The effect of gastric electrical stimulation on canine gastric slow waves

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Xing, Jinhong, Frederick Brody, Michael Rosen, J. D. Z. Chen, and Edy Soffer. The effect of gastric electrical stimulation on canine gastric slow waves. Am J Physiol Gastrointest Liver Physiol 284: G956–G962, 2003. First published February 12, 2003; 10.1152/ajpgi.00477.2002.—This study determined the most efficient parameters of low-frequency/long-pulse gastric electrical stimulation (GES) required to entrain gastric slow waves and also evaluated the effect of entrainment and high-frequency, short-pulse GES on gastric electrical activity (GEA). Nine dogs were fitted with stimulation wires along the greater curvature. Entrainment was observed in six or seven animals, with long-pulse GES at six cycles per minute (cpm), at various combinations of current and pulse width and was directly related to the energy delivered. Entrainment was observed in four to seven animals, with long-pulse GES at 12 cpm, and the maximal driven frequency was 6 cpm. Entrainment did not significantly increase the dominant power of GEA. High-frequency, short-pulse GES, using pulse trains of 14 Hz, 5 mA, and 330 μs, with 0.1 s on and 5 s off, and pulse trains of 40 Hz, 10 mA, and 330 μs, with 2 s on 3 s off, did not affect variables of GEA. We conclude that acute low-frequency GES but not high-frequency, short-pulse GES can entrain slow waves; the power of slow waves is not affected by either type of stimulation.

low-frequency, long-pulse gastric electrical stimulation; high-frequency, short-pulse gastric electrical stimulation

GASTRIC ELECTRICAL ACTIVITY (GEA) normally originates from the interstitial cells of Cajal, located in the proximal stomach, along the greater curvature, and propagates distally to the antrum. This rhythmic GEA, also known as gastric slow waves, controls the maximal frequency and direction of gastric contractions and coordinates gastric motor function. Impaired GEA (tachygastria, bradygastria, and dysrhythmias) may be present in gastroparesis and is associated with nausea and vomiting (17, 18), whereas normalization of gastric dysrhythmias is associated with relief of such symptoms (17).

Patients with refractory gastroparesis can be treated with gastric electrical stimulation (GES), a novel therapy incorporating an implantable stimulator that delivers electric current to the gastric muscle. Two types of GES have been tried: low-frequency, long-duration pulses (in ms) and trains of high-frequency, short-duration pulses (in μs). Studies in humans indicate that both patterns of GES, although different in nature, benefit patients with severe gastroparesis (1, 21, 23a, 30a). Low-frequency, long-pulse GES may improve symptoms through entrainment of gastric slow waves and regulation of gastric dysrhythmias, although symptomatic relief by this modality was observed in patients without dysrhythmia (21). Stimulation parameters required for entrainment of GEA by low-frequency, long-pulse GES were determined in patients with gastroparesis (20). Only limited data are available on the effect of high-frequency, short-pulse GES on regulation of GEA (10, 11, 22, 23). There are no data on the effect of GES at parameters investigated for obesity on variables of GEA.

The aims of the present study were 1) to determine the most efficient stimulation parameters of low-frequency, long-pulse GES that can entrain gastric slow waves; 2) to evaluate the effect of entrainment on the power of the GEA; 3) to evaluate the effect of high-frequency, short-pulse GES, currently in use for patients with gastroparesis and being investigated for the treatment of obesity, on GEA.

MATERIALS AND METHODS

Preparation of Animals

Nine healthy female mongrel dogs weighing 17–21 kg were anesthetized with intravenous infusion of thiopental sodium (20 mg/kg) and maintained with isoflurane (1–2%). Midline laparotomy was performed, and four pairs of temporary stimulation wires (A&E Medical) were implanted within the seromuscular layer of the anterior gastric wall along the greater curvature. The distance between the two electrodes in each pair was 1 cm, and the distance between two adjacent pairs was 4 cm, with the most distal pair 2 cm proximal to the pylorus (Fig. 1). The wires were brought out through the abdominal wall along the right trunk, properly labeled, and secured. During a 2-wk recovery period, all animals were trained to stand quietly in a Pavlov sling. The protocol was approved by The Cleveland Clinic Institutional Animal Care and Use Committee.

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Experimental Procedure

All experiments were conducted in the morning after an overnight fast on alert and conscious animals. Animals underwent low-frequency long-pulse GES, with various combinations of stimulation parameters (frequency, current intensity, and pulse width (PW)) to determine the most efficient parameters required to achieve entrainment of gastric slow waves. With the use of these parameters, the effect of entrainment on the power of GEA was also determined. In a separate set of experiments, high-frequency, short-pulse GES, using two sets of stimulation parameters, was applied to determine the effect on the frequency and power of GEA.

GES

The most proximal pair of electrodes (14 cm from the pylorus) was used for GES, whereas the other pairs were used for recording.

Low-frequency, long-pulse GES. Low-frequency, long-pulse GES was generated by a portable electrical stimulator (Neurocontrol, Cleveland, OH), with rectangular pulses with a width of 0–650 ms and current intensity of 1–6 mA. Two stimulation frequencies, 6 and 12 cycles per minute (cpm), were tested (Fig. 2A). The frequency of 6 cpm was 10–20% above the intrinsic frequency of the gastric slow waves in the dogs. This frequency was chosen because optimal entrainment of gastric slow waves is achieved at a stimulation frequency that is slightly higher than the intrinsic GEA in humans (20). The frequency of 12 cpm was used to test the effect of higher frequency on GEA variables. High-frequency pulse trains at 12 cpm are used in the treatment of gastroparesis.

After a 20-min baseline recording, a series of stimuli at 6 and 12 cpm, with amplitudes of 1, 2, 4, and 6 mA, was randomly delivered. At each current, the PW was gradually increased every 3 min until entrainment was achieved, and recording was then continued for 10 min. The 3-min increments were used because entrainment of GEA occurred within this period of time. Stimulation was discontinued for 3 min between successive sessions. The 3-min interval was sufficient, because intrinsic slow waves resumed within <1 min after cessation of GES.

High-frequency, short-pulse GES. High-frequency, short-pulse trains were generated by an implantable Irel-III pulse generator (Medtronic, Minneapolis, MN). Two sets of stimulation parameters were tested on separate days: 1) pulse trains of 14 Hz, 4 mA, and 330 μs with 0.1 s on and 5 s off (Fig. 2B), currently used in the management of patients with gastroparesis; and 2) pulse trains of 40 Hz, 10 mA, and 330 μs with 2 s on 3 s off (Fig. 2C). GES using these parameters is currently being investigated as a potential treatment for obesity, with electrodes implanted along the greater curvature (3). In both conditions, a baseline recording of 30 min was obtained and compared with a subsequent period of GES given for 30 min.

Recording of GEA

GEA was recorded using a multichannel recorder (Biopac Systems, Santa Barbara, CA). All signals were displayed on a computer monitor and saved on a hard disk by an HP Pentium III PC. The low and high cutoff
frequencies of the amplifier were 0.05 and 35 Hz, respectively, and the sampling frequency was 20 Hz. The recordings were then low-pass filtered with a frequency of 1 Hz and resampled at a frequency of 24 Hz to reduce the volume of data and potential artifacts before the final review.

Analysis of GEA

All tracings were subjected to visual inspection. GEA was considered entrained when it was phase-locked at a fixed ratio with electrical stimulus after the initiation of GES. Complete entrainment was defined as entrainment during which the intrinsic frequency of gastric myoelectrical activity was driven to the same frequency of the external electrical stimulus (20).

The dominant frequency (DF) and dominant power (DP) of gastric myoelectrical activity were determined by spectral analysis of gastric slow waves using a validated computer software (4). The power corresponding to the DF in the power spectrum was defined as DP. The percentage of power (%power) of GEA within the frequency of 4–6 cpm (normal range in dogs) was calculated for sessions of high-frequency, short-pulse GES. To avoid stimulation artifacts, only the most distal channel was selected for spectral analysis.

Gastric slow-wave coupling was visually inspected. It was considered coupled when gastric slow waves, originated from the proximal stomach, propagated distally and were recorded at different recording sites along the greater curvature with persistently similar time shift. If entrained, the time during which the slow waves propagated from one proximal site to the immediate distal one (P2 to P3, and P3 to D1; Fig. 1) was manually estimated (peak to peak), and the corresponding conduction velocity of slow waves was calculated by dividing the distance of the pairs with the propagation time (cm/s). The analysis was performed only on the recordings at baseline and during 6-cpm GES. The data with 12-cpm GES were not analyzed, because stimulation at 12 cpm yielded more stimulation artifacts in the tracings, making it difficult to accurately identify the peaks of the slow waves in some cases.

Statistical Analysis

For low-frequency, long-pulse GES, the PW required for entrainment and DP (dB) of the entrained gastric slow waves were determined. Values of DP at various sessions and PW required for entrainment were analyzed with ANOVA; the conduction velocity of the gastric slow waves with entrainment was compared with baseline using a paired t-test; for high-frequency, short-pulse GES, the DF, DP, and the %power of GEA within normal frequency range of 4–6 cpm were compared with those of baseline with paired t-test. All data were presented as means ± SE, P < 0.05 for significance.

RESULTS

Entrainment with Low-Frequency, Long-Pulse GES

The baseline intrinsic frequency of the slow waves was 5.1 ± 0.2 cpm, ranging from 4.5 to 5.5 cpm. During low-frequency, long-pulse GES, entrainment of gastric slow waves was observed in six of seven animals at 6 cpm and four of the seven animals at 12 cpm. In two animals, entrainment failed at 12 cpm but was achieved at 6 cpm. Entrainment could not be achieved in only one animal at both 6 and 12 cpm.

When entrainment could be achieved, it was induced within 1 min after initiation of stimulation. Of those entrained, the stimulation frequency of 6 cpm was 17.6 ± 4.2% (range 7.1–33.3%) higher than the baseline frequencies, whereas the 12 cpm was 132.3 ± 9.7% higher, with a range of 114.3–166.6%. Comparable values were observed in animals in which entrainment could not be achieved.

Entrainment at 6 cpm

Most animals could be fully entrained, at a 1:1 ratio, to 6 cpm (Fig. 3). The rate of entrainment was directly related to the energy delivered (Table 1). Pulse duration required for entrainment was inversely related to the current used, with durations required at 1 and 2 mA being significantly longer than those required at 6 mA (Table 1). Despite a sixfold reduction in current intensity, entrainment could be achieved by just a twofold increase in pulse duration, suggesting that pulse duration is the dominant factor in determining entrainment. Once entrainment was achieved, it persisted during the 10-min stimulation sessions with currents from 1 to 6 mA. Entrainment of gastric slow waves at 6 cpm did not significantly increase the DP of gastric myoelectrical activity (Table 1).

Slow-wave coupling was consistently observed in all animals at baseline and during GES (entrainment). Entrainment of slow waves did not significantly affect the conduction velocity of slow waves. From P2 to P3, the conduction velocity was changed from 0.80 ± 0.10 cm/s of control to 0.96 ± 0.10 cm/s (n = 6; P = 0.51); from P3 to D1, the conduction velocity was slightly increased from control 2.5 ± 0.6 to 3.0 ± 0.6 cm/s with entrainment (n = 6; P = 0.077).

Entrainment at 12 cpm

Entrainment with stimulation at 12 cpm was less successful compared with 6 cpm. Fewer animals showed a clear 2:1 fixed ratio of external to internal frequency (Fig. 4). Intrinsic frequency could not be driven above 6 cpm, or 50% that of the external stimulus. Entrainment of gastric slow waves at 12 cpm did not significantly increase the DP of gastric myoelectrical activity (Table 2).

High-Frequency, Short-Pulse GES and GEA

High-frequency, short-pulse GES, using pulse trains of 14 Hz, 4 mA, and 330 µs with 0.1 s on and 5 s off and pulse trains of 40 Hz, 10 mA, and 330 µs with 2 s on 3 s off did not affect gastric slow-wave frequency. DF, DP, and %power were not significantly affected by either pattern (Table 3).

DISCUSSION

A number of studies has shown that intrinsic gastric slow waves can be paced (entrained) when an external electric stimulus at a slightly higher frequency is applied (2, 9, 20, 21, 27). When the stimulus is applied to the proximal stomach, the entrained electrical activity normally propagates distally, in the normal direction. The ability of GES to entrain the slow-wave activity is...
largely dependent on stimulation parameters including the frequency, amplitude, and width of the stimulus (9, 20, 27).

Controlling and regulating GEA for therapeutic purposes is an attractive concept. Abnormal GEA is frequently observed in gastroparesis, both diabetic and idiopathic (7, 17, 25). Experimentally generated tachygastria or bradygastria, evoked by circular vection, develops 1–2 min before the initial report of nausea (28, 34), and both symptoms and gastric dysrhythmia can be suppressed by anticholinergic agents such as atropine and scopolamine (13, 31). Because gastric slow waves determine the frequency and direction of gastric contractions, it is assumed that abnormalities in gastric contractile activity and emptying may be related, in part, to abnormal gastric electrical rhythm. Furthermore, nausea and vomiting, common in gastroparesis, are also common in other conditions associated with abnormal GEA such as motion sickness and pregnancy (14, 16). Thus regulation of abnormal GEA may potentially improve gastric emptying and symptoms in gastroparesis. Indeed, in a canine model of gastroparesis induced by truncal vagotomy and an injection of glucagon, gastric emptying was improved during application of a pacing stimulus that entrained GEA (2). A recent open-labeled study in patients with refractory gastroparesis showed that low-frequency, long-duration GES (4 mA, 300 ms, and frequency 10% higher than intrinsic frequency of gastric slow waves) entrained GEA and significantly improved gastric emptying of solids and gastroparetic symptoms (21).

Table 1. Entrainment of gastric slow waves with long-pulse GES at 6 cpm and its effect on DP

<table>
<thead>
<tr>
<th>Animals</th>
<th>Entrained to 6 cpm</th>
<th>Time to Entrain, min</th>
<th>Pulse Width, ms</th>
<th>DP, dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mA</td>
<td>4/7</td>
<td>0.41 ± 0.05</td>
<td>157.5 ± 7.5</td>
<td>4.7 ± 1.1</td>
</tr>
<tr>
<td>2 mA</td>
<td>5/7</td>
<td>0.56 ± 0.2</td>
<td>130.0 ± 11.3</td>
<td>6.9 ± 1.3</td>
</tr>
<tr>
<td>4 mA</td>
<td>5/7</td>
<td>0.36 ± 0.06</td>
<td>94.8 ± 10.8*</td>
<td>5.6 ± 1.7</td>
</tr>
<tr>
<td>6 mA</td>
<td>6/7</td>
<td>0.39 ± 0.11</td>
<td>76.8 ± 6.0*</td>
<td>6.5 ± 1.7</td>
</tr>
</tbody>
</table>

Values in parenthesis refer to the range of time from beginning of gastric electrical stimulation (GES) to entrainment. ANOVA. *P < 0.05, pulse width compared with that of 1 mA. Dominant power (DP) at entrainment was not significantly different from that at baseline, which was 6.6 ± 1.6 dB, cpm, cycles/min.
to be 300 ms, 4 mA at a frequency of 10% higher than the intrinsic slow-wave activity (20). The studies cited indicate that optimal frequency for entrainment should be slightly above the frequency of the intrinsic slow wave. For this reason, we chose to apply a stimulus with a frequency of 6 cpm, which was slightly higher than the frequency of GEA measured in the dogs. We were, however, interested to study a wide range of combinations of current and PW to determine the most efficient values of such variables required for entrainment. We found an inverse relationship between current and PW required for entrainment, which could be achieved with as low a current as 1 mA, given an appropriate increase in PW duration. It thus appears that pulse duration may be the dominant factor, because small increases in pulse duration can compensate for a substantial reduction in the current needed for entrainment. These findings may be of clinical relevance, because pulse parameters can be individualized if low-frequency, high-energy GES will be used in the treatment of gastroparesis.

Comparable with other studies (20, 24, 27), we found that GEA cannot be driven to frequencies much higher than the intrinsic frequency. Sarna and Daniel (27) showed in a canine model that the intrinsic frequency could be driven to a maximum of 7.4 cpm, which was ~42.3% higher than that of the basal intrinsic one. In a study of patients with gastroparesis, Lin et al. (20) found that the maximum driven frequency of the GEA was 4.3 cpm, although GES at a frequency of up to four times the normal intrinsic frequency in humans was applied. Similarly, we found that application of GES at a frequency of 12 cpm could entrain GEA but could not drive the intrinsic frequency to a higher frequency. These data suggest that the frequency of the external stimulus required for entrainment, unlike other variables, has a narrow range of values.

In contrast to low-frequency long pulses, we found that high-frequency, short-duration pulses given at trains with a frequency of 12 cpm did not affect the frequency of gastric slow waves. In this type of stimulation, we were able to entrain GEA at a 2:1 ratio to 6 cpm with a frequency of 6 cpm, which was 17.6% (7.1–33.3%) higher than intrinsic frequency in our animal group. These data suggest that the frequency of the external stimulus required for entrainment, unlike other variables, has a narrow range of values.

Table 2. Entrainment of gastric slow waves with long-pulse GES at 12 cpm and its effect on DP

<table>
<thead>
<tr>
<th>Animals Entrained to 6 cpm</th>
<th>Time to Entrain, min</th>
<th>Pulse Width, ms</th>
<th>DP, dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mA</td>
<td>4/7</td>
<td>0.38 ± 0.13</td>
<td>209.3 ± 56.7</td>
</tr>
<tr>
<td>4 mA</td>
<td>2/7</td>
<td>0.46 ± 0.29</td>
<td>137.7 ± 43.1</td>
</tr>
<tr>
<td>6 mA</td>
<td>3/7</td>
<td>0.67 ± 0.16</td>
<td>100.0 ± 39.0</td>
</tr>
</tbody>
</table>

Values in parenthesis refer to the range of time from beginning of GES to entrainment. ANOVA. DP at entrainment was not significantly different from that at baseline, which was 6.6 ± 1.6 dB. Pulse widths required for entrainment were not significantly different.

Table 3. Effect of high-frequency, short-pulse GES on variables of gastric electrical activity

<table>
<thead>
<tr>
<th>GES-1 (n = 5)</th>
<th>GES-2 (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GES-1 (n = 5)</td>
<td>GES-2 (n = 8)</td>
</tr>
<tr>
<td>Baseline</td>
<td>GES</td>
</tr>
<tr>
<td>Baseline</td>
<td>GES</td>
</tr>
<tr>
<td>Baseline</td>
<td>GES</td>
</tr>
<tr>
<td>DF, cpm</td>
<td>5.3 ± 0.3</td>
</tr>
<tr>
<td>DF, dB</td>
<td>9.0 ± 2.2</td>
</tr>
<tr>
<td>Power, %</td>
<td>13.6 ± 2.4</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of dogs. GES-1 parameters used for gastroparesis (trains of 14 Hz, 4 mA, and 330 μs with 0.1 s on and 5 s off); GES-2 parameters used for weight control (trains of 40 Hz, 10 mA, 330 μs with 2 s on 3 s off). Paired t-test. Variables with GES were not significantly different from control.
luation, individual pulses are delivered at a Hertz frequency with duration in microseconds, which is ~1,000 times shorter than the duration used in low-frequency GES (in ms). Because the energy delivered by the stimulus is directly related to its duration, high-frequency GES is also referred to as low-energy stimulation. Our results suggest that high energy is indeed required to control the elements that regulate GEA, and that can be achieved by low-frequency, long-pulse GES.

The amplitude of GEA (or the power at the DF) increases following a meal (5). This effect is likely to reflect increased contractility of the stomach (6) rather than gastric displacement by food, because data in humans showed that postprandial changes in electrogastrogram (EGG) correlate with serosal recording (19). A reduction in or absence of the expected postprandial increase in the EGG power correlates with delayed gastric emptying and antral hypomotility (7, 8). The DP of GEA was not affected by either type of GES we used, suggesting these types of GES may not be able to induce or enhance gastric muscle contractions.

These data raise the question on the mechanisms of action of GES currently in use for the treatment of gastroparesis. Previous open-label clinical studies have shown that treatment of patients with gastroparesis using high-frequency, short-pulse GES provides substantial relief of symptoms of nausea and vomiting (1, 23a, 30a). The presumed mechanisms responsible for the beneficial effect of this type of GES were thought to be through the regulation of GEA and improved gastric emptying. However, currently there are no solid data supporting this assumption. In a small number of patients studied within 1 wk after surgical implantation, high-frequency, short-pulse GES did not significantly improve gastric dysrhythmias or affect the frequency of serosal GEA (22), although an increase in DP was observed with surface EGG (23). The results of our study suggest that entrainment of GEA cannot be achieved with high-frequency, short-pulse GES currently in clinical use. It has also been shown that this type of GES does not enhance the gastric emptying of solids (23a). Consequently, other mechanisms may be responsible for the symptomatic relief observed with this therapy.

It has been postulated that this type of GES may act on afferent pathways, resulting in modulation of central control mechanisms for nausea and vomiting. However, there are no data to support this view as of now. Another possible explanation is that GES may enhance gastric accommodation in response to food. Patients with diabetic gastroparesis often have impaired gastric relaxation in response to balloon distension or a meal (26, 32), which is thought to contribute to their symptoms. Restoring gastric accommodation can significantly improve meal-induced satiety in patients with functional dyspepsia (30). In fact, short-pulse GES in patients with gastroparesis enhanced gastric accommodation to meal and balloon distension (29). In the same study (29), the authors also found that this type of stimulation reduced pain perception induced by balloon distension. Interestingly, low-frequency, long-duration GES was also found to induce gastric relaxation in dogs (33). Thus it appears that GES of different types can induce gastric relaxation. The effect is likely induced by local gastric mechanisms, because we observed no increase in pancreatic polypeptide, the indicator of vagal cholinergic activity, in response to GES at low or high frequency (unpublished data).

In conclusion, we found that entrainment of gastric slow waves can be achieved with low-frequency, long-pulse, high-energy GES. Our data on the various pulse width and current amplitude required for effective entrainment may be of importance in the development of alternative types of GES. Acute application of high-frequency, short-pulse GES does not affect slow-wave frequency. The power of the GEA signal is not affected by either type of stimulation. The mechanisms by which long-pulse and short-pulse GES benefit patients with gastroparesis are not fully understood and warrant further investigation.

REFERENCES


