Therapeutic Potential of Synchronized Gastric Electrical Stimulation for Gastroparesis: Enhanced Gastric Motility in Dogs

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Short running head: Synchronized GES enhances gastric motility

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Abstract

The aim of this study was to determine the effects and mechanism of synchronized gastric electrical stimulation (SGES) on gastric contractions and gastric emptying. **Methods:** The first experiment was designed to study the effects of SGES on antral contractions in 4 randomized sessions. Sessions 1 (control) and 2 (atropine,) were performed in the fasting state, composed of three 30-min periods (baseline, stimulation and recovery). Sessions 3 (control) and 4 (SGES performed during 2nd 20-min period) were performed in the fed state, consisting of two 20-min periods; glucagon was injected after the first 20 min recording. The 2nd experiment was designed to study the effect of SGES on gastric emptying and consisted of two sessions (control and SGES). SGES was delivered with train duration of 0.5-0.8s, and a pulse frequency of 40Hz, width of 2ms and amplitude of 4mA. **Results:** 1) SGES induced gastric antral contractions in the fasting state. The motility index was $1.3 \pm 0.5$ at baseline and $6.1 \pm 0.7$ ($P=0.001$) during SGES. This excitatory effect was completely blocked by atropine. 2) SGES enhanced postprandial antral contractions impaired by glucagon. 3) SGES significantly accelerated glucagon-induced delayed gastric emptying. Gastric emptying was $25.5 \pm 11.3\%$ without SGES and $38.3 \pm 10.7\%$ with SGES ($P=0.006$ vs. control). **Conclusions:** This novel method of SGES induces gastric antral contractions in the fasting state, enhances glucagon-induced antral hypomotility in the fed state and accelerates glucagon-induced delayed gastric emptying. The effect of synchronized GES on antral contractions is mediated via the cholinergic pathway.

**KEY WORDS:** Gastric electrical stimulation; gastroparesis; gastric emptying; gastrointestinal motility.
Introduction

Gastroparesis is defined as delayed emptying of solids from the stomach and is reported in 30% to 50% of patients with type I or type II diabetes (15, 16, 37). Common symptoms of gastroparesis include nausea, vomiting, early satiety and abdominal bloating. Treatment options for gastroparesis are limited. These include medical therapy, surgical therapy and nutritional support. Surgical procedures, such as gastrectomy and antrectomy, are the last options of treatment since they involve the removal of all or part of the stomach.

Recently, the therapeutic potential of gastric electrical stimulation (GES) for gastroparesis has been explored (2, 5, 9, 10, 12, 13, 19-21, 23, 30, 33). GES is performed via a pair of electrodes implanted on the serosal surface of the stomach. According to its stimuli, GES can be classified into long pulse stimulation and short pulse stimulation. Long pulse GES is usually performed at a frequency slightly higher than the physiological frequency of the gastric slow wave and has been shown to normalize gastric dysrhythmias with limited effects on symptoms (23). Short pulse GES is delivered at a frequency several times higher than the physiological frequency of the gastric slow wave and has been reported to improve nausea and vomiting in patients with gastroparesis with limited or no effect on gastric motility (2, 19, 33). However, there has been no concrete data suggesting the induction or enhancement of gastric contractions with either method of GES.

When GES is performed, two electrical events occur in the stomach: an artificial electrical stimulus and the intrinsic physiological electrical activity. With the existing methods of GES, there is not a perfect match between these two electrical events. The electrical stimulus is delivered at a frequency slightly higher or much higher than the intrinsic electrical activity (2, 19, 23, 33). In this study, we proposed a novel method of GES: synchronization of GES with the intrinsic gastric slow waves. The electrical stimulus is applied only upon the detection (occurrence) of the peak of each intrinsic electrical event (or slow wave). Since each gastric slow wave represents the depolarization of gastric smooth muscles, electrical stimulation performed upon the occurrence of the slow waves is expected to enhance the depolarization process and possibly induce or enhance gastric contractions and accelerate gastric emptying.

The principal objectives of this study were, therefore, to study the effect of gastric electrical stimulation synchronized with intrinsic gastric slow waves on gastric contractions and gastric emptying in dogs and to investigate the underlying mechanism of these actions.
Methods

Animal preparation

Thirteen healthy female hound dogs (15-22 kg) were involved in this study. After an overnight fast, anesthesia was induced in each dog with Pentothal (sodium thiopental 11mg/kg, intravenous; Abbott Laboratories, North Chicago, IL, USA) and maintained on 2%-4% IsoFlo (Abbott Laboratories, North Chicago, IL, USA) in Oxygen (1L/min) carrier gases delivered from a ventilator after endotracheal intubation. A gastric cannula was placed on the anterior side of the stomach, approximately 10 cm proximal to the pylorus, for the assessment of gastric contractions in 8 dogs. In 5 dogs, a duodenal cannula was placed in the duodenum, 20 cm beyond the pylorus, for the assessment of gastric emptying. Three pairs of 28-gauge stainless steel cardiac pacing wires (A&E Medical, Farmingdale, New Jersey) were implanted on the serosal surface along the greater curvature at an interval of 4 cm with the distal pair 2 cm proximal to the pylorus. The two electrodes in each pair were 1 cm apart. The electrode wires were tunneled through the anterior abdominal wall subcutaneously along the right side of the trunk, and placed outside the skin around the right hypochondrium for attachment to the recording or stimulation equipment. After surgery, each dog was transferred to a recovery cage. All studies were initiated after the dogs had completely recovered, usually 2 weeks after surgery.

Experimental protocol

The study is composed of two experiments. The first experiment was designed to investigate the effect of SGES on antral contractions in the fasting and fed states and performed in 4 sessions in eight dogs implanted with 3 pairs of gastric serosal electrodes and a gastric cannula. The order to perform these four sessions was randomized. Sessions 1 and 2 were performed in the fasting state and recording of gastric motility was initiated during Phase I of the migrating motor complex. Session one was composed of three 30-min periods (baseline, stimulation and recovery). Session two was the same as session one except atropine (0.02mg/kg) was injected after the 30-min baseline recording and GES was initiated 20 minutes after the injection of atropine. The dose of atropine was believed to be sufficient to block the cholinergic pathway. Tests before the initiation of this formal study showed that atropine at this dosage did not induce gastric dysrhythmia. Sessions 3 and 4 were performed in the fed state, consisting of two 20-min periods. Glucagon
(0.1mg/kg) was injected after the first 20 min recording in both sessions. No SGES was performed in session 3 and SGES was performed in session 4 after first 20 minute recording. Antral contractions were measured using a manometric catheter with four side holes via the gastric cannula. Four channels of signals were recorded simultaneously. The channel with best signal was used to calculate motility index. Glucagon was chosen because it is known to induce hyperglycemia, a clinical condition often seen in patients with diabetes. The dosage of glucagon was determined based on preliminary experiments in a few dogs: it inhibited antral contractions but did not induce gastric dysrhythmia.

The 2nd experiment was designed to study the effect of SGES on gastric emptying and consisted of two sessions (control and SGES). It was performed in 5 dogs with a chronic duodenal cannula and gastric serosal electrodes. The number of the animals was determined based on power analysis and previous data on gastric emptying in dogs. Each dog was given glucagon IV (0.1mg/kg) and immediately fed with a 237ml liquid meal mixed with phenol red. Gastric emptying was monitored for 90 min by collecting chyme from the duodenal cannula every 15 minutes (35). Gastric slow waves were recorded from all three pairs of electrodes at baseline and from the two most distal pairs of electrodes during stimulation and recovery. Gastric electrical stimulation was performed via the most proximal pair of electrodes using trains of pulses with train duration of 0.5-0.8s, and a pulse frequency of 40Hz, width of 2ms and amplitude of 4mA. The selection of these parameters was based on our previous studies in which non-synchronized GES was found capable of altering gastric tone.

**Measurement and analysis of intrinsic gastric slow waves**

A multi-channel recorder (Acqknowledge, EOG 100A, Biopac Systems, Inc. Santa Barbara, CA) was used to record gastric slow waves throughout the study. All signals were displayed on a computer monitor and saved on the computer’s hard disk. The low and high cutoff frequencies of the amplifiers were 0.05Hz and 35Hz, respectively. The signals were initially sampled at a frequency of 100Hz and then down-sampled to 2Hz after low pass filtering with a cut-off frequency of 1 Hz.

Spectral analysis was performed to derive the following parameters related to gastric slow waves:

- **Dominant frequency and power of the slow wave:** The frequency at which the power spectrum of an entire 30-min recording had a peak power was defined as the dominant frequency.
The power at the dominant frequency in the power spectrum was defined as the EGG dominant power. These two parameters were calculated by using the smooth-power spectral analysis method (6). Decibel (dB) units were used to represent the power of the gastric slow wave.

**Percentage of normal gastric slow waves:** The percentage of normal gastric slow waves was defined as the percentage of time during which regular 4 to 6 cpm (cycles/min) slow waves were present over the entire recording period. It was computed by using the adaptive spectral analysis method. In this method, each recording was divided into blocks of 1 min without overlap. The power spectrum of each 1-min recording was calculated and examined to see if the peak power was within the range of 4-6 cpm. The 1-min recording was categorized as normal if the peak power was within the 4-6 cpm range; otherwise it was categorized as dysrhythmia. The selection of the normal frequency range of 4-6 cpm in the stomach was based on the analysis of gastric slow waves measured from the serosal electrodes at baseline.

**GES synchronized with gastric intrinsic slow waves**

Three pairs of electrodes were implanted on the serosal surface along the greater curvature at an interval of 4 cm in each dog. Slow waves from these three channels were recorded during the baseline period. The phase-shift between the proximal channel and middle channel was calculated. During the synchronized GES period, the proximal channel was used as the stimulation channel. The middle and the distal channels were used as the recording channels. The stimuli were delivered based on the slow wave recorded from the middle channel after adjustment of phase-shift between the proximal channel and middle channel.

**Measurement and analysis of antral motility**

Antral contractile activity was recorded from four pressure sensors (1cm apart) of the manometric catheter. The recording was made via a PC polygraf HR system (Synectics Medical, Stockholm, Sweden) and a microcapillary infusion system (Medtronic Synectics, Stockholm, Sweden). The catheter was inserted into the distal antrum via the gastric cannula. All recordings were displayed on a computer monitor. A parameter, called the motility index, was used to represent the contractile strength of the distal stomach (38). It was defined as the total number of contractions times the average amplitude of contractions within each recording period. The data presented in this study was obtained from channel 3 which showed the highest quality of the recording. Propagation of antral contractions was evaluated among all four channels.
Measurement and analysis of gastric emptying

Gastric emptying was assessed using a validated method in our lab (28, 32, 36). The liquid test meal (a can of Ensure, 237ml, 225Kcal) was evenly mixed with 100mg of phenol red, and gastric emptying was determined by the assessment of the amount of phenol red in each collection obtained from the duodenal cannula. For each collection of the gastric effluent (every 15 minutes for a total of 90 minutes), the volume was recorded and a sample of 5ml was taken and stored in a freezer. The samples were analyzed all together at the end of the study using a spectrophotometer. Gastric emptying was assessed by computing the amount of phenol red recovered from each collection of the gastric effluent.

Statistical Analysis

The data are expressed as mean ± SE. The Student’s t-test was used to compare the differences between two parameters. P values < 0.05 were considered statistically significant.

Results

Intrinsic gastric slow waves

Normal gastric slow waves were recorded at the baseline in both control and atropine sessions. The mean frequency of the gastric slow waves was 5.39±0.10 cycles/min and the percentage of normal 4-6 cpm slow waves was 94.5±1.5%. A typical tracing is shown in Figure 1. The injection of atropine at the given dose did not alter gastric slow waves. The mean frequency of the gastric slow waves was 5.41 ± 0.07 cycles/min (P = 0.8 vs. baseline) and the percentage of normal slow wave was 92.4 ± 0.8% (P = 0.3 vs. baseline) after injection of atropine.

Synchronized GES had excitatory effects on gastric antral contractions in fasting state.

Gastric electrical stimulation synchronized with gastric slow waves significantly induced or enhanced gastric antral contractions. The motility index was 1.3±0.5 at baseline and 6.1±0.7 (P=0.001) during SGES. The number of contractions per minute was 1.49±0.55 at baseline, 2.55±0.34 (P=0.002 vs. baseline) with synchronized GES and 2.18±0.35 during recovery period. The average amplitude of contractions was 36.7±8.1mmHg at baseline, 65.0±10.3mmHg (P=0.06 vs. baseline) with synchronized GES and 58.9±10.2mmHg during recovery period. More than
50% of contractions induced by synchronized GES were propagated from the proximal antrum to the distal antrum; some of the contractions were not propagated; retrograde propagation was not noted. Figure 2 presents antral contractions at baseline (2a) and synchronized GES-induced propagated (2b) and non-propagated (2c) contractions in the fasting state. Figure 2b indicates that synchronized GES induced contractions not only in the proximal antrum and but also in the distal antrum, i.e., the synchronized GES-induced contractions were capable of propagating all way to the most distal channel. In some cases, however, synchronized GES was only able to induce local contractions and the contractions were not able to propagate to the distal end of the stomach as shown in Figure 2c.

**Synchronized GES enhanced postprandial antral contractions impaired by glucagon**

In the control session, the motility index was 9.9±1.8 at baseline and reduced to 1.6±0.4 (P=0.004) after glucagon. However, the corresponding motility index after glucagon in the SGES session was increased to 4.7±0.5 (P=0.001 vs. control) (See Fig. 3).

**Synchronized GES significantly accelerated glucagon-delayed gastric emptying**

Typically, gastric emptying is more than 60% at 90 min in dogs. After glucagon, gastric emptying at 90 min was decreased to 25.5±11.3%. A 50% improvement in gastric emptying was noted with SGES. Gastric emptying was increased to 38.3±10.7% with SGES (P=0.006 vs. control).

**Involvement of cholinergic pathway**

Atropine completely blocked the excitatory effect of synchronized GES on antral contractions in the fasting state. The motility index was 1.1 ± 0.7 at baseline, 1.0±0.5 after injection of atropine, 1.6 ± 0.8 during stimulation (P=0.2 vs. baseline) and 2.0±0.9 in recovery period. See Fig.4

**Discussion**

In this study, we found that gastric electrical stimulation synchronized with intrinsic gastric slow waves induced gastric antral contractions in the fasting state, enhanced glucagon-induced antral hypomotility in the fed state, and accelerated glucagon-induced delayed gastric emptying; the effects of synchronized GES on antral contraction were blocked by injection of atropine.
Gastroparesis, also known as delayed gastric emptying, is a disorder in which the stomach takes too long to empty its contents. It is known that gastric motility is a critical physiological function of the human gut. Without coordinated motility, digestion and absorption of dietary nutrients cannot take place. To accomplish its functions effectively, the gut needs to generate not just simple contractions, but contractions that are coordinated in order to produce transit of luminal contents (peristalsis). Thus, coordinated gastric contractions are necessary for the emptying of the stomach.

Similar to the heart, there is electrical activity in the stomach. Gastric electrical activity consists of two components: slow waves and spike potentials (14). Slow waves are omnipresent and occur at regular intervals whether or not the stomach contracts. They originate in the proximal stomach and propagate distally toward the pylorus. The gastric slow wave determines the maximum frequency, propagation velocity, and propagation direction of gastric contractions. When spike potentials (similar to an action potential) are superimposed on the gastric slow wave, a strong lumen-occluded contraction occurs. The normal frequency of the gastric slow wave is about 3 cycles/min in humans and 5 cycles/min in dogs.

GES has been proposed for treating gastroparesis (1, 3, 4). Long pulse GES is capable of entraining (pacing) physiological electrical activity of the stomach in both animals and humans (7, 17, 18, 20, 24). Single channel GES with long pulses has no effects on gastric emptying in healthy dogs but is capable of improving gastric emptying in a canine model of gastroparesis and a rodent model of diabetes (5, 11, 22). Whereas, two or four-channel GES with long pulses is able to improve gastric emptying in both healthy and diseased model of canines (8, 32); similar results (improvement in liquid and solid gastric emptying) were also observed with multi-channel sequential GES of trains of pulses with pulse width in the order of a few ms (25, 26). In a non-controlled clinical study on 9 patients with gastroparesis, GES with long pulses has shown promising results with significant improvement in symptoms and marginal improvement in gastric emptying (23). The efficacy of short pulse GES was investigated in multi-center clinical studies with a substantial reduction in the frequency of nausea and vomiting but no consistent improvement in gastric emptying.

When GES is performed, there are two kinds of electrical events occurring in the stomach: an artificial electrical stimulus and the intrinsic physiological electrical activity. With the current
methods of GES, there is not a perfect match between these two electrical events. For short pulse GES, the frequency is 3 times higher and the energy is much lower than the intrinsic gastric electrical activity. Laboratory data showed that such stimulation has no effect on the intrinsic gastric electrical activity (17). For long pulse GES, the frequency is usually slightly higher than that of the intrinsic electrical activity and the applied electrical stimulus is not in phase with the intrinsic electrical event. That is, the stimuli are applied at random without considering the occurrence of the intrinsic electrical activity.

In this study, we used synchronized GES, in which, the electrical stimulus is applied only upon the detection (occurrence) of each intrinsic electrical event (or slow wave). Since each gastric slow wave represents the depolarization of gastric smooth muscles, the electrical stimulation performed upon the occurrence of the slow waves is expected to enhance the depolarization process and thus induce or enhance gastric contractions. This is similar to inducing a stronger vibration/oscillation in a target (such as a bridge) by stimulating it at its intrinsic frequency. Gastric electrical stimulation was performed via the most proximal pair of electrodes using trains of pulses with train duration of 0.5-0.8s, and a pulse frequency of 40Hz, width of 2ms and amplitude of 4mA. Our results showed that GES synchronized with gastric slow waves was able to induce or enhance antral contractions in the fasting state. The average number of contractions per minute increased significantly and the average amplitude of contractions increased marginally.

Glucagon consists of 29 amino acid residues and is released from A-cells of the pancreatic islets. Exogenously administered glucagon inhibits gastrointestinal motility in humans and dogs (27, 34). Glucagon inhibits the postprandial elevation of the serum gastrin concentration and thus inhibits postprandial antral motility (31). Because of this, glucagon is frequently used as a pharmacological agent to provide temporary inhibition of gastrointestinal movements. In our study, glucagon was used to inhibit gastric contractions and delay gastric emptying. It was found that GES synchronized with gastric slow waves was able to induce antral contractions after inhibition by glucagon and accelerate gastric emptying delayed by glucagon. That suggests that SGES maybe a good method to treat hypomotility and delayed gastric emptying for gastroparesis patients.
We also found that, like GES, the effects of synchronized GES on antral motility were mediated via the cholinergic pathway. Atropine, a competitive antagonist of acetylcholine and other muscarinic agonists, can effectively inhibit the effects of vagal impulses, thus decreasing gastric tone and motility. Our results show that the administration of atropine inhibited antral motility, and synchronized GES could not enhance antral contractions, indicating that the effect of synchronized GES on antral motility was mediated via the cholinergic pathway. This is similar to the effect of GES in rodents, where vagal afferent fibers are activated when antral contractions were induced with GES (29).

This study has presented an innovative method for the treatment of gastroparesis. In addition, a similar method may be applied to the small intestine to treat intestinal pseudo-obstruction and to the colon to treat patients with constipation. The implementation of this therapy is relatively easy and minimally invasive. It requires the implantation of 2 pairs of electrodes (one for the detection of gastric slow waves and the other for stimulation) and a subcutaneous stimulator. This can be achieved by a laparoscopic procedure. The safety of this procedure has already been proven by the Enterra Therapy (short pulse GES) in more than 100 patients (2, 33).

In conclusion, gastric electrical stimulation with trains of pulses synchronized with gastric intrinsic slow waves is able to induce gastric antral contractions and accelerate gastric emptying. This effect is mediated via the cholinergic pathway. This novel method of GES has a potential for the treatment for disorders with hypotensive gastric motility.

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Figure Legends

Fig. 1. A typical tracing of normal slow waves recorded from three channels.

Fig. 2. Manometric recordings at baseline and after SGES.
  a) Baseline tracing before stimulation in the fasting state (no contractions)
  b) SGES induced propagated contractions in the fasting state
  c) SGES induced non-propagated contractions in the fasting state

Fig. 3. Effect of synchronized GES on antral motility expressed in the fed state.
  A. Glucagon impaired postprandial antral contractions.
  B. Synchronized GES significantly increased glucagon-impaired antral motility.

Fig. 4. Manometric tracings showing the effects of synchronized GES on antral motility with and without administration of atropine in the fasting state.
  A. Synchronized GES induced antral motility
  B. Excitatory effect of synchronized GES on antral motility was abolished by administration of atropine
Fig. 1. A typical tracing of normal slow waves recorded from three channels.
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c) SGES induced non-propagated contractions in the fasting state
Fig. 3. Effect of synchronized GES on antral motility expressed in the fed state.

C. Glucagon impaired postprandial antral contractions.

D. Synchronized GES significantly increased glucagon-impaired antral motility.
Fig. 4. Manometric tracings showing the effects of synchronized GES on antral motility with and without administration of atropine in the fasting state.

C. Synchronized GES induced antral motility

D. Excitatory effect of synchronized GES on antral motility was abolished by administration of atropine