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Two- channel gastric pacing with a novel implantable gastric pacemaker accelerates glucagon-induced delayed gastric emptying in dogs

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Abstract

Backgrounds— The aim of this study was to investigate the efficacy of two-channel gastric electrical stimulation (GES) with a custom-made implantable pacemaker on delayed gastric emptying and gastric dysrhythmia induced by glucagon in dogs.

Methods— Six dogs were studied in four randomized session (saline, glucagon, glucagon with single-channel or two-channel GES). GES was applied via the first pair of electrodes for single-channel GES or the first and third pairs of electrodes for two-channel GES. Gastric emptying was assessed for 90 minutes and gastric slow waves were recorded at the same time.

Results— Both single-channel and two-channel GES improved gastric dysrhythmia ($P < 0.05$ vs. glucagon session). Two-channel GES but not single-channel GES improved glucagon-induced delayed gastric emptying at 30min, 45min, 60min, 75min and 90min.

Conclusion— Two-channel GES with a novel implantable pacemaker is more efficient and effective than single-channel GES in improving delayed gastric emptying induced by glucagon. This implantable multipoint pacemaker may provide a new option for treatment of gastric motility disorders.

Keywords

Gastric pacing; Implantable pacemaker; Gastroparesis; Gastric emptying; Gastric dysrhythmia

Introduction

Gastroparesis, or delayed gastric emptying, is a common cause of chronic nausea and vomiting as seen in gastroenterology practice. Diabetic cause remains one of the most common forms of gastroparesis. Patients with gastroparesis have frequent hospital admissions, lost employment, and poor quality of life. Diabetic gastroparesis may be attributed to impaired

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motor activity and /or impaired myoelectrical activity associated with hyperglycemia (1–5). Treatment options for gastroparesis remain very limited. Prokinetic agents, such as erythromycin, domperidone, tegaserod, are most commonly used for the treatment of gastroparesis. However, a fair number of patients are refractory to prokinetic agents (6), and up to 40% of patients can not tolerate chronic use of prokinetic agents due to side effects (7). Surgical options, such as gastric resection, have not been uniformly helpful and have accompanying mortality and morbidity (8).

Gastric electrical stimulation (GES) has been introduced as a potential therapy for gastric motility disorders (9,10). Long-pulse stimulation, also called electrical or gastric pacing, represents a promising new treatment for gastric motility disorders. In this method, electrical stimulus is composed of repetitive single pulses with a pulse width in the order of milliseconds (10–600 ms), and a stimulation frequency in the vicinity of the physiological frequency of the gastric slow wave. It is able to normalize gastric dysrhythmia (11,12). However, its effects on gastric emptying have been controversial. It appears that single-channel GES with long pulses may improve gastric emptying in both patients with gastroparesis and animal models of gastroparesis but has no effects on gastric emptying in healthy dogs or humans (13–16). Whereas, two or four-channel GES with long pulses has been reported to improve gastric emptying in both healthy and diseased models of canines (17,18). Compared with single-channel GES, multi-channel GES is substantially more efficient (requiring lower stimulation energy) in entraining gastric slow waves, and more effective in accelerating gastric emptying.

Unfortunately, so far, there have been no implantable devices capable of generating pulses with a width longer than 2ms. An implantable device necessitates miniaturization of circuits and lower power consumption. The advantages of multi-channel stimulation in efficacy and energy efficiency make it more practical for GES to be delivered by a permanent implantable device. Recently, a novel implantable multi-point gastric pacemaker has been custom-made. This device is capable of generating long pulses. It mimics long pulses by a series of biphasic pulse trains. In addition, a special technology, called Q-stim, has been applied. Q-Stim technology is an energy efficient alternative to traditional constant current or constant voltage stimulation. Based on the prescribed parameters, the stimulation generator calculates the charge needed at each channel of the pacing lead. It periodically tests the interface between this lead and the patient, obtaining a real-time electrical characterization, including measures of impedance and of the rate at which energy dissipates into the tissue. Based on these tests, and on the stimulation profile, the generator sends a precisely measured amount charge to the electrode-tissue interface – the connection between the pacing lead and the patient – Q-Stim intelligently compensates for aging of the system and changes in the patient's tissue condition. Q-Stim ensures that only the charge needed for stimulation is sent to the patient. In this way, it promotes patient safety, guarding against over-stimulation. It also maximizes energy efficiency, revolutionizing the state of the art in pacemaker technology. Older pacemakers could not adapt their stimulation on the basis of frequent and complete electrical characterization of the tissue interface, and so generated excess charge to prepare for a worst-case scenario. This, however, wasted energy and shortened battery life. Q-Stim, by contrast, uses its proprietary adaptive technology to maximize energy efficiency, and to conserve the lives of both the system battery and the pacing lead. That, in turn, promotes patient safety by reducing the need to replace the pacemaker over time.

Glucagon has been shown to increase blood glucose (BG) levels, impair gastric slow waves, and inhibit gastric motility (19–22). It has been used to establish an acute model of gastroparesis in various animal studies (23,24).

The aim of this study was to investigate the efficacy of two-channel GES using this newly developed implantable multi-point pacemaker in a canine model of delayed gastric emptying and gastric dysrhythmia induced by glucagon.

Materials and Methods

Animal Model

A group of 6 healthy female dogs (20–28kg) were involved in the study. The dogs were surgically prepared. After an overnight fast, the dogs were anesthetized with an initial intravenous infusion of sodium thiopental (5 mg/kg; Abbott Laboratories, North Chicago, IL) and maintained on IsoFlo (1.5% isoflurane, inhalation anesthesia; Abbott) in oxygen–nitrous oxide (1:1) carrier gases delivered from a ventilator following endotracheal intubation. Laparotomy was performed. Four pairs of 28-gauge cardiac pacing wires (A&E Medical, Farmingdale, NJ) were implanted on the gastric serosa along the great curvature at an interval of 4 cm with the most distal pair 2 cm above the pylorus. Two electrodes in each pair were arranged in the circumferential direction with a distance of about 0.5–1.0 cm. The electrodes penetrated into the subserosal layer and were affixed to the serosa by nonabsorbable sutures. The connecting wires of the electrodes were tunneled through the anterior abdominal wall subcutaneously along the right side of the trunk and placed outside the skin around the right hypochondrium for the attachment to the recorder (World Precision Instruments, Sarasota, FL). A cannula was placed in the duodenum, 20 cm beyond the pylorus, for the assessment of gastric emptying. The dogs were transferred to a recovery cage after receiving medications for postoperative pain control. The study was initiated after the dogs were completely recovered from the surgery (usually 2 weeks after the surgery). The study was approved by the Institutional Animal Care and Use Committees of the University of Texas Medical Branch at Galveston and performed at the University of Texas Medical Branch.

Experimental Design

The study consisted of two experiments using the following protocols.

Experiment 1—This experiment was designed to find the most efficient stimulation parameters to entrain gastric slow waves in the distal stomach. The custom-made implantable pacemaker described in the previous section was used for stimulation with adjustable frequency, amplitude, pulse width and time delay among different channels. After a 30-min baseline recording, a series of sessions with different parameters were performed in the fasting state, each lasting 10 min. A 5-min recording without GES was made between two consecutive periods with GES of different parameters. The stimulation frequency was fixed at 1.1 times of the intrinsic frequency (IF) of the gastric slow wave (25,26). The pulse width was gradually increased (one step per 5 min) until complete entrainment was achieved. The stimuli were applied via the first pair (the most proximal pair) of electrodes for single-channel GES, with amplitude 4 mA, or the first and third pairs (14 and 6cm above the pylorus) of electrodes for two-channel GES, with amplitude of 1mA for the first channel and 0.5mA for the third channel. The difference in current between the two pairs of stimulation electrodes was to prevent retrograde propagation of the stimulation current. The current in the proximal stimulation channel was higher than that in the distal stimulation channel. These stimulation parameters were based a previous study performed in our lab (17). During stimulation, gastric slow waves were recorded via the other two pairs (2nd and 4th pairs) of electrodes.

Experiment 2—The aim of this experiment was to investigate the effects of single-channel or two-channel GES on gastric emptying, gastric dysrhythmia induced by glucagon using the most efficient parameters derived from Experiment 1 for each specific configuration. The study was performed in four sessions (saline, glucagon alone, glucagon plus single-channel GES and

glucagon plus two-channel GES) on four separate days (at least 3 days apart) in a randomized order. Each session consisted of a 30-min fasting period and a 90-min postprandial period (broken into 4 periods for analysis: 15-min, 15-min, 30-min and 30-min). In the saline session, a small balloon was placed into the small intestine 5 cm distal to the duodenal cannula and inflated with 10 ml of air to block distal flow of gastric effluent. After a 30-min baseline recording in the fasting state, the animals were fed with 237ml liquid meal (240 kcal; total fat: 4.0g; total carbohydrate: 41.0 g; protein: 10.0g; Boost; Novartis Medical Nutrition, Minneapolis, MN, USA). Saline was injected intravenously immediately after feeding. Gastric effluent was collected from the cannula every 15 minutes for 90 minutes. Postprandial gastric myoelectrical activities were recorded for 90 minutes simultaneously with the collection of gastric effluent. BG levels were measured at 0, 15, 30, 60, 90minutes after feeding using a blood glucose monitor (Relion[®], Solartek Products Inc, Alameda, CA, USA). The protocol of the glucagon session was the same as the saline session except the dogs were given glucagon (IV, 0.01mg/kg) instead of saline to induce gastric dysrhythmia and delay gastric emptying. This dose was reported to reliably induce dysrhythmia and delay gastric emptying (27). The procedure of the single-channel or two-channel GES session was the same as those of the glucagon session expect that GES was continuously applied during the entire 90-min postprandial period.

Gastric electrical stimulation

The stimulus was generated by the custom-made implantable pacemaker but used externally (Model MGP-2, multi-point gastric pacemaker, Virginia Technologies Inc, Charlottesville, VA, USA Figure 1). The stimulation parameters were determined based on Experiment 1. The lowest parameters that were effective in entraining gastric slow waves were used for the experiment. Single-channel GES was delivered via the first pair (most proximal) of electrodes and composed of pulse trains with train on-time of 300–500 ms, pulse amplitude of 4 mA and pulse frequency of 50Hz. The frequency of the trains was 10% higher than the IF of the gastric slow waves (Figure 2A). Two-channel GES was applied via electrode pairs 1, 3 with train on-time of 200–400ms, pulse amplitude of 1mA for the first pair and 0.5 mA for the third pair (Figure 2B). The phase shift of electrical stimuli between the two channels was adjusted to be the same as the intrinsic phase shift calculated from the baseline recording.

Measurement and Analysis

Gastric emptying—The liquid test meal (a can of Boost, 237 ml, 240 kcal) was evenly mixed with 100 mg of phenol red, and gastric emptying was determined by the assessment of the amount of phenol red in each collection obtained from the duodenal cannula. For each collection of the gastric effluent, the volume was recorded and a sample of 5 ml was taken and stored in a freezer. The samples were analyzed all together at the end of the study using a spectrophotometer. Gastric emptying was assessed by computing the amount of phenol red recovered from each collection of the gastric effluent.

Gastric myoelectrical activities—Gastric myoelectrical activities were recorded from the fourth pairs of gastric serosal electrodes (distal antrum) using a special amplifier (Acknowledge III, EOG 100A; Biopac Systems, Inc, Santa Barbara, CA, USA) with a cutoff frequency of 35 Hz. A previous study showed that the highest prevalence of dysrhythmia was in the distal antrum (28). All signals were displayed on a computer monitor, digitized at a frequency of 100 Hz, and saved on the hard disk by a PC. For the spectral analysis of the gastric slow waves, the recorded myoelectrical signal was filtered by a digital low-pass filter with a cutoff frequency of 1 Hz and down-sampled at 2 Hz. Gastric myoelectrical activity is composed of rhythmic slow waves with a frequency of 4–6 cycles/min and spikes with a frequency of about 2–10 Hz. The recorded signal after low-pass filter (a cutoff frequency of 1 Hz) was composed of only slow waves as spikes were filtered out. The following parameters were derived from the

spectral analyses of the myoelectrical recordings. Percentage of normal slow waves reflects the regularity of gastric slow waves. The percentage of 4–6 cycles/min (cpm) gastric slow waves was defined as the percentage of time during which the recorded signal had a dominant frequency in the range of 4–6 cpm. It was computed using the adaptive spectral analysis method. In this method, each recording was divided into blocks of 1 min without overlapping. The power spectrum of each 1-min recording was calculated and examined to see if the peak power was within the range of 4–6 cpm. The 1-min recording was called normal if the peak power was within this range. Otherwise it was defined as dysrhythmia. The definition of the normal frequency range of 4–6 cycles/min was based on our previous study (29).

Statistical Analysis

All data are presented as mean $\pm$ SE. One-way analysis of variance (ANOVA) was applied to assess the difference among four sessions or three or more periods. Paired Student's t-test was used to test the difference between paired samples. Pearson correlation analysis was applied to study the correlation between the BG level and gastric emptying or gastric slow waves. A P value of <0.05 was considered significant.

Results

Optimization of stimulation parameters

The gastric slow waves were entrained in every dog by GES with the following parameters. The lowest parameters required to entrain the slow waves in the most distal channel recording included a train on-time of 300–500ms and pulse amplitude of 4 mA for single-channel GES and a train on-time of 200–400 ms, and pulse amplitude of 1 mA for the first channel and 0.5 mA for second channel for two-channel GES. Typical gastric slow waves during GES are presented in Fig 3 A. The minimum energy required was 6400 ± 584.2 ms mA² for single channel GES and 483 ± 10.5 ms mA² for two-channel GES. This represented a saving of more than 90% of energy over the single-channel GES.

Blood glucose levels

The BG levels were only slightly increased after the test meal in the control session. In the glucagon session, BG levels rose steeply from a mean of 67.2 ± 1.6 mg/dl to a mean of 201.7 ± 7.4 mg/dl, and remained above the normal range of 120mg/dl for at least 60 min after the glucagon injection. Neither single-channel GES nor two-channel GES altered the high glucose levels induced by glucagon (see Figure 4).

Effects of GES on glucagon- induced delayed gastric emptying

Glucagon delayed gastric emptying ($P < 0.001$, ANOVA) (see Figure 5). A significant negative correlation (Pearson correlation $r = -0.75$, $p < 0.001$) was found between the percentage of gastric emptying and the BG concentration (see Figure 6). In comparison with saline, glucagon significantly and substantially decreased gastric emptying of liquids at 15 min (0.65 ± 0.32 vs. $20.69 \pm 8.2\%$; $P = 0.048$), 30 min (1.26 ± 0.44 vs. $39.21 \pm 9.59\%$; $P = 0.01$), 45 min (2.19 ± 0.49 vs. $49.21 \pm 9.2\%$; $P = 0.005$), 60 min (6.39 ± 1.88 vs. $59.3 \pm 7.96\%$; $P = 0.0007$), 75 min (17.41 ± 5.34 vs. $66.3 \pm 6.29\%$; $P = 0.0001$), and 90 min (30.04 ± 7.38 vs. $71.12 \pm 5.13\%$; $P = 0.0004$) after feeding.

Compared with glucagon without GES, single-channel GES tended to improve glucagon-induced delayed gastric emptying, but statistically not significant ($P > 0.05$, ANOVA; see Fig 5) at all time after feeding. Two-channel GES significantly improved delayed gastric emptying induced by glucagon ($P < 0.01$, ANOVA; see Fig 5) at 30 min (14.96 ± 3.68 vs. $1.26 \pm 0.44\%$; $P = 0.02$), at 45 min (21.76 ± 3.64 vs. $2.19 \pm 0.49\%$; $P = 0.004$), at 60 min (29.76 ± 3.01 vs.

$6.39 \pm 1.88 \%$; $P=0.0008$), at 75 min (43.51 ± 3.32 vs. $17.41 \pm 5.34 \%$; $P=0.004$), and at 90 min (63.89 ± 5.68 vs. $30.04 \pm 7.38 \%$; $P=0.02$).

Effects of GES on glucagon-induced dysrhythmia

Glucagon injection provoked gastric dysrhythmia in all 6 dogs (Figure 7). The dysrhythmia appeared as early as 1 min but no later than 5 min post-injection in all dogs. The percentage of normal gastric slow waves was negatively correlated with the BG concentration (Pearson correlation $r=-0.58$, $p < 0.01$) (see Figure 8). The percentage of normal 4- to 6-cpm slow waves in the antrum was $93.0 \pm 2.2 \%$ in the control session and dramatically decreased to $31.2 \pm 8.2 \%$ in the first 15-min period after the glucagon injection ($p=0.0002$ vs. control), then rose to $79.9 \pm 6.8 \%$ and $84.9 \pm 6.8 \%$ during the second and third periods ($p=0.12$ and 0.38 , respectively, vs. control), and $87.9 \pm 4.6 \%$ during the fourth period. Figures 3B and 3C present typical tracings of regular gastric slow waves in the saline session and irregular slow waves 5 minutes after the injection of glucagon in the glucagon session.

Both single channel and two-channel GES improved gastric dysrhythmia induced by glucagon ($p < 0.05$, ANOVA) (see Figure 7). In the GES sessions, the percentage of 4- to 6-cpm slow waves for single-channel and two-channel GES in the antrum was $71.4 \pm 8.4 \%$ and $72.6 \pm 7 \%$ during the first 15-min after glucagon injection ($P=0.026$ and 0.004 vs. the corresponding periods in the glucagon session without GES, respectively). Figure 3D presents typical tracings of normalized slow waves in the two-channel GES session.

Discussion

In the present study, we found that glucagon increased BG levels, delayed gastric emptying of liquids and induced gastric dysrhythmia. These inhibitory effects on the stomach were associated with the high blood glucose levels. Both single channel and two-channel gastric pacing with the implantable pacemaker improved glucagon-induced gastric dysrhythmia. Two-channel, but not single-channel, gastric pacing significantly accelerated glucagon-induced delayed gastric emptying of liquids without altering BG levels. Two-channel gastric pacing was substantially more efficient in entraining gastric slow waves and more effective in accelerating gastric emptying than single channel gastric pacing.

Gastroparesis is one of the most common motility disturbances in diabetes mellitus and affects up to 58% of diabetics (30). In diabetic patients, the degree of glycemic control can influence the magnitude of gastric motor and myoelectric dysfunctions. However, maintaining a good control of blood glucose level is difficult. It is well known that gastric motility is paced by myoelectrical activity of the stomach; normalizing gastric myoelectrical activity may lead to improvement in gastric motility. The use of GES to treat gastroparesis has been proposed by investigators for decades, because the stomach, like the heart, has natural pacemakers and the myoelectrical activity they generate may be entrained by electrical pacing. That is, electrical pacing may normalize gastric dysrhythmia. It is conceivable that the success of GES in the treatment of gastroparesis mainly depends on stimulation parameters. Low-frequency, high-energy stimulation (long-pulse) has been shown to have the ability to improve gastric dysrhythmias (13,31), whereas high-frequency, low-energy stimulation (short pulse) is capable of reducing symptoms of nausea and vomiting but not gastric dysrhythmia in either animal models or patients with gastroparesis (32–34). One-point or single-channel GES with either long pulses or short pulses does not seem to be potent enough to accelerate gastric emptying (35).

Recently, multi-channel GES has been proposed. Previous studies have shown that multi-channel electrical stimulation provides better performance and requires less energy than single channel electrical stimulation (17,18,36). It is clear that although the gastric slow wave

originates in the proximal stomach, it has a higher propagation velocity and amplitude in the distal stomach. It is also known that the distal stomach plays a more crucial role than the proximal stomach in gastric emptying. Abnormalities in both myoelectrical activity and motility are often related to the distal stomach. Accordingly, electrical stimulation of the stomach should be better applied to the distal stomach. In single-channel electrical stimulation, however, stimulus can not be directly applied to the distal stomach, because this would result in a retrograde propagation of the slow wave and delay the emptying of the stomach. Multi-channel stimulation can be designed to accurately mimic the natural propagation and characteristics of the slow wave. MGP2, a custom-made multi-point implantable gastric pacemaker, delivers electrical pulses to multiple locations (up to 4 locations) along the greater curvature of the stomach through electrodes in the seromuscular layer, by adjusting the phase, timing, amplitude and duration of the pulse and pulse trains provided by each channel, peristaltic electrical waves can be generated to propagate progressively toward the pylorus. Consequently, the effect of electrical stimulation can be maximized in the distal stomach. The efficacy of this device was investigated in this study.

In the present study, glucagon caused significant delay in gastric emptying and induced gastric dysrhythmia. Gastric dysrhythmia was evoked almost immediately after the glucagon injection. The percentage of normal gastric slow waves was dramatically decreased during the first 15-min period after glucagon injection. This inhibitory effect was correlated with the high BG concentration. In the control session, the postprandial BG level was only slightly increased because of the low carbohydrate meal. After the glucagon injection, the BG level was significantly increased to over 200mg/dl. It is well known that the rate of gastric emptying in diabetes is affected by the BG concentration. A BG concentration of 140 mg/dl was able to delay gastric emptying when compared to euglycemia of 70mg/dl in both diabetes patients and normal subjects (37). The gastric motility abnormalities induced by glucagon in the present study were similar to those observed in diabetic patients. However, it should be noted that the acute injection of glucagon is not a good model of diabetic gastroparesis as glucagon does not induce any autonomic neuropathy.

The present results also showed that two-channel gastric pacing was more potent than single-channel gastric pacing and was capable of accelerating glucagon-induced delayed gastric emptying of liquids in every dog. As shown in Fig 5, gastric emptying was severely delayed with glucagon but dramatically accelerated (more than one fold increase) with two-channel GES. This increase would be of clinical significance if the same were achieved in patients. In addition, the two-channel gastric pacing required only about 7.5% of the energy required by the single-channel gastric pacing for the entrainment of gastric slow waves. However, neither the single-channel nor the two-channel gastric pacing altered blood glucose levels. This suggested that gastric pacing improved glucagon-induced gastric dysrhythmia and two-channel gastric pacing improved delayed gastric emptying by directly acting on gastric smooth muscle without altering blood glucose level. The limitation of this study was that the efficacy of two-channel GES was investigated only in an acute model of delayed gastric emptying and dysrhythmia. Further studies are required to confirm its therapeutic efficacy for diabetic gastroparesis in chronic and more appropriate model such as animals with vagotomy.

The findings of the present study indicate that the newly developed implantable pacemaker, MGP2, is suitable for the treatment of gastric motility disorders. Although the method is invasive, it can be performed relatively easily using laparoscopic surgery for the placement of the pacing electrodes. Patients will need to stay in the hospital for only a few days to recover from the surgery (32) or can be discharged the same day. On the other hand, the same methodology may be applied to treat motor disorders of other parts of the gut, such as the small intestine and the colon.

In conclusion, two-channel gastric pacing with a newly developed implantable pacemaker (MGP2) is capable of improving glucagon-induced gastric dysrhythmia and accelerating delayed gastric emptying. Two-channel gastric pacing is substantially more efficient and more effective than single-channel gastric pacing in improving delayed gastric emptying and gastric dysrhythmia induced by glucagon. This implantable multipoint pacemaker may provide a new device for the treatment of gastric motility disorders.

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Figure 1.
Implantable pacemaker (Model MGP-2).

Figure 2.

Stimulation parameters applied in single-channel and two-channel GES: A) signal-channel GES: 50 Hz, 4 mA, 300–500ms; B) two-channel GES: 50Hz, ch-1 1mA and ch-3 0.5mA, 200–400ms.

Figure 3.

Typical tracing of gastric slow waves recording in channel 4 (distal stomach). A: Recording of stimulation and slow waves in fasting state. Slow waves were entrained with GES. B: Normal gastric slow waves 5 min after feeding. C: Recording of dysrhythmia 5 min after glucagon injection. D: Recording of normalized gastric slow waves 5 minutes after glucagon injection in GES session.

Figure 4. Blood glucose levels in the saline, glucagon, single-channel GES and two-channel GES sessions. The data shown in the figure are mean $\pm$ SE (N=6).

Figure 5. Percentage of gastric emptying of liquids in the saline, glucagon, single-channel GES and two-channel GES sessions. The data shown in the figure are mean $\pm$ SE (N=6).

Figure 6.

The correlation between the percentage of gastric emptying and blood glucose levels (Pearson correlation $r=-0.75$, $p<0.001$).

Figure 7. Percentage of normal 4–6 cpm gastric slow waves during different recording periods in the saline, glucagon, single-channel GES and two-channel GES sessions. The data shown in the figure are mean±SE (N=6).

Figure 8.
The correlation between the normal percentage of gastric slow waves and blood glucose levels (Pearson correlation $r=-0.58$, $p<0.01$).