Pacing the Gut in Motility Disorders

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Opinion statement

Similar to cardiac pacing, gastrointestinal (GI) pacing is an attractive idea and may become a promising therapy, as the GI organs, like the heart, have their own natural pacemakers. Over the past 10 years, electrical stimulation of the gut has received increasing attention among researchers and clinicians. Several clinical studies have shown that gastric electrical stimulation (GES) with short pulses is able to reduce nausea and vomiting in patients with gastroparesis and that GES with long pulses is able to pace the intrinsic gastric slow waves and thus normalize gastric dysrhythmia. However, possible placebo effects cannot be ruled out, although recent animal studies have revealed various peripheral and central mechanisms involved with GES. Electrical stimulation of the small intestine, colon, or anal sphincter also has been reported for the treatment of dumping syndrome, constipation, and fecal incontinency. Similarly, there is a lack of placebo-controlled studies. In our opinion, pacing of the gut has great potential for the treatment of various GI motor disorders. However, none of the commercially available devices is designed for pacing the gut. The lack of well-suited devices and the invasive nature of gut pacing slow down the progress and clinical applications of gut pacing.

Introduction

Gastrointestinal (GI) electrical stimulation or pacing was advocated as a possible treatment for gastric motor dysfunctions as early as 1963. The first intent of gut pacing was to treat postoperative ileus using intraluminal electrical stimulation [1]. The efforts were interrupted due to conflicting results [2–4]. In the late-1960s and early-1970s, experiments, primarily in the canine model, began to elucidate the nature of GI myoelectrical activity and its relation to contractile activity [5,6]. These results and the development of techniques of myoelectrical recording were critical to further research in GI pacing. Since that time there have been numerous reports on the applications of electrical stimulation to affect GI motility both acutely and chronically [7–10].

Several stimulation parameters are involved in electrical stimulation, including frequency, pulse width, and amplitude (usually in the order of a few milliamperes without much variation). Various methods of electrical stimulation are derived from the variations of electrical stimuli. These include long-pulse stimulation, short-pulse stimulation, and stimulation with trains of pulses rather than repetitive single pulses.

LONG-PULSE STIMULATION

This method is most frequently reported in the literature (but mostly limited to animals) because it is able to “pace” or entrain natural slow waves. It is also called electrical pacing or gut pacing. In this method, the electrical stimulus is composed of repetitive single pulses with a pulse width in the order of milliseconds (10 to 600 ms) and a stimulation frequency in the vicinity of the physiologic frequency of the gastric/intestinal slow wave (Fig. 1A). However, it should be noted that currently there are no implantable devices capable of generating pulses with a width longer than 2 ms available on the market. Consequently, little information on its clinical efficacy is available.

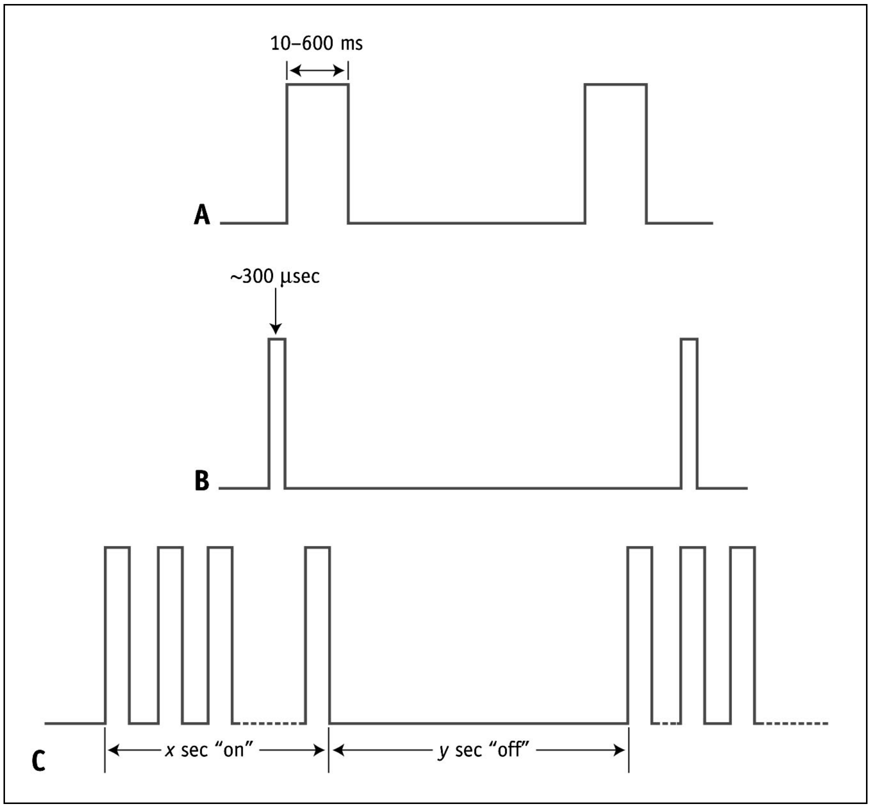

Figure 1. Electrical stimuli using three different methods of gastric electrical stimulation. **A,** Long-pulse. **B,** Short-pulse. **C,** Trains of short pulses. µsec—microseconds.

SHORT-PULSE STIMULATION

In contrast to long-pulse stimulation, the pulse width in this method is substantially shorter and is in the order of a few hundred microseconds (µsec). The stimulation frequency is usually a few times higher than the physiologic frequency of the gastric slow wave (Fig. 1B). Most of the commercially available cardiac pacemakers or nerve stimulators are capable of generating short pulses.

TRAINS OF SHORT PULSES

In this method, the stimulus is composed of repetitive trains of short pulses and is derived from the combination of two signals: a) continuous short pulses with a high frequency (in the order of 5 to 100 Hz); and b) a control signal to turn the pulses on and off, such as *x* seconds "on" and *y* seconds "off." The addition of *x* and *y* then determines the frequency of the pulse train (Fig. 1C). This kind of stimulation has been used frequently in nerve stimulation. Commercially available stimulators are capable of generating trains of pulses with a pulse width of less than 2 ms. Recently, gastric electrical stimulation (GES) with trains of short pulses has been introduced in the treatment of obesity [11–13]. If its clinical efficacy in reducing weight is proven, it would have a great impact on society, as obesity affects approximately one third of the general population in most countries [14].

Technically, GI electrical stimulation can be achieved via different positioning of stimulation electrodes summarized as follows:

1. Serosal electrodes. Most commonly, stimulation electrodes are placed directly on the serosal surface of the GI tract. The advantage of this method is the guaranteed contact and direct effect on the targeted organ. The disadvantage is its invasiveness. Surgical procedure is required using either laparotomy or laparoscopy.
2. Intraluminal or mucosal electrodes. Alternatively, electrodes may be placed on the mucosal surface of the GI tract. The major disadvantage of this method is that the contact between the stimulation electrodes and mucosa is not guaranteed when suction electrodes or intraluminal electrodes are used, especially for electrical stimulation of the stomach. However, intestinal electrical stimulation using intraluminal ring electrodes is feasible [15,16].

This review is focused on clinical applications or implications of GES/intestinal electrical stimulation. More detailed information on basic research and mechanistic data may be found in a number of recent reviews [7–10].

Treatment

GES

- Two methods of GES have been applied to treat patients with gastroparesis: short-pulse GES and long-pulse GES. In the literature, they are also called high-frequency/low-energy GES and low-frequency/high-energy GES, respectively. Most clinical studies have been performed using short-pulse GES. This is because the therapy, called Enterra® therapy (Medtronic, Inc., Minneapolis, MN), has been approved by the US Food and Drug Administration (FDA) for humanitarian use, and the implantable pulse generator is commercially available.

Short-pulse GES (Enterra® therapy)

Standard parameters

The configuration of electrical stimuli in this method is similar to that of trains of short pulses (Fig. 1C). There are two pulses in each train, and the interval between the two pulses is 71.43 ms (or a frequency of 14 Hz); the train is repeated every 5 seconds. Typically, the pulse has a width of approximately 0.33 ms or 330 μsec and an amplitude of approximately 5 mA [17••].

Indications and contraindications

The device is approved for humanitarian use in treating nausea and vomiting in patients with gastroparesis. Three groups of gastroparesis have been studied: diabetic, idiopathic, and postsurgical [17••,18–21,22•,23–25]. No significant difference has been reported in treating nausea and vomiting among these three groups of patients. Because the effects of the therapy on gastric emptying are conflicting, whereas the effects on nausea and vomiting are more consistent, it is better to apply this method of GES in patients with severe nausea and vomiting rather than severe gastroparesis. Adverse events, other than technical failure, such as pocket infections, are rare; thus, there are no clear contraindications for the therapy.

Efficacy of therapy

The most consistent improvement with this therapy is seen with nausea and vomiting, although improvement in other physiologic measurements and/or clinical profiles also has been reported. It also should be noted that most of the studies were not placebo-controlled.

Symptoms A leading multicenter clinical trial in 33 patients with diabetic or idiopathic gastroparesis showed a 50% reduction in weekly vomiting frequency with the therapy during the randomized phase of GES "on" and GES "off" [17••]. However, the total symptom score was not significantly altered during this controlled period. In the open-label period, the weekly vomiting frequency was substantially dropped, from 17.3 at baseline to 2.6 at 6 months and 4.8 at 12 months after the treatment. However, the improvement in the total symptom score or quality of life SF-36® (Medical Outcomes Trust, Inc., Boston, MA) score was not substantial, although it was statistically significant. Consistent results were noted in other studies, with the major improvement being in vomiting frequency [18–21,22•,23–25]. Overall, success in treating nausea and vomiting was reported in about 50% to 75% of patients, varying from one center to another. This variation could be attributed to the placebo effect, as no noticeable variations in the therapy, such as different stimulation parameters, have been reported.

Although the placebo effect cannot be ruled out, controlled basic research data in animals also showed significant improvement in vomiting and behavior suggestive of nausea with the therapy but not as dramatic as reported in open-label clinical studies [26••]. These basic and clinical findings seem to suggest that the therapy does improve nausea and vomiting, but the improvement may be augmented by the placebo effect.

Gastric motility The short-pulse GES has been repeatedly shown to be ineffective in altering or pacing gastric slow waves and thus is not capable of normalizing gastric dysrhythmia [26••,27]. This is due to the narrowness of pulses used in this method. No clinical data on the effects of the therapy on gastric contractions are available. Gastric emptying was shown to be improved in some studies but not in others [17••,19,21,23,24]. In our opinion, the improvement in gastric emptying reported in some studies could be attributed to the improvement in overall clinical profiles of the patients rather than the direct effect of the short-pulse GES.

Clinical profiles Overall improvement in clinical profiles, including a reduction in hospitalization and medications, and improvement in nutritional status and quality of life are commonly seen with the therapy [22•,28,29]. Approximately 50% of patients who required nutritional support with a feeding jejunostomy tube do not need the feeding tube after long-term GES [22•].

Diabetes Improvement in diabetes was reported in a few studies involving patients with diabetic gastroparesis reflected as a significant decrease in HbA1c [18,23,30].

Cost effectiveness

One recent study compared the health care costs between the GES therapy and the standard pharmacologic therapy and reported a significant and substantial reduction in the cost with the GES therapy during the second and third years after implantation of the pulse generator [31].

Special points

As the therapy may not be effective in a certain percentage of patients, screening of patients before the surgical implantation of the pulse generator is advantageous. The method for such screening is described by Ayinala et al. [32]. Temporary GES is performed via pair of stimulation electrodes attached to gastric mucosa under endoscopy, with the connecting wires coming from the mouth.

Pros and cons of therapy

Pros This therapy is effective in treating nausea and vomiting in more than 50% of patients who are refractory to medical therapy; it is reversible, although minimally invasive surgical procedure (laparoscopy) is involved; and its side effects are rare.

Cons The stimulation parameters used in this method are limited due to the availability of the implantable device and have not been optimized clinically, although a recent canine study does seem to support the selection of stimulation parameters used in clinical studies [33]; there is a lack of mechanistic studies, and major mechanisms involved in the improvement of nausea and vomiting remain unclear; its effects on gastric motility are limited; and it is questionable whether gastroparesis can be resolved with the therapy.

Long-pulse GES

- Whereas long-pulse GES is the most commonly used method in animal research, its clinical applications have been limited due to the fact that the method has not been FDA approved and that there have been no commercially available implantable stimulators capable of generating long pulses.

Standard parameters

The configuration of electrical stimuli for long-pulse GES is shown in Figure 1B. The stimulus is composed of repetitive single long pulses with a pulse width of about 300 ms and amplitude of 5 mA. These values may be adjusted to ensure the entrainment of natural slow waves (the slow waves are phase locked with the stimuli). The stimulation frequency should be the same as or slightly higher than the intrinsic frequency of the gastric/intestinal slow waves [34,35••].

Indications and contraindications

Best candidates for long-pulse GES are those with refractory gastroparesis and known gastric dysrhythmia measured by noninvasive electrogastrography [36]. Patients with severe nausea and vomiting unrelated to gastric dysrhythmia may not be good candidates for long-pulse GES.

Efficacy of therapy

Gastric dysrhythmia Unlike short-pulse GES, electrical stimulation with long pulses is able to entrain or pace slow waves of the gut, including the stomach. Accordingly, this method of electrical stimulation is called electrical pacing or pacing. However, it should be noted that complete entrainment (the natural slow waves are phase locked with electrical stimuli) can only be achieved when the stimulation frequency is slightly higher than the natural frequency of the slow wave and that the maximum entrainable frequency of gastric slow waves in humans is about 40% higher than its intrinsic normal frequency [34]. Although it has been theorized that slow waves of the gut are generated by interstitial cells of Cajal (ICC), recent studies seem to indicate that gastric/intestinal slow waves can be paced in the absence of ICC [37,38].

Normalization of gastric dysrhythmia, such as tachygastria in gastroparesis and postsurgical dysrhythmia, has been consistently reported in clinical studies [35••,39,40]. These clinical findings have been confirmed by various animal studies [26••,40–42]. The normalization of bradygastria is achieved by pacing or entrainment, whereas the normalization of tachygastria is accomplished by overriding because tachygastria is usually originated in the distal stomach and pacing is performed via the proximal stomach.

Gastric emptying There has been only one open-label clinical study showing an acceleration of gastric emptying with short-term, long-pulse GES (4 weeks) in patients with gastroparesis [35••]. However, alterations of gastric emptying with GES of long pulses have been reported in a number of animal studies. It seems that single-channel GES with long pulses has no effect 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 [43–45], whereas two- or four-channel GES with long pulses is able to improve gastric emptying in both healthy and diseased models of canines [46,47].

Conversely, retrograde GES with long pulses delivered via electrodes placed at the distal antrum was reported to delay gastric emptying in both dogs and humans [48–50]. It was further reported that the inhibitory effects of retrograde GES on gastric emptying in healthy volunteers were associated with reduced food intake and reduced gastric accommodation [50,51].

Gastric tone No clinical data are available on the effect of long-pulse GES on gastric tone. However, canine studies have consistently shown inhibition of both fundic and antral tone with long-pulse GES in an energy-dependent manner [52,53]. With low-stimulation energy, long-pulse GES may change gastric tone slightly, which may be beneficial to patients with impaired gastric relaxation. With high-stimulation energy, GES could substantially inhibit gastric tone and result in substantial distention of the stomach, which may actually lead to early satiety and be applied for treating obesity rather than gastroparesis.

Symptoms One single-center clinical study reported a significant reduction in dyspeptic symptoms after 4 weeks of GES of long pulses in patients with gastroparesis [35••]. However, canine studies have shown that long-pulse GES is not capable of alleviating vasopressin-induced vomiting and behaviors suggestive of nausea [26••].

Pros and cons of long-pulse GES

Pros Conceptually, GES with long pulses is more suited to the stimulation of smooth muscles of the stomach or gut than GES with short pulses; it is able to pace gastric slow waves and thus normalize gastric dysrhythmia; and it is capable of altering gastric motility such as gastric tone and gastric emptying.

Cons The method is not FDA approved, and none of the commercially available implantable stimulators is capable of delivering long pulses; there is a lack of clinical studies; and its direct effects on nausea and vomiting may be limited.

Emerging therapies on electrical stimulation

- Several new methods of GES have been proposed recently. These methods have been tested in animals, with promising results. However, clinical studies are needed to probe their clinical validities.

Dual-pulse GES

This novel method of GES has recently been proposed by combining short and long pulses. In this method, the stimulus of GES is composed of a short pulse (in the order of a few hundred microseconds) followed with a long pulse (in the order of a few hundred milliseconds). A canine study has shown that dual-pulse GES is capable of both normalizing gastric dysrhythmia and alleviating symptoms suggestive of nausea and vomiting induced by infusion of vasopressin [54]. Apparently, the proposed method of dual-pulse GES is more attractive than the conventional method of electrical stimulation, in which only short pulses or long pulses (but not both) are utilized.

Synchronized GES

Conventionally, GES is performed at a fixed frequency delivered at random without consideration of the occurrence of the intrinsic gastric slow waves. Although GES performed at the tachygastrial frequency has a potent effect on inhibiting gastric contractions, no solid evidence is available in the literature that GES performed at the physiologic frequency is capable of enhancing gastric contractions. A novel method has recently been proposed: synchronized GES [55], which requires the implantation of two pairs of electrodes, one for the detection of gastric slow waves and the other for stimulation. In this proposed method, each electrical stimulus is delivered upon the detection of an intrinsic slow wave peak. That is, GES is performed at the occurrence of cyclic physiologic electrical events of the stomach. By synchronizing each electrical stimulus with the intrinsic slow wave, it is hypothesized that it is capable of enhancing gastric contractions. A recent canine study showed that synchronized GES in fasting state significantly increased the amplitude of gastric contractions and improved impaired postprandial antral motility induced by glucagons [55]. Apparently, this method can only be applied in patients with normal gastric slow waves but antral hypomotility. It would fail if gastric slow waves were dysrhythmic.

Optimal method of GES

Pathophysiology of gastroparesis includes impaired gastric or fundic relaxation, visceral hypersensitivity, gastric dysrhythmia, antral hypomotility, and delayed gastric emptying. Based on findings in the literature and emerging technologies proposed in animal research, an optimal method of GES may include all elements of GES that are beneficial to addressing various pathophysiologic factors. Such a method may be called multichannel synchronized dual-pulse GES. In this method, GES is performed using two or more channels, which is known to improve gastric emptying even in healthy animals. Second, the electrical stimuli are composed of both short pulses (to stimulate nerves and alleviate nausea and vomiting) and long pulses (to stimulate smooth muscles and to normalize dysrhythmia and enhance the relaxation of the stomach). Third, the stimuli are delivered in synchronization with gastric slow waves (to enhance gastric contractions). However, there is a need to prove this concept in patients with motility disorders and to design and develop such a kind of implantable stimulator.

Intestinal/anorectal electrical stimulation

- In addition to GES, electrical stimulation also has been performed in the small intestine, colon, and anorectum. However, most studies were performed in animals, except in the case of anal electrical stimulation (AES).

Small intestinal electrical stimulation

Forward intestinal pacing

Intestinal electrical stimulation with long pulses has been shown capable of entraining intestinal slow waves [56], normalizing intestinal dysrhythmia [57], and accelerating delayed intestinal transit induced by ileal brake [58].

Backward intestinal pacing

Several canine studies have demonstrated that backward intestinal pacing slows intestinal transit, induces retrogradely propagated intestinal contractions, and improves intestinal absorption [59,60]. A number of other studies have shown similar effects of backward intestinal stimulation in canine models of short bowel and dumping syndromes [61–64].

Colonic electrical stimulation

Clinical studies

A few studies have reported on colonic pacing in patients from one single center [65–67]. The preliminary clinical data seem to suggest that colonic pacing (with long pulses) is able to improve defecation in constipation patients with colonic inertia [66] and alter colonic slow waves in patients with irritable bowel syndrome [65].

Animal studies

Improvement in colonic transit has been reported in a number of animal studies with colonic electrical stimulation. In a canine study with sequential (multichannel) colonic electrical stimulation, propagated colonic contractions were generated, and the movement of colonic content was accelerated [68,69]. Similar acceleration of colonic transit also was noted in rats [70].

Anorectal electrical stimulation

Clinical studies

A few studies were reported in the literature regarding AES in patients with fecal incontinence, with limited success [71–73]. AES in these clinical studies was performed using trains of short pulses. An increase in anal sphincter pressure was consistently reported; however, long-term efficacy in treating fecal incontinence has not been demonstrated, likely attributable to the phenomenon of muscle fatigue. Sacral nerve stimulation seems to be more effective in treating fecal incontinence [74].

Animal studies

A similar increase in anal sphincter pressure with AES was reported in dogs [75,76]. Moreover, recent canine studies also have shown an increase in rectal compliance and the involvement of the α-adrenergic pathway with AES.

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