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# Mechanisms of High-Frequency Electrical Stimulation of the Stomach in Gastroparetic Patients

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*Abstract*—**Previous studies have demonstrated that high frequency and low energy gastric electrical stimulation (GES) reduced nausea and vomiting in gastroparetic patients without improving gastric emptying. The mechanisms of action for this have not been clarified. The aim of our study was to investigate the effects of GES on autonomic function, gastric distention and tone, and central control mechanism in gastroparetics patients. 10 gastroparetic patients refractory to standard medical therapy participated in this study and data were collected at baseline session, within two weeks before surgery for implantation of GES system, and at follow-up sessions between 6 to 12 weeks after GES therapy. In each session, electrocardiogram and gastric barostat measurements were conducted before and after a caloric liquid meal. Positron Emission Tomography (PET) brain scans were performed on a separate day. Analysis of autonomic function was accomplished through power spectral analysis of heart rate variability which revealed that the sympthovagal balance was significantly decreased after GES therapy, indicating a significant increase in vagal activity. Results from gastric barostat measurements demonstrated that during GES there was a significant increase in the discomfort threshold for both pressure and volume. Quantitative analysis of PET imaged cerebral activity showed that chronic GES increased thalamic activity. This study suggests that the symptomatic efficacy achieved by GES may be partly attributed to enhanced vagal autonomic function, decreasing gastric sensitivity to volume distention which simulates a postprandial adaptation, and the activation of central control mechanisms for nausea and vomiting through thalamic pathways during GES.**

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## I. INTRODUCTION

AS in the human heart, there is a pacemaker in the stomach, located in the midcorpus along the greater curvature. It paces gastric electric activity generated by smooth muscles, yielding a so-called slow wave which propagates circumferentially and distally toward the pylorus with an increasing amplitude and velocity. The gastric slow wave is omnipresent, and its normal frequency in humans is about 3 cycles/min. (cpm) [1]. It is known that the frequency and propagation of gastric contractions are determined by the gastric slow wave. Gastric contractions occur when spikes (action potentials) are superimposed on the slow wave. Because gastric motility is controlled by electric activity of the stomach abnormalities in gastric electric activity may result in gastric motility disorders such as gastroparesis [2].

Gastroparesis is a chronic disorder of gastric motility. It is characterized by delayed gastric emptying of solids without evidence of mechanical obstruction and presents with nausea, early satiety in mild cases and chronic vomiting, dehydration and weight loss in severe cases [3]. Patients with this condition have frequent hospital admissions, lost employment, and a poor quality of life. The most common treatment for gastroparesis is to use prokinetic agents, such as erythromycin and domperidone. These agents are developed to stimulate gastric motility, i.e., contractility of smooth muscles of the stomach [3]. However, only two agents are currently available in the USA and side effects from these agents result in up to 40% of patients being unable to tolerate chronic use. Those who are refractory to the prokinetic agents often undergo an abdominal surgery for the placement of a feeding jejunostomy tube (J-tube). The J-tube is only for nutritional support and does not eliminate symptoms.

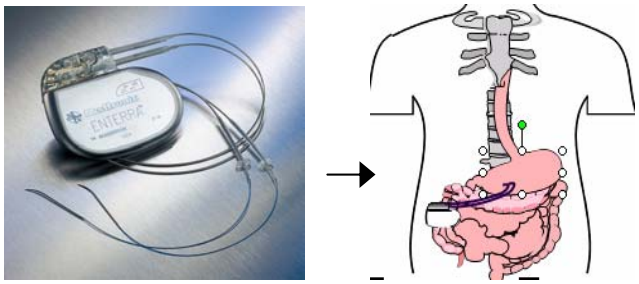
Gastric electrical stimulation (GES) is an emerging therapy for refractory gastroparesis [4]. Based on the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS) data [5], the US FDA approved GES with high frequency and low energy parameters (ENTERRA™

Therapy System, Medtronic, Minneapolis, MN) in March 2000 under a Humanitarian Device Exemption for symptomatic relief in patients with diabetic and idiopathic gastroparesis. Since then a number of publications have shown that GES by the Enterra device does produce a significant and sustained improvement in symptoms and nutritional status in most patients with intractable symptomatic gastroparesis [4-6]. Since gastric emptying is not consistently improved and gastric dysrhythmias are not converted to normal rhythm then other reasons to explain the substantial improvement in nausea and vomiting must be considered. Therefore the aim of our study is to identify possible mechanisms that could help explain how GES is effective in treating nausea and vomiting associated with refractory gastroparesis.

## II. METHODOLOGY

### *A. Surgical and GES Techniques*

This study was performed in 10 patients (2 men and 8 women; mean age: 44 years; range: 20-58 years) with severe gastroparesis (7 diabetic, 3 idiopathic) refractory to standard medical therapies. The GES system used in this study consisted of 3 components: a battery-powered implantable pulse generator (Model 7425G, Medtronic, Minneapolis, MN) and 2 intramuscular electrodes (Model 4300, Medtronic) (see Figure 1a) and an external programmer to adjust the output parameters of the pulse generator (Model 7432, Medtronic). One pair of permanent electrodes (about 1 cm apart) was inserted by laparotomy into the muscularis propria layer on the greater curvature at 9.5 and 10.5 cm proximal to the pylorus. The electrodes were secured to the serosa of the stomach using a 5-0 silk sutures and a plastic disk. The other end of each electrode was connected to the pulse generator which was positioned in a subcutaneous pocket on the top of the abdominal wall fascia to the right of the umbilicus (see Figure 1b). The load impedance of the circuit was checked both before and after the GES device was placed in the pocket using the external programmer. The pulse generator was usually activated in the operating room or within 48 hours after surgery and initially programmed to standardized parameters: pulse width, 330 μs; (current) amplitude, 5 mA; frequency, 14 Hz; cycle ON: 0.1 seconds; cycle OFF, 5.0 seconds. At various intervals of follow-up after the implant, those parameters can be adjusted based on patient's symptomatic status or changes in impedance reading.



(a) (b)

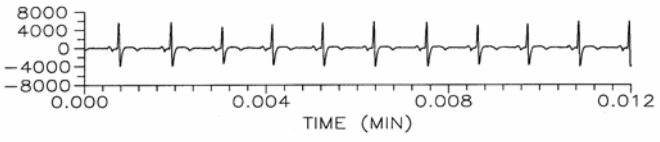
Fig. 1 (a) Gastric electrical stimulation (GES) system and (b) its location. The GES system comprised a pair of leads sutured on the serosal surface of the stomach wall, 9.5 and 10.5 cm proximal to the pylorus, 1 cm apart, and connected to an implantable battery-powered pulse generator positioned subcutaneously in the abdominal wall.

### *B. Study Protocol*

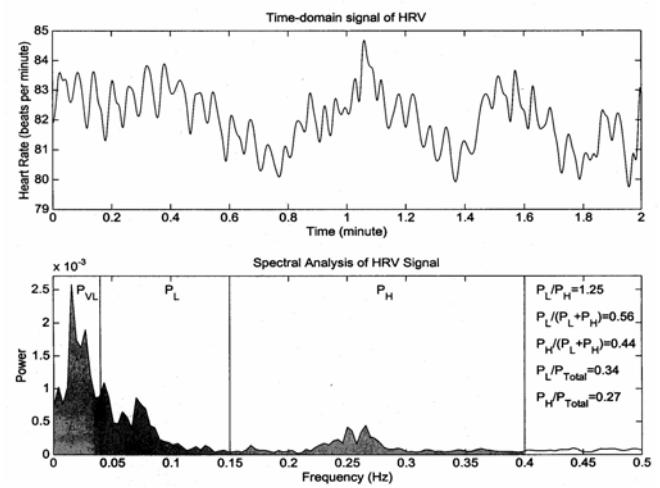
This study consisted of a baseline session, within two weeks before implantation of GES system and a follow-up session between 6 to 12 weeks after GES therapy. In each session, total symptom score (TSS) derived from 7 upper GI symptom sub-scores (vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain and burning) using a 5-point scale (0=none, 4=extremely severe) was assessed, electrocardiogram (ECG), gastric barostat and Fluoro-Deoxy Glucose (FDG) Positron Emission Tomography (PET) scans of brain were performed on two separate days.

### *C. Recording and Analysis of Heart Rate Variability (HRV)*

After the patient fasted for at least 6 hours, one-channel ECG was measured for at least 30 minutes using the UFI Bio-Amplifier (UFI, Morro Bay, CA). Prior to the attachment of three electrodes, the chest where electrodes were to be positioned was shaved if hairy and cleaned with sandy skin-prep paste to reduce the impedance. Analysis of autonomic function was accomplished through power spectral analysis of heart rate variability (see Figure 2). The following parameters were computed from the ECG recordings [7]: (a) average and standard deviation of the heart rate, (b) spectral components of HRV in low frequency band (PL: 0.04 – 0.15 Hz) and in high frequency band (PH: 0.15 – 0.4 Hz); (c) the percentage of power in low frequency band, P1 =PL/(PL+PH) % and the percentage of power in high frequency band, P2 =PH/(PL+PH) % and (d) PL/PH, which measures sympthovagal balance, with higher value indicating greater overall sympathetic dominance.




(a)




(b)

Fig. 2 (a) An example of an ECG recording, b) Time-domain signal of heart rate variability (up panel) and spectral analysis of heart rate variability signal (low panel).

*D. Gastric Barostat Study*

After an overnight fast for at least 12 hours, a double-lumen polyvinyl tube, with a finely folded adherent plastic bag (1200-ml capacity; maximal diameter: 17 cm), was introduced through the mouth and secured to the patient's chin with adhesive tape. The polyvinyl tube was then connected to a programmable barostat device (G & J Electronics, Ontario, Canada). The position of the bag in the gastric fundus was considered appropriate once a slight resistance was met (reaching the fundic wall and diaphragm). The patient was then positioned in a supine manner on a bed to keep him or her comfortable. After a 30-min adaptation period, minimal distending pressure (MDP) was first determined by increasing intrabag pressure by 1 mm Hg every 1.5 minutes until a volume of 30 ml was reached. (a) Assessment of Perception: Subsequently, isobaric distensions were performed in stepwise increments of 2 mm Hg starting from MDP, each lasting for 2 minutes, while the corresponding intragastric volume was recorded. Patients were instructed to score their perception of upper abdominal sensations at the end of every distending step, using a graphic rating scale that combines verbal descriptors on a scale graded 0-6. The end point of each sequence of distensions was established at an intrabag volume of 1000 ml, or when the patients reported discomfort or pain (score 5 or 6). This pressure level equilibrated the intra-abdominal pressure. (b) Assessment of Gastric Accommodation: After a 15-min adaptation period with the bag completely deflated, the pressure level was set at MDP + 2 mm Hg for 75 minutes. After 15 minutes, the patient ingested a liquid meal (200 ml, 240 kcal). In all patients, gastric tone measurement wase continued for 60 minutes after the meal. Discomfort threshold was defined as the first level of pressure and corresponding volume that provoked a score of 5 or more. Pressure thresholds are expressed both as pressure relative to MDP and as absolute pressures. The amplitude of the meal-induced fundal relaxation was calculated by subtracting the difference between the average volume during the 15-minute period before and the 60-minite period after the administration of the meal [8].

*E. Positron Emission Tomography (PET) Imaging of Brain*

The patient was fasted for at least 4 hours prior to this study. Diabetic patients had their glucose blood levels checked prior to the injection of fluoro-deoxy glucose (FDG). Twenty minutes after being placed in an environment controlled for light and sound, the patient was injected with 10 mCi of FDG. Forty-five minutes thereafter, brain metabolic activity data were acquired in the 2D mode using a Discovery ST PET/CT scanner (GE Healthcare –Americas, Milwaukee, WI, USA). Quantitative count data from 240 separate areas of the brain of each patient were displayed as 47 anatomical regions and compared to a standardized database, which was derived from the PET brain scans of 50 normal subjects acquired at a major research medical center in the United States and licensed as a commercial package under the name Neuro Q (9). .

## III. RESULTS

Severity of nausea and vomiting and TSS was significantly reduces after GES therapy (see TABLE I).

*A. Effect on Autonomic Function*

The results of heart rate (HR), power in the low frequency band (0.04-0.15 Hz), power in the high frequency band (0.15-0.4 Hz) and power ratio (PL/PH) are summarized in TABLE II. The sympthovagal balance (PL/PH) was significantly decreased after GES therapy (16.5±8.7 vs. 0.6±0.2), indicating a significant increase in vagal activity during GES.

*B. Effect on Gastric Tone and Accommodation*

After GES therapy there was a significant increase in the discomfort threshold for pressure from 21 mm Hg at baseline to 25 mm Hg at follow-up, and for volume from 561 ml at baseline to 713 ml ($p<0.05$). Also an increase in the amplitude of gastric accommodation to the meal was observed between baseline (38ml) and follow up (68ml), although not achieving statistical significance.

*C. Changes in Cerebral Activity on PET Images*

Through comparison with a standardized PET brain scans database from 50 normal subjects, the cumulative data from 35 separate regions of the brain of each patient showed a 3% mean increase in counts in the regions of the thalamus after GES therapy. Figure 3 shows an example of PET brain images from a gastroparetic patient before (left panel) and during GES therapy (right panel) at 3-month follow-up visit.

TABLE I

Results of gastroparetic symptoms

| | Before GES | During GES | P value (t-test) |
|---|---|---|---|
| Nausea score (0-4) | 3.8±0.1 | 1.7±0.4 | <0.05 |
| Vomiting score (0-4) | 2.2±0.4 | 1.8±0.5 | <0.05 |
| TSS in severity (0-28) | 23.1±0.8 | 11.5±2.6 | <0.01 |

Note: TSS, total symptom score; GES, gastric electrical stimulation.

TABLE II

Comparison of HRV before and during gastric electrical stimulation

| | Mean HR (beats/min) | SD | P1 (%) | P2 (%) | PL/PH |
|---|---|---|---|---|---|
| Before GES | 98.7 | 60.1 | 69 | 31 | 15.0 |
| During GES | 88.2 | 40.0 | 34 | 66 | 0.6 |
| P values (t-test) | | | | 0.04 | 0.04 |

Note: HR, heart rate, SD, standard deviation; PL, power in low frequency band; PH, power in high frequency band.

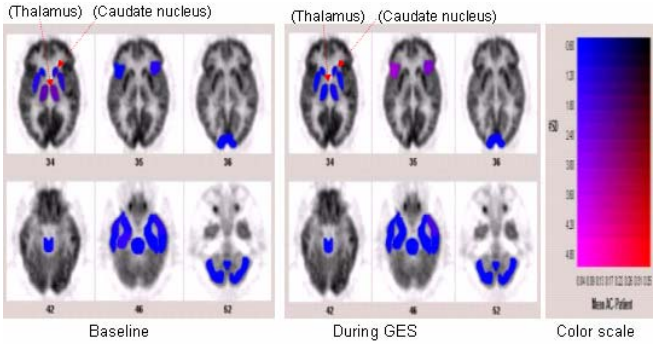



Fig. 3 Results of PET images of brain before (left panel) and during gastric electrical stimulation (right panel).

## IV. DISCUSSION AND CONCLUSION

In this paper, power spectral analysis of HRV showed that the sympthovagal balance was significantly decreased after GES therapy, indicating a significant increase in vagal activity. Results from gastric barostat measurements demonstrated that duirng GES there was a significant increase in the discomfort threshold for both pressure and volume. Quantitative analysis of PET imaged cerebral activity showed that chronic GES increased thalamic activity. These findings suggest that the symptomatic efficacy achieved by GES may be partly attributed to enhanced vagal autonomic function, decreasing gastric sensitivity to volume distention which simulates a postprandial adaptation, and the activation of central control mechanisms for nausea and vomiting through thalamic pathways during GES.

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