Absence of the Interstitial Cells of Cajal in Patients With Gastroparesis and Correlation With Clinical Findings

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The interstitial cells of Cajal (ICCs) are fundamental in the generation of gastric slow waves. The role of these cells in gastroparesis has not been established. We studied 14 gastroparetic patients (9 diabetic, 4 idiopathic, and 1 postsurgical) for whom standard medical therapy had failed and who had been treated with a gastric electrical stimulator for at least 3 months. All patients had a full-thickness antral gastric wall biopsy at the time of surgery. The biopsy samples were stained with c-*kit* and scored for the presence of ICCs. Baseline electrogastrogram recordings were obtained for 30 minutes in the fasting state and for 2 hours after a test meal. The patients assessed their total symptom score at baseline and at 3 months. Five patients had almost no ICCs and were compared with nine patients with 20% to normal cell numbers. Both groups did respond symptomatically to gastric electrical stimulation. However, patients with depleted ICCs had significantly more tachygastria and had significantly greater total symptom scores at baseline and after 3 months of gastric electrical stimulation. ICCs are absent in some patients (up to a third) with diabetic or idiopathic gastroparesis, and the absence of these cells is associated with abnormalities of gastric slow waves, worse symptoms, and less improvement with gastric electrical stimulation. (J GASTROINTEST SURG 2005;9:102–108) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Electrogastrogram, gastric myoelectrical activity, gastric electrical stimulation, gastroparesis, interstitial cells of Cajal

The condition of gastroparesis predominately affects patients with longstanding diabetes but may occur after surgery or without a known etiology (idiopathically). Patients suffer from a variety of symptoms, including nausea, vomiting, epigastric pain, premature satiety, abdominal fullness, bloating, epigastric pain, and weight loss.[1] The major diagnostic abnormality is gastric dysmotility, which is commonly measured scinitigraphically. The presence of more than 10% of a standard meal remaining at 4 hours has been suggested to be the gold standard diagnostic test.[2]

Treatment has long focused on improving gastric motility with prokinetic medications, including metoclopramide, domperidone, and erythromycin, and on treating nausea with antiemetics.[3] If standard medical therapy fails, surgical options include placement of a feeding gastrostomy or jejunostomy or performing a vagotomy and pyloroplasty, partial gastrectomy, or a total gastrectomy.[4,5] Electrical pacing of the stomach to promote contractions has been introduced, but the treatment requires an external stimulator and transabdominal electrodes.[6] This technique additionally converts the abnormal gastric rhythm of

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tachygastria to a normal rhythm. Recently, an implantable device (Enterra Therapy, Medtronic, Minneapolis, MN), initially termed, incorrectly, a gastric pacemaker, has become available from Medtronic for treatment of gastroparesis. Our initial published report demonstrated a marked reduction in both nausea and vomiting and a mild effect on gastric emptying in 25 patients suffering from longstanding gastroparesis.[7] This device does not promote contractions or normalize tachygastric rhythms[17] and should be called a gastric electrical stimulator (GES).

Networks of the interstitial cells of Cajal (ICCs) pace gastrointestinal phasic motor activity necessary for the orderly propulsion of digested food, by producing slow waves. The ICCs were discovered by Dr. Cajal in 1893 and thought originally to be fibroblasts.[8–10] These slow waves are initiated by inward currents in the ICCs, which depolarize in the muscularis propria smooth muscle. The depolarizations activate ion channels, which initiate contractions ensuring coordinated motor responses to neural reflexes. In the stomach, the networks of ICCs in the myenteric plexus pace these slow waves. These cells occur throughout the gastrointestinal tract and are in close proximity to enteric nerves. They stain for CD117, and on electron microscopy have dense granules.[10,11] Their loss has been implicated in the gastroparesis of diabetes based on a strain of mice that spontaneously become both diabetic and gastroparetic as ICCs are lost.[12] There are no published data addressing ICCs in patients with diabetes or other types of gastroparesis.

We hypothesized that the ICCs may play a role in gastroparetic patients. We obtained full-thickness biopsies of the antrum of the stomach during the surgery to place the GES and specially stained these biopsy samples for the presence of ICC. The presence of ICCs was correlated with both gastric electrical recordings and the patient's self-assessed total symptom score (TSS). We learned that those patients with absent or deficient ICC populations had dysrhythmic gastric myoelectric activity and more severe symptoms of gastroparesis.

MATERIALS AND METHODS

Subjects

The gastric wall biopsy samples of 14 patients with refractory gastroparesis (9 diabetic, 4 idiopathic, and 1 postsurgical) undergoing laparotomy for GES placement were analyzed. The research protocol was approved by the Human Subjects Committee at The University of Kansas Medical Center, and written consent forms were obtained from all subjects.

Surgical Procedure

The GES system used consisted of three components: the implanted pulse generator, two leads, and the stimulator programmer (Medtronic). During the abdominal surgery, one pair of unipolar electrodes was placed into the muscularis propria of the stomach 9.5 and 10.5 cm proximal to the pylorus on the greater curvature. The electrodes were secured to the serosa of the stomach using 5-0 silk sutures. The other ends of the electrodes were connected to the pulse generator, which was placed in a subcutaneous pocket above the abdominal wall fascia to the right of the umbilicus.[7] The GES was initiated within 48 hours of surgery. The stimulus parameters used in this study were low energy and high frequency parameters: pulse width, 330 μsec; pulse (current) amplitude, 5 mA; and frequency, 14 Hz, cycle ON time of 0.1 second and cycle OFF time of 5.0 seconds. During the implantation surgery, gastric wall biopsy samples were taken from the antrum and preserved in formalin. These biopsies were taken by cutting out 1 cm^2 of gastric wall and leaving the mucosa intact. The defect was closed with interrupted 3-0 silk sutures.

Immunohistochemistry

Immunohistochemical staining was performed using the Dako Autostainer (Dako, Carpenteria, CA). Monoclonal antibodies purchased from Dako were used according to the standard protocol. To this end, the paraffin-embedded tissue was deparaffinized in xylene and alcohol, rehydrated, and placed into 10 mmol/L citrated buffer, pH 6, antigen retrieval solution. The tissue covered with buffer was placed into the microwave for 10 minutes, followed by blockage of endogenous peroxidase in 0.3% hydrogen peroxide for 30 minutes. The primary antibodies to CD117, neurofilaments, and S-100 were applied for 30 minutes, washed, and incubated with the secondary horseradish peroxidase−labeled antibodies and streptavidin peroxidase. For color development, diaminobenzidine hydrogen peroxide was used creating a brown reaction. Ethyl green was used for counterstaining.

All slides were examined microscopically and scored by a pathologist (I.D.) blinded to the clinical status of the patient for the presence of ICCs. The findings were expressed as follows: normal number of ICCs, equivalent to normal controls; reduced number of ICCs equivalent to 20–40% of the control: almost complete loss of ICCs, to the point that not more than 5 cells were seen per 10 high-power fields (<10% of the control). The slides stained with antibodies to neurofilaments and S-100 were used for general orientation and to ascertain that nerve cells

and ganglia are present in the specimen and that they can be demonstrated by using a immunohistochemical approach.

Recording and Analysis of Gastric Myoelectrical Activity

Gastric myoelectrical activity was measured with surface electrogastrography (EGG) for 30 minutes in a supine position in the fasting state and for 2 hours after the ingestion of a meal as previously described.[13] Before the placement of electrodes, the epigastric skin was shaved, cleaned, and abraded with sandy skin-prep jelly (Omni Prep; Weaver & Co., Aurora, CO) to reduce the impedance. Two silver-silver chloride ECG electrodes (DNM, Dayton, OH) were placed: the first one at the midpoint between the xiphoid process and the umbilicus and the second on the subject's left side, just below the ribcage and above the level of the first electrode. A reference electrode was placed on the left costal margin, horizontal to the first active electrode. These electrodes were connected to a portable battery-operated recorder (Synectics Medical Inc., Irving, TX) with cutoff frequencies of 1 and 18 cpm. On-line digitization was done at a sampling frequency of 4 Hz, and digitized samples were stored on the recorder. All recordings were made in a quiet room, and the subject was asked not to talk and to remain as still as possible during the recording to avoid motion artifacts. These measurements were made before placement of the GES or activation of the GES.

At the end of the recording, the EGG data were downloaded to an IBM 586 personal computer for data analysis. After the EGG segments with motion artifacts were identified by visual analysis and removed by using a locally developed program, the following parameters were computed from the EGG data using spectral analysis methods: (1) EGG dominant frequency, the frequency at which the power spectrum of the EGG recording had peak power (range, 0.5–9 cpm); (2) EGG dominant power, the power at the dominant frequency in the power spectrum of the EGG recording; (3) the change of postprandial EGG dominant power (δP), the difference between the EGG dominant power before and after test meal consisting of a turkey sandwich or scrambled egg substitute and two slices of bread; (4) the percentage of normal slow waves (2–4 cpm), the percentage of tachygastria (4–9 cpm), and the percentage of bradygastria (0.5–2 cpm) present over the entire observation period.[14] To be called a dysrhythmia, the abnormal rhythm had to be recorded for at least 2 minutes, with the normal signal simultaneously absent.

Symptom Assessment and Total Symptom Scores

Each patient completed a self-assessment form at baseline and at 3 months. This form assessed the symptoms of gastroparesis occurring during the 2 weeks before the interview for severity and frequency of vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain, and epigastric burning. The severity of each symptom was graded by the patients as 0 = absent, 1 = mild (not influencing the usual activities), 2 = moderate (diverting from, but not urging modifications, of usual activities), 3 = severe (influencing usual activities, severely enough to urge modifications), and 4 = extremely severe (requiring bed rest) and frequency of each symptom as 0 = absent, 1 = rare (1/week), 2 = occasional (2–3/week), 3 = frequent (4–6/week), and extremely frequent (⩾7/week). The TSS is the sum of the grades of these seven symptoms for both severity and frequency.

Statistical Analysis

Results are reported as mean ± SEM. Student's *t* test was performed to investigate the difference of the EGG parameters between baseline and at 3 months (Microsoft Excel, Redmond, WA). Analysis of variance (ANOVA) was used to compare the TSS between the two groups at baseline and 3 months (SuperANOVA; Abacus Concepts, Inc., Berkeley, CA). $P < 0.05$ was considered to be significant.

RESULTS

Based on the analysis of the gastric wall biopsy samples, five patients had a normal number of ICCs, four patients had reduced numbers of ICCs, and five had almost none or depleted numbers of ICCs (Table 1). Representative microscopic images are presented in Fig. 1. Because we were interested in whether the ICC number was important for gastric myoelectric activity, we compared the group of nine patients with some or adequate number of ICCs (ICC+ group) with the group of five patients with depleted or no ICCs (ICC− group). The two groups were demographically similar in that the average age of the ICC+ group (35.9 ± 3.8 years) was no different than the age (37 ± 1.8 years) of the ICC− group; seven of the patients in the ICC+ group and all five patients in the ICC− group were female. In addition, the etiologies were similar; five of the patients in the ICC+ group were diabetic, three were idiopathic, and one was identified to have gastroparesis after a vagotomy and pyloroplasty. In the ICC− group, four patients were diabetic and the fifth was idiopathic.

Table 1. Patient information

Patient	Age (yr)	Gender	Etiology of gastroparesis	Years with diabetes	Years with gastroparesis	No. of interstitial cells of Cajal (ICC)
1	27	F	Diabetes	15	2	Normal (+)
2	32	M	Diabetes	8	6	Normal (+)
3	30	F	Diabetes	19	2.5	Normal (+)
4	31	F	Diabetes	11	5	Normal (+)
5	22	F	Idiopathic	—	2.5	Normal (+)
6	44	F	Idiopathic	—	6	Reduced (+/−)
7	36	M	Diabetes	20	19	Reduced (+/−)
8	60	F	Postsurgical	—	4	Reduced (+/−)
9	41	F	Idiopathic	—	6	Reduced (+/−)
10	39	F	Idiopathic	—	1.25	None (−)
11	38	F	Diabetes	26	2	None (−)
12	36	F	Diabetes	12	2	None (−)
13	31	F	Diabetes	24	6	None (−)
14	41	F	Diabetes	30	20	None (−)

Normal number of ICC equivalent to normal controls; reduced number of ICC equivalent to 20–40% of controls; none equivalent to less than 10% of control.

The EGG recordings of the two groups revealed marked differences (Table 2). In the fasting state, the ICC− group patients had significantly more tachygastria (slow wave frequency, >4 cpm) than the ICC+ group (54 ± 36% versus 11 ± 13%, $P < 0.05$) and hence less percentage of time in normal rhythm. Postprandially, the ICC− group continued to have significantly less normal rhythm (81 ± 4.9% versus 42 ± 17%, $P < 0.05$) and associated dominant tachygastria.

In terms of the TSS, the ICC+ group had a significantly lower TSS than the ICC− group at baseline and after 3 months of GES (Fig. 2). Both groups responded to the GES with a significant decrease in both the severity and frequency of gastrointestinal symptoms. However, as noted in Fig. 2, the ICC− group had

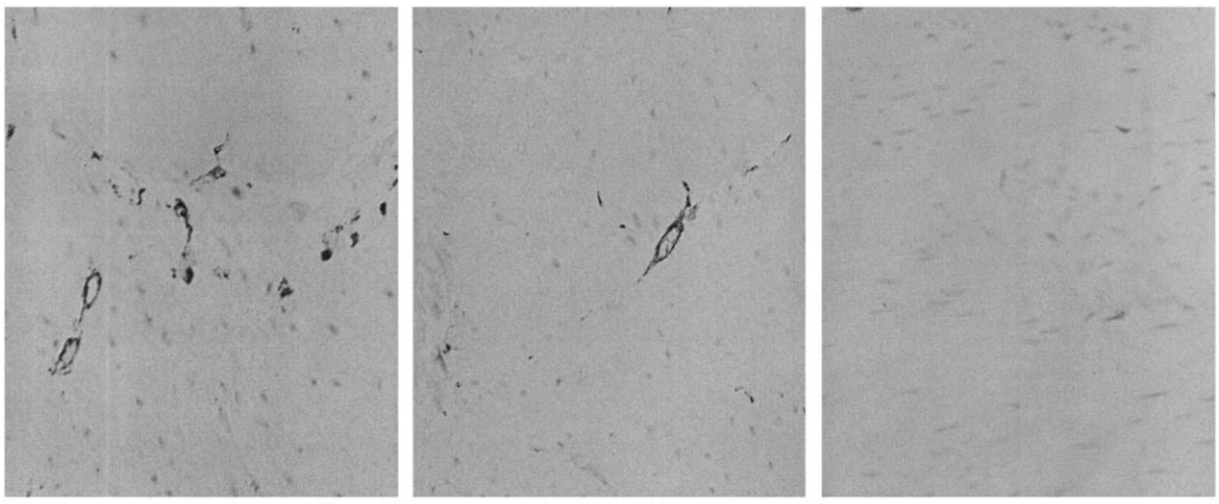

Fig. 1. Microscopic images of antral gastric wall biopsy samples. These images were taken at ×160 magnification of formalin-preserved full-thickness 1-cm^2 surgically obtained gastric antral biopsy samples, with staining of CD117. These images are representative of the three grades that were assigned for the numbers of interstitial cells of Cajal (ICCs) that could be stained. Specifically, a normal result is A, where normal numbers of ICCS would be approximately 10 cells per high-powered field; 20–40% of normal numbers of ICCS was graded as B, and depleted numbers of ICCS (<10% of normal) was graded as C.

Table 2. Results of electrocardiogram (ECG) analysis

	DF (cpm)	2–4 cpm (%)	T (%)	B (%)	δP (dB)
Preprandial EGG					
ICC−	4.0 ± 0.68	41 ± 16	54 ± 16	4.8 ± 3.0	—
ICC+	3.2 ± 0.24	73 ± 5.0	11 ± 5.3*	17 ± 4.9	—
Postprandial EGG					
ICC−	4.2 ± 0.73	42 ± 17	50 ± 21	8.4 ± 4.0	−1.0 ± 2.4
ICC+	3.2 ± 0.22	81 ± 4.9*	11 ± 5.2	8.5 ± 2.2	0.65 ± 1.9

Patients with depleted interstitial cells of Cajal (ICC) had significantly more tachygastria and a tendency to less bradygastria and less normal slow waves before a meal than did those with ICC. After a meal, the patients with no ICC had significantly less slow waves in the normal frequency range and tended to have more tachygastria.
DF = EGG dominant frequency; 2–4 cpm = percent normal slow waves; T = percent tachygastria; B = percent bradygastria; δP = EGG postprandial power change.
*$P < 0.05$ compared with ICC− group.

on average a 39% reduction in their symptoms, whereas the ICC+ group had a 66% reduction. By ANOVA, there was a significant effect of both time and ICC group but not in their interaction.

DISCUSSION

In this retrospective analysis of prospectively gathered data, the presence of the ICCs in the antral gastric wall was associated with less tachygastria by cutaneous EGG measurements and less symptoms in this group of medically recalcitrant gastroparetics requiring treatment with GES. The patients in this study are a highly selected group of gastroparetics requiring GES treatment because all standard medical therapies had failed and some of the patients required surgical placement of a gastrostomy tube or nutritional assistance with parenteral or enteral approaches. Five of the patients, or 30% of the group of 14, had depleted ICCs. This observation could be relevant to their clinical outcomes, which was only a 39% reduction in TSS. On the other hand, the ICC-intact patients had a 66% reduction in TSS, similar to the

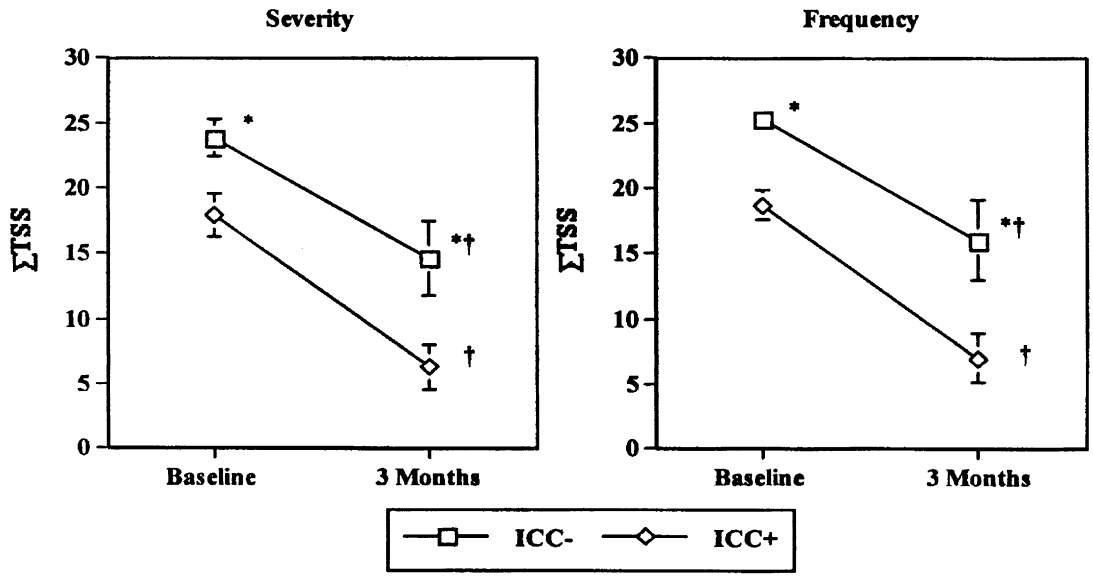

Fig. 2. Total symptom scores (TSSs) at baseline and after 3 months of gastric electrical stimulation (GES). TSS was calculated for each patient based on self-assessment of symptoms at baseline and at 3 months. Patients with depleted interstitial cells of Cajal (ICCs) had greater symptoms for both severity and frequency than those with normal or adequate ICCs at both time points; both groups experienced a reduction in symptoms after GES. *Significant difference between two groups at baseline and at 3 months by analysis of variance (ANOVA) ($P < 0.05$). †Significant difference in TSS at 3 months compared with baseline by ANOVA ($P < 0.05$).

expected levels that have been reported for GES therapy.[15,16] One could hypothesize that patients deemed to be less responsive or treatment failures may have depleted ICC populations, contributing to their refractoriness to both medical and GES approaches.

The importance of ICCs is to maintain normal gastric electrical activity. The cutaneous measurement of this electrical activity (EGG) demonstrated evidence of marked tachygastria in the ICC− group, whereas the ICC+ group remained in the normal range. It is interesting that about one third of the last 100 patients in whom we have evaluated and who underwent placement of the GES system had tachygastria on their EGG,[17] consistent with the percentage of patients in the current report who had ICC depletion. In the future, it may be better to stimulate this subset of patients with different parameters, specifically a higher energy (long pulse trains), to either induce smooth muscle contractions directly and/or convert dysrhythmia into a regular rhythm of 2–4 cycles per minute.

What pathophysiologic ramifications result from our observation of depleted ICCs in some patients with gastroparesis? Dysrhythmia represents an attempt at remodeling of the impaired myoelectrical network related to areas where ICCs are depleted. Tachygastria is the observed dysrhythmia and prevents electromechanical coupling, and hence contractions are diminished, and this results in gastroparesis. By our study, low numbers of ICCs may permit normal rhythms, but when ICCs are truly depleted or absent, an abnormal gastric rhythm results. We believe that our definition of *depletion* is defendable. Although the ICC distribution could be patchy, our large full-thickness surgically obtained sample of the antrum should adequately represent the status of the cells. We have recently had the opportunity to examine the distribution of ICCs in the body and antrum of total gastrectomy specimens from patients with severe diabetic gastroparesis. ICC depletion is selectively manifested in the antrum and not the body, and within the antrum, the depletion is relatively uniform.[18] Hence, our full-thickness surgical biopsy of the antrum is an adequate representative of the status of ICCs in these chronic gastroparetic patients.

Clearly, from the animal studies, diabetics have ongoing loss of ICCs.[12] Patients who suffer from idiopathic gastroparesis may have become gastroparetic due to a viral illness that damaged their gastric nerves and/or their ICCs. Patients who became gastroparetic after gastric surgery or vagotomy would be unlikely to have a loss of ICCs. Here we believe gastroparesis is related to preoperative gastric outlet obstruction and prolonged distention with food plus the postoperative effects of vagotomy. In fact, the one postgastric surgery patient in our group had normal numbers of ICCs, as did the completion gastrectomy specimens we recently studied from Billroth I and II patients.[18]

Patients with some or normal numbers of ICCs had clearly fewer symptoms before and after 3 months of GES. Thus, the ICC number was important in gastric function and as well in the response to GES. The manner by which the GES improves symptoms remains unclear. Although the majority of the patients had a marked reduction in symptoms, only a minority of patients had improved gastric emptying after GES.[7] On average, there was no improvement in gastric emptying at 3 months, suggesting that the GES may not improve gastric motility.

There are two identified regions of ICCs. The ICCs associated with the myenteric plexus initiate the slow wave or basal electrical rhythm and then conduct it to the smooth muscle layer by inducing depolarization. The other region of ICCs termed the intramuscular ICCs (IM) is deeper in the muscularis propria smooth muscle layer. The IM amplifies the gastric slow wave signal so that it may achieve an action potential level, which results in muscle contractions through activation of calcium channels. Hence, the ICCs in the myenteric plexus layer are fundamental for initiating the slow wave frequency in the smooth muscle, whereas the IM propagates the slow wave and permits peristalsis.

If there are no ICCs (IM), then short-pulse duration (low energy, in microseconds) electrical stimulation (Enterra Therapy) could not influence gastric slow wave frequency or motility. However, long train (high energy, in milliseconds) could entrain or pace the smooth muscle directly even if the IM is absent. In gastric biopsy samples from normal patients, the ICCs (IM) are preferably stained by the c-*kit* technique used in our study. In our gastroparetic patients, the ICC layer that is depleted represents this deeper layer (IM) because those ICCs (IM) are more vulnerable to initial damage or loss. The short-duration pulse stimulation utilized by the Enterra device does not require intact ICCs (IM), because short-pulse stimulation does not affect motility. However, this low-energy or neural stimulation could be conducted afferently to the central nervous system and influence central control of nausea and vomiting, leading to relief of symptoms via this pathway. Further studies to pursue the mechanisms of action of the Enterra device are in progress.

CONCLUSION

This work describes for the first time that ICC populations are impaired in gastroparetic patients.

ICCs were absent in about a third of the studied population of gastroparetic patients for whom standard medical therapy failed and who required a GES. The absence of ICCs was associated with increased abnormalities of gastric slow waves, more severe symptoms, and a poorer response to GES. The EGG could be a clinical marker for depleted ICCs and a possible predictor of treatment response to GES. In the future, a different stimulating device with high-energy and low-frequency parameters may be necessary to induce muscular contractions in the group with depleted ICCs, given the evolving knowledge regarding the role of ICC subgroups in controlling gut myoelectric function.

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