Intraluminal modulation of gastric sensitivity to distension: effects of hydrochloric acid and meal

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Received 31 July 2000; accepted in final form 1 December 2000

In recent years, sensory dysfunction has been implicated in the pathogenesis of functional gut syndromes such as noncardiac chest pain (26), chronic idiopathic dyspepsia (17), and irritable bowel syndrome (27). Gut stimuli mainly induce unperceived reflex responses (3), but under certain circumstances they may also induce conscious sensations, which are modulated at different levels of the brain-gut axis. As far as the gut level is concerned, different conditions may modify conscious sensations. Gastric tone by itself modulates sensations because symptoms are more intense during isobaric distensions performed on a relaxed stomach than under basal conditions, and the reverse is true during isovolumetric distensions (24). Temporospatial interactions between two stimuli may also modulate conscious perception. A synergistic effect was evidenced between two concomitant mechanical intestinal distensions (31), and in the esophagus, hydrochloric acid (HCl) infusion decreased the pain threshold to balloon distension (21). In the stomach, meal ingestion (22) and duodenal lipid infusion (5) also decreased the threshold of discomfort to gastric isobaric distensions. In the rectum, infusion of biliary acids reduced the rectal volume required to induce a desire to defecate (12).

The two key functions of the stomach, i.e., motor activity and acid-peptic secretion, are highly interrelated. Gastric distension modulates the rate of gastric secretion, and conversely, HCl modulates gastric motor activity (18). Conscious sensations in response to distension or to direct intragastric HCl infusion have been separately studied (8, 13, 17, 20) in healthy subjects or in patients with chronic idiopathic dyspepsia, but sensations in response to concomitant administration of both stimuli remain undetermined.

Our working hypothesis was that symptoms induced by gastric distension could be modulated by the chemical content of the stomach. Gastric distension tests were therefore performed in healthy subjects during continuous intragastric infusion of saline or HCl in the fasting state and after meal ingestion. Because previous studies (24) demonstrated that sensory responses of the stomach were affected by the modality of the distension, both isobaric and isovolumetric distensions were performed by using an electronic barostat.

Subjects and Methods

Participants. Nine healthy volunteers (7 males, 2 females, 24–38 years) gave written informed consent to the protocol approved by the Ethics Committee of Saint-Louis Hospital (Paris, France). All subjects were healthy on physical examination. No subjects had gastrointestinal symptoms or previ-
ous abdominal surgery (except for appendectomy) or were taking any medication during the study.

Tube assembly and distending device. Gastric distensions and infusions were performed by using a three-lumen tube assembly that incorporated a two-lumen gastric tube (French no. 12 polyvinyl tube, Sherwood Medical, Petit-Rechain, Belgium) and an infusion tube (5 mm OD). At the tip of the gastric tube, a polyethylene bag (capacity, 1,100 ml; maximal diameter, 19 cm) was sealed airtight, and its orad extremity was connected to an electronic barostat (Institut National de la Recherche Agronomique, Toulouse, France) (4, 15). In the barostat mode, it measures volume variations, as a reflection of gastric tone, when set at low pressure, and performs graded pressure (isobaric) distensions by an electronic feedback mechanism. In the pump mode, it allows graded volume (isovolumetric) distensions to be performed (4, 15). To produce isobaric distension, the desired pressure level is set using a pressure selector dial that increases the pressure within the intragastric bag, while changes in gastric volume are recorded. To produce isovolumetric distension, the desired level is set using a volume selector dial that increases the volume within the intragastric bag, while changes in gastric pressure are recorded. Both pressure and volume inside the bag were recorded on a paper polygraph (model L6514, Linseis). The infusion tube, with a latex balloon containing 25 g of mercury fixed at its distal tip, allowed intragastric infusion to be performed over a 20-cm length by multiple side holes. The tube was connected to an infusion system to perform continuous infusions at a rate of 4 ml/min.

Experimental design. Two experiments separated by a 7-day period were performed in a randomized double-blind order. The same design was used on both experimental days. On one day, participants received an intragastric infusion of HCl, and on the other day, isotonic saline was perfused at the same rate.

The participants were intubated after an 8-h fast. The tube assembly, i.e., the bag of the barostat finely folded and the infusion tube, was introduced through the mouth into the stomach. Its position was checked by fluoroscopy. The bag was located in the gastric fundus, while the distal tip of the infusion tube was in the antrum. Each participant was seated comfortably on a chair. First, the gastric juice was aspirated by the infusion tube. Next, to unfold the intragastric bag, one lumen of the gastric tube was connected to a pressure transducer, and the bag was slowly inflated through the other lumen with 300 ml air under controlled pressure (<20 mmHg). The bag was then completely deflated and connected to the barostat. The minimal distending pressure, defined as the lowest pressure level that provided an intrabag volume of 30 ml or more (24), was determined by increasing intrabag pressure by 1 mmHg every 2 min using the pressure selector of the barostat. A baseline gastric pressure of 1 mmHg above the minimal distending pressure was set and then continuous infusion (4 ml/min) of saline or HCl was performed and maintained until the end of the experiment. The output of HCl infused was individually determined by taking into account the calculated maximal acid output according to sex, age, and body weight as defined in a French population (7). This resulted in infusion rates ranging from 18.9 to 37.6 mmol/h (mean ± SE, 28.1 ± 4.1 mmol/h). A 15-min basal period was then observed, and subjects were asked to report any sensations. Thereafter, isobaric or isovolumetric distensions were performed in a randomized order. Isobaric distensions were performed in stepwise increments of 2 mmHg starting from the baseline gastric pressure; isovolumetric distensions were performed in stepwise increments of 100 ml starting from 0 ml. Distensions were 3 min in duration, and between each step, the bag was deflated until the minimal distending pressure or 0 ml was reached during isobaric or isovolumetric distension, respectively, and a 1-min rest period was observed. At the end of each distension step, type and intensity of sensations were noted by using a graded questionnaire that included four types of sensations: pressure, bloating, nausea, and heartburn. Other perceived sensations were specified by participants in an open-box questionnaire. The intensity of sensations was scored by using a graded (scores 0–6) questionnaire (24). Score 0 represented no sensation, score 5 discomfort, and score 6 a painful sensation that was not intended and was to be instantaneously reported for immediate discontinuation of the stimulus. Distensions were stopped at the maximal distension step defined as the distending pressure or volume that induced discomfort or pain (≥score 5) or when a distending volume of 1 l was reached to stay in an infinitely compliant system. Between each distending protocol (isobaric and isovolumetric), a 5-min rest period was observed. Lastly, a 375-ml liquid meal (500 kcal; 15% protein, 35% lipid, and 50% carbohydrate; Sondalis HP, Laboratoires Sopharga, Paris, France) was ingested within 10 min. After a new 15-min basal period during which subjects were asked to report any sensations, isobaric and isovolumetric distensions were randomly performed according to the same distending protocol described above.

Data analysis. During each 15-min basal period, intrabag volume was measured for 1 min and averaged. For each distending step, the dependent variable (volume during isobaric distensions and pressure during isovolumetric distensions) was the mean value recorded during the last 2 min of the distension. Volumes were corrected for air compressibility. The perception score corresponding to each distension was computed; when more than one sensation was scored, only the sensation with the maximal score was computed for comparison. For each distending protocol (isobaric and isovolumetric) during the intragastric infusions of saline and HCl under fasting conditions and after meal ingestion, the maximal distension step was defined as the distension that induced a sensation ≥score 5 or, if participants did not experience discomfort, a sensation <score 5, when the volume of distension was equal to 1 l. We also calculated the percent distribution of the specific sensations elicited by each type of distension. Pressure-symptom curves during isobaric distensions and volume-symptom curves during isovolumetric distensions were constructed from the maximal distension step. Compliance was determined by constructing compliance curves from the imposed and the dependent variables. Pressure was calculated from the balloon estimated radius (r; derived from $V = 4/3πr^3$, in which V represents the volume of the sphere) and the transmural pressure (p; defined as the absolute distending pressure minus the minimal distending pressure) using Laplace's law ($T = p × r/2$, in which $T = $ wall tension) (14), assuming that the volume within the gastric bag conformed to a spherical shape (20, 24).

Statistical analysis. Results are expressed as means ± SE. Statistical comparisons were performed by paired Wilcoxon's test for nonparametric data and ANOVA with repeated measures for continuous variables, followed by the Newman-Keuls test for multiple comparisons. $P < 0.05$ was considered to be significant.

RESULTS

Volume infused. The mean volume infused was not different during the saline (404 ± 65 ml) and the HCl periods (402 ± 59 ml) ($P = 0.87$).
Basal periods. The basal pressure measured in the fasting state before distensions did not vary significantly between the 2 experimental days. It was $4.2 \pm 0.4$ and $3.9 \pm 0.3$ mmHg during the saline and HCl infusions, respectively ($P = 0.49$). At these pressure levels, the mean gastric volumes measured during the 15-min basal periods were not significantly different during the saline and HCl infusions ($83 \pm 15$ and $75 \pm 17$ ml, respectively; $P = 0.63$). No sensations were reported by participants either during saline or HCl infusions.

Meal ingestion induced a rapid increase in intrabag volume (i.e., gastric relaxation). At the end of the 15-min basal period, the mean intrabag volumes were $245 \pm 53$ and $263 \pm 63$ ml during the saline and HCl infusions ($P = 0.35$). Three participants reported a mild sensation of satiety immediately after the end of meal ingestion on both experimental days.

Isobaric distensions. In the fasting period, the pressure-symptom curve demonstrated that HCl significantly increased sensations during isobaric distension (Fig. 1A). At the maximal distension step, the pressure was significantly lower during HCl than during saline infusion ($11.8 \pm 0.6$ vs. $13.7 \pm 0.8$ mmHg, respectively; $P = 0.01$). For instance, at the maximal distending pressure tested in both conditions ($11.8 \pm 0.6$ mmHg) the symptom score was nearly two times higher during HCl than during saline ($4.6 \pm 0.6$ vs. $2.7 \pm 0.4$, respectively; $P = 0.02$). The decrease in the maximal distension step noted during HCl infusion compared with saline was not associated with a significant modification in the intrabag volume ($912 \pm 27$ vs. $876 \pm 57$ ml, respectively; $P = 0.51$) but was associated with a significant decrease in the wall tension ($17.2 \pm 1.2$ vs. $19.7 \pm 1.5$ mmHg·cm, respectively; $P = 0.01$).

In the postprandial period, the pressure-symptom curve tended to be shifted to the left during HCl infusion, but the differences were not significantly different ($P = 0.24$) (Fig. 1B). At the maximal distension step, no significant differences were observed between HCl and saline for the intrabag volume ($812 \pm 59$ vs. $796 \pm 96$ ml; $P = 0.35$), the intensity of sensations (4.3 vs. 4.0; $P = 0.6$), and the wall tension (15.5 vs. 2.5 vs. 13.8 vs. $1.8$ mmHg·cm; $P = 0.29$).

Compared with the fasting state, meal ingestion significantly increased sensations felt during saline infusion and the maximal distension step was significantly lower during saline infusion ($13.7 \pm 0.8$ vs. $11.7 \pm 0.4$ mmHg; $P = 0.01$). However, meal ingestion had no further effect on the maximal distension step during HCl infusion ($11.8 \pm 0.6$ vs. $10.8 \pm 0.7$ mmHg; $P = 0.24$) (Fig. 1, A and B).

Isovolumetric distensions. In the fasting period, HCl infusion did not modify the volume symptom curve compared with saline ($P = 0.45$) (Fig. 1C). At the maximal distension step, HCl did not significantly modify the intrabag pressure ($10.8 \pm 1.3$ vs. $12.3 \pm 1.2$ mmHg; $P = 0.21$) and the wall tension (15.5 vs. 2.5 vs. 18.2 vs. $2.3$ mmHg·cm; $P = 0.19$).

Likewise, HCl infusion in the postprandial period did not modify the volume-symptom curve compared with saline ($P = 0.39$) (Fig. 1D). At the maximal distension step, no significant differences were observed for the intrabag pressure ($9.1 \pm 0.6$ vs. $9.4 \pm 0.9$ mmHg; $P = 0.82$) and the wall tension ($13.3 \pm 1.1$ vs. $14 \pm 2.1$ mmHg·cm; $P = 0.36$). Compared with the fasting state, the volume-symptom curves were not significantly different after the meal during saline ($P = 0.34$) and HCl infusions ($P = 0.43$) (Fig. 1, C and D).

Compliance. In the fasting period, gastric compliance was significantly increased by HCl infusion compared with saline during both isobaric ($P = 0.004$) and isovolumetric distensions ($P = 0.005$) (Fig. 2). In contrast, compliance measured in the postprandial period during isobaric and isovolumetric distensions was not
significantly different when saline and HCl were infused \( (P = 0.22 \text{ and } P = 0.10, \text{ respectively}) \) (Fig. 3).

**Frequency of symptoms.** The relative frequency of symptoms was not different during isovolumetric and isobaric distensions in both the fasting and postprandial periods (results not shown). Thus an overall analysis was performed. As shown in Fig. 4, the frequency of bloating, pressure, and heartburn was roughly similar under the four conditions. The frequency of nausea tended to increase during HCl and fasting \( (14\% \pm 5\%) \), saline and meal \( (15\% \pm 6\%) \), and HCl and meal \( (12\% \pm 7\%) \) compared with during saline and fasting \( (4\% \pm 4\%) \), but differences were not significant \( (P = 0.19) \).

**DISCUSSION**

We have shown in the present study that HCl infusion sensitized the stomach to isobaric but not isovolumetric distensions in fasting healthy subjects. This sensitizing effect of HCl was abolished by meal ingestion. Compared with fasting, meal ingestion also decreased sensory thresholds during isobaric but not isovolumetric distensions, when saline was infused.

To detect a putative effect of HCl on gastric sensitivity, we used direct intragastric instillation with HCl concentrations close to the maximal acid output in a normal population \( (7) \) and not after subcutaneous or intravenous pentagastrin injection. Indeed, a pentagastrin test reflects the submaximal gastric acid secretion by parietal cells, but its injection may induce symptoms \( (30) \), stimulate gastric phasic activity \( (9) \), and decrease gastric tone \( (19) \). In the present study, we did not measure intragastric acidity, and the summation of exogenously administered and endogenously secreted acid could have achieved supraphysiological levels of gastric acid. However, recent data using standardized gastric distension with the barostat suggest that distension did not modify significantly gastric acid secretion \( (30) \). Moreover, under physiological conditions, H+ secretion is rapidly inhibited by different negative feedback mechanisms triggered at the gastric level, including the H+ gastric concentration \( (16) \). To suppress endogenous gastric acid secretion, gastric acid inhibitors could have been used, but such drugs decrease gastric motility \( (25) \).

Gastric emptying was not assessed during this study. However, the results we noted on sensations during isobaric distensions did not appear to be due to fluid accumulation, because mean volumes of saline and HCl infused were similar during both experimental days and HCl gastric infusion did not modify the basal volume and magnitude of immediate postprandial gastric relaxation. On the other hand, it could be hypothesized that gastric distensions enhanced gastric emptying, leading to increased HCl in the duodenum. In this case, it might be supposed that the stimulation of duodenal receptors modulates the gastric sensitivity to isobaric distension by a central reflex mechanism. However, it has been shown that constant isobaric distension did not significantly modify gastric emptying assessed by scintigraphy \( (22) \), and the intensity of sensation was clearly proportional to the intensity of gastric distensions as shown in Fig. 1.
This sensitization of the stomach by HCl can be explained by different mechanisms. First, HCl infusion significantly increased gastric compliance. Previous studies showed that an increase in gastric compliance, as obtained after glucagon injection (24) or meal ingestion (22), sensitized the stomach during isobaric distensions, probably by decreasing the stimulation of mechanoreceptors sensitive to wall tension. This hypothesis is partly supported by the fact that at the maximal pressure tested in both conditions the transmural tension was decreased during HCl infusion while intensity of symptoms was increased. However, according to this mechanistic model, we should have observed a significant decrease in sensations also during isovolumetric distensions (24), suggesting that compliance changes induced by HCl cannot fully explain these differences. The second hypothesis is to consider that gastric mechanoreceptors and gastric acid sensitive receptors are independently stimulated but converge at the same level in the spinal cord or in the brain stem. At this level, the summation of these two stimuli onto a second neuron, which conveys information toward the central nervous system, may increase conscious sensations. Somatovisceral convergence has been demonstrated in animals and suggested in humans (2). It probably explains the somatic referral pain during gut distensions. However, viscerovisceral convergence still remains hypothetical. Studies (23, 31) showing the sensory summation of two distensions applied in two adjacent parts of the gut might be explained by such phenomenon. Finally, the third hypothesis is that the stimulating threshold of some mechanoreceptors is decreased by concomitant application of HCl, making them act as polymodal receptors. Such interactions were demonstrated in animal studies (11) where the stimulation thresholds of some true mechanoreceptors may be decreased by previous or concomitant application of non- or irritating chemical substances. It is likely that these mechanoreceptors are located in the very superficial part of the gastric wall, probably the mucosa. Whatever the physiological mechanism, temporal summation of chemical and mechanical stimulation has been previously reported (12, 21) in the human gut. For instance, in the esophagus, HCl infusion decreased the pain threshold to balloon distension in both controls and patients with noncardiac chest pain (21), and in the rectum, infusion of deoxycholic acid decreased the rectal volume required to induce a desire to defecate during balloon distension in healthy subjects (12).

Meal ingestion induces gastric relaxation (1, 22, 28), which increases gastric compliance, as we found in our study. Hence the meal is accommodated without increments in intragastric pressure. It is believed that a defective gastric relaxation increases intragastric pressures and symptoms in patients with postsurgical gastroparesis (4) and during functional dyspepsia (32, 33). In the saline period, we confirmed that the maximal distension step was lower after meal ingestion than during fasting by performing isobaric distensions (22), whereas we did not find any similar effect during isovolumetric distensions. These discrepancies cannot be explained by a difference in compliance during both modalities of distension. They suggest that postprandial symptoms are mostly related to a sensitization of mechanoreceptors stimulated during isobaric distensions. During isobaric distensions, the sensitizing effect of HCl was abolished by meal ingestion. This could be because the meal has a buffering effect or once the meal has exerted its influence the response is maximal or submaximal and HCl could have no further effect on sensations.

Relationships between quality of symptoms and type of receptor stimulated (mechanical, chemical, or polymodal) remain largely unknown. We expected that HCl could significantly modify the quality of symptoms, but this was not confirmed because participants reported mainly one kind of sensation throughout the experimental procedure, during all test periods. Only intensities varied proportionally to the stimulation, as previously noted (3) during gut distension tests.

In conclusion, we have shown that HCl infusion and meal ingestion sensitized the stomach to isobaric distensions, but not to isovolumetric distensions. This effect might be related to an increase in gastric compliance or to acting on the threshold of stimulation of some mechanoreceptors. During isobaric distensions, these changes might act in the same direction with an increase in sensation due to decreased wall tension as well as mechanoreceptor sensitization, whereas during isovolumetric distension they might act in opposite directions (a decreased sensation due to decreased wall tension, but increased sensation due to mechanoreceptor sensitization), making the net HCl effect similar to saline. These hypotheses could be confirmed by performing fixed tension gastric distensions, as recently proposed (10). Additional pathophysiological considerations may be derived from our study. Patients with chronic idiopathic dyspepsia present gastric hypersensitivity during gastric balloon distensions (8, 17, 20), whereas gastric hypersensitivity to HCl remains controversial (6, 15) but duodenal hypersensitivity to HCl has recently been demonstrated (29). Because dyspeptic patients are hypersensitive to wall tension, and not to gastric wall elongation (20), the sensitizing effect of HCl on gastric sensation elicited by distensions warrants further study to understand its role in the genesis of symptoms of dyspepsia.

REFERENCES


