Symptom hypersensitivity to acid infusion is associated with hypersensitivity of esophageal contractility

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Bhalla, Vikas, Jianmin Liu, James L. Puckett, and Ravinder K. Mittal. Symptom hypersensitivity to acid infusion is associated with hypersensitivity of esophageal contractility. Am J Physiol Gastrointest Liver Physiol 287: G65–G71, 2004. First published February 19, 2004; 10.1152/ajpgi.00420.2003.—Several investigators have observed that repeated acid infusions induce stronger symptoms (symptom hypersensitivity). The goal of our study was to determine whether symptom hypersensitivity is associated with esophageal contractile hypersensitivity. Subjects with chronic heartburn symptoms underwent simultaneous pressure and ultrasound imaging of the esophagus. Normal saline and 0.1 N HCl were sequentially infused into the esophagus, and subjects scored heartburn symptoms on a 1–10 scale. Saline and HCl infusions were repeated in 10 subjects with a positive Bernstein test. Esophageal contraction amplitude and duration and muscularis propria thickness were measured using a computerized method during recording. Acid infusion induced heartburn. Esophageal contractions had higher amplitudes (pressure 114.2 ± 7.0%) and duration (116.8 ± 4.4%) during acid infusion compared with saline infusion. Average muscle thickness was greater during acid infusion than saline infusion (107.0 ± 2.0%). Sustained esophageal contractions (SECs) were identified during acid infusion. A second acid infusion (acid-2) induced heartburn with shorter latency (93.0 ± 15.0 vs. 317.0 ± 43.0 s) and stronger severity (8.5 ± 0.5 vs. 5.3 ± 0.8) than the first acid infusion (acid-1). Contraction amplitudes (140.2 ± 13.0%), average muscle thickness (118.0 ± 3.3%), and contraction duration (148.5 ± 5.6 vs. 116.8 ± 4.4%) were higher during acid-2 than acid-1. Also, numbers of SECs were greater during acid-2 than acid-1 (31 in 8 subjects vs. 11 in 6 subjects). Our data show that acid infusion into esophagus induces esophageal hypersensitivity and that a close temporal correlation exists between symptom hypersensitivity and contractility hypersensitivity.

ACID INFUSION INTO THE ESOPHAGUS in susceptible individuals induces heartburn (positive Bernstein test) (2, 5, 7, 13, 20, 21, 23, 24). The precise mechanism by which acid induces heartburn is not known; however, it is generally believed that acid-sensitive nerve endings located in the mucosa and submucosa of the esophagus are the transducers of heartburn sensation. Siegel and Hendrix (19) in 1965 observed that acid infusion into the esophagus induces dysmotility and proposed that heartburn sensation may be the result of esophageal dysmotility. Richter et al. (14), using improved infusion techniques to monitor esophageal motility, found that acid infusion in the esophagus increased esophageal contraction durations but had no effect on the esophageal contraction amplitude and concluded that motor dysfunction induced by acid infusion is not the cause of heartburn sensation. More recently, using a high-frequency intraluminal ultrasound imaging technique, we (12) found that heartburn sensation during acid infusion was preceded by a sustained esophageal contraction (SEC). The latter most likely represents a contraction of the longitudinal muscle of the esophagus (4, 10).

Smith et al. (21) observed that acid infusion into the esophagus induces esophageal hypersensitivity, i.e., a second acid infusion in the esophagus provokes stronger symptoms than the first acid infusion. The mechanism of acid-induced hypersensitivity is not clearly understood. Sarkar et al. (17) found that acid infusion in the distal esophagus of normal subjects and patients with reflux disease results in an increased sensitivity to the electrical stimulus-induced esophageal sensation in the distal as well as the proximal esophagus. They suggest that the mechanism of acid-induced hypersensitivity may be related to the sensitization of neurons in the central nervous system, i.e., spinal cord or the brain (16, 17).

We hypothesized that if acid infusion-related dysmotility is related to heartburn sensation, the acid-induced symptom hypersensitivity should be related to an increase in the esophageal contractility. The goal of our study was to determine the motor correlate of acid hypersensitivity of the esophagus. We studied motor correlates of acid-induced symptom hypersensitivity using manometry and high-frequency intraluminal probe ultrasonography (HFUS).

MATERIALS AND METHODS

Studies were performed in 10 patients (4 men and 6 women; mean age, 34 yr; range, 23–46 yr). All subjects experienced symptoms of chronic heartburn and esophageal chest pain for at least 6 mo before the study. These patients were followed by one of the investigators at the University of California, San Diego (UCSD) gastrointestinal clinics. The Human Investigation Committee of University of California, San Diego approved the study protocol, and each subject signed an informed consent before participation in the study protocol.

Study protocol. Subjects fasted overnight and reported to the UCSD gastrointestinal motility function laboratory in the morning. Their nostrils were anesthetized by using 2% xylocaine jelly, and their throats were anesthetized with a lignocain spray. A catheter assembly consisting of a 3-mm diameter water-perfused manometry catheter and a 2-mm diameter HFUS probe equipped with a 30-MHz transducer (Olympus Optical, Tokyo, Japan) was placed through the nose into the esophagus. The catheter assembly was positioned in such a way that one of the side holes of the manometry catheter and the ultrasound transducer were located 5 cm above the lower esophageal sphincter (LES). Subjects were in the right recumbent position during the entire study period. After 5–7 swallows of 5 ml water per patient, the water infusion was stopped for all the manometry channels except for the

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MANOMETRIC DETERMINATION OF ESOPHAGEAL CONTRACTILE HYPERSENSITIVITY IN BERNSTEIN TEST

Determination of SEC. SEC was defined as an increase in muscle thickness ≥95th percentile for 8 s or more and/or >75th percentile of baseline (saline period) muscle thickness for 17 s or more.

Statistical analysis. Paired t-test was used to compare the saline infusion period as control with the acid infusion period. Data are presented as means ± SE.

RESULTS

Effect of acid infusion on the esophageal symptoms. All 10 subjects responded to acid infusion with symptoms similar to their spontaneous heartburn. Three subjects also experienced chest pain during the acid infusion. These chest pain symptoms were experienced several minutes after the onset of heartburn sensation and after the peak of heartburn sensation. One subject reported chest pain during both acid infusion periods, and the other two subjects reported them during the second acid infusion only. Figure 2 shows the esophageal contraction pressure, muscle thickness, and symptom score during the saline (Fig. 2A), first acid (acid-1) (Fig. 2B), second saline, and second acid (acid-2) (Fig. 2C) infusion periods. Latency of symptom response after the first acid infusion was 317.0 ± 43.0 s (Fig. 3). Saline infusion relieved heartburn/chest pain in all subjects after the first acid infusion. The second acid infusion elicited heartburn with a shorter latency period compared with the first acid infusion (93.0 ± 15.0 s, P < 0.005). The maximal heartburn score during the second acid infusion was significantly greater compared with the first acid infusion (8.5 ± 0.5 vs. 5.3 ± 0.7, P < 0.005). The incidence of chest pain was not different during the two acid infusion periods.

Effect of acid infusion on the amplitude and duration of esophageal contractions. The number of esophageal contractions during the first saline period, the first acid infusion, and the second acid infusion periods were not different (22.3 ± 3.6, 24.4 ± 3.9, 26.1 ± 3.5, respectively). The contraction amplitude during the first saline infusion was 66.4 ± 12.3 mmHg. The first acid infusion resulted in a small increase in the contraction amplitude (71.9 ± 9.3 mmHg, 114.2 ± 7.0% of the saline period, P = 0.07). Duration of esophageal contractions was significantly greater during the acid infusion period compared with the saline period 4.9 ± 0.6 s vs. 4.4 ± 0.6 s, respectively (117.0 ± 4.4% of the saline period, P < 0.01). The second acid infusion resulted in a greater increase in the contraction amplitude (84.0 ± 9.0 mmHg, 143.0 ± 14.0% of the saline period) compared with the first acid infusion period (P < 0.05). The contraction duration was also significantly greater during the second compared with the first acid infusion, 6.4 ± 0.9 s (148.5 ± 5.6% of the saline period, P < 0.001) (Fig. 4).

Effect of acid infusion on the thickness of esophageal muscularis propria. The esophageal muscle thickness was analyzed in two different ways. First, the muscle thickness was averaged for the entire saline, first acid infusion, and second acid infusion periods. Second, the muscle thickness at the peak

one located at the level of the ultrasound transducer. The ultrasound images were recorded in real time using an Olympus ultrasound system (model EU-M30; Olympus America, Melville, NY). Images were recorded on videotape using a videocassette recorder (model AG1980P; Panasonic, Osaka, Japan). Pressures were recorded by using a physiological acquisition system (Polygraf ID; Medtronic, Minneapolis, MN) and a computer. Ultrasound images and pressure recordings were synchronized by using a time-stamp device on the video recordings and event markers on the Polygraf software.

Experimental design. After placement of the catheter assembly, normal saline and 0.1 N hydrochloric acid were infused into the esophagus in an alternating fashion. Patients were blinded to the order of the solution being infused. Each of the two solutions was infused into the esophagus at a rate of 6 ml/min for 10 min or less if the patient could not tolerate symptoms. The site of infusion was 15 cm above the LES. Subjects were asked to record the onset and severity of symptoms, i.e., heartburn/chest pain, continuously during the entire recording period. Heartburn was defined as a burning sensation in the retrosternal region and chest pain as the pressure or squeezing sensation in the chest. The severity of symptoms was graded on a scale of 1 to 10 using a visual analog scale with 10 representing the worst severity. Any change in the nature and symptom severity was recorded in real time as it occurred. Normal saline was infused after the first acid infusion for 10–15 min until there was complete resolution of symptoms. Acid infusion was then initiated again, which was followed by normal saline infusion. The second acid infusion was only performed if a patient experienced symptoms during the first acid infusion.

Data analysis. Ultrasound images during the entire recording period were digitized every 3 s using a computer and software program (Adobe Premier Software). Images were analyzed for the thickness of muscularis propria using computer software (Sigma Scan; Jandel Scientific, San Rafael, CA). The muscle thickness was measured at three places around the circumference of the esophagus, and a mean muscle thickness was obtained for each ultrasound image (Fig. 1). The mean muscle thickness was averaged for the entire period for each infusion period with the saline infusion period as the baseline. In addition, the duration of contraction was determined for each infusion period. Contractions with amplitude ≥15 mmHg above the end-expiratory esophageal pressure were scored for this analysis. In addition, the duration of contraction was determined for each esophageal pressure wave of ≥15 mmHg. Latency of symptom response to the acid infusion was defined as the duration between the start of infusion and the onset of the symptom.

Determination of SEC. SEC was defined as an increase in muscle thickness ≥95th percentile for 8 s or more and/or >75th percentile of baseline (saline period) muscle thickness for 17 s or more.
of manometric pressure waves during each infusion period was determined. Muscle thickness during the first acid period was greater compared with the normal saline infusion period (1.57 ± 0.08 mm vs. 1.46 ± 0.07 mm, P < 0.05). During the second acid infusion, the increase in muscle thickness was even greater than the first acid infusion period (1.71 ± 0.08 mm, P < 0.005). Similarly, the peak muscle thickness was significantly higher during the first acid infusion (2.20 ± 0.10 mm) compared with saline (2.07 ± 0.10 mm, P < 0.001), and the second acid infusion period (2.34 ± 0.10 mm) was significantly higher than the first acid infusion period (P < 0.001) (Fig. 5).

SECs. SECs were identified intermittently in six subjects during the first acid infusion period and in eight subjects during the second acid infusion period (Figs. 6 and 7). The incidence of occurrence of SECs was significantly higher during the second acid infusion period (3.9/subject) compared with the first acid infusion period (1.8/subject).
DISCUSSION

Our data show that acid infusion in the esophagus is associated with an increase in amplitude and duration of esophageal contractions. In addition, ultrasound images show an increase in the thickness of the muscularis propria during the acid infusion periods. SECs are found during the acid infusion periods. A second acid infusion into the esophagus reduces latency of symptom response and increases intensity of heartburn. Symptom hypersensitivity induced by acid infusion is associated with the hypersensitivity of esophageal contractility as revealed by a greater increase in the contraction amplitude, contraction duration, muscle thickness, and incidence of SECs during the second acid infusion compared with the first.

A number of investigators have observed the symptom hypersensitivity in association with the repeated acid infusion in the esophagus. Smith et al. (21), while studying the effects of pH of a solution on the onset of heartburn, found that the repeat acid infusion produced symptoms with a shorter latency and greater intensity. Prolonged pH recordings have shown that repeated acid reflux is more likely to induce heartburn than isolated acid reflux episodes (11, 15, 18). Janssen et al. (6) coined the term “acid burden,” which is inclusive of hydrogen ion concentration and duration of acid reflux, and suggested that a greater acid burden is a better predictor of heartburn than the duration of acid reflux or pH changes in the esophagus. Our finding of an increase in symptom sensitivity with repeat acid infusion is consistent with observations of all these investigators. Symptom sensitivity in our study was reflected by a shorter latency of the onset of heartburn as well as a stronger intensity of symptoms with a second acid infusion. The symptom hypersensitivity we studied is different from the one studied by Sarkar et al. (16, 17), who found that acid infusion in the distal esophagus induces hypersensitivity of the electrical stimulus-induced esophageal sensation in both the distal (primary hypersensitivity) and the proximal esophagus (secondary hypersensitivity). These investigators found that the mechanism of acid-induced symptom sensitivity is related to a central mechanism, i.e., at either the level of the spinal cord or higher.

Several investigators (1, 3, 8, 19, 14) have studied the effects of acid infusion on the esophageal motility. Siegel and Hendrix (19) observed that acid infusion in the esophagus was associated with an increase in the spontaneous (dry) swallow-induced contraction amplitude and simultaneous esophageal contractions and felt that heartburn symptoms were related to the esophageal dysmotility induced by acid. Richter and colleagues (14), as well as Burns and Venturatos (3), using improved infusion manometry technique and standardized swallow-induced esophageal contractions failed to find a significant increase in the contraction amplitude during acid infusion. However, an increase in the contraction duration was observed by these investigators. Our study shows that an increase in the contraction duration but not contraction amplitude is statistically significant during the first acid infusion period compared with saline. Changes in amplitude and duration of contraction during repeat acid infusion are significantly higher compared with the first acid infusion period.

In an earlier study, we found a strong temporal correlation between heartburn and SEC (12). The SEC is observed on the ultrasound images as a prolonged increase in thickness of the muscularis propria. These changes in the thickness of the muscularis propria are not necessarily associated with the sustained increase in intraluminal pressure and most likely represent contraction of the longitudinal muscle of the esophagus. In the present study, we found intermittent periods of SECs during the two acid infusion periods with a greater number of subjects and higher frequency of SECs during the second compared with the first acid infusion period. The reason for the intermittent occurrence of SECs during the infusion period is because the swallow-associated distension of the...
esophagus in the presence of SEC causes its disruption. Furthermore, distension of the esophagus associated with infusion of saline and acid in the esophagus reduces muscle thickness and thus makes SEC detection difficult.

The current hypothesis is that acid in the esophagus, in the presence of a leaky esophageal epithelium (9, 22), enters the mucosa and submucosa and stimulates acid-sensitive nerves. Our data show that acid-induced symptom sensitivity and hypersensitivity is associated with an increase in esophageal contractility and hypercontractility. It is possible that increased contractility leads to myosclerosis of the esophageal wall, which in turn is responsible for symptoms. The strong temporal association between contractility and hypercontractility with heartburn and its hypersensitivity suggests but does not prove the cause-and-effect relationship between contractility and heartburn. The ultimate proof of the causality would be if inhibition of contraction abolishes symptoms.

Fig. 6. A: ultrasound images at an interval of 2 s during normal saline infusion period. Note an increase in the muscle thickness in image taken at time 0:02. This increase in the muscle thickness was associated with a manometric contraction. B: ultrasound images show esophageal muscle thickness at an interval of 2 s during acid infusion period. Note an increase in the muscle thickness (markers of contractility) that lasted for several seconds (from time 0:08 to 0:20).
Our data provide a basis for the peripheral mechanism (increased contractility) of visceral hypersensitivity. The current understanding is that acid-induced hypersensitivity is mediated at the level of the central nervous system (16, 17). Sensitization of acid-induced contractility could be a possible peripheral mechanism of visceral hypersensitivity. The significance of our observation is that the pharmacological therapies to address visceral pain related to a central mechanism is likely to be associated with significant side effects, and it may be easier to address the peripheral mechanisms of visceral hypersensitivity than a central mechanism. Further studies should be undertaken to better define the cause and effect relationship between esophageal contractility and esophageal symptoms.

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Fig. 7. A: muscle thickness and heartburn score during saline infusion. B: muscle thickness and heartburn score during acid perfusion. Note the sustained esophageal contraction (SEC) (marked with the dual-head arrows).