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BRIEF ARTICLES

Effect of two-channel gastric electrical stimulation with trains of pulses on gastric motility

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Abstract

AIM: To investigate the effect of two-channel gastric electrical stimulation (GES) with trains of pulses on gastric emptying and slow waves.

METHODS: Seven dogs implanted with four pairs of electrodes and equipped with a duodenal cannula were involved in this study. Two experiments were performed. The first experiment included a series of sessions in the fasting state with trains of short or long pulses, each lasted 10 min. A 5-min recording without pacing was made between two sessions. The second experiment was performed in three sessions (control, single-channel GES, and two-channel GES). The stimulus was applied *via* the 1st pair of electrodes for single-channel GES (GES *via* one pair of electrodes located at 14 cm above the pylorus), and simultaneously *via* the 1st and 3rd channels for two-channel GES (GES *via* two pairs of electrodes located at 6 and 14 cm above the pylorus). Gastric liquid emptying was collected every 15 min *via* the cannula for 90 min.

RESULTS: GES with trains of pulses at a pulse width of 4 ms or higher was able to entrain gastric slow waves. Two-channel GES was about 50% more efficient than single-channel GES in entraining gastric slow waves. Two-channel but not single-channel GES with trains of pulses was capable of accelerating gastric emptying in healthy dogs. Compared with the control session, two-channel GES significantly increased gastric emptying of liquids at 15 min (79.0% ± 6.4% *vs* 61.3% ± 6.1%, $P < 0.01$), 30 min (83.2% ± 6.3 % *vs* 68.2% ± 6.9%, $P < 0.01$), 60 min (86.9% ± 5.5 % *vs* 74.1% ± 5.9%, $P < 0.01$), and 90 min (91.0% ± 3.4% *vs* 76.5% ± 5.9%, $P < 0.01$).

CONCLUSION: Two-channel GES with trains of pulses accelerates gastric emptying in healthy dogs and may have a therapeutic potential for the treatment of gastric motility disorders.

Key words: Gastric electrical stimulation; Gastric slow waves; Gastric emptying; Gastrointestinal motility; Gastric pacing

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INTRODUCTION

Gastrointestinal functional or motor disorders are common, affecting 25% of the United State population[1,2] and 5%-10% of Asian population[3]. The patients often complain of a series of dyspeptic symptoms such as nausea and vomiting[4]. Gastric dysrhythmia has been observed in a variety of gastrointestinal motility disorders, including unexplained nausea and vomiting[4], gastroparesis[4,5], type Ⅱ diabetes[2,5], early pregnancy[6], gastroesophageal reflux disease[7], after vagotomy and surgery[8] or after bone marrow or stem cell transplant[9]. In these circumstances, the frequency of gastric slow wave becomes either abnormally high (tachygastria) or low (bradygastria). Gastric emptying is delayed in patients with gastroparesis and in about 30%-65% of patients with functional dyspepsia.

The commonly used medical therapy for gastroparesis is prokinetic agents, such as metoclopramide, cisapride, domperidom and erythromycin[10]. However, there are a considerable number of patients who are refractory to these medical therapeutic agents and side effects also limit their usage. While a number of studies have shown that some prokinetics have anti-dysrhythmic effects, but none of them has been developed for the normalization of gastric dysrhythmia[5,11].

Gastric electrical stimulation (GES) or pacing has been under investigation as a potential therapy for gastrointestinal motility disorders[12,13]. A number of studies have been performed to investigate the effect of gastric pacing, but the majority of them seem to indicate that gastric pacing is able to entrain gastric slow waves[14-20], accelerate gastric emptying in patients with gastroparesis[21,22] or in animal model of gastroparesis[18-20]. Three distinct methods have been used in GES, including long pulse stimulation, short pulse stimulation, and stimulation with trains of short or long pulses. In long-pulse stimulation, the pulse width is in the order of milli-seconds and the stimulation frequency is usually in the vicinity of the physiological frequency of gastric slow wave[23-25]. In short pulse stimulation, the pulse width is substantially shorter and is in the order of a few hundred micro-seconds. The stimulation frequency is usually a few times higher than the physiological frequency of gastric slow wave[12,26]. It has been reported that long-pulse stimulation can normalize gastric dysrhythmia, entrain the slow wave[13,17,25,27,28], accelerate gastric emptying in human beings and dogs, and short-pulse stimulation is effective against nausea and vomiting with no or little effect on gastric dysrhythmia, slow waves, or gastric emptying[18,26]. Trains of pulses are composed of a repetitious train of pulses and are derived from the combination of two signals: a continuous signal with a high frequency (in the order of 5-100 Hz) and a control signal to turn the pulses on and off, such as x seconds “on” and y seconds “off”. This kind of stimulation has been frequently used in electroacupuncture[29]. Most previous studies were performed using long- or short-pulse GES in patients and in animal model of gastroparesis. Commercially available implantable stimulators are capable of generating short pulses or trains of pulses but not long pulses that are technically difficult to produce. That is, long pulse GES is practically not feasible or much less feasible than GES of pulse trains and has to be replaced by GES with trains of pulses. Accordingly, it is important to study whether the GES with trains of pulses is able to mimic the functions of long pulse GES. However, to the best of our knowledge, few studies have investigated the effect of GES with trains of pulses on gastric motility, such as gastric slow waves and gastric emptying.

This study was to investigate the effect of GES with trains of pulses on gastric slow waves and gastric emptying in health dogs.

MATERIALS AND METHODS

Animal preparation

Seven healthy female beagle dogs, weighing 14-21 kg, were used in this study. After an overnight fasting, the dogs were anesthetized with 2% sodium thiopental (0.6 mL/kg, intravenous) and underwent abdominal surgery. Their tongue color, pulse rate and breath rate were monitored. Four pairs of stainless steel cardiac pacing wires were implanted on the serosal surface of stomach in an arching line along the greater curvature. The most distal pair was placed 2 cm above the pylorus, and the distance between adjacent pairs of electrodes was 4 cm. The bipolar electrodes in each pair were 0.5 cm apart. The electrodes were affixed to the gastric serosa with an unabsorbable suture in the seromuscular layer of stomach. The wires were brought out through the anterior abdominal wall, channeled subcutaneously along the left side of the trunk, and placed outside the skin for pacing or recording gastric myoelectric activity. Each dog was equipped with a duodenal cannula 20 cm beyond the pylorus for the assessment of gastric liquid emptying. The study was initiated after the dogs were completely recovered from surgery, usually 2 wk after surgery. The Animal Care and Use Committee of the Union Hospital of Tongji Medical College approved the surgical and experimental protocols.

Experimental protocol

The study was composed of two experiments using the following protocols. Experiment 1 was designed to assess the optimal stimulation parameters (lowest stimulation energy) to entrain gastric slow waves in the dogs. The dogs were fasted overnight and received no medication before the study. A 30-min baseline recording was made *via* all electrodes in the stomach. Then, an adjustable multi-channel electrical stimulator (model A300, World Precisio Instruments, Sarasota, Florida) was used for stimulation in a constant current mode, and the stimulus consisted of periodic trains of bipolar pulses with adjustable pulse widths. In order to get effective pacing parameters for the entrainment, a series of sessions with various pacing parameters were performed in the fasting state, 10 min each session. A 5-min recording without pacing was made between two consecutive pacing sessions. The pulse width was gradually increased (0.3 ms, 0.5 ms, 0.7 ms, 0.9 ms, 1 ms, 2 ms, 3 ms, 4 ms …) until entrainment of gastric slow waves was achieved. Other parameters for GES were fixed. The stimulus was delivered *via* the 1st channel for single-channel GES (a train on-time of 3 s and off time of 8 s, a pulse frequency of 30 Hz, an amplitude of 5 mA) or *via* both the 1st and 3rd channels for two-channel (channel one: 3 s-on and 8 s-off, 30 Hz, 2 mA; channel three: the same as channel one except for pulse amplitude of 1.6 mA). With this setting, the frequency of pulse train was about 5.5 trains/min, which is similar to the physiological frequency of gastric slow wave. Time delays among different channels were determined

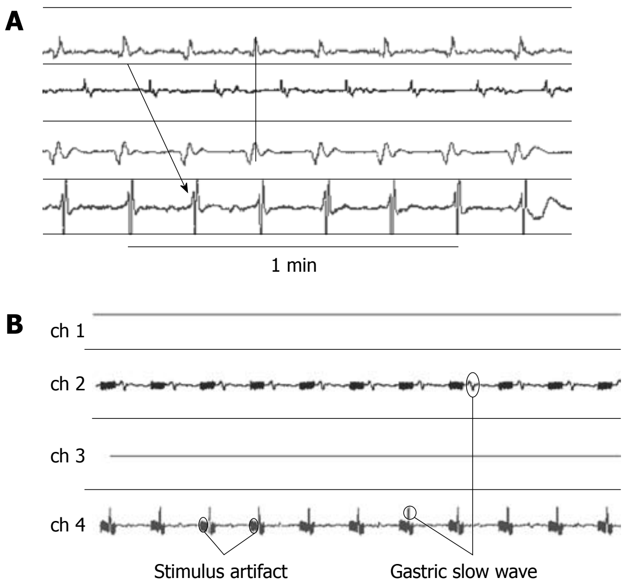

Figure 1 Gastric slow waves at the baseline and with two-channel GES (A), and recordings of gastric slow waves at baseline during 2-channel GES *via* the first and third channels (B).

based on the propagation speed of intrinsic gastric slow waves during the baseline recording. The peak of slow waves occurred simultaneously at the 1st and 3rd channels (a phase shift of 360 degree). Accordingly, stimulation applied in these two channels was synchronic or simultaneous (Figure 1).

Experiment 2 was to investigate the effect of two-channel GES with trains of pulses on gastric emptying. The stimulation parameters were determined as in experiment 1. The study was performed in three sessions (control, single-channel GES, two-channel GES) on three separate days (at least 3 d apart) in a randomized order. Each session consisted of four consecutive 30-min periods of gastric slow wave recordings. During each study session, the dogs were fed with a liquid meal composed of 43 g Nutrison (Nutricia, Holland) and 100 mg phenol red mixed with 100 mL water, immediately after a 30-min baseline recording in the fasting state (the dogs were fasted for 12 h or more). The total volume was 237 mL with a total energy of 250 kcal (6 g fat, 40 g carbohydrate, and 9 g protein). The emptied chyme containing gastric secretion and the ingested liquid meal were collected every 15 min *via* the intestinal cannula for 90 min. The collected volume and the amount of phenol red in each collection were used for the assessment of gastric emptying. Session two was the same as session one, except that GES was performed *via* the 1st channel during the entire postprandial period (Figure 2) with a train on-time of 3 s and off time of 8 s, a pulse frequency of 30 Hz, an amplitude of 5 mA, and width of 4 ms (the optimal pulse width obtained from experiment 1). Session three was the same as session two, except that GES was performed *via* channels one and three (pulse amplitude of 2 mA for channel one and 1.6 mA for channel three). The reduced pulse amplitude in the distal (channel three) stimulation channel was designed to avoid retrograde propagation of stimulation.

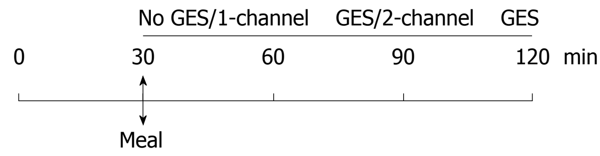

Figure 2 Experiment protocol.

Recording and assessment of gastric slow waves

A multi-channel recorder (AcqknowledgeIII, EOG 100A, Biopac System, Inc. Santa Barbara, CA) was used to record gastric slow waves *via* the serosal electrodes during the entire study. All signals were displayed on a computer monitor and saved on the hard disk with an IBM-compatible 486PC. The low and high cutoff frequencies of the amplifier were 0.05 and 35 Hz, respectively. The most distal recording was used to identify whether gastric slow waves are entrained with GES. Complete entrainment was defined as the frequency of gastric slow waves that was the same as the pacing frequency and phase-locked with the pacing stimulus. The percentage of entrainment of gastric slow waves was defined as the ratio of difference between the recorded slow wave frequency during pacing (f) and the intrinsic frequency before pacing (fi), and the difference between the pacing frequency (fp) and the intrinsic frequency before pacing. It was represented as % of entrainment = (f - fi)/(fp - fi)[28].

Gastric emptying

The test liquid meal contained 100 mg of phenol red as a marker, and gastric emptying was determined by assessment of the amount of phenol red in each collection of gastric effluent as previously described[19]. During the study, the volume of each collection was recorded and a sample of 5 mL was taken and stored in a freezer. At the end of study, these samples were analyzed using a spectrophotometer to detect the amount of phenol red in each sample. Gastric emptying was assessed by calculating the amount of phenol red recovered from each collection of gastric effluent.

Statistical analysis

Results were reported as mean ± SE. The analysis of variance (ANOVA) was used to assess the difference in three sessions of gastric emptying. Paired Student *t* test was used to investigate the differences in gastric emptying between the stimulation and control sessions. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of GES with trains of pulses on gastric slow waves

Gastric slow waves were entrained in each dog with single-channel or two-channel GES using trains of pulses with a greater pulse width. The relation between the entrainment of slow waves and stimulation pulse width is presented in Figure 3. The percentage of entrainment of gastric slow waves with single- or two-channel GES

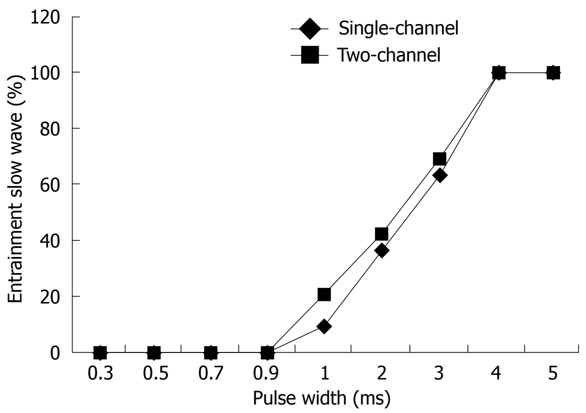

Figure 3 Percentage of slow wave entrainment with GES as a function of stimulation pulse width.

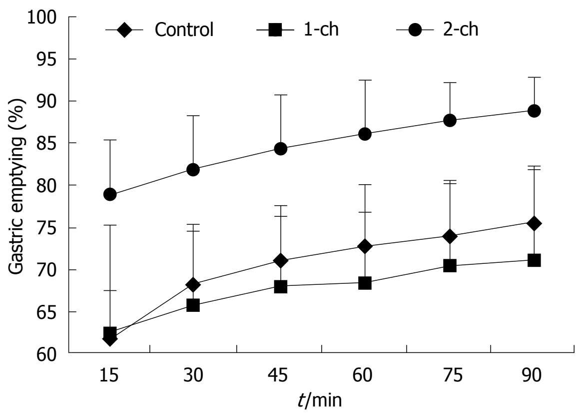

Figure 4 Gastric emptying in the control sessions and sessions with single-channel or two-channel GES. $P < 0.01$ (2-ch *vs* control).

was 7.75% ± 1.62% or 19.25% ± 9.04% at 1 ms, 36.62% ± 5.75% or 42.82% ± 5.45% at 2 ms, 62.34% ± 7.38% or 67.75% ± 9.80% at 3 ms and 100% ± 0% or 100% ± 0% at 4 ms, respectively. A complete entrainment was achieved with GES with a pulse width of 4 ms or greater. Some typical recordings at the baseline and during GES are shown in Figure 1. The entrainment of gastric slow waves usually occurred a few minutes after gastric pacing as demonstrated by the fact that the slow waves were phase-locked with the pacing stimulus a few minutes after the initiation of pacing.

To compare the stimulation energy required to completely entrain the gastric slow waves, the following formula was used for the calculation of stimulation energy (E): E = (cycles/min) × (frequency) × (pulse width) × (amplitude)^2. Accordingly, the minimum energy required by single-channel GES was 16 500 ms × mA^2, whereas that for the two-channel GES was 8421.6 ms × mA^2, which represents about 51.04% of the energy required by single-channel GES or a saving of 48.96% of energy.

Effect of GES with trains of pulses on gastric emptying

Two-channel GES with trains of long pulses (pulse width: 4 ms) could accelerate gastric emptying in the healthy dogs ($P < 0.01$, ANOVA) (Figure 4). Compared with the control session, two-channel GES significantly increased gastric emptying of liquids at 15 min (79.0% ± 6.4% *vs* 61.3% ± 6.1%, $P = 0.001$), 30 min (83.2% ± 6.3 % *vs* 68.2% ± 6.9%, $P = 0.005$), 60 min (86.9% ± 5.5% *vs* 74.1% ± 5.9%, $P = 0.010$), and 90 min (91.0% ± 3.4% *vs* 76.5% ± 5.9%, $P < 0.0037$), respectively, after feeding. However, no significant difference was noted in gastric emptying between single-channel GES and control sessions.

DISCUSSION

In the present study, GES with trains of wider pulses (width ⩾ 4 ms) but not short pulse could entrain gastric slow waves. Two-channel GES but not single-channel GES, significantly accelerated gastric emptying of liquids in healthy dogs.

Most previous studies showed that long pulse GES can entrain gastric slow waves in human beings and animals[19,20,22-25,27]. None of these studies has investigated the effect of GES with trains of pulses on gastric slow waves. It has been shown that GES with trains of short pulses can improve symptoms, such as nausea and vomiting of patients with gastroparesis[24,26], but cannot entrain gastric slow waves or normalize gastric dysrhythmia. In this study, GES with trains of pulses entrained gastric slow waves as long as the width of pulses in the train was 4 ms or greater. The energy required to completely entrain gastric slow waves with two-channel GES was less than that with single-channel GES, which might be due to the fact that each stimulation was responsible for entraining slow waves in a smaller region (about 50%) of the stomach with two-channel GES, compared with single-channel GES.

Conventionally, long-pulse GES is performed using a single pair of electrodes or single-channel GES. It has been reported that single-channel GES with long pulses accelerates gastric emptying in patients with gastroparesis[22] and in animal models of gastroparesis[30], and has no effect on gastric emptying in healthy dogs[18,19,30]. Recent studies on the effect of multi-channel GES on gastric emptying and entrainment of slow waves indicate that multi-channel stimulation with long pulses is more efficient than single-channel stimulation for the entrainment of slow waves, and can accelerate gastric emptying[18-20,31]. It has been shown that four-channel long pulse GES can accelerate gastric emptying in healthy dogs[18], whereas two-channel long pulse GES can normalize vasopressin-induced delayed gastric emptying in dogs[19]. To date, no study is available on the effect of multi-channel GES with trains of pulses on gastric emptying. In the present study, we used single-channel (14 cm above the pylorus) and two-channel (6 and 14 cm above the pylorus) GES to investigate their effect on gastric emptying. Compared with the control session, two-channel but not single-channel GES with trains of pulses significantly accelerated gastric emptying, which is consistent with the previous findings.

It is well known that gastric emptying of liquid and solid occurs separately, involving different areas of stomach. It is believed that the antrum undergoes orderly peristaltic contractions and acts as a pump, while the proximal segment functions as a reservoir[32]. Gastric emptying demands accommodated motion of the proximal and distal stomach. The motility of stomach follows an orderly pattern in which gastric peristaltic contractions are phase-locked with gastric pacesetter potentials, which sweep distally from the corpus toward the pylorus. It is also known that gastric contractions are controlled by gastric slow waves. Multi-channel GES more accurately mimics the natural propagation and characteristics of gastric slow waves[18,30], thus controlling gastric contractions more effectively.

In this study, two-channel GES with trains of pulses entrained gastric slow waves and accelerated gastric emptying in healthy dogs, suggesting that two-channel GES with trains of pulses might be applicable in treatment of gastroparesis and normalization of gastric dysrhythmia. Technically, it is more feasible to make an implantable stimulator using trains of pulses than using repetitive long pulses due to the current charge balance. Accordingly, GES with trains of pulses is technically more attractive than long pulse GES. Currently, most commercially available implantable stimulators use trains of pulses. However, none of them is able to generate pulses with a width of 4 ms or greater. Therefore, new hardware design and development are needed before two-channel GES with trains of pulses can be used in clinical practice.

In conclusion, entrainment of gastric slow waves is feasible using GES with trains of pulses at a pulse width of 4 ms or greater. Two-channel GES with trains of pulses can accelerate gastric emptying in healthy dogs and may have a therapeutic potential for the treatment of gastric motility disorders.

COMMENTS

Background

Gastric dysrhythmia and delayed gastric emptying have been observed in a variety of gastric motility disorders. Treatment options for such disorders include medical therapy, surgical therapy, and nutritional support.

Research frontiers

Gastric electrical stimulation (GES) or pacing has been under investigation as a potential therapy for gastrointestinal motility disorders. However, few studies are available on the effect of two-channel GES with trains of pulses on gastric slow waves and gastric emptying.

Innovations and breakthroughs

In this study, the authors used single-channel (14 cm above the pylorus) and two-channel (6 and 14 cm above the pylorus) GES to investigate their effect on gastric emptying. Compared with the control session, two-channel but not single-channel GES with trains of pulses significantly accelerated gastric emptying, which is consistent with the previous findings.

Applications

Two-channel GES could entrain gastric slow waves and accelerate gastric emptying in healthy dogs, suggesting that two-channel GES with trains of pulses can be used in treatment of gastroparesis and normalization of gastric dysrhythmia.

Terminology

GES with trains of pulses, composed of a repetitious train of pulses, is derived from the combination of a continuous pulse singal with a high frequency (in the order of 5-100 Hz) and a control signal to turn the pulses on and off, such as x seconds "on" and y seconds "off". This kind of stimulation has been used in electroacupuncture.

Peer review

The authors have demonstrated that entrainment of gastric slow waves is feasible with GES of trains of pulses at a pulse width of 4 ms or greater and two-channel GES with trains of pulses can accelerate gastric emptying in healthy dogs, thus having a therapeutic potential for the treatment of gastric motility disorders.

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