Effects of pacing parameters on entrainment of gastric slow waves in patients with gastroparesis

Z. Y. Lin, R. W. McCallum, B. D. Schirmer, and J. D. Z. Chen. Effects of pacing parameters on entrainment of gastric slow waves in patients with gastroparesis. Am. J. Physiol. 274 (Gastrointest. Liver Physiol. 37): G186–G191, 1998.—The aim of this study was to investigate the effect of pacing parameters on the entrainment of gastric slow waves in patients with gastroparesis. Four pairs of cardiac pacing wires were placed on the serosal surface of the stomach in 13 patients with gastroparesis. After a baseline recording for 30 min, gastric pacing was performed in a number of sessions with different effective parameters, each lasting for 30 min. The following parameters were found to be effective for the entainment of the gastric slow wave: a pacing frequency 10% higher than the intrinsic gastric slow wave frequency (IGF), 300 ms pulse width, and 4 mA pacing amplitude. A reduction of pacing amplitude from 4 to 2 mA and 1 mA reduced the percentage of entrainment of the gastric slow wave to 79 ± 10% and 50 ± 11%, respectively. Pacing with a pulse width of 30 or 3 ms was not able to entrain the gastric slow wave in any of the patients. An ectopic pacemaker of tachygastria found in three patients was reversed with gastric pacing. It was concluded that gastric pacing at a frequency up to 10% higher than the IGF and with an amplitude of 4 mA and a pulse width of 300 ms is able to completely entrain the gastric slow wave and normalize gastric dysrhythmias in patients with gastroparesis.

As in the heart, there is a pacemaker in the stomach, located in the midcorpus along the greater curvature. It paces gastric myoelectrical activity generated by smooth muscles, yielding so-called “slow waves” propagating circumferentially and distally toward the pylorus with an increasing amplitude and velocity. The gastric slow wave is omnipresent, and its frequency in humans is about three cycles per minute (cpm) (2, 12, 16). The frequency and propagation of gastric contractions are determined by the gastric slow wave. This is because second or spike potentials are phase-locked with the gastric slow wave.

Gastroparesis is a chronic disorder of gastric motility, defined as delayed gastric emptying of a solid meal in the absence of any organic or structural etiology. Gastroparesis may be attributed to impaired motor activity and/or impaired myoelectrical activity (1, 3, 6). These include gastric hypomotility, uncoordinated antral contractions, and uncoupled or dysrhythmic gastric myoelectrical activity. It is known that tachygastria is associated with gastric hypomotility and that uncoupled or dysrhythmic gastric myoelectrical activity leads to a lack of coordinated gastric contractions or peristalsis.

Electric stimulation has made a recognized therapeutic contribution in the field of cardiology. However, the role for electrical stimulation in the gastrointestinal tract remains controversial, and conflicting results have been reported (2, 7, 9, 13, 14, 17–19, 21, 22, 24, 25, 27, 28). No systematic studies have been performed in humans to derive effective parameters for gastric pacing. Without optimization of pacing parameters, some investigators claimed success in entraining the gastric slow wave with gastric pacing, whereas others reported failure. Only in very few patients with gastroparesis was electrical stimulation performed (13). The aim of this study was to derive effective pacing parameters and attempt to entrain the gastric slow waves in patients with gastroparesis.

Materials and Methods

Subjects. Thirteen patients (3 male, 10 female, ages 19–52 yr) with a history of severe gastroparesis participated in the study. Gastric emptying of a solid test meal (4) was performed in nine of the 13 patients, and all showed delayed gastric emptying, a percentage of retention in 2 h equal to or larger than 70%, a gastric half-emptying time (t½) greater than 150 min, or both (see Table 1). Four patients were either not able to eat the solid test meal or vomited during the test. The common symptoms of these patients were severe nausea, vomiting, abdominal pain, weight loss, and anorexia. All patients were refractory to standard medical therapy and underwent abdominal surgery for the placement of a jejunostomy feeding tube for nutritional support. The study protocol was approved by the Human Investigation Committee at the University of Virginia Health Science Center, and written consent forms were signed by all subjects before the study.

Placement of pacing electrodes. Four pairs of temporary 28-gauge cardiac pacing wires (A&E Medical, Farmingdale, NJ) were placed on the serosal surface of the stomach during the scheduled surgery for the placement of a feeding jejunostomy tube. The pacing wires were arranged in an arching line along the greater curvature from the corpus to the pylorus. The distance between two electrodes in the pair was 1 cm, and the distance between adjacent pairs of electrodes was 4 cm. The most distal electrodes were 2–4 cm above the pylorus. The pacing electrodes were affixed to the gastric serosa by partially embedding the wire in the seromuscular layer of the stomach. The wires were brought out through the abdominal wall percutaneously and placed under a sterile dressing. One of the pairs was used for gastric pacing, and the rest were to record gastric myoelectrical activity.

Protocol for gastric pacing. Three days or more after the surgery and the placement of the pacing wires, while the patients were still in the hospital, myoelectrical activity of the stomach was recorded via the pacing wires in the fasting state for at least 1 h to confirm that the pacing wires were in the right position and functioning.

The study on gastric pacing was initiated 1 wk or more after the surgery, when the patients had recovered. On the
day of the study, each patient was fasted for 6 h or more and given no medications with known effects on gastrointestinal motility. First, a 30-min baseline recording was made via all the pacing wires. Then an adjustable electrical stimulator (model A310; World Precision Instruments, Sarasota, FL) was used in a constant current mode, and the stimulus consisted of periodic rectangular pulses with adjustable frequency, amplitude, and pulse width. To optimize gastric pacing for the entrainment of the gastric slow waves, a series of sessions with different pacing parameters was performed in the fasting state, each lasting for 30 min. There was a sham pacing for 5–10 min between two consecutive study sessions. The pacing frequencies tested included frequencies 10% lower and 10% higher than the intrinsic gastric slow wave frequency (IGF), and 4, 5.5, and 12 cpm. Three different pulse width values were used: 3, 30, and 300 ms. The amplitude of the pulse changed from 1 to 4 mA.

Recording and analysis of gastric myoelectrical activity. Gastric myoelectrical activity was recorded from the electrodes distal to the pacing electrodes during the entire study. All signals were displayed on a Dynograph chart recorder and simultaneously recorded on a tape recorder. The low and high cutoff frequencies were 0.02 to 30 Hz, respectively. All recorded signals were subjected to both visual analysis and computerized spectral analysis. For the computerized data analysis, all recorded signals were played back from the tape recorder, digitized by a 12-bit analog-to-digital converter, and stored in ASCII files on an IBM-AT computer. The sampling frequency was 60 Hz. To reduce the volume of data, the digitized serosal recording was filtered by a digital low-pass filter with a cutoff frequency of 0.5 Hz and sampled again at 2 Hz. A smoothed power spectral analysis method called the periodogram method (23) was applied to compute the power spectrum of the recording. The frequency of the gastric slow wave with and without gastric pacing was obtained from the power spectrum. The gastric slow wave was defined as bradygastria if its frequency was lower than 2 cpm and had a duration of longer than 2 min. Similarly, the gastric slow wave was defined as tachygastria if its frequency was greater than 4 cpm.

Percent entrainment was defined to quantitatively assess the effect of pacing parameters. Percent entrainment was defined as the ratio of the difference between the recorded slow wave frequency during pacing and the intrinsic baseline frequency, and the difference between the pacing frequency and the intrinsic baseline frequency. Entrainment was defined as 100% if the recorded frequency was exactly the same as the pacing frequency. If the intrinsic frequency was 3.0 cpm, the pacing frequency was 3.3 cpm, and the recorded frequency during pacing was 3.2 cpm, the percent entrainment would be 67% \(\left[\frac{3.2 - 3.0}{3.3 - 3.0}\right]\).

### RESULTS

Entrainment of the gastric slow wave and normalization of gastric dysrhythmia. Effective pacing parameters for the complete entrainment of the gastric slow wave were found to be as follows: pacing frequency, 10% higher than the IGF; pacing pulse amplitude, 4 mA; pacing pulse width, 300 ms. With these parameters, the entrainment of the gastric slow wave was achieved in all 13 patients. The entrainment usually occurred a few minutes after gastric pacing was initiated (see Figs. 1 and 2). The entrainment of the gastric slow wave was demonstrated by the fact that the slow waves were phase-locked with the pacing stimulus a few minutes after the initiation of pacing, as seen in Fig. 1. The mean time required for the complete entrainment was 5 min (see Fig. 2). It was also observed that the stomach exhibited a brief memory, with the gastric slow wave remaining entrained for a few cycles after the termination of gastric pacing. After that brief period, the frequency of the gastric slow wave was reduced to a level below the IGF for a few cycles and then returned to the baseline frequency before pacing. In the baseline recording, the gastric slow wave showed a regular pattern in nine of the subjects. As shown in Fig. 3, the gastric slow wave propagated distally with an increasing amplitude and velocity. The frequency of the gastric slow wave in these patients ranged from 2.60 to 3.0 cpm, with a mean value of 2.86 ± 0.06 cpm (mean ± SE).

Tachygastria of higher than 4 cpm was observed in four of the patients. Three patients showed ectopic gastric dysrhythmia in the antrum. As shown in Fig. 4, the gastric slow wave in the proximal stomach had a regular frequency of 3 cpm, whereas the gastric slow

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Table 1. Patient information

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, Yr</th>
<th>Gastroparesis</th>
<th>GE, t</th>
<th>GE, %</th>
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<tbody>
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<td>1</td>
<td>M</td>
<td>39</td>
<td>Diabetic</td>
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<tr>
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<td>F</td>
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<td>85</td>
<td>260</td>
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<tr>
<td>4</td>
<td>F</td>
<td>48</td>
<td>Postvagotomy</td>
<td>89</td>
<td>790</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>38</td>
<td>Diabetic</td>
<td>ND</td>
<td></td>
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<td>F</td>
<td>45</td>
<td>Idiopathic</td>
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<td>202</td>
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<tr>
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<td>77</td>
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<td>F</td>
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<td>Idiopathic</td>
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<td>170</td>
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<tr>
<td>9</td>
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<td>198</td>
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<tr>
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<td>F</td>
<td>41</td>
<td>Postvagotomy</td>
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<td></td>
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<tr>
<td>13</td>
<td>F</td>
<td>36</td>
<td>Diabetic</td>
<td>ND</td>
<td></td>
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</table>

GE, gastric emptying; %, percentage of gastric retention after 2 h; GE, t, time for half of solid meal to be emptied; ND, not done because the patient could not tolerate the isotope-labeled solid meal for GE study. M, male; F, female.
wave in the antrum showed tachygastria of higher than 4 cpm. Table 2 summarizes the frequencies of the gastric slow waves in these three patients before, during, and after gastric pacing. The proximal stomach had regular frequency and the distal stomach exhibited tachygastria or dysrhythmia. Pacing at a frequency higher than the IGF of the proximal stomach was able to entrain the proximal stomach as well as the distal stomach. The time required for the entrainment (or normalization) varied from 2 to 10 min. It took more time to entrain the distal stomach than the proximal stomach. More importantly, the gastric slow wave remained in regular rhythm even when gastric pacing was terminated. Typical tracings illustrating the normalization of tachygastria are presented in Fig. 5.

The fourth patient showed tachygastria of 4.0 to 4.2 cpm on postoperative days 3 and 5. Unlike in the other three patients, the tachygastria observed in this particular patient was not ectopic and did not originate in the antrum but originated in the pacemaker area and propagated distally toward the pylorus. Gastric pacing at a frequency of 3.2 cpm was not able to reduce this elevated frequency of the gastric slow wave on postoperative days 5 and 7. After postoperative day 7, however, the gastric slow wave in this patient was reduced spontaneously to 3.2 cpm, and gastric pacing at a frequency 10% higher than the IGF was able to entrain the gastric slow wave.

Effects of pacing parameters. Although gastric pacing at a frequency 10% higher than the IGF was able to entrain the gastric slow wave, it was found that there

Table 2. Effects of gastric pacing on frequency of the gastric slow wave in 3 patients with ectopic gastric dysrhythmia

<table>
<thead>
<tr>
<th>Position/Patient</th>
<th>Patient: DH</th>
<th>Patient: JC</th>
<th>Patient: BS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency, cpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before pacing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Proximal</td>
<td>2.7</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Distal</td>
<td>4.6</td>
<td>Dysrhythmia</td>
<td>6.8</td>
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<tr>
<td>During pacing</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>3.0</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Distal</td>
<td>3.0</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>After pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>2.8</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Distal</td>
<td>2.8</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Time for entrainment, min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Distal</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Pacing frequency was 3.0 cpm for patient DH, 3.3 cpm for patient JC, and 3.5 cpm for patient BS.
was an upper limit beyond which the gastric slow wave could not be driven. As shown in Fig. 6, there was no linear relationship between the pacing frequency and the actual driven frequency. Gastric pacing at a frequency equal to or higher than 4 cpm was able to increase the frequency of the gastric slow wave but was not able to completely entrain the gastric slow wave. The percentage of entrainment was substantially reduced as the pacing frequency was further away from the intrinsic baseline frequency. The maximum driven frequency of the gastric slow wave was found to be 4.3 cpm, achieved at a pacing frequency of 5.5 cpm. One of the patients showed gastric arrhythmia during gastric pacing at a frequency of 5.5 cpm and vomited during gastric pacing at a frequency of 12 cpm. Gastric pacing at a frequency 10% lower than the IGF was not able to entrain the gastric slow wave but slightly reduced the frequency by 3.0 ± 0.1%.

Figure 7 shows the effect of pacing pulse amplitude on the entrainment of the gastric slow wave. An amplitude of 4 mA yielded 100% entrainment, whereas amplitudes of 2 and 1 mA resulted in 79 ± 10% and 50 ± 11% entrainment, respectively.

The pulse width of the pacing stimulus was also found to affect the entrainment of the gastric slow wave. With a fixed pacing frequency 10% higher than the IGF and a fixed pacing pulse amplitude of 4 mA, gastric pacing with a pulse width of 300 ms was able to entrain the gastric slow wave completely, whereas gastric pacing with pulse widths of 30 and 3 ms only entrained the gastric slow wave by 45 ± 15% and 14 ± 8%, respectively.

DISCUSSION

This study has shown that the result of gastric pacing was associated with every pacing parameter, including pacing frequency, pacing amplitude, and pulse width. The gastric slow wave in patients with gastroparesis was successfully entrained using the parameters derived in this study. Ectopic tachygastria or dysrhythmia in the antrum could be normalized by gastric pacing at a frequency of ≈ 3 cpm.

It is conceivable that the variable success of gastric pacing in the literature can be attributed to variabilities in the pacing parameters incorporated. In a well-designed experiment, Kelly (15) studied the effect of different pacing parameters on the performance of gastric pacing and derived appropriate pacing parameters for the entrainment of the gastric slow wave in dogs. The effect of gastric pacing parameters on the entrainment of the gastric slow wave in patients with gastroparesis has not previously been investigated. The pacing parameters used in human studies were usually chosen on the basis of animal studies, which might have contributed to conflicting results reported...
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previously in the literature. A few studies suggested that the entrainment of the gastric slow wave became more difficult with increased time after surgery (14, 20). With the optimized pacing parameters, we have found that the entrainment of the gastric slow wave was possible even 1 wk or more after surgery. This study also indicates that the entrainment of the gastric slow wave was possible only when the pacing frequency was slightly higher than the IGF. One of the early studies, however, reported the entrainment of the gastric slow wave with a pacing frequency lower than the IGF (18). Although gastric pacing was able to entrain the gastric slow wave, our data showed that the entrainment lasted only for a few cycles when gastric pacing was terminated. This was in agreement with the findings reported in the literature (14). These data suggest that a permanent stimulation device would be necessary if gastric pacing is to be considered as a therapeutic approach.

Although gastric pacing was not able to entrain the gastric slow wave to a frequency lower than the IGF, it was capable of overriding ectopic tachygastria originating in the antrum. In the three patients with ectopic tachygastria in the distal stomach, the gastric slow wave in the proximal stomach had normal rhythms but apparently was not able to propagate distally and not able to override the antral dysrhythmia. During and after pacing, however, the antral dysrhythmia was normalized to a frequency identical to that in the proximal stomach, indicating that the propagation of the gastric slow wave from the proximal stomach to the distal stomach was restored. Similar findings on the normalization of gastric dysrhythmia were previously reported in postsurgical patients with and without gastroparesis (14). The entrainment of the gastric slow wave and normalization of ectopic tachygastria observed in this and previous studies suggest that gastric pacing may be an effective therapeutical approach for the treatment of patients with gastric dysrhythmia.

Although the gastric slow wave could be driven to a higher frequency, there seemed to be a maximum driven frequency. The mean maximum driven frequency in patients with gastroparesis found in this study was 4.2 cpm. This maximum driven frequency may prevent the stomach from being paced into the range of tachygastria (4–9 cpm). It is well known that the stomach does not contract when tachygastria occurs. That is, entrainment of the gastric slow wave at a frequency higher than 4 cpm may lead to gastric hypomotility. Pacing at a frequency higher than 4 cpm may lead to improvement in symptoms but should not be aimed at entrainment. A similar maximum driven frequency was previously observed in dogs (18, 21). An early study reported that the frequency of the gastric slow wave in dogs could be entrained from 5 to 8 cpm (18). In a recent study, the gastric slow wave in dogs was entrained from 5 cpm to a maximum of 6 cpm (10). Pacing at a frequency much higher than the IGF was also reported (10, 11, 21, 24). Some investigators reported the introduction of gastric contractions by gastric pacing at a frequency of 30 or 1,200 cpm (10, 11).

The earliest gastric pacing studies used a pacing frequency of 50 Hz (or 3,000 cpm). However, there seemed to be no significant improvement in the clinical symptoms with gastric pacing at that high frequency (21, 24). A recent study revealed a dramatic improvement in the symptoms of nausea and vomiting with gastric pacing at a frequency of 12 cpm and a pulse width of 300 µs, 1,000 times smaller than that used in our present study (10a). With a pulse width of 300 ms, however, pacing at a frequency of 12 cpm may induce an adverse effect such as gastric dysrhythmia or symptoms of nausea and vomiting, as we observed in some patients. Side effects of excessive belching were also reported in a previous study with a pacing frequency of 50 Hz (24).

The strength or energy of the pacing stimulus was found in this study to be important in the entrainment of the gastric slow wave. The pacing energy was determined by the pulse width and the pulse amplitude. Our data indicated that an amplitude of 4 mA and a width of 300 ms are the minimum requirements for the entrainment of the gastric slow wave in patients with gastroparesis. Gastric pacing with energy below this level may not be able to completely entrain the gastric slow wave. The values of these two parameters used in some previous studies were lower than those used in this study, which may explain the failure or partial entrainment of the gastric slow wave.

The effects of gastric pacing on gastric emptying and symptoms were investigated in nine of the 13 patients (5). Using the effective parameters derived in this study, gastric pacing was performed daily for 1 h before and 2 h after the meal for a period of 35 days or more in these nine patients. A significant improvement in gastric emptying and symptoms of gastroparesis was observed. This might be attributed to the entrainment of the gastric slow wave and normalization of dysrhythmia.

In summary, the entrainment of the gastric slow wave is associated with the pacing frequency and energy. With enough pacing energy and a frequency slightly higher than the IGF, the entrainment of the gastric slow wave can be achieved in patients with gastroparesis. Ectopic tachygastria or dysrhythmia may be normalized by gastric pacing at a frequency of ~3 cpm. Appropriate gastric pacing may be a therapeutic approach for the treatment of patients with gastric dysrhythmias.

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