Normalization of atropine-induced postprandial dysrhythmias with gastric pacing

LI WEI QIAN, XU MEI LIN, AND J. D. Z. CHEN
Lynn Institute For Healthcare Research, Oklahoma City, Oklahoma 73112

Qian, Liwei, Xuemei Lin, and J. D. Z. Chen. Normalization of atropine-induced postprandial dysrhythmias with gastric pacing. Am. J. Physiol. 276 (Gastrointest. Liver Physiol. 39): G387–G392, 1999.—Gastric pacing has received increasing attention recently. However, few studies have systematically assessed the effect of pacing on gastric dysrhythmias. The aims of this study were to investigate the effect of gastric pacing on gastric dysrhythmia and to explore whether the effect of gastric pacing was mediated via cholinergic nerves.

Eight hound dogs implanted with three pairs of serosal electrodes were studied. Three study sessions were performed on each dog. The experiment was conducted sequentially as follows: a 30-min myoelectrical recording immediately after a meal, intravenous injection of atropine or saline, and three sequential 20-min myoelectrical recordings with or without gastric pacing during the second 20-min recording. The percentage of regular slow waves (3.5–7.0 cycles/min) was calculated using spectral analysis. The percentage of the regular slow waves was progressively reduced from 96.7±1.7% at baseline to 29.6±9.0 (P<0.001), 23.1±7.1 (P<0.001), and 27.3±4.3% (P<0.001), respectively, during the first, second, and third 20 min after atropine injection. Normalization of the gastric slow wave was achieved with gastric pacing 2.3±1.0 min after the initiation of pacing. The percentage of regular slow waves was significantly increased both during pacing (93.6±2.4 vs. 23.1±7.1, P<0.002) and after pacing (70.9±6.8 vs. 27.3±4.3%, P<0.003) in comparison with the session without pacing. We conclude that 1) atropine induces gastric myoelectric dysrhythmia in the fed state, 2) gastric pacing is able to normalize gastric postprandial dysrhythmia induced by atropine, and 3) the effect of gastric pacing is not mediated by vagal cholinergic mechanism.

Gastric myoelectric activity; gastric motility; electrogastrography; cholinergic mechanism; electrical stimulation

GASTRIC DYSRHYTHMIA has been found in a number of clinical settings (6, 10), including unexplained nausea and vomiting (15), gastroparesis (1, 5), early pregnancy (29, 37), vagotomy (16, 36), and postsurgery (9). In these circumstances the frequency of the gastric slow wave becomes either abnormally high (tachygastria), abnormally low (bradygastria), or arrhythmic. Sometimes, an ectopic pacemaker may exist in the antrum. Gastric dysrhythmias are associated with gastric motor disorders and gastrointestinal symptoms. Abnormalities in the frequency of the gastric slow wave may lead to gastric hypomotility and/or uncoordinated or unpropagated antral contractions, yielding delayed emptying of the stomach. Therefore, it is conceivable that the normalization of gastric dysrhythmia may lead to an improvement in gastric motility, gastric emptying, and/or gastrointestinal symptoms.

Recently, gastric pacing has received increasing attention among researchers and clinicians. A number of studies have been performed to investigate the acute effect of gastric pacing on gastric motility, gastric emptying, and gastrointestinal symptoms in both dogs (3, 11, 14, 18, 23, 26) and humans (13, 17, 21, 22, 24, 32, 34). Although some of the results are still controversial, the majority of these studies seem to indicate that gastric pacing is able to entrain gastric slow waves, accelerate gastric emptying in patients with gastroparesis or the animal model of gastroparesis, and improve gastrointestinal symptoms. However, few studies have systematically assessed the effect of gastric pacing on gastric dysrhythmias (21, 35). None has ever investigated the mechanism of gastric pacing and whether the effect of gastric pacing would last when pacing is terminated. The aims of this study were to establish a postprandial model of gastric dysrhythmia in dogs, to investigate the effect of gastric pacing on gastric dysrhythmia, and to study whether the effect of gastric pacing is mediated via the cholinergic mechanism.

MATERIALS AND METHODS

Subjects. Eight healthy female hound dogs (14.5–22.6 kg) were implanted with pacing electrodes by laparotomy. Three pairs of 28-gauge cardiac pacing wires (A&E Medical, Farmingdale, NJ) were implanted on the serosal surface of the stomach along the greater curvature. The most distal pair was 2 cm above the pylorus, and the distance between adjacent pairs of electrodes was 4 cm. The electrodes in each pair were 1 cm apart. The electrodes were affixed to the gastric serosa by unabsorbable suture in the seromuscular layer of the stomach. The wires were brought out through the anterior abdominal wall, channeled subcutaneously along the right side of the trunk, and placed outside the skin for the attachment of pacing or recording. The most proximal pair of electrodes was used for forward pacing, whereas the remaining two were used for recording gastric myoelectric activity. The study was initiated about 10 days after the surgery. The protocol was approved by the animal committee of the Veterans Affairs Hospital (Oklahoma City, OK).

Study protocol. Each dog was studied in three sessions on three different days in a randomized order. In session 1 gastric myoelectric activity was recorded for 90 min after a test meal (225 g dry food, 838 kcal). Atropine (0.25 mg/kg; Elkin-Sinn, Cherry Hill, NJ) was given intravenously at the 31st min. Session 2 was the same as session 1 except for the replacement of atropine with saline. Session 3 followed the same protocol of session 1, except that forward gastric pacing was applied during the 2nd 20 min after the injection of atropine. The pacing signal was given at the most proximal pair of electrodes (10 cm from the pylorus) and was composed of periodic rectangular electrical pulses with a width of 550 ms, amplitude of 6 mA, and frequency of 6.67 cycles/min.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
These pacing parameters were previously shown to be able to entrain gastric slow waves in dogs (31).

Recording and analysis of gastric myoelectrical activity. Gastric myoelectrical activity was recorded from the two distal pairs of electrodes during the whole study using a multichannel recorder (Acknowledgement; Biopac Systems, Santa Barbara, CA). All signals were displayed on a computer monitor and saved on the hard disk by an IBM-compatible 486 PC. The low and high cutoff frequencies of the amplifier were 0.5 and 35 Hz, respectively. To lower the computational load, the signals were low-pass filtered again by software with a cutoff frequency of 10 Hz and sampled at 20 Hz. For the spectral analysis of the gastric slow wave, the signal was further filtered and sampled at 1 Hz. Adaptive spectral analysis was applied to compute the running spectra of the recording on a minute-by-minute basis (7). The percentage of regular gastric slow waves was used to assess the effects of atropine and pacing. It was defined as the percentage of time during which a dominant peak was observed in the range of 3.5–7.0 cpm in the running spectra. The definition of regular slow waves as 3.5–7.0 cpm was based on the analysis of baseline data in all 8 dogs. The dominant peak in the range of 0.5–3.5 cpm was defined as bradygastria. The dominant peak in the range of 7.0–12.0 cpm was defined as tachygastria. The corresponding recording period was called arrhythmia if there was no dominant peak in the range of 0.5–12.0 cpm (Fig. 1).

Statistical analysis. To investigate the effects of atropine and pacing, the 60-min postinjection data were divided into three 20-min periods. ANOVA was applied to assess the difference among the data obtained during the three 20-min periods after atropine or saline. To investigate the effect of pacing on atropine-induced dysrhythmia, the data obtained in session 1 (no pacing) and session 3 (with pacing) were compared using paired Student's t-test. All values are expressed as means ± SE. P < 0.05 was considered significant.

RESULTS

Effects of atropine. Regular gastric slow waves of 3.5–7.0 cpm were observed in all dogs in the fed state before the injection of atropine or saline (Fig. 2A), and the mean dominant frequency was 4.34 ± 0.16 cpm. Atropine consistently induced gastric dysrhythmia...
(bradygastria or tachygastria), which lasted at least 60 min (Fig. 2, B and C). The percentage of 3.5–7.0 cpm slow waves was progressively reduced from 96.7 ± 1.7% before atropine to 29.6 ± 9.0% (P < 0.001), 23.1 ± 7.1% (P < 0.001), and 27.3 ± 4.3% (P < 0.001) during the 1st, 2nd, and 3rd 20 min after atropine injection (Fig. 3). Saline had no effects on the gastric slow wave; the percentage of the 3.5–7.0 cpm slow wave was 94.0 ± 3.0, 99.4 ± 0.6, 95.6 ± 2.6, and 96.1 ± 2.3% during the corresponding recording periods (Fig. 3). Two dogs showed dominant tachygastria with a frequency of 9.53 ± 0.35 cpm. The other six dogs presented bradygastria with a frequency of 3.26 ± 0.08 cpm.

Effects of pacing. The normalization occurred a few minutes after gastric pacing was initiated. The time required for normalization of the atropine-induced bradygastria in the six dogs was 1.12 ± 0.36 min and for normalization of tachygastria in the two dogs, 5.97 ± 1.15 min. The average time for the normalization was 2.3 ± 1.0 min. After this transient period the gastric slow wave was actually completely entrained with the pacing stimulus.

Gastric pacing was found to be able to normalize atropine-induced dysrhythmias, and the effect seemed to last at least for 20 min after the termination of pacing. Both bradygastria and tachygastria were entrained at the pacing frequency during pacing and remained at the normal frequency range of 3.5–7.0 cpm after pacing (Figs. 4 and 5). The percentage of 3.5–7.0 cpm slow waves was increased to 93.6 ± 2.4% during pacing (P < 0.02 in comparison with that before pacing) and 70.9 ± 6.8% during the 20 min after pacing (P <
0.05 in comparison with that before pacing; Fig. 6). It can also be seen from Fig. 6 that the percentages of 3.5–7.0 cpm slow waves during and after pacing were significantly higher than the corresponding periods in the session of atropine without pacing ($P < 0.003$). All values presented were calculated from the recordings obtained from the most distal pair of electrodes. However, these were not different from the data obtained from the middle pair (Table 1).

**DISCUSSION**

This study demonstrated that atropine was able to induce gastric dysrhythmia and gastric pacing was capable of normalizing atropine-induced dysrhythmia. There was a transient time of a few minutes before normalization took place when pacing was initiated. The effect of pacing lasted for at least 20 min more when pacing was terminated. The normalization in the six dogs with dominant bradygastria occurred earlier than that in the two dogs with dominant tachygastria.

Gastric dysrhythmia is defined as abnormal myoelectrical rhythm of the stomach. It is further classified as tachygastria, bradygastria, and arrhythmia (6). It is not only found in a number of clinical circumstances but is also induced by chemical agents such as epineph-
of the vagal activity by atropine. The current study might be attributed to the inhibition of gastric myoelectric activity in the fed state was decreased dose-dependently by bolus injection of atropine. Sonesson and Lindberg (20) found that the frequency of gastric slow waves, its mechanism is still unclear. Although atropine was used to block the vagal activity in this study, pacing could still entrain and normalize tachygastria (bring the frequency up by 10.220.33.6 on June 24, 2017 http://ajpgi.physiology.org/ Downloaded from
Efficacy of gastric pacing is largely dependent on pacing parameters (32). The parameters that are most effective in entraining gastric slow waves are considered as the optimal parameters. Frequency, amplitude, and width of the pacing stimulus are the three important parameters that contribute to the success or failure of entrainment. It has been reported that the complete entrainment of gastric slow waves was possible only when the pacing frequency was slightly higher than the intrinsic gastric frequency (32, 34). One of the early studies, however, reported the entrainment of gastric slow waves with a frequency lower than the intrinsic gastric frequency (26). Furthermore, recent reports showed that pacing at frequencies much higher than the intrinsic slow-wave frequency (20–1,200 cycles/min) induced antral contractions (13, 14, 19). In a recent study it was found that energy of pacing stimuli, which was determined by the pulse width and the pulse amplitude, was equally important in achieving complete entrainment in patients with gastroparesis (33). The parameters used in this study were found to be the most effective for the entrainment of gastric slow waves in the canine model (31). Using these parameters, complete entrainment was achieved after a transient period of a few minutes both in the dogs with dominant bradygastria and in the dogs with dominant tachygastria. It seemed easier (or faster) to normalize bradygastria (bring the frequency up by pacing) than to normalize tachygastria (bring the frequency down).

Recently, a number of studies have indicated that gastric pacing with appropriate parameters is able to entrain gastric slow waves and improve gastric motility and emptying both in dogs and in humans. Bellahsene et al. (3) demonstrated that gastric pacing could accelerate gastric emptying in the canine model of gastroparesis. McCallum et al. (33) reported an improvement of gastric emptying and symptoms in patients with gastroparesis. Using high-frequency stimulation, Familoni et al. (13) observed an increase in gastric motility in dog. However, few studies have systematically investigated the effect of gastric pacing on gastric dysrhythmias (21, 35), and none has studied this effect quantitatively. In this study we quantitatively investigated the effect of gastric pacing on the canine model of atropine-induced postprandial gastric dysrhythmias and found that gastric pacing could markedly normalize the abnormality of gastric myoelectric activity. In addition, we noted that the effect could last at least 20 min after pacing was terminated.

Although gastric pacing could abolish abnormal gastric electrical rhythms and restore a healthy pattern of slow waves, its mechanism is still unclear. Although atropine was used to block the vagal activity in this study, pacing could still entrain and normalize the irregular rhythm of the gastric slow wave. This suggests that the mechanism of gastric pacing is not via the cholinergic nerves and may be via some other neurohumoral pathways.

<table>
<thead>
<tr>
<th>Table 1. Normalization of atropine-induced dysrhythmia measured from middle and distal pairs of electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regular Slow Waves in Pacing Session, %</strong></td>
</tr>
<tr>
<td>Baseline (no pacing)</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Distal pair</td>
</tr>
<tr>
<td>Middle pair</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 dogs. Slow wave, 3.5–7.0 cycles/min.
We thank Loretta Dunnaway for assistance in the preparation of the manuscript.

This study was supported by a biomedical research grant from the Whitaker Foundation.

Address for reprint requests: J. D. Z. Chen, Lynn Institute for Healthcare Research, 5300 N. Independence Ave., Suite 130, Oklahoma City, OK 73112.

Received 11 March 1998; accepted in final form 23 October 1998.

REFERENCES


