Mechanosensory properties in the human gastric antrum evaluated using B-mode ultrasonography during volume-controlled antral distension

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Mechanosensory properties in the human gastric antrum evaluated using B-mode ultrasonography during volume-controlled antral distension. Am J Physiol Gastrointest Liver Physiol 290: G876–G882, 2006. First published November 17, 2005; doi:10.1152/ajpgi.00131.2005.—The aims of this study were to evaluate gastric antral mechanical behavior and distension-induced sensorimotor responses in the human gastric antrum using transabdominal ultrasound scanning. Ten healthy volunteers underwent volume-controlled ramp inflation of a bag located in the antrum with volumes up to 125 ml. The active and passive circumferential tensions and stresses were calculated from measurements of pressure, diameter, and wall thickness before and during the administration of the anticholinergic drug butylscopolamine. The bag distensions elicited contractions in the antrum and sensory responses below the pain threshold. Butylscopolamine abolished the contractions and significantly reduced the sensory response. The length-tension diagram known from in vitro studies of smooth muscle strips could be reproduced as tension-volume diagrams in the human gastric antrum. The number of induced contractions and the contraction pressure amplitude (afterload) showed a parabolic behavior as function of the distension volume (preload), with maximum approximately at 70 ml. At the sensation threshold, the luminal circumference showed the lowest variation coefficient (13–25%), whereas the variation coefficient was more than 100% for the pressure, tensions, and stresses. We conclude that the muscle length-tension diagram and typical preload-afterload curves ad modem the Frank-Starling cardiac law can be obtained in the human gastric antrum. The sensory responses were most closely associated with the luminal circumference, indicating that the sensation during antral distension depends on deformation rather than on tension.

MATERIALS AND METHODS

Ten normal volunteers (5 women, 5 men) were included in the study. The median and ranges of the volunteers’ age, weight, and height were 25 yr (range, 22–56), 60 kg (range, 54–83), and 173 cm (range, 160–184), respectively. The median body mass index was 21.9 (range, 19.0–24.7). The volunteers did not take any drugs and did not abuse alcohol. None of them was a regular smoker. The subjects did not experience chest pain, heartburn, dyspepsia, irritable bowel syndrome-like symptoms, or any other kind of chronic symptoms and pain. There were no restrictions on food intake in the days before the study. The regional ethics committee approved the study protocol, and the experiments were conducted in accordance with the revised Declaration of Helsinki. All volunteers were asked to provide written, informed consent to participate in the trial.

Probe design and equipment. A specially designed distension probe was constructed. The probe was 120 cm long and contained a 30-μm-thick polyesterurethane bag 6 cm from the tip of the probe.
The cylindrical bag was 5 cm long and could be inflated with fluid through an infusion channel of 3.5 mm to a volume of 120 ml (diameter ~6 cm) without stretching the bag wall. The size of the bag was chosen on the basis of previous experience from ultrasonographic studies of the antrum (16, 20). The probe contained a metal clip in the middle of the bag as a marker for ultrasound. A side hole for pressure measurements was placed in the middle of the bag. The lumen and side hole both had diameters of 0.5 mm. The perfusion rate for the pressure channel was 0.1 ml/min. The pressure was measured by a low-compliance perfusion system connected to external transducers (Medex). The pressure data were amplified and converted from analog to digital form at a sampling rate of 10 Hz using a motility data acquisition system from GMC-Medical (Hornslet, Denmark). The digitized data were stored on a personal computer for later analysis.

The ultrasound equipment for two-dimensional scanning of the antrum was a digital sector scanner (System Five; Vingmed Sound, Horten, Norway) with a 5- to 8-MHz linear or curved array transducer. The resolution in the focus point was for 5.0 focused linear array (axial: 0.4 mm, lateral: 0.6 mm, slice thickness: 1.4 mm). This system allowed measurement of the cross-sectional area of the antrum during resting conditions and distension.

Experimental procedures. The volunteers were scanned after an overnight fast; during scanning, volunteers sat in a chair, leaning slightly backward. The probe was passed into the stomach via the nostrils after calibration of the pressure measuring system. The ultrasound transducer was placed in the epigastrium. The depth of scanning was 4–8 cm during the experiments. The positioning of the probe was guided by ultrasound imaging, and the middle of the bag was placed ~3 cm proximal to the pylorus. The zero pressure level for the distension series was determined using manometry.

The distension protocol was performed as volume-controlled ramp distensions at a rate of 100 ml/min up to a maximum bag volume of 125 ml of fluid. A syringe pump was used for the infusions. The distensions were started in antral phase 1 or early phase 2. The antrum was first preconditioned by distending the bag several times until a reproducible area and symptomatic response were obtained. The last of these preconditioning distensions was used for further analysis. One more ramp distension at the same infusion rate was done during intravenous administration of 20 mg of the anticholinergic drug butylscopolamine. None of the volunteers experienced significant side effects, such as double vision, from the anticholinergic action of the drug. Distensions were separated by at least a 2-min resting period; i.e., the volume was withdrawn from the bag at the same volume rate as during infusion, and the bag pressure was kept slightly negative during these periods to ensure complete emptying of the bag. During this period, the subjects were asked to report any visceral perception resulting from the previous distension. Ultrasonographic images were obtained during the distensions. All selected ultrasound images were scanned in expiration, and standardized image sequences were frozen before digital storage. The localization of the metal marker on the probe ensured that the same section was scanned each time. The total investigation time never exceeded 1.5 h.

Sensory assessment. The sensory intensity was assessed continuously during the experiments using an electronic visual analog scale (GMC. Hornslet, Denmark). Before the experiments, the subjects were instructed how to use the 0–10 visual analog scale. The electronic data were amplified, digitized, and stored on the computer for later analysis. A scale for both painful and painful sensations was used as described in previous studies in the upper gut (6, 11, 26). The intensities of the nonpainful sensations were scored with the following descriptors added to facilitate the scoring: 1 = vague perception of mild sensation, 2 = definite perception of mild sensation, 3 = vague perception of moderate sensation, 4 = definite perception of moderate perception, and 5 = the pain threshold. For the painful sensations, the patients used the scale from 5–10 anchored at 5 = pain threshold to 10 = unbearable pain, with the following anchor words: 6 = slight pain, 7 = moderate pain, 8 = medium pain intensity, 9 = intense pain, and 10 = unbearable pain. The scale was previously described in detail (6). It is robust and discriminates sensations in the gastrointestinal tract with high accuracy (6–8). The subjects were carefully instructed to score the evoked sensations and to differentiate these sensations from the unpleasantries in the nose and throat caused by the probe.

Data collection and analysis. The collection of personal data was performed by interview and recorded on a registration form. Analyses of the pressure recordings and the sensory data were done by means of computer software (Openlab version 2.11; GMC-Medical).

In the analysis of the ultrasonic data, several layers of the gastric wall could be visualized in the anterior part of the antrum in most cases. The thickness of the wall was defined as the radial distance through the wall, including muscularis propria, submucosa, and mucosa. The balloon wall usually did not appear on the images. All selected ultrasound images were frozen before digital storage on the scanner and transferred to a personal computer workstation. A designated software package (EchoPAC-3D; GE Vingmed Ultrasound, Horten, Norway) installed on a separate workstation equipped with the Windows 2000 operating system was used for measurement of gastric sizes. The tracing algorithm was previously evaluated and demonstrated good agreement as well as low intra- and interobserver errors (12, 13, 20). The inner echogenic layer of the stomach, corresponding to the interface between the bag and the mucosa of the gastric wall, was outlined. The luminal circumference and the minor diameters of the antral lumens were then measured. Ultrasound images were acquired in a sagittal section of the antrum, in the regions where the aorta and the mesenteric vein were visualized. The thickness of the wall was estimated three times, and the mean value was fitted to obtain more accuracy. The person doing the measurements on the ultrasound images was experienced in these measurements and was not blinded.

The steady-state pressure, diameters, and wall thickness values at each volume distension step were used for the computation of circumferential wall tension and wall stress during distension.

The circumferential wall tension, $T_o$, was computed according to Laplace’s law for circular pressure vessels as follows:

$$T_o = \Delta P r$$

where $\Delta P$ is the transmural pressure (antrum pressure minus abdominal pressure) and $r$ is the hydraulic radius of the antrum (14, 17). The bag pressure at the lowest volume was assumed to be equal to the resting pressure of the antrum, i.e., the intra-abdominal pressure. Hence, the transmural pressure during distension was considered to be equal to the difference between the bag pressure and the resting pressure. The circumferential wall stress ($\sigma_o$) was defined as the tension divided by the wall thickness, thus

$$\sigma_o = \frac{\Delta P r}{h}$$

where $h$ is the wall thickness. This stress is also called the Cauchy stress or hoop stress (14).

The wall stress was decomposed into active and passive components. The total wall stress ($\sigma_{total}$) reflects both active and passive tissue properties and was determined from the distension test without the administration of butylscopolamine. The readings were done between the phasic contractions. Thus the total stress (and tension) represents the tonic component of muscle contraction. The passive stress ($\sigma_{passive}$) results from passive components such as the extracellular collagen and was obtained from the test done during butylscopolamine. The active stress ($\sigma_{active}$) contributed by tonic smooth muscle activity was computed using the equation

$$\sigma_{total} = \sigma_{active} + \sigma_{passive}$$

These wall stresses were plotted as a function of the distending volume to represent an in vivo smooth muscle length-tension diagram.
similar to the well-known length-tension diagram obtained from muscle strips in vitro (9, 10).

The distension-induced contractile activity was also analyzed in terms of the number of contractions and the afterload pressure as functions of the preload volume. The preload volume was determined immediately preceding the contractions, and the afterload pressure was defined as the peak pressure during a contraction minus the pressure immediately before the contraction. This is analogous to the Frank-Starling analysis of heart function (10).

Statistical analysis. The results are expressed as means ± SD unless otherwise stated. ANOVA was used to evaluate the variation of the various parameters as a function of the distension volume and to compare the distension values obtained during or without the administration of butylscopolamine. To analyze with which geometric and mechanical factors the sensation is most closely associated, the variation coefficient (SD/mean) was computed for a number of parameters at the first sensory threshold. Differences were considered significant if $P < 0.05$.

RESULTS
Preconditioning behavior. More than 60 distensions were done in the 10 subjects. Twenty preconditioned distensions were used for further analysis. Of these distensions, half were done during butylscopolamine administration. During the preconditioning distensions, we noticed some variability in the perception score and biomechanical parameters before the responses became repeatable in each subject. It demonstrates that preconditioning is necessary for investigation of sensation and biomechanics in the gastric antrum. All subjects admitted that it was easier to report the perception score after they had experienced the bag distension at least once. The distensions did not change the motility pattern of the antrum between the distensions.

Basic preconditioned distension data. Figure 1 shows representative distension data before and during infusion of butylscopolamine. The pressure increased as function of the volume. Before administration of butylscopolamine, the distensions induced contractions, primarily during inflation of the bag. These contractions typically had amplitudes of 15–20 cmH₂O. Butylscopolamine removed by far the most contractile activity. Between the contractions, the pressure was higher before administration of butylscopolamine compared with the curves during butylscopolamine infusion. This indicates a significant tonic muscle component in antral function. The

Fig. 1. Illustration of ramp distension curves in the human gastric antrum from 1 subject. The thick vertical line (middle) illustrates the reverse point for the distensions at 125 ml. Top and middle: pressure and sensory tracings, respectively, during the distensions. The black tracings are from the distension before butylscopolamine administration, whereas the gray tracings represent the butylscopolamine data. It is apparent that the gastric antrum exhibits both phasic and tonic contractions during distension and that butylscopolamine lowers the contractile activity and the sensory response. Bottom: averaged sensory data as a function of the distension volume.
corresponding sensory data are also shown in Fig. 1. Typically, the sensory score was lower and shorter lasting during the butylscopolamine infusion than before it was initiated. The sensory score tracings were most often skewed, meaning that the sensation did not decrease immediately after the pump was reversed at a volume of 125 ml in the bag. Figure 1, bottom, shows the median sensory data from all subjects. There was no notable effect of butylscopolamine on the sensory score up to a volume of 90 ml. At higher volumes, the sensory data obtained before butylscopolamine were significantly higher than those obtained during the infusion ($P < 0.05$). None of the volunteers reached the pain threshold during the distensions. Sensation of fullness was the symptom most often reported.

**Geometric and tension-stress data.** Figure 2 shows the pressure and morphometric data in terms of luminal circumference and wall thickness as functions of the distension volume before and during administration of butylscopolamine. Only data obtained between the phasic contractions were used in the analyses, thus representing tonic curves before butylscopolamine infusion. The pressure increased as a function of volume (Fig. 2, top; $P < 0.001$). The pressure increase was relatively minor until a volume of 80 ml was reached. The pressure was highest before butylscopolamine infusion. The luminal circumference increased as a function of volume (Fig. 2, middle; $P < 0.001$), without any difference observed between the curves before and during butylscopolamine, which was to be expected because a volume-controlled distension protocol mainly shows changes in pressure rather than in associated geometric variables. The wall thickness decreased (Fig. 2, bottom; $P < 0.01$) as a function of the volume, without any difference observed between the curves obtained before and during butylscopolamine. The average wall thickness before and during butylscopolamine was 4.93 and 5.12 mm. The luminal cross-sectional area and the diameter curves were similar to the circumference curve (not shown).

The circumferential tension and stress increased slowly until a 100-ml volume was reached before administration of butylscopolamine (total tonic tension and stress data; Fig. 3). The tension and stress increases were much larger at volumes $>100$ ml. The passive tension and stress increased less than the total tension and stress and followed an exponential pattern. The total and passive curves differed at volumes $>100$ ml ($P < 0.05$). Figure 3, bottom, shows the computed average active

![Fig. 2. Pressure (top), circumference (middle), and wall thickness (bottom) as a function of volume during the distensions before and during administration of butylscopolamine (buscopan).](image-url)
tonic stress. This curve follows the passive curve but seems to level off at the highest volumes.

**Preload-afterload contraction analysis.** Figure 4 shows the number of contractions during distension and the afterload pressure as functions of the preload volume. Both the number of contractions and the afterload pressure showed parabolic curves with an ascending leg, with a maximum obtained at ~75-ml volume, and part of a descending leg. Thus, when the antrum contains a high volume, it cannot contract with high force.

**Relationship of sensory data to the mechanical parameters.** Comparing the sensory data in Fig. 1 with the tension and stress data in Fig. 3, we see some correlation between sensation and the mechanical force in terms of tension or stress. However, the sensation levels off, whereas tension and stress increased steeply at high volumes. At high volumes (where the antrum is filled and starts to stretch in the circumferential direction, as verified by the pressure increase in Fig. 2, top), the sensation curve seems to have more similarities with the circumference curve. To look further into the issue of which mechanical stimulus causes the sensation, we plotted the geometric and mechanical parameters and their variation at the first sensation threshold (Fig. 5). The variation coefficient was considered a reverse indicator of the dependence of the parameter. The variation coefficient was lowest for the circumference (13–25%) and cross-sectional area (29–46%), whereas it was >100% for pressure, tension (not shown in Fig. 5), and stresses.

**DISCUSSION**

The active and passive mechanical properties of the gastric antrum are important for the understanding of its function in health and disease. In past decades, distensions have become popular in experimental clinical studies as a tool for evaluation of gastric antral function. Pressure-volume measurements have been used extensively for distension purposes in the esophag-
Gus; however, it is difficult to derive mechanical data from such studies. In a recent study, we demonstrated that ultrasonography is useful in combination with antral distension to obtain data on the mechanical behavior of the gastric antrum (16). However, the bag design limited the study, and data on the mechanosensory properties were not obtained. In this study, we overcame these limitations by using a larger bag and ramp protocols that were easier to interpret from a mechanical point of view. Furthermore, we have introduced a new way of studying antral muscle function on the basis of cardiac function tests. Methodological aspects related to ultrasonography, the ability of butylscopolamine to fully relax the muscle, and tension and stress computations have been addressed previously (16) and are not further described here.

Tissue and muscle mechanical aspects. In this study, we demonstrate that the distensibility in vivo depends not only on the passive properties but also on the physiological state of smooth muscle. Smooth muscle tone is pronounced during the distensions as verified by the difference between the curves obtained before and during infusion with butylscopolamine. The active tonic tension and stress level off at the largest volumes (Fig. 3), whereas the phasic muscle contractility has its maximum at lower volumes (Fig. 4). This indicates that phasic and tonic muscle contractions are regulated differently (14, 15). The maximum active tension is presumably reached at a level of optimum overlap between the sliding filaments in the muscle cells (25, 29). The passive curves were exponential, in accordance with findings in other soft tissues (5, 10). The exponential behavior protects the tissue against overstress and damage at high luminal pressure loads while distending easily and facilitating flow in the physiological pressure range.

The preload in this study was considered to be the volume representing the initial muscle length preceding the contraction during the distension, whereas the afterload was evaluated as the pressure amplitude during the contraction. In cardiac physiology, the preload is usually considered to be the end-diastolic radius and the afterload is considered to be the arterial pressure during systole (18). The explanation of the Frank-Starling mechanism is that, when an extra amount of blood flows into the ventricles, the cardiac muscle itself is stretched to a greater length. This in turn causes the muscle to contract with increased force because the actin and myosin filaments then are brought to a more nearly optimal degree of interdigitation for force generation. In cardiac physiology, the importance of the concept of preload and afterload is that in many abnormal functional states of the heart and circulation, the pressure during filling of the ventricle or the arterial pressure against which the ventricle must contract, or both, are severely altered from normal levels. Transferring this concept to gastric antral physiology, the results described herein are of interest for evaluation of normal antral physiology and in the pathophysiology of functional dyspepsia.

Mechanosensory properties. The distensions did not cause pain but only symptoms in the nonpainful range. Functional dyspepsia, in which evidence suggests that the antrum is important to symptom generation (3, 19), is characterized not by pain but rather by more vague symptoms. As shown in Fig. 1, the sensory data exhibit hysteresis, i.e., the descending curve is skewed compared with the ascending curve. Because this phenomenon cannot be explained by the tonic and phasic contractility and by the distension load, it points to a central component such as temporal summation (6). Butylscopolamine clearly decreased the sensation, which intuitively indicates active stress as being important for symptom generation. In fact, the sensation curve (Fig. 1) and the active stress curve (Fig. 3) are very similar. However, this does not exclude other factors but merely points to gastric antral tone being important. The data obtained during butylscopolamine infusion demonstrate that passive stretch also can elicit symptoms.

To further evaluate the sensory response, we also undertook an analysis of the parameters at the first sensation threshold. Because pain was not elicited, we could not do the analysis at the pain threshold, which usually is easier to determine in gastrointestinal distension studies. We plotted the geometric and mechanical parameters and their variation at the sensation threshold (Fig. 5). The coefficient of variation was taken as a reverse indicator of the dependence of the parameter. This analysis showed that circumference and cross-sectional area had much lower variation coefficients than pressure, tension, and stresses. Because changes in the circumference is a proxy of antral deformation, this points to circumferential strain being important for symptom generation. This is consistent with our findings in the esophagus, small intestine, and rectum (1, 11, 27) and with other studies demonstrating that energy intake and appetite are related to antral area (28).

To summarize the mechanosensory findings, the passive stretch, muscle tone, and central mechanisms such as temporal summation all play a role. It is also of interest to note that the
sensory responses are elicited at higher volumes that the contractile response. In fact, the motor response starts even before the antrum wall is stretched (according to the pressure volume curve in Fig. 2). At low volumes, the antrum changes geometry (bending deformation) rather than stretches (i.e., the ratio between the major and minor diameter decreases). This indicates that the mechanosensitive receptors or the sensitivity of the afferent pathways differ for sensory and motor responses.

Conclusions and future clinical applications. We have devised a new way to obtain data on the distensibility, muscle function, and mechanosensory function of the gastric antrum. The antral muscle shows a behavior that can be compared with that of heart muscle. The new test may have applications in the testing of drugs on antral motor function and disease states. The present study attracts attention regarding patients with gastroparesis, diabetic autonomic neuropathy, and functional dyspepsia in whom gastric motor disturbances have been detected. Especially regarding patients with functional dyspepsia characterized by a wide gastric antrum (19) and hypersensitivity (3), there is an obvious need to carry out research to enhance understanding of the pathophysiology underlying symptom induction. On the basis of the literature (3, 19), it may be hypothesized that patients with functional dyspepsia have altered antral mechanosensory properties that can be detected using this test. Together, there is an obvious need to carry out research to enhance our understanding of the pathophysiology underlying the symptom induction in dyspeptic patients.

GRANTS
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