain. We found that the duration of SECs associated with spontaneous heartburn events (44.9 ± 29.6 s) differed significantly from the duration of SECs (68.0 ± 38.9 s) observed in the chest pain study (P = 0.02) (1). In the present study, there was a strong trend for the SECs associated with the heartburn events accompanied by chest pain to be longer in duration than the SECs associated with heartburn alone. However, the number of analyzed episodes was too small to reach statistical significance.

We only analyzed 40 of the 107 episodes recorded in this study because of the limitation of the ultrasound image analysis technique. The analysis of one heartburn episode required processing of 210–270 images. A total of 21,120 images were analyzed for the measurement of 40 symptomatic episodes, matched control periods, and acid perfusion tests. We feel that the heartburn episodes that we analyzed are indeed representative of the overall symptoms observed in the study because there was no significant difference between the severity scores of analyzed versus nonanalyzed episodes. Another concern about our study may be that the absolute changes in muscle wall thickness are rather small. Could errors have been made during measurement of the muscle wall thickness? Ultrasonographic images were magnified 12 times the original size and were analyzed by a single investigator using a standardized technique. The investigator was blinded to the time of the onset of symptoms and pH changes. In addition, the investigator was blinded to the result of the Bernstein test, both in terms of a positive or a negative response and to the timing of symptoms. Therefore, it is unlikely that an observer bias played a significant role in the interpretation of our results.

If SEC is indeed the motor correlate of esophageal symptoms, why is it detected during only two-thirds of the episodes? One explanation may be that we used criteria that were too strict in defining a SEC (1). In the previous report (1), a SEC was defined as an increase of esophageal wall thickness greater than the mean (± 2 SD) of the baseline thickness for a duration of 8 s, followed by a wall thickness greater than the mean thickness for a duration of at least 10 s. In this study, our criteria were even more strict, 95th and 75th percentile instead of mean ± 2SD and mean, respectively. We felt that the latter definition was more accurate because the distribution of esophageal thickness value has a non-Gaussian distribution. It is very possible that we may have underestimated the frequency of SECs. However, using these definitions, we found a clear separation between normal subjects and patients as well as between the symptomatic versus symptom-free periods.

In summary, our findings suggest that SECs are important motor events that are associated with symptoms of heartburn and esophageal chest pain. If our observations are indeed confirmed by other investigators, a number of important paradoxes may be explained on the basis of SECs. It may explain why heartburn can occur before the drop in esophageal pH or even in the absence of an acid reflux event. Heartburn and chest pain unresponsive to acid inhibition therapy (26) could be secondary to SECs.

We thank Dr. Joseph H. Steinbach for assistance. Present address of N. Pehlivanov: Division of Gastroenterology, University of Kansas Medical Center.

This study was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grants R01-DK-51604-04A1 and R03-DK-52094.

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