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REVIEW ARTICLE

Methods of gastric electrical stimulation and pacing: a review of their benefits and mechanisms of action in gastroparesis and obesity

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Abstract *Development of gastric electrical stimulation techniques for treatment of gastric dysmotility syndromes and obesity has been a long-standing goal of investigators and clinicians. Depending on stimulus parameters and sites of stimulation, such methods have a range of theoretical benefits including entrainment of intrinsic gastric electrical activity, eliciting propagating contractions and reducing symptomatology in patients with gastroparesis and reducing appetite and food intake in individuals with morbid obesity. Additionally, gastric stimulation parameters have extragastrointestinal effects including alteration of systemic hormonal and autonomic neural activity and modulation of afferent nerve pathways projecting to the central nervous system that may represent important mechanisms of action. Numerous case series and smaller numbers of controlled trials suggest clinical benefits in these two conditions, however better controlled trials are mandated to confirm their efficacy. Current research is focusing on novel stimulation methods to better control symptoms in gastroparesis and promote weight reduction in morbid obesity.*

Keywords *diabetes, gastric electrical stimulation, gastric emptying, gastroparesis, obesity, vagus nerve.*

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HISTORY OF GASTRIC ELECTRICAL STIMULATION

Investigations since the 1960s suggest that exogenous electrical stimulation methods exhibit the potential to alter gastric neuromuscular activity and perception, offering the promise that such methods might be effective therapies to accelerate gastric emptying or reduce nausea and vomiting in gastric dysmotility syndromes such as gastroparesis and to blunt appetite and reduce food intake in morbid obesity. In the earliest report of gastric pacing using temporary electrodes in humans, 7 s impulses delivered every 60 min reduced paralytic ileus to 28 h compared to 57 h with nasogastric suction.[1] Subsequent pioneering investigations in animals demonstrated that gastric pacing could entrain slow waves at 0.8–1.6 times the intrinsic frequency and could reverse spontaneous slow wave dysrhythmias.[2] Responses to gastric pacing were dependent on stimulus intensity, with shorter duration stimuli needed when impulse strength increased. Furthermore, the antrum could be paced to significantly higher frequencies than more proximal gastric regions.[3] More recent studies in dogs in whom gastroparesis was induced by atropine or by vagotomy plus glucagon, gastric pacing at 1–1.1 times the normal slow wave frequency reversed dysrhythmic activity and accelerated emptying.[4] In humans with postoperative gastroparesis, gastric pacing entrained the slow wave in 10 of 16 patients but did not enhance emptying.[5] These studies provide the foundation for rigorous exploration into potential benefits of electrical stimulation in gastroparesis and obesity.

PATTERNS OF GASTRIC ELECTRICAL STIMULATION

Although electrical protocols for gastroparesis and obesity are different, there are similarities in patterns of the stimulus that are common for all devices. All stimuli are phasic, with an initial ON time during which a pulse or series of pulse bursts are administered followed by an OFF period of no current delivery. ON times range from 0.1 to 4 s with OFF times of 1–5 s. Series of pulse bursts within each ON time administration exhibit frequencies of 10–100 Hz. Each individual pulse exhibits a width or duration from 100 μs to 500 ms. Each parameter can be modified to elicit different motor and symptom responses.

GASTRIC PACING AND ELECTRICAL STIMULATION IN GASTROPARESIS

Gastroparesis presents with nausea, vomiting, bloating, fullness, early satiety and discomfort in association with delayed gastric emptying. The role of gastric retention in pathogenesis of symptoms is controversial. Other potential symptom causes include impaired fundic relaxation, dysrhythmic slow waves and heightened afferent activation. Parameters of gastric stimulation have been characterized that entrain slow waves (and reverse dysrhythmias), promote propagative antral contractions, enhance gastric emptying, elicit fundic relaxation, and blunt afferent vagal transmission.

Parameters of stimulation – pacing *vs* neurostimulation

In animal and human studies, selected gastric stimulation parameters entrain slow waves and restore phasic antral motor activity. Such pacing methods employ depolarizations at frequencies slightly above the intrinsic slow wave frequency with long duration pulses. In humans, pacing is accomplished at a frequency of 3.3 cycles per minute (cpm), a current of 4 mA, and a pulse width of 300 ms.[6] Reducing pacing currents to 2 and 1 mA decreases slow wave entrainment to 79 ± 10 and 50 ± 11%, respectively, while decreasing the pulse width to 30 ms eliminates entrainment.[6] Pacing decreases gastric retention from 86% to 68% in dogs with gastroparesis induced by vagotomy plus glucagon.[4] In dogs with gastroparesis and gastric dysrhythmias evoked by atropine and vasopressin, long pulse duration pacing increases normal slow waves and reverses tachyarrhythmias. In the only trial in humans, long pulse duration pacing was delivered for 1 month in nine patients with gastroparesis (five diabetic, three idiopathic and one postvagotomy) through a single pair of serosal electrodes 14–16 cm proximal to the pylorus.[7] Pacing wires were brought out through the skin and current from an external current source was delivered during and after meals. Slow wave entrainment was achieved in all patients, dysrhythmias were reversed in two individuals, and 2 h gastric retention decreased from 77 ± 3% to 57 ± 9%. Symptoms decreased by nearly 50% and eight patients discontinued jejunal feedings. Implementation of pacing as treatment of gastroparesis has been hampered by the energy requirements of a reliable pacing system. Because slow wave entrainment requires long duration pulses, all devices to date have employed unwieldy current sources that are too large to be portable or implantable.

Because of these limitations, protocols with lower energy requirements were examined. In initial validation studies in dogs, electrical stimulation with short duration pulses (0.3 ms) at 2 mA and frequencies varying from 0.6 to six times that of the intrinsic slow wave determined that higher frequencies (≥4 times the slow wave frequency) provided optimal enhancement of gastric motor activity.[8] In the first case report employing these short pulse duration parameters in a human with gastroparesis, electrical stimuli were delivered through serosal electrodes at several sites along the greater curvature.[9] The most effective response was observed with electrodes implanted in the distal corpus and proximal antrum in this individual. Subsequent studies in dogs confirmed that short pulse duration stimuli (0.1–0.3 ms) delivered with an ON time of 0.1 s every 5 s with series of pulse bursts at 14–40 Hz exhibited potent anti-emetic actions to the effects of vasopressin without any entrainment of intrinsic electrical activity.[10] Direct comparisons in animals highlight the differences between pacing and stimulation parameters. Short pulse stimulation (0.3 ms) reduces vomiting via vagal pathways but does not prevent slow wave dysrhythmias or uncoupling caused by vasopressin.[11] Conversely, long pulse duration (500 ms) pacing normalizes vasopressin-evoked slow wave disruptions but has little effect on vomiting.[11] Because of the low energy requirements of short pulse duration stimulation, pulse generators and battery systems can be miniaturized to provide long-term stimulation in a device that can be implanted under the skin.

Results of clinical studies

Initial uncontrolled case series using an implantable stimulator that provided low energy ON stimuli every

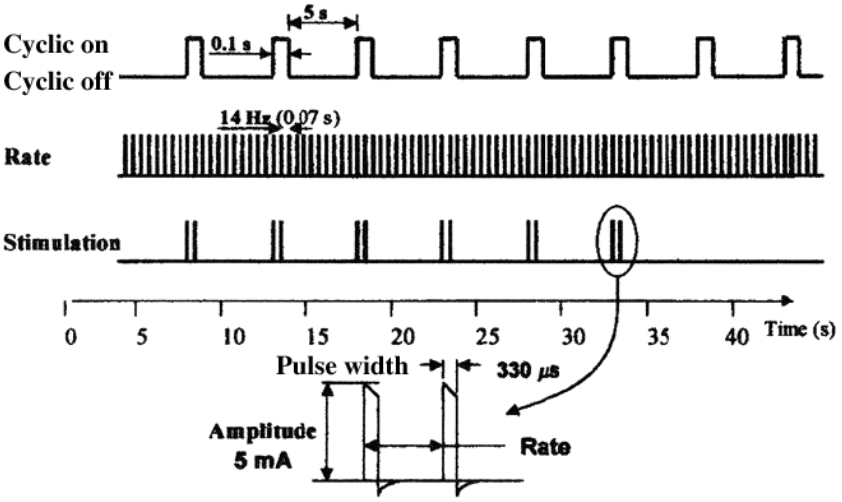

Figure 1 The pulse characteristics for the gastric electrical stimulator are shown. In the top tracing, the waveform is cyclic with an ON time of 0.1 s and an OFF time of 5 s. This yields a frequency of approximately 12 cycles per minute. Within each delivery of an ON stimulus, phasic pulses are delivered at a rate of 14 Hz (second and third tracings). The expanded view of an individual ON stimulus shows that each pulse has a width of 330 μs and a current of 5 mA.[14]

5 s (four times the intrinsic slow wave frequency) at 5 mA with a pulse width of 0.33 ms with pulse trains at 14 Hz reported impressive improvements in nausea and vomiting in patients with medication-refractory diabetic or idiopathic gastroparesis (Fig. 1).[12] As a result, the gastric stimulator was granted approval as a humanitarian use device (HUD) in 2000 by the United States Food and Drug Administration (FDA). A humanitarian device exemption (HDE) was conferred allowing the device (Enterra; Medtronic, Minneapolis, MN, USA) to be used in patients with refractory diabetic or idiopathic gastroparesis. An HUD is a device which treats conditions affecting <4000 patients/year when other therapies are ineffective or do not exist. An HDE authorizes marketing of an HUD. Under FDA guidelines regulating use of HUDs, gastric electrical stimulator implantation is restricted to institutions where Institutional Review Board approval has been obtained. Because controlled trials showing definitive benefits had not been performed, the stimulator was not approved for unrestricted marketing.

As its initial FDA review, several uncontrolled trials have reported significant gastric symptom improvements in diabetic and idiopathic gastroparesis (Table 1). Many of these investigations originate from a small number of centres and may include overlapping patient populations. Initial series of 2–55 patients observed 80% reductions in nausea and vomiting that persisted for at least 12 months.[13–19] In one study, patients receiving gastric stimulation responded better than those managed with medications alone.[16] More recent series of >200 patients report continued reductions in at least one symptom of gastroparesis a median of 4 years after implantation.[20] Taken together, the response rates to chronic gastric electrical stimulation in these case series range from 50% to 92%. However, some centres have discontinued device implantation because of lesser observed benefits.

To date, only one trial comparing electrical stimulation to a sham stimulus has been published. In this study, 33 patients with gastroparesis (17 diabetic and 16 idiopathic patients) were randomized to stimulation ON or OFF for 1 month in blinded, cross-over fashion after implantation.[21] The device was then activated in all patients and uncontrolled assessments were made at 6 and 12 months. During the blinded phase, weekly vomiting frequency decreased significantly from 13.5 (range 5.5–25.4) to 6.8 (3.9–16.5) but total symptom scores showed no change (13.9 ± 1.1 OFF *vs* 12.5 ± 1.0 ON) (Fig. 2). Reductions in vomiting frequency were observed in diabetics but not in patients with idiopathic gastroparesis. In the uncontrolled phase at 6 and 12 months, vomiting frequencies were reduced by >80% in both groups. Nausea decreased in diabetics but not idiopathic patients. No reductions in early satiety, bloating, and postprandial fullness were observed and inconsistent decreases in pain were noted. In a follow-up letter to the Editor, it was noted that, in the initial submission to the United States FDA, no differences in vomiting frequency were observed with the device ON *vs* OFF during the controlled phase of the study.[22] This raised the concern of a *post hoc* change in the primary study endpoint in the preparation of the final manuscript. Because benefits in this trial were modest, a second controlled, blinded, multicentre trial of gastric stimulation in diabetic and idiopathic gastroparesis was initiated. The results of this trial are pending.

Laparotomy was employed for device implantation in most early patients, however modifications in the operative technique were introduced to improve

Table 1 Case series (>5 patients) of gastric electrical stimulation for gastroparesis

Investigator	Number of patients	Patient characteristics	Study duration	Findings
Forster (2001)	25	19 diabetic, 3 idiopathic, 3 postsurgical	1 year	Decreased nausea and vomiting
Abell (2002)	38	9 diabetic, 24 idiopathic, 5 postsurgical	1 year	35/38 had >80% decreases in nausea and vomiting, 5.5% weight gain, 9/14 discontinued supplemental nutrition
Abell (2003)	12	3 diabetic, 9 idiopathic	5 years	Maintained symptom response at 5 years, weekly vomiting frequency decreased from 3.9 at baseline to 1.7
Abell (2003)	33	17 diabetic, 16 idiopathic	1 year	Open extension of sham stimulation controlled trial, decreased total symptoms and vomiting frequency, improved quality of life
Forster (2003)	55	39 diabetic, 7 idiopathic, 9 postsurgical	1 year	Decreased total symptoms, improved quality of life, increased body mass index, decreased hospital admissions, decreased haemoglobin A1c
Lin (2004)	48	All diabetic	1 year	Decreased total symptoms, improved quality of life, 17/22 discontinued supplemental nutrition, decreased hospitalizations, decreased haemoglobin A1c
Al-Juburi (2005)	36	NA	Mean 28.8 months (laparoscopy), mean 42.7 months (laparotomy)	Decreased length of stay with laparoscopy *vs* laparotomy, health care utilization similar for both approaches
Cutts (2005)	18	2 diabetic, 16 idiopathic	3 years	Better symptom reductions, decreased costs *vs* medication therapy, no difference in days hospitalized
Forster (2005)	14	9 diabetic, 4 idiopathic, 1 postsurgical	3 months	Total symptoms higher at baseline and with stimulation in patients with absent interstitial cells of Cajal on biopsy
Lin (2005)	37	24 diabetic, 8 idiopathic, 5 postsurgical	1 year	8/27 discontinued prokinetics, 9/26 discontinued anti-emetics, hospitalizations decreased from 50 to 14 days/year
Mason (2005)	29	24 diabetic, 5 idiopathic	Mean 20 months	Decreased symptoms in 19/27, discontinued supplemental nutrition in all, increased body mass index
McCallum (2005)	16	All postsurgical	1 year	Decreased total symptoms, improved quality of life, 4/7 discontinued supplemental nutrition, decreased hospitalization
Oubre (2005)	6	All postsurgical	Up to 46 months	Decreased weekly vomiting from 3.2 to 1.4, decreased total symptom score from 36.5 to 20.5
Van der Voort (2005)	17	All diabetic	1 year	Decreased nausea and vomiting, decreased haemoglobin A1c from 8.6 to 6.5%
De Csepel (2006)	16	7 diabetic, 7 idiopathic, 1 postsurgical, 1 other	>6 months	Decreased nausea and vomiting, decreased prokinetic medication use, decreased pyrosis, improved quality of life
Lin (2006)	55	39 diabetic, 9 idiopathic, 7 postsurgical	>3 years	10 deaths unrelated to device, 6 explanted, total symptoms decreased 62%, decreased hospitalizations, medication use, and haemoglobin A1c, 10/15 discontinued supplemental nutrition
Anand (2007)	214	146 idiopathic, 45 diabetic, 23 postoperative	4 years	Decreased symptoms, improved quality of life, 90% had reductions in at least one symptom
Gourcerol (2007)	15	8 delayed emptying, 7 normal emptying	6 months	Similar improvements in quality of life, similar reductions in nausea and vomiting in both groups

Table 1 (Continued)

Investigator	Number of patients	Patient characteristics	Study duration	Findings
Salameh (2007)	6	All post-Roux-en-Y gastric bypass	Mean 6 months	Decreased total symptoms, decreased nausea and vomiting
Filichia (2008)	13	All post-transplant	Mean 1 year	Decreases in nausea, vomiting, and bloating similar to or greater than diabetics undergoing gastric stimulation
Islam (2008)	9	All children	8–42 months	Decreased total symptoms, decreased nausea and vomiting
Lin (2008)	63	38 diabetic, 11 idiopathic, 14 postsurgical	>1 year	Decreases in nausea, vomiting, and pain correlated with improvements in gastric retention in patients with normalization of gastric emptying
Maranki (2008)	28	12 diabetic, 16 idiopathic	Mean 148 days	14/28 improved, 6/28 worsened, decreased nausea and vomiting but not bloating or pain, diabetics responded better than idiopathics, opiate use reduced responses

Comment: Consecutive case series from single centres may include overlapping and partially duplicated patient populations.

Figure 2 Vomiting episodes per week are shown under baseline conditions, during controlled ON gastric stimulation *vs* OFF sham stimulation and during open gastric stimulation at 6 and 12 months after implantation. Reductions in vomiting frequency were significant in diabetics but not idiopathic gastroparesis patients during the controlled study phase. Vomiting frequencies were markedly reduced during the open trial phase in both groups of gastroparesis patients.[21]

outcome from surgery. Some centres offer minilaparotomy as a method to reduce postoperative morbidity. Laparoscopy can insert electrodes into the gastric wall and implant the pulse generator in the subcutaneous pocket with no increase in postoperative complications. In one study, mean length of stay after implantation was shorter for laparoscopic surgery (1.1 days) than for laparotomy (6.4 days) while operative times and symptom reductions were similar.[23] Another group has employed intraoperative endoscopic ultrasound to confirm positioning of the electrodes within the gastric smooth muscle.[24]

In addition to exhibiting efficacy in diabetic and idiopathic gastroparesis, gastric stimulators may reduce symptoms in other populations. Individuals with postsurgical gastroparesis exhibit symptom reductions of >50% which persist for at least 12 months after implantation.[25] Likewise, the device has benefits after oesophagectomy for oesophageal carcinoma or for scintigraphically defined gastroparesis or rapid gastric emptying after Roux-en-Y gastric bypass.[26] One exclusion criterion in early case series was use of immunosuppressive medications. However, recent series report symptom reductions after stimulator implantation in patients with gastroparesis after organ transplants including heart–lung and kidney–pancreas procedures.[27] Gastric stimulation reduced vomiting in three patients with hereditary intestinal

pseudo-obstruction and one individual with postsurgical pseudo-obstruction indicating possible benefits in generalized dysmotility syndromes.[28] Lastly, improvements in nausea and vomiting reportedly are similar in patients with delayed and normal gastric emptying suggesting that the presence of gastroparesis may not be requisite for device efficacy.[29] Likewise, adolescents exhibit reduced nausea and vomiting with gastric stimulation regardless of emptying rates.[30]

Uncontrolled series report several associated benefits of gastric stimulation (Table 1). Improvements in nutritional parameters including body mass index (BMI), serum albumin and needs for enteral or parenteral nutrition have been observed.[13–15,18] Use of antiemetic or prokinetic medications is reduced in some studies.[17] Metabolic control as assessed by haemoglobin A1c measurements exhibits improvement in some diabetics.[15,18,31] Physical and mental composite scores of health-related quality of life have shown increases.[14,15,17,21] Finally, a parameter of healthcare utilization, days of inpatient hospitalization, show reductions in many series.[15–18]

Recent investigations have delineated factors predictive of response to gastric stimulation. Individuals with predominant nausea and vomiting report greater improvements than patients with prominent bloating or pain.[19] Opiate use at the time of implantation blunts responses to stimulation.[19] Diabetics exhibit greater symptom reductions than individuals with idiopathic disease.[19,21] In another investigation, energy requirements for successful stimulation were higher for patients with postsurgical gastroparesis than for diabetic or idiopathic gastroparesis suggesting the postoperative group may be less responsive to electrical therapy.[32] Reductions in gastric retention at 4 h correlate with gastric stimulation-evoked symptom improvements in the patient subset exhibiting normalization of gastric emptying.[33] Symptoms at baseline and after 3 months of stimulation are higher in patients with a loss of interstitial cells of Cajal on full-thickness antral biopsies.[34] Use of endoscopically placed temporary stimulating electrodes has been proposed to facilitate prediction of symptom responses to permanent gastric stimulator therapy.[35] However, no rigorously controlled trials of this method have been convincingly performed.

It is possible to adjust several stimulator settings using a handheld programming device, however there has been limited study of the benefits of adjusting any of these parameters. Anecdotal reports suggest that increasing the voltage, ON time, or pulse frequency can improve symptoms, however no publications have addressed this issue and no evidence-based recommendations can be made for patients initially unresponsive to stimulation.

Several complications may develop after gastric stimulator implantation. Infection of the subcutaneous pocket occurs in up to 15% of patients.[18,20,21] Other complications include gastric wall perforation, lead erosion into the small intestine, and generation of intra-abdominal adhesions with subsequent bowel obstruction. These all are managed by surgical revision; those cases with associated infection mandate device explantation. Battery life with standard stimulator settings has not been well defined; however, unpublished longitudinal case series report the need for repeat surgery for battery replacement in some patients followed for <10 years.[36]

Proposed mechanisms of action

Gastric and extragastric mechanisms are proposed to underlie any benefits of gastric stimulation. The importance of accelerating gastric emptying as a means of reducing symptoms is unproved. Many case series and some animal models report decreased retention with gastric stimulation.[13,31,37] In some human studies, acceleration of gastric emptying was absent initially but was observed only on long-term follow-up.[13] Other uncontrolled investigations observe little or no effect of gastric stimulation on emptying despite reporting impressive clinical responses.[21,25] More recently, one group reported 7% reductions in gastric retention at 4 h in a cohort of 63 gastroparetics treated with gastric electrical stimulation.[33] In this investigation, improvements in nausea, vomiting and pain correlated with reductions in gastric retention only in those patients who exhibited normalization of their gastric emptying rate. The lack of a consistent, prompt prokinetic effect of electrical stimulation on gastric emptying raises questions about causation. Although few natural history studies have been performed, it has been reported that many patients with idiopathic gastroparesis (especially with a postviral aetiology) exhibit spontaneous recovery of impaired gastric motor function over months to years.[38] This raises the possibility that any apparent benefits of gastric stimulation on emptying may result from inherent reestablishment of normal gastric neuromuscular function rather than any motor stimulatory action of electrical therapy. Verification of any prokinetic effects of gastric stimulation awaits controlled comparison with sham stimulation.

Other gastrointestinal mechanisms may contribute to the benefits of gastric stimulation in gastroparesis. In dogs, reduced fundic tone and increases in volume

are observed with long-pulse stimulation.[39] Volume increases persist after vagotomy and are blunted by nitric oxide synthase inhibitors, suggesting mediation by non-vagal nitrergic pathways.[39] The effect of short pulse gastric stimulation on the accommodation reflex is less clear with different studies showing enhancement and reduction of the response. Most investigations observe no effect of gastric stimulation on slow wave activity as measured by electrogastrography.[30] Other effects of gastric stimulation of uncertain importance include increased lower oesophageal sphincter pressure, inhibition of gastric juice secretion and enhanced pancreatic elastase release. No consistent changes in levels of pancreatic polypeptide, motilin, gastrin and neurotensin have been observed.

Evidence suggests that the purported benefits of gastric stimulation in gastroparesis may stem from effects on extrinsic neuronal function. In animal models and gastroparesis patients, short pulse duration stimulation modifies sympathovagal activity as measured by heart rate variability.[40] In rats, gastric stimulation also modulates activity in thoracic spinal neurons that are responsive to gastric distention.[41] On central nervous system imaging with positron emission tomography, gastric stimulation increases activity in the thalamus of gastroparesis patients.[40] In rats, gastric stimulation with parameters similar to those for gastroparesis modulate activity in neurons in the paraventricular nucleus of the hypothalamus – a region involved in regulating food intake.[42]

Future directions

Ongoing research is focusing on developing new stimulus protocols for the next generation of gastric electrical stimulators for gastroparesis. The main drawback of single channel gastric pacing is the high energy requirement that precludes use of a portable or implantable pulse generator. Multichannel pacing devices in which long pulse duration stimuli are administered in sequential fashion to elicit propagating contractions offer promise in this area. In dogs, sequential, synchronized long pulse duration stimulation at frequencies slightly above that of the slow wave through 2–4 electrode pairs entrains slow waves, increases contractions and accelerates emptying.[43] The stimulation energy required for four channels stimulation is only 1% that of the single channel protocol.[43] Similar sequential stimulation methods reverse glucagon- and vasopressin-evoked gastric dysrhythmias and delays in gastric emptying.[44] The first use of multichannel pacing in humans has been reported in 16 patients with diabetic gastroparesis.[45] In this investigation, sequential pacing at 16 and 8 cm from the pylorus reduced symptoms by nearly two-thirds and accelerated emptying in most patients.

Another approach has been to modify the electrical properties of the gastric stimulus. One centre demonstrated acceleration of glucagon-delayed gastric emptying and induction of propagating antral contractions in dogs stimulated with train durations of 0.5–0.8 ms, pulse frequencies of 40 Hz, pulse widths of 2 ms, and amplitudes of 4 mA that were delivered only upon detection of intrinsic slow waves.[46] A second group has employed 4 s trains of 50 Hz depolarizations at 14 V rectangular voltage (Fig. 3).[47] In dogs, this method employs four electrode pairs that are activated sequentially with 4 s lag times between consecutive electrodes to elicit circumferential contractions that propagate anorally in the stomach in a manner that is

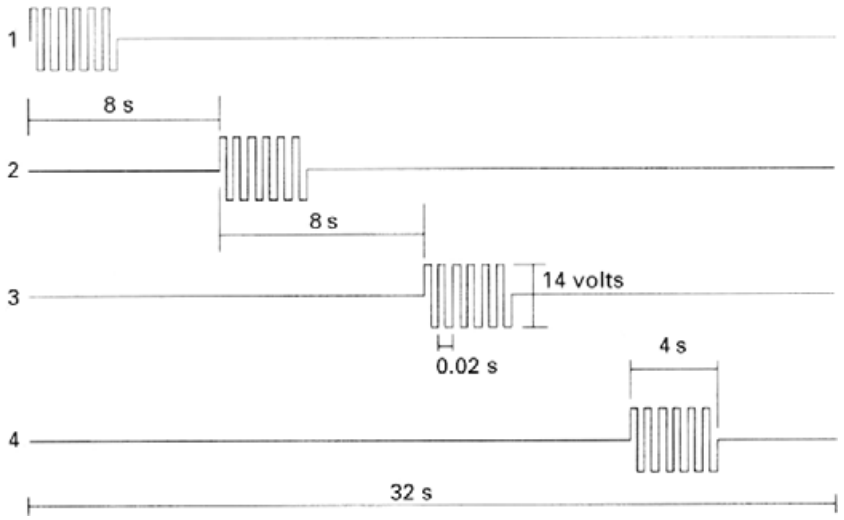

Figure 3 Characteristics of one sequential gastric pacing stimulation protocol in dogs are shown from the proximal (1) to the distal (4) lead. Four second pulse trains with an amplitude of 14 V and a frequency of 50 Hz are delivered in synchronized fashion with a 4 s lag between adjacent stimulus sites.[47]

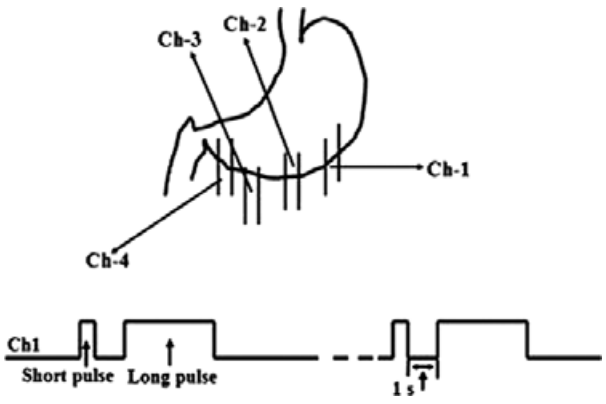

Figure 4 A sample dual pulse stimulus is shown being delivered to the most proximal electrode site in a canine model. The long pulse is a pacing stimulus that can entrain slow wave activity and promote motor activity while the short pulse exhibits anti-emetic actions.[49]

independent of intrinsic slow waves and is atropine-sensitive. Similar circumferential antral contractions were observed using these parameters in a gastroparesis patient at the time of laparotomy.[47] Recently, an implantable radiofrequency-controlled multichannel device was developed which delivers bipolar pulse trains at a frequency of 50 Hz at 8–16 V, with pulse trains of 1–120 s and 2 s to 1 h pauses between stimulation sessions.[48] These advances bring the reality of a clinical feasible gastric pacemaker system closer to reality.

Another stimulus modification involves delivery of variable stimuli at each electrode site to exert beneficial effects both on symptoms and motor function. In dogs in whom two electrode pairs are implanted, stimulation with pulses of short duration (0.3 ms) alternating with pulses of long duration (500 ms) exerts anti-emetic effects and reverses slow wave dysrhythmias evoked by vasopressin (Fig. 4).[49] This dual stimulation protocol combines the most effective features of current gastric pacing and stimulation methods.

Finally, investigators are evaluating novel methods for permanent implantation of stimulation electrodes that do not require laparotomy or laparoscopy. One group has developed a percutaneous electrode system to deliver short pulse duration gastric stimulation. With this method, a plastic cannula with an internal needle is introduced percutaneously through the abdominal wall and the gastric serosa and muscularis to the submucosal region.[50] Endoscopy is performed to verify that luminal perforation has not occurred. Saline is injected through the cannula to create a fluid filled space, a specially designed, self-anchoring electrode is introduced and the cannula is withdrawn leaving the electrode in position in the antral submucosal space. This method has been perfected in pigs and has been employed as a means of delivering stimulation to 24 patients for up to 8 weeks.[51] A second group has devised an electrode system that can be introduced percutaneously under endoscopic guidance at the time of gastrostomy placement.[52] This technique has been demonstrated to deliver pacing stimuli that could entrain intrinsic slow wave activity for several weeks. Such an anchored electrode system theoretically could be employed to deliver long pulse duration stimulation from an external current source without surgery or use of exposed intraperitoneal electrodes that could become infected. Other device companies have proposed miniaturized endoscopically paced stimulation systems which also would bypass the need for surgical placement.

GASTRIC ELECTRICAL STIMULATION IN OBESITY

Morbid obesity is prevalent and results from alterations in food intake coupled with reduced activity levels. Although subtle gastric motor abnormalities have been characterized in some patients with obesity, it is probable they play relatively minor roles in causing weight gain. Rather, morbid obesity more likely results from dysregulation of peripheral and central neurohumoral pathways that control food intake. Nevertheless, gastric electrical stimulation methods have been characterized that reduce food intake and promote modest weight reduction via action on gastric motor and afferent function and on extragastric neurohormonal activities.

Parameters of stimulation

Several gastric stimulation protocols have demonstrated efficacy in weight reduction in patients with morbid obesity and animal models of obesity. Each stimulus method for obesity is distinct from that employed by the gastric stimulator for gastroparesis. One method, the Transcend Implantable Gastric Stimulator (Medtronic), delivers 2 s pulse trains with a frequency of 40–100 Hz, a current of 3–10 mA, and a short pulse duration of 0.18–0.4 ms with intervening 3 s periods of no stimulation.[53,54] Two electrode positions along the lesser curvature of the stomach have been used – low insertions 6 cm proximal to the pylorus and high insertions just distal to the oesophagogastric junction.[53] Although this method may inhibit gastric motor function, it is believed to modulate food intake primarily via action on vagal afferent pathways.

A second method, the Tantalus system (MetaCure, Orangeburg, NY, USA), involves surgical placement of three electrode pairs – one pair in the fundus detects food intake, two pairs in the antrum detect intrinsic slow waves and deliver stimuli in synchrony with these slow waves.[55] Gastric stimulation begins when food enters the stomach and is delivered only postprandially. The device is postulated to work by augmenting antral contractions. This stimulated phasic motor activity enhances satiety that is elicited by postprandial gastric distention.[56] Stimulation parameters which enhance phasic antral contractions (termed gastric contractility modulation) include a frequency of 80 Hz, a pulse width of 1–2 s, and a current of 0.5–1 mA.[56] Because of its energy requirements, the device must be recharged weekly by an external charger.

Other stimuli have been tested in animal models and in non-clinical studies in humans. In dogs, retrograde stimulation through two electrode pairs positioned proximal to the pylorus for 8 s at a frequency of 50 Hz at a voltage of 16 V with intervening periods of no stimulation elicits retrograde contractions, reduces food intake and promotes weight reduction.[57] In healthy humans, retrograde stimulation through endoscopically placed mucosal electrodes 5 cm proximal to the pylorus at 9 cpm with a pulse width of 500 ms and a current of 5 mA reduces maximal water and food consumption by 13% and 16%, respectively, and delays gastric emptying.[58] These effects are accompanied by induction of satiety, bloating, discomfort, abdominal pain and nausea.

Results of clinical studies

Most studies of electrical stimulation to treat morbid obesity have employed the Transcend implantable gastric stimulator (Table 2). Clinical response is most often defined as excess body weight lost in these investigations. For example, a 5 foot 10 inch patient with a weight of 244 pounds has a BMI of 35 kg m^{-2}. If a BMI of 25 kg m^{-2} is considered ideal, then this patient should weigh no more than 174 pounds. A therapy that reduces ideal body weight by 20% of excess body weight will promote a weight loss of 14 pounds. The earliest device implantations were performed in 1995.[54] Two individuals followed >5 years from this group lost 38% and 67% of excess body weight. Four large trials have been subsequently performed using this method. A longitudinal follow-up of 65 European obese patients reported significant reductions in weight.[59] In the multicentre European Laparoscopic Obesity Stimulation Survey trial, 69 patients with a mean BMI of 41 kg m^{-2} (range 35–57 kg m^{-2}) exhibited 21 ± 5% reductions in excess body weight.[60] An initial sham-controlled trial in 103 patients in the United States reported no greater weight loss at 7 months in those with the device activated *vs* those with sham stimulation.[61] However on open label follow-up, patients exhibited 20% loss of excess body weight. In the open label Dual-Lead Implantable Gastric Electrical Stimulation Trial, 30 patients reported 23% reductions in excess body weight at 16 months with associated reductions in appetite and

Table 2 Case series (>5 patients) of gastric electrical stimulation for morbid obesity

Investigator	Number of patients	BMI on entry (kg m^{-2})	Study duration	Findings
Cigaina (2002)	24	>40	3 years to >5 years	24% decrease in excess body weight
D'Argent (2002)	12	42.7	9 months	30% decrease in excess body weight
Cigaina (2003)	11	46	6 months	10.4 kg weight loss, decreased postprandial cholecystokinin and somatostatin, decreased basal leptin and GLP-1
Cigaina (2004)	65	46.9	6 months	Decreased weight, decreased symptoms of acid reflux, improved glucose tolerance
De Luca (2004)	69	41	15 months	21% decrease in excess body weight
Favretti (2004)	20	40.9	10 months	23.8% decrease in excess body weight
Shikora (2004)	101	46	29 months	Approached 20% decrease in excess body weight (US-01 trial)
Shikora (2004)	30	42	16 months	23% decrease in excess body weight (DIGEST trial)
Champion (2006)	24	30–34.9	6 months	5.9% decrease in excess body weight
Hoeller (2006)	8	41	23 months	All patients had failed prior laparoscopic adjustable banding, no improvement in weight
Bohdjalian (2006)	12	43.2	>20 weeks	Study of Tantalus system, 9 kg weight loss, improved blood pressure

DIGEST, Dual-Lead Implantable Gastric Electrical Stimulation Trial.

enhancement of satiety.[61] Likewise in a study of 19 patients, stimulation for 6 months reduced appetite and meals consumed, and increased satiety (Table 3).[60] Other studies of 12–24 obese patients have reported reductions in excess body weight from 24% to 30% at 9–36 months after implantation.[53,54] In addition to reducing excess body weight, the implantable gastric stimulator for obesity decreases symptoms of gastroesophageal reflux disease and improves glucose tolerance.[59] In 2005, Medtronic issued a press release stating that a 200 patient double-blind, controlled trial of the Transcend device did not meet its study endpoint. This device has been used clinically in Europe and Canada but is not approved by the United States FDA.

The implantable gastric stimulator has been further investigated in selected obese patient subsets. In eight patients with failed laparoscopic adjustable banding surgery for obesity who subsequently underwent device implantation, gastric stimulation produced no reduction in BMI compared to preoperative values.[62] In another study of 24 patients with modest obesity (BMI 30–34.9 kg m^{-2}) who underwent stimulator implantation, the device produced losses of only 5.9% excess body weight after 6 months of therapy.[63]

Complications of the implantable gastric stimulator for obesity are similar to those of the device for gastroparesis. Intragastric lead perforations can occur after surgery and lead dislodgement has been observed in 20–25% of patients.[53]

One study has reported on the benefits of the Tantalus gastric contractility modulation device (Table 2).[55] In 12 patients, body weight decreased from 129 ± 5 to 120 ± 6 kg after 20 weeks. In nine patients followed for 52 weeks, weight further decreased to 112 ± 4 kg. Weight reductions were associated with improved blood pressure control. As with the Transcend system, the Tantalus device is available in Europe but is not FDA approved in the United States.

Proposed mechanisms of action

The different electrical methods for weight reduction reduce food intake via a variety of gastric and extragastric mechanisms. In dogs, a protocol similar to the Transcend device inhibits postprandial antral contractions – an effect blocked by guanethidine indicating sympathetic mediation.[64] Likewise in humans, stimulation through temporary fundic mucosal electrodes reduced food and water intake more than a sham stimulus and delayed gastric emptying in the initial 45 min after eating.[65] Similarly, retrograde stimulation delays emptying of solids and liquids and decreases antral tone.[66] Conversely, stimulation parameters similar to the Tantalus system augmented gastric emptying in 11 obese patients.[67] The abilities of these varied stimuli to reduce weight while having opposite effects on gastric retention suggests that modulation of gastric emptying may play only a minor role in the beneficial effects of stimulation in obesity.

Electrical stimulation also modulates other gastric functions. Parameters similar to the Transcend stimulator increase fundic volume via nitrergic activation and raise lower esophageal sphincter pressure in dogs (Fig. 5).[68] Retrograde stimulation increases gastric volumes, impairs accommodation, disrupts slow wave rhythm, and induces slow wave uncoupling. Stimulation-evoked tachygastria was antagonized by propranolol and phenotamine in one study, demonstrating participation of α- and β-adrenoceptor pathways.[69]

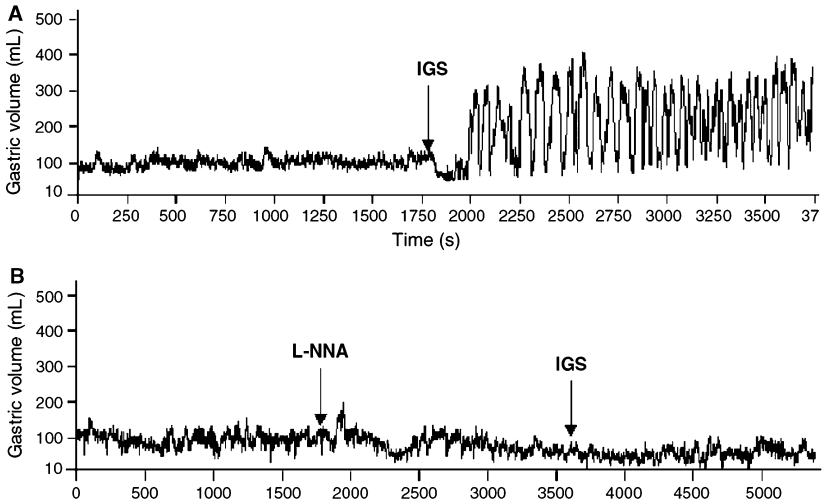

Figure 5 The effects of the implantable gastric stimulator (IGS) on gastric volume are shown in a dog model. Initiation of stimulation elicits a prompt and marked increase in gastric volume (A). In a second experiment in which the nitric oxide synthase inhibitor L-NNA is given, gastric stimulation no longer produces gastric relaxation indicating mediation of the effects of the electrical device by activation of nitrergic pathways (B).[68]

Table 3 Appetite and satiety in 19 patients before and after gastric electrical stimulation for morbid obesity

Months	Preprandial appetite	Postprandial satiety	Interprandial satiety	Number of meals
0	6.9 ± 2.0	1.3 ± 2.0	3.8 ± 2.8	3.4 ± 1.2
1	4.3 ± 3.3**	8.5 ± 2.5***	6.8 ± 3.2*	2.5 ± 0.5**
2	5.7 ± 3.1	3.2 ± 4.1*	7.0 ± 2.9**	2.1 ± 0.3***
3	4.0 ± 2.9***	7.6 ± 3.0***	7.2 ± 2.8**	2.3 ± 0.5**
4	4.8 ± 1.9**	7.1 ± 2.7***	5.5 ± 3.0*	2.2 ± 0.4***
6	4.7 ± 1.7**	7.6 ± 2.6***	6.1 ± 2.2**	2.1 ± 0.3***

All scores on scale from 0 to 10. Results at months 1–6 compared to month 0.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (from Ref. 60).

Although humoral abnormalities contribute to the pathogenesis of obesity, effects of gastric stimulation for obesity show no consistent alterations in hormone release. Stimuli similar to the Transcend system exert uncertain effects on ghrelin release, with studies showing increases, no effect or decreases in levels. Other humoral effects of stimulation include enhanced meal-evoked cholecystokinin and somatostatin release and increased basal GLP-1 and leptin in one study but no effects on cholecystokinin and leptin in others.[70,71] Insulin release was reduced in one investigation.[71] Other hormones involved in satiety including obestatin and colonic peptide YY are unaffected by stimulation. In a study of the Tantalus device, stimulation reduced ghrelin levels.[67] Retrograde stimulation decreased insulin release but had no effect on leptin or glucagon levels.[72]

Evidence suggests that reduced food intake with gastric stimulation stems from action on extrinsic nerve transmission to brain regions involved in appetite control. Vagal afferent fibres transmit information from the stomach to the nucleus tractus solitarius, arcuate nucleus and thalamus. Direct electrical stimulation of the vagus, ventromedial thalamus or lateral hypothalamic nucleus reduces food intake.[73–75] Gastric stimulation with parameters similar to the Transcend device decreases vagal parasympathetic activity as determined by heart rate variability. T9–T10 spinal neurons also are activated by gastric stimulation, suggesting additional participation of non-vagal pathways.[76] Such stimuli exert excitatory effects on the nucleus tractus solitarius, ventromedial hypothalamus and brain regions normally associated with drug craving in addicted subjects (orbitofrontal cortex, hippocampus, cerebellum and striatum).[77] Gastric stimulation increases expression of neurons containing oxytocin (reduces appetite) and decreases expression of neurons containing orexin (increases appetite) in the hypothalamus.[78] In another study, increases in ghrelin-immunoreactive neurons in the paraventricular nucleus of the hypothalamus were observed within 2 h of electrical stimulation and increases in cholecystokinin-immunoreactive neurons and CCK mRNA in the hippocampus were observed after 2 weeks.[79]

PERSPECTIVE

The literature suggests that there may be significant benefits from gastric electrical stimulation in treating gastroparesis and morbid obesity. Extensive investigations in humans and in animal models of gastric dysmotility and satiety provide insight into the mechanisms of stimulation techniques in each clinical setting. There are several issues to be addressed before the technique should be confidently embraced in either condition. There is a paucity of controlled data comparing responses of gastric stimulation to medications or other surgical techniques. The data in gastroparesis is limited to one small study which showed modest symptom reductions during sham stimulation, but more impressive benefits in the unblinded, follow-up period of active stimulation.[21] It has been postulated that the limited initial response stemmed from prolonged postoperative inhibitory effects on gastric motor function that masked the benefits of stimulation. However, it is established that many diabetics do not exhibit worsening gastric function over time despite progression of neuropathy and that many idiopathic gastroparetics resolve their symptoms and motor dysfunction within a few years after disease onset.[38,80] These observations raise the possibility that the observed benefits of electrical stimulation in gastroparesis may be artificially enhanced because the natural history of disease predicts spontaneous symptom improvement regardless of choice of therapy. Most series of gastric stimulation in obesity report significant weight reductions, but many have observed only modest decreases in BMI (20–25% of excess body weight). This contrasts with the more impressive benefits of another similarly invasive procedure,

laparoscopic adjustable gastric banding, that can produce reductions of up to 87% of excess weight and the similar reductions (22% of excess body weight) of non-surgical approaches of diet restriction and medications.[81] These observations mandate the performance of controlled comparisons of gastric stimulation with sham techniques and other established treatments to validate their purported benefits.

Additional investigation is warranted to better define optimal stimulation protocols to treat gastroparesis and obesity. There has been a lack of standardization of inclusion and exclusion criteria, electrical pulse properties and anatomic stimulation sites. With nausea and vomiting, is abnormal gastric retention an appropriate parameter for patient selection? If so, what degree of gastroparesis is likely to benefit from electrical therapy? Should gastric stimulation be considered only for certain aetiologies for gastroparesis (e.g. diabetes) and denied for other causes (e.g. idiopathic)? If so, this would suggest important differences in the pathogenesis of different forms of gastroparesis. Nausea and vomiting appear to respond to stimulation, but is there a role for electrical methods in the controlling other symptoms? If the technique acts partly via modulating afferent transmission, does the method have a role in managing discomfort and pain that can be dominant in some gastroparetics? Do distinct stimulation parameters differentially control nausea, bloating, and discomfort? With obesity, there is less consensus about which stimulation parameters are best for effecting weight reduction. Different stimulation protocols delay, accelerate or have no effect on gastric emptying and have no consistent action on gastric and extra-gastric hormonal factors. In animal and human models, direct electrical stimulation of the vagus or brain suppress appetite suggesting that modulating gastric function may not be important for electrical techniques to reduce food intake. Finally, are there undefined electrical protocols that can elicit greater weight reduction that can make gastric stimulation a more attractive option to treat obesity?

Despite these concerns, gastric electrical stimulation is likely to continue to play significant roles in managing gastroparesis and may become more important for obesity. Future investigations will improve our understanding of gastric factors that contribute to each condition and will characterize novel stimulation parameters with increased efficacy in reducing symptoms of gastric dysmotility and controlling food intake. Progress in battery technologies, non-surgical means of electrode implantation and miniaturization of electrical devices may expand options for each condition. These advances promise to improve care in these conditions in the coming years.

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COMPETING INTEREST

The author has no competing interests.

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