

Frequency of gastric pacesetter potential depends on volume and site of distension

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Lin, Henry C., Xiao-Tuan Zhao, Benjamin Chung, Yu-Guo Gu, and Janet D. Elashoff. Frequency of gastric pacesetter potential depends on volume and site of distension. *Am. J. Physiol.* 270 (*Gastrointest. Liver Physiol.* 33): G470–G475, 1996.—Little is known about the response of the frequency of gastric pacesetter potential (PP) to luminal distension. When volume distension occurs as a result of a meal, gastric emptying may play an important role, since the site of distension shifts as the meal is displaced from the stomach to the small bowel. In this study, using dogs equipped with duodenal fistulas and serosal electrodes on the antrum, we compared the frequency of gastric PP during the course of gastric emptying while isolating the volume distension to either the stomach or the small bowel. We found that 1) the frequency of gastric PP decreased linearly with greater initial meal volume when volume distension was isolated to either the stomach [$P < 0.05$, analysis of variance (ANOVA)] or small bowel ($P < 0.01$, ANOVA), and 2) the frequency of gastric PP decreased linearly with increased volume remaining in the stomach or increased volume entering the small intestine. We conclude that the frequency of gastric PP depends on volume and site of distension.

gastrointestinal motility; gastric emptying; stomach; small intestine

ALTHOUGH THE FREQUENCY of gastric pacesetter potential (PP; also termed slow waves or electrical control activity) (5, 31) in the fasted state has been reported to vary between 4.5–5.7 cycles per minute (cpm) in dogs (6, 24, 27) and 3.5–4.5 cpm in humans (18), the distending effect of different meal volumes on these “normal” frequencies is not well known. The available information is incomplete, conflicting, and without data on dose response. Distending the canine stomach with a 500-ml balloon decreased the frequency of gastric PP by 30%, but a water meal at the same volume only decreased the frequency by 11% (17). Although 250 and 350 ml of water instilled into the stomach in humans slowed the frequency of gastric PP by ~15% (26), a 250-ml yogurt meal decreased the frequency of gastric PP (as recorded by cutaneous electrogastrography) by 23% in the first 10 min (13).

Since volume distension decreases for the stomach but increases for the small intestine as the meal shifts its location with gastric emptying, we hypothesized that the effect of meal distension on the frequency of gastric PP may depend on both volume and site of distension. In this study, we used dogs equipped with duodenal fistulas and antral electrodes to evaluate the change in the frequency of gastric PP that occurs in the course of gastric emptying of 150–1,800 ml of pH 7.0

nonnutrient solutions. Gastric output was diverted completely at the duodenal fistula to isolate the distension effect to either the stomach (*part 1*) or the small intestine (*part 2*).

METHODS

General Experimental Design

Nonnutrient solutions (150–1,800 ml) were used to test for the effect of volume distension on the frequency of gastric PP. In *part 1* of the study, to isolate distension to the stomach, gastric output was diverted completely out of the duodenal fistula of the dog undergoing recording of antral myoelectrical activity ($n = 6$ dogs). In *part 2* of the study, to isolate distension to the small intestine, two dogs were used in each experiment so that the test solution could be instilled into a dog that was designated as the “donor” while its gastric output was diverted completely and returned to the small intestine of a “recipient” dog ($n = 6$ recipient dogs, 1 donor dog; Fig. 1). The frequency of gastric PP was then measured from the recipient dog. By limiting gastric distension to the donor dog, this paired model allowed the volume entering the small intestine, and thereby the frequency of gastric PP of the recipient dog, to follow the pattern of surge and wane that is characteristic of physiological gastric emptying. Outcome measures for this study were the frequency of gastric PP and either the volume remaining in the stomach (*part 1*) or the volume entering the small intestine (*part 2*).

Preparation of the Dog Model

The procedures used in this study were approved by the Institutional Animal Care and Use Committees at Cedars-Sinai Medical Center, Los Angeles, CA, and the Sepulveda Veterans Affairs Medical Center. Seven mongrel dogs were each surgically prepared with a chronic duodenal fistula fitted with a modified Thomas cannula located across from the pancreatic duct ~10 cm from the pylorus (21). With the flanges of the cannula resting against the inner surface of the duodenal wall, the cannula was fixed against rotation by suturing. Just distal to the fistula, a length of Tygon tubing with a diameter of 2 mm was looped around the intestine and fixed by suture through the visceral peritoneum to the intestinal wall. The length of tubing used was individualized to be as short as possible without a tightening effect on the lumen. This tubing provided a stent against which an inflated Foley balloon could be pulled to provide a water-tight seal. Since gastric myoelectrical activities are best recorded from bipolar electrodes implanted in the distal stomach (17), three silver-tipped, bipolar electrodes were implanted 1 cm apart on the anterior serosal surface of the antrum. These electrodes were placed along the longitudinal axis of the antrum 1, 2, and 3 cm proximal to the pylorus. The proximal ends of the Teflon-coated wires leading from these electrodes terminated onto an electrical coupler embedded within a cannula. The cannula, modified from a 20-mm plastic syringe barrel,

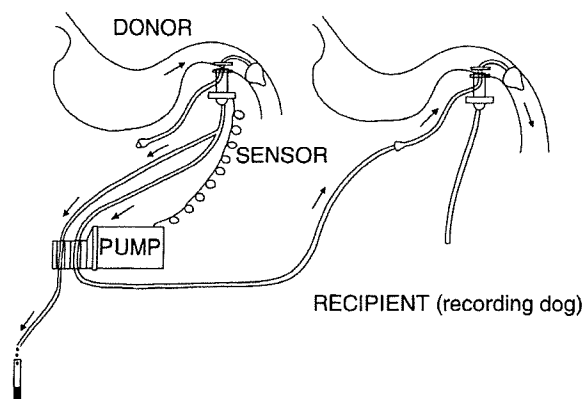


Fig. 1. Method of isolating volume distension to the small bowel (*part 2*). The gastric output of "donor" dog was diverted completely and pumped into the small intestine of "recipient" recording dog. This paired model limited distension of the stomach to the donor.

was brought out through an incision in the abdominal wall. All dogs were given a recovery period of 4 wk and underwent testing only after normal feeding behaviors were reestablished postoperatively. This preparation had good survival, and the seven dogs remained healthy with stable body weights, unaffected demeanor, and functioning electrode for >12 mo of observation.

Distension by Liquid Meals

Dogs were deprived of food but not water for an 18-h period before each experiment. The dogs weighed ~25 kg. They were fed once a day. The volume of their regular meal was ~1,500 ml. Thirty minutes before each experiment, the duodenal cannula was uncorked so that a Foley catheter could be placed into the distal limb of the duodenal fistula, and the stomach was allowed to drain freely. The catheter balloon was inflated with 10 ml of water and cinched up against the Tygon ring (21). At the start of each experiment, 150, 300, 600, 1,200, or 1,800 ml of 300 mosM phosphate buffer (pH 7.0) was delivered in <2 min into the stomach of the recording dog via a temporarily placed orogastric tube (*part 1*). For *part 2* of the study, 300, 600, 1,200, or 1,800 ml of the same buffer solution was similarly delivered into the donor dog. The maximal volume used for this study was 1,800 ml, since this was the highest volume that was well tolerated by the dogs. The order of administration followed a randomization schedule. Each solution was labeled with ~0.05 mCi ^{99m}Tc chelated to diethyltriamine pentaacetic acid (DTPA) (9).

Methods of Limiting Distension to Stomach or Small Intestine

In *part 1*, to isolate the effect of volume distension to the stomach, gastric output was allowed to drain freely and rapidly out of the duodenal fistula by gravity. Since the first 10 cm of duodenal lumen became continuous with ambient air once the duodenal cannula was uncorked, the luminal pressure within the postpyloric duodenum could not exceed the atmospheric pressure (22). Thus the distension effect of the liquid meals was effectively limited to the stomach of the recording dog. In *part 2* (Fig. 1), to isolate the effect of volume distension to the small intestine, the gastric output of the donor dog was diverted and pumped into the small intestine of the recipient dog via a Foley catheter placed into the distal limb of its duodenal fistula. Thus, using this paired model, the stomach of the donor, but not the recipient dog, was dis-

tended. In contrast, the small bowel beyond the duodenal fistula was distended in the recipient recording dogs.

Gastric emptying is not a constant event. The volume entering the duodenum in *part 2* and, therefore, the distension of the small bowel by gastric emptying, is also variable. This transit-dependent variable distension of the small intestine by gastric output would be most appropriately studied if the rate of volume entry into the recipient dog were to be synchronized to the gastric emptying of the donor dog. A dual-headed pumping system was used for this purpose (21) (Fig. 1). The output from the duodenal fistula of the donor dog was diverted into an optical chamber that was attached to the fistula. An optical sensor (Skanamatic Systems, Elmhurst, NY), placed around the chamber, was used to detect any rise in the fluid level as the luminal content drained into it. The sensor, in turn, triggered a dual-headed peristaltic pump (Masterflex, Cole-Palmer, Chicago, IL). As the optical chamber fluid level drained down to the baseline, the pump was turned off until the next surge of flow. Driven by the same motor, the two pump heads would move fluids to separate destinations at the same rate. Thus one head was used to deliver 92% of the solution that had been diverted from the donor dog into the small intestine of the recipient dog, while the other smaller head pumped 8% of the diverted solution into the collection tubes for later radioactivity counting (20).

Measurement of Gastric Emptying

The recovery of ^{99m}Tc -DTPA from the output of the duodenal fistula was used to calculate either the volume of the meal remaining in the stomach (*part 1*) or the volume entering the small intestine (*part 2*). After each solution was instilled into the stomach, the content emptying out of the stomach was sampled from the drainage of the duodenal fistula every 5 min for 30 min. One-milliliter aliquots of the test solution and duodenal samples were then counted in a well counter (Chicago Nuclear, Chicago, IL). All counts were corrected to *time 0*.

Fraction emptied = $(V_d \times C_d)/(V_o \times C_o)$, where V_d is the volume (in ml) emptied from the duodenal fistula, C_d is the concentration (in counts \cdot min $^{-1} \cdot$ ml $^{-1}$) of the radioactive marker in the duodenal output, V_o is the initial meal volume (in ml), and C_o is the concentration of the radioactive marker in the original solution. The cumulative fraction emptied equals the sum of the fraction emptied by that time. The cumulative volume emptied equals the cumulative fraction emptied multiplied by V_o .

The volume of the meal left in the stomach was then calculated as the difference between the original meal volume and the cumulative volume emptied into the duodenum (*part 1*). The cumulative volume entering the small intestine of the recipient dog was the cumulative volume emptied into the duodenum of the donor dog (*part 2*).

Myoelectrical Recordings

To obtain recordings of gastric myoelectrical activity from the antral electrodes, a ribbon cable was used to connect the electrical coupler of the dog to a physiograph (Beckman Instruments, Anaheim, CA), which was equipped with a chart recorder that was set for a paper speed of 1 mm/s. At this speed, the number of slow-wave cycles per 5 min (frequency of gastric PP) of each 30-min myoelectrical recording was easily counted by visual inspection. The recording for each experiment began at least 5 min before instillation of the test solution that occurred during phase II of interdigestive myoelectrical complex. For uniformity, one of us (H. C. Lin), blinded to the conditions of the experiment, counted all of the

recordings at the completion of the full experimental schedule. Before his reading, the recordings were grouped by dog and randomly mixed within each group. Readings were initially obtained in each dog (in the first 3 experiments analyzed) by determining the frequency of gastric PP in all three antral channels. Since the results of the three channels only confirmed one another, we completed the analysis by reading the distal-most antral channel (17). After the frequency of gastric PP was determined for each 5-min time period, this value was converted to cpm.

Statistical Analysis

Gastric emptying was represented as the volume of meal remaining in the stomach (*part 1*) or the volume entering the small intestine (*part 2*). Since these volumes varied smoothly over the 30-min recording period with similar shapes for each of the liquid meal volumes, analysis concentrated on comparing results at 5 min across the meal volumes (early response) and at 30 min across the meal volumes (late response). Results for each of these two outcomes were analyzed using repeated measures of analysis of variance (ANOVA; BMDP 2V) (11) in which the repeated measures factor was meal volume (5 levels in *part 1* and 4 levels in *part 2*). In each case, a planned linear contrast across meal volumes and contrasts directed at detecting evidence of nonlinearity were tested, since this provides more power for the hypothesis of interest than following a significant ANOVA with multiple-comparison *t*-tests.

The frequency of gastric PP was analyzed using a repeated measures ANOVA with two repeated measures factors, time and meal volume. For both *parts 1* and *2*, a planned linear contrast across times from 5 to 30 min, a planned linear contrast across meal volumes, and their interaction were tested; contrasts directed at detecting evidence of nonlinearity were also tested. In addition, since there was some crossover in time curves, separate analyses concentrated on comparing results at 5 min across the meal volumes (early response) and at 30 min across the meal volumes (late response). As for gastric emptying, results for each of these two time points were analyzed using a repeated measure ANOVA in which the repeated measures factor was meal volume, and a planned linear contrast across meal volumes and contrasts directed at detecting evidence of nonlinearity were tested.

RESULTS

Part 1. Distension of the Stomach

Gastric emptying: milliliters left in stomach. Gastric emptying of the liquid meals followed a time course that appeared exponential in shape (Fig. 2). At 5 min, the volume of the meal remaining in the stomach showed a linear increase with increasing initial volumes. Emptying was nearly complete by 30 min irrespective of the initial volume. In the first 5–10 min, the volume distension of the stomach was proportionally greater with meals of larger starting volumes.

Frequency of gastric PP. At 5 min, the frequency of gastric PP (in cpm) is lower for higher meal volumes, with a significant linear contrast across meal volumes ($P < 0.05$), whereas, at 30 min, significant differences between the meal volumes do not show a monotone tendency for higher volumes to have lower frequencies of gastric PP (Fig. 3). When the data from 5 to 30 min were all included in the same analysis, the frequency of

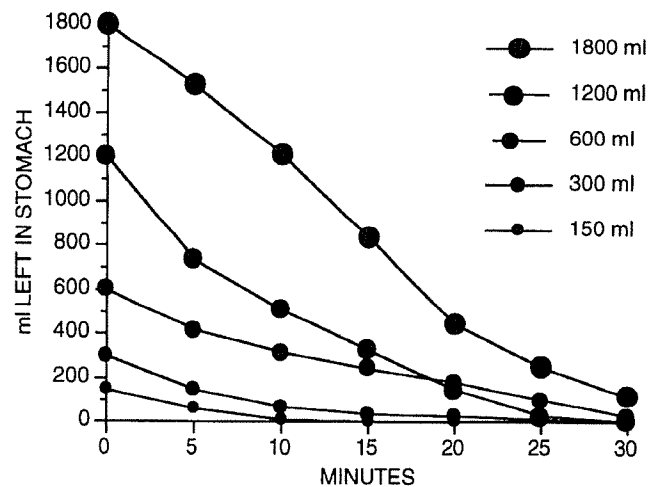


Fig. 2. *Part 1*: gastric emptying of 150- to 1,800-ml solutions as represented by volume remaining in stomach over 30 min (data are mean values, $n = 6$). SE values ranged from 5 for small volumes remaining to 160 for large volumes remaining.

gastric PP showed a significant linear trend toward lower average values for higher meal volumes ($P < 0.05$, ANOVA). An interaction of the linear time and linear volume components reflected a volume effect on the frequency of gastric PP in the early periods.

Part 2. Distension of Small Bowel

Gastric emptying: milliliters entering small bowel. As expected, we see a significant pattern of increase over time in the amount entering the small bowel. The amount at any given time depends on the initial meal volume (Fig. 4).

Frequency of gastric PP. When the data from 5 to 30 min were all included in the same analysis, slopes of frequency of gastric PP over time showed a significant difference between meal volumes ($P < 0.01$, ANOVA). Figure 5 shows that the steepest slope was seen for the 1,800-ml solution. Detailed examination of plots of the relationship between frequency of gastric PP and cumulative volume entering the small bowel showed a linear decline in frequency of gastric PP as the volume entering the small bowel increased from 352 ml at 5 min to 1,106 ml at 20 min and a leveling off beyond 1,106 ml.

When *part 1* of the study was compared with *part 2*, two major differences were apparent. 1) The maximal decline of the frequency of gastric PP was immediate with gastric distension (maximum reached by 5 min) but delayed with intestinal distension (maximum reached by 20 min). 2) The volume required to achieve the suppressive effect on the frequency of gastric PP was greater with intestinal than with gastric distension.

DISCUSSION

By isolating the distending effect of solutions of varying volumes to the stomach or the small bowel, we found that the frequency of gastric PP decreased linearly with increasing starting volumes. This study extended previous observations (17, 26) by showing

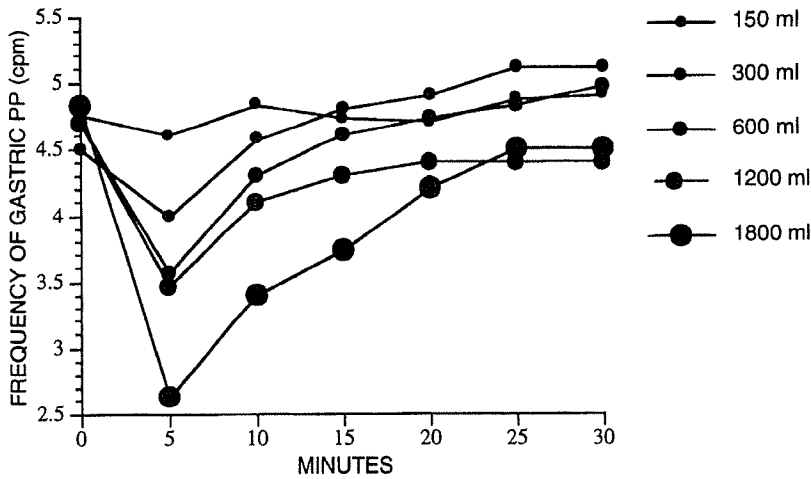


Fig. 3. Part 1: frequency of gastric pacesetter potential (PP) in cycles per minute (cpm) during gastric emptying of 150- to 1,800-ml solutions while distension was isolated to the stomach (data are mean values, $n = 6$). SE values ranged from 0.1 to 0.3.

that 1) the frequency of gastric PP is decreased by meal distension in a volume-dependent fashion, whether volume distension is isolated to the stomach or small bowel; 2) although maximal decline in the frequency of gastric PP occurred immediately when distension was isolated to the stomach, the effect was delayed (by ~20 min) when distension was isolated to the small bowel; and 3) the frequency of gastric PP decreased linearly with increased volume remaining in the stomach or increased volume entering the small intestine. Thus the frequency of gastric PP is determined by the rate of gastric emptying and the effect of emptying in shifting the site of volume distension from the stomach to the small bowel.

Volume distension by a meal is not constant. During the course of gastric emptying, distension of the stomach decreases as distension of the small bowel increases. Previously, using fixed volume balloon (17) or the ingestion of 250- to 350-ml liquid meals (13, 26) as the distending stimulus, only distension of the stomach was known to decrease the frequency of gastric PP. The relationship between the frequency of gastric PP and gastric emptying was, however, unknown. In this study, we were able to describe this relationship by separating the effect of gastric from intestinal distension using a fistulated dog model that allowed for the complete diversion of the gastric output. In single and paired

(donor and recipient) animal experiments, we were able to preserve the dynamic effects of gastric emptying on volume distension of the stomach and small bowel, respectively. Since this study was focused on the response to volume distension, we also eliminated the potential confounding effect of chemo-specific intestinal feedback (25) by using a nonnutrient solution as the distending volume. Specifically, a 300 mosM phosphate buffer (pH 7.0) was used to nullify the potential effect of inhibitory feedback generated by acidity (20), nutrient load (21), or osmolarity (22).

The normal frequency of gastric PP in dogs has been reported to range from 4.5 to 5.7 cpm (6, 24, 27). In this study, we showed that the frequency of gastric PP may vary widely depending on the magnitude of volume distension. Across the range of meal volumes commonly found in the postprandial stomach (e.g., volume of intake of 1–2 liters is common when an athlete drinks fluids after a workout, a college student binges on alcohol (33), or a diner eats a meal at a buffet), we found that the frequency of gastric PP ranged between 2.6 and 5.1 cpm over the 30-min recording period. In corroboration with earlier reports in dogs and humans when lower volumes were tested (17, 26), we found that the decrease in the frequency of gastric PP was 11% for the 300-ml meal and 23% for the 600-ml meal when distension was isolated to the stomach. However, we

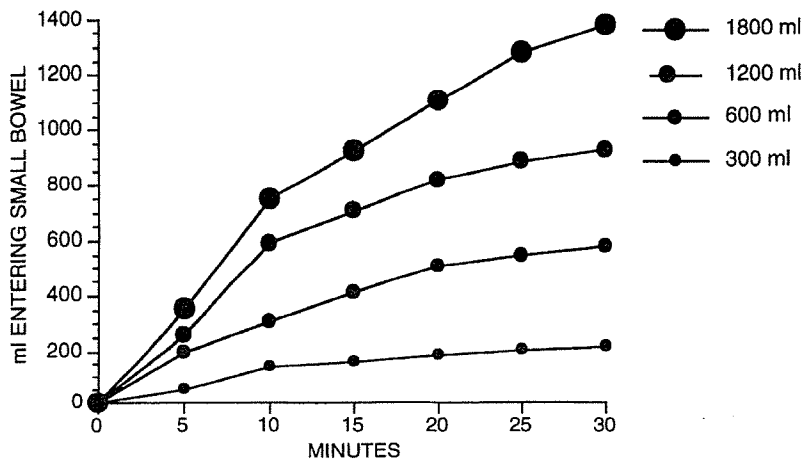


Fig. 4. Part 2: gastric emptying of 300- to 1,800-ml solutions as represented by volume entering small bowel of recipient dog over 30 min (data are mean values, $n = 6$). SE values ranged from 17 for small volumes to 150 for large volumes.

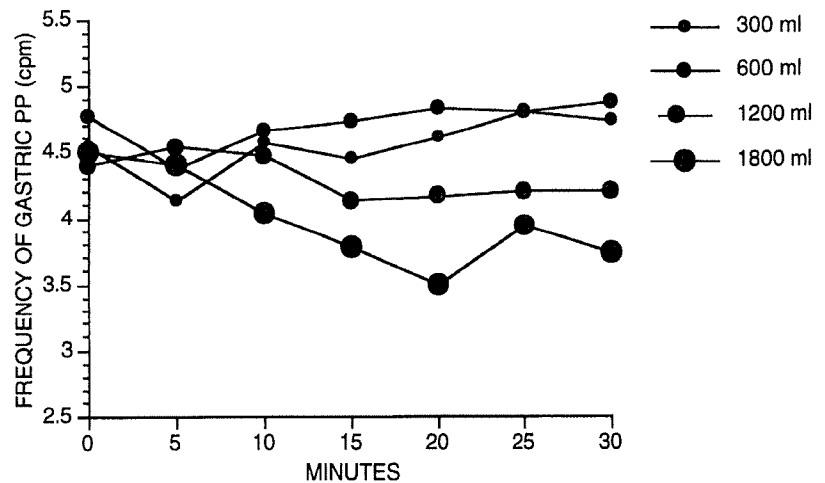


Fig. 5. Part 2: frequency of gastric PP (in cpm) of recipient dog during distension of small bowel (data are mean values, $n = 6$). SE values ranged from 0.1 to 0.4.

found that the potential range of the frequency response was much greater than reported, since the maximal frequency change for the 1,800 ml was 46% in the first 5 min.

The capacity of the dog stomach has been reported to be 100 ml/kg (for our dogs that averaged 25 kg, the capacity would be 2,500 ml) (12). The capacity of the stomach in humans and dogs is comparable. In humans, the capacity is 1,000–6,000 ml (32) and intragastric pressure increases significantly only after a volume of 1,600 ml has been reached (7). Thus distending the stomach by a volume of 1,800 ml is both physiologically and commonly encountered.

Gastric emptying of a nonnutrient-containing liquid solution follows first-order kinetics (23). Accordingly, the rate of gastric emptying of the buffer solution (pH 7.0) depended on the starting volume. This meal size-dependent acceleration of the rate of gastric emptying rapidly reduced gastric distension to minimal volumes by 30 min regardless of the initial volume (Fig. 2). Correspondingly, the frequency of gastric PP recovered by the end of each experiment to nearly baseline levels (Fig. 3) so that the frequency of gastric PP recovered to 4.5 cpm by 30 min even after the 1,800-ml solution.

The dynamics of gastric emptying also determined the volume of intestinal distension and its effect on the frequency of gastric PP. The rapid gastric emptying associated with the higher gastric distending volumes rapidly displaced large volumes from the stomach to the small bowel. Accordingly, when 1,106 ml had shifted to the small bowel by 20 min (Fig. 4), the frequency of gastric PP decreased from 4.5 to 3.5 cpm for the 1,800-ml experiment (Fig. 5).

The timing and magnitude of maximal suppression of the frequency of gastric PP depended on the site of distension. Although the stomach was distended maximally, immediately on the instillation of each solution, similar magnitude of distension for the small bowel required progressive accumulation of emptied volume over time. Correspondingly, the nadir of the frequency response was reached immediately when distension was isolated to the stomach but was delayed (by ~20 min) when distension was isolated to the small bowel. In contrast to volume distension of the stomach, higher

meal volumes were required to demonstrate a significant slowing effect of intestinal distension on the frequency of gastric PP. The weaker effect of intestinal volume distension may be related to the greater capacity of the small intestine. The sensitivity of the mechanoreceptive neural pathways in these two regions of the gut may also be important to the difference in the magnitude of the frequency response to volume distension (Fig. 3 and 5).

The frequency of gastric PP as recorded from the distal antrum directly mirrors the activity of the pacemaker of the stomach. Along the greater curvature, in the corpus of the stomach, cells with the highest intrinsic oscillator frequency dominate as the pacemaker of the organ and entrain the distal two-thirds of the stomach (31). Although the antrum lags slightly behind the pacemaker in the timing of its depolarization (to permit a proximal to distal pattern of depolarization), the frequency of the pacemaker potential, as recorded from the antrum, is the same as the firing frequency of the gastric pacemaker.

The response of the frequency of gastric PP to volume distension, as observed in this study, was likely the result of the triggering of a mechanoreceptive neural reflex (3, 10, 16, 28) to the gastric pacemaker. Afferent fibers sensitive to luminal distension (mechanoreceptors) are located in the mucosa, the muscularis, the serosa, and the mesentery of the entire gastrointestinal tract. These fibers are part of vagal (primarily from mucosa and muscularis) and splanchnic (from serosa and mesentery) pathways (14).

The mechanoreceptors located in the stomach and the duodenum have been well studied. In the stomach, these mechanoreceptors provide a monitoring function during filling of the stomach and are essential for the accommodation reflex (2) and for the coordination of the corpus and antrum (30). In the small intestine, these mechanoreceptors determine perception and reflex relaxation of the stomach (4).

By developing a response that is proportional to the magnitude of distension, these afferent pathways provide detailed information on meal volume so that the response is appropriate for the luminal content. The information is precise enough to regulate food intake

(29) and control effector responses such as volume-dependent inhibition of gastric motility (1, 8, 19). These inhibitory responses are primarily vagovagal in circuitry and are triggered by both gastrogastic (1) and intestinogastric reflexes (8, 19). Although the neural mechanism for the reflex response of the gastric PP to volume distension has not been studied, the linear response of the frequency of gastric PP to volume distension described in this study suggests the contribution of similar, highly precise reflex mechanisms.

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