

Treatment of Diabetic Gastroparesis by High-Frequency Gastric Electrical Stimulation

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OBJECTIVE — To investigate the long-term efficacy of high-frequency gastric electrical stimulation (GES) for treating diabetic gastroparesis.

RESEARCH DESIGN AND METHODS — This is a retrospective review of 48 adult diabetic patients with refractory gastroparesis who had a GES system implanted surgically and had follow-up evaluations at 6 and 12 months. The outcome measures were total symptom score (TSS), derived from six upper gastrointestinal (GI) symptom subscores; health-related quality of life (HQOL), including physical composite score (PCS) and mental composite score (MCS) assessed by SF-36 questionnaire, radionuclide gastric emptying test, nutritional status, HbA_{1c}, and adverse events.

RESULTS — In comparison with baseline, TSS, all six upper GI symptom subscores, PCS, and MCS were significantly improved at 6 months, with the improvement sustained at 12 months. Of 13 patients receiving nutritional support at baseline by tube feeding, only 5 required supplemental enteral feeding at 12 months, and none of the 9 on total parenteral nutrition continued this support. The mean number of hospitalization days during the year after GES was significantly reduced by 52 days compared with the prior year. HbA_{1c} levels were significantly reduced at 12 months. Gastric emptying was only minimally and not significantly faster. Because of infections at the pulse generator pocket site, four patients had their GES systems removed 3–17 months postsurgery.

CONCLUSIONS — In diabetic patients with refractory gastroparesis, high-frequency GES by a permanently implanted system significantly improved upper GI symptoms, HQOL, nutritional status, glucose control, and hospitalizations with an acceptably low complication rate.

Diabetes Care 27:1071–1076, 2004

D iabetic gastroparesis (DGP), defined as delayed gastric emptying (GE) in the absence of mechanical obstruction (1–4), affects 20–50% of the diabetic population, most often those individuals with long-standing, poorly controlled diabetes (5,6). The most common symptoms of DGP are nausea and vomit-

ing accompanied by early satiety, postprandial fullness, belching, abdominal pain, bloating, and weight loss (2).

The standard treatment of symptomatic DGP consists of glycemic control, dietary manipulation, medications, and, in severe cases, surgical procedures. Medications include antiemetic therapy com-

bined with prokinetic agents, such as metoclopramide, erythromycin, and domperidone. However, only metoclopramide and erythromycin are commercially available in the U.S. and both have side effects that make them intolerable for >40% of patients (7). Glycemic control recommendations are to maintain glucose levels <180 mg/dl to avoid inhibiting gastric myoelectric control and motility. The main modalities of dietary modification consist of small frequent meals of low-fat and low-fiber content. In severe cases, patients may be placed on a liquid diet. If those approaches fail, palliative surgical therapies include tube gastrostomy for decompression and jejunostomy for feeding. Other surgical options have focused on improving GE with pyloroplasty and antrectomy (8). Total gastrectomy remains the ultimate surgical option (9).

Recently, gastric electrical stimulation (GES) has been investigated as a new approach for treating medically refractory gastroparesis (10). GES is achieved by delivering electric current via electrodes to gastric smooth muscle. Two methods of GES have been reported in the literature. The first uses electrical stimulation with a low frequency (i.e., frequency similar to or slightly higher than that of the native slow wave, ~3 cpm) and high-energy (width of ~300 msec) pulses. Studies in both animals and humans have indicated that this method is able to entrain the gastric slow wave, normalize gastric dysrhythmias (11–13), and significantly improve GE and dyspeptic symptoms in patients with refractory gastroparesis (11). Unfortunately, the external devices used in this latter study allowed for only 3- to 6-month use and were somewhat cumbersome (11). In contrast, an implantable neurostimulator with a high-frequency (12 cpm), low-energy (pulse width 330 μ sec) output, manufactured by Medtronic (Minneapolis, MN) and approved by the Federal Drug Administration in 2000 as Enterra Therapy, can be permanently implanted into the abdomen via laparotomy or laparoscopy. Published

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Received for publication 3 October 2003 and accepted in revised form 11 February 2004.

R.W.M. is the recipient of grant/research support from Medtronic, Inc.

Abbreviations: DGP, diabetic gastroparesis; GE, gastric emptying; GES, gastric electrical stimulation; GI, gastrointestinal; HQOL, health-related quality of life; MCS, mental composite score; PCS, physical composite score; TPN, total parenteral nutrition; TSS, total symptom score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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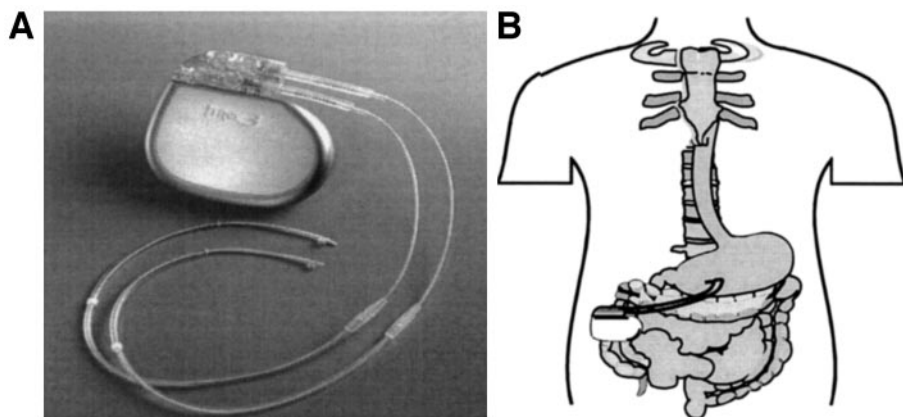


Figure 1—Implantable GES system and its location. A: The implantable GES system is comprised of a pair of leads and a battery-powered pulse generator. B: The pair of electrodes are inserted by laparotomy or laparoscopy into the muscular propria of the greater curvature at 9.5 and 10.5 cm proximal to the pylorus and connected to the pulse generator positioned subcutaneously in the abdominal wall. (Pictures courtesy of Medtronic).

reports (14–18) have shown a significant improvement in symptoms and nutritional status, and a variable improvement in GE in patients with refractory gastroparesis after 6 and 12 months of GES. However, patients with different etiologies of gastroparesis were included in those studies, resulting in relatively small numbers of patients in each etiology. Because DGP constitutes the largest group with a common pathophysiology of motility disorder, we retrospectively reviewed all patients undergoing GES implantation at the University of Kansas Medical Center (KUMC) since 1998 and now report the effects of GES on symptoms, health-related quality of life (HQOL), nutritional status, GE, and the degree of glucose control in 48 patients who have ≥ 12 months of follow-up available.

RESEARCH DESIGN AND METHODS

Participants in this trial included 48 patients with DGP who had a GES system (Medtronic) implanted from April 1998 to June 2002 at KUMC. The key inclusion criteria were 1) documented diagnosis of gastroparesis for >1 year and refractoriness to antiemetics and prokinetics, 2) over seven emetic episodes per week, and 3) delayed GE (gastric retention $>60\%$ at 2 h and $>10\%$ at 4 h) based on a 4-h standardized radionuclide solid meal (19). Patients were excluded if they had organic or pseudo-obstruction, previous gastric surgery, primary eating or swallowing disorders, chemical dependency, positive pregnancy test, or psychogenic vomiting. The study protocol was approved by the Human Subjects Com-

mittee at KUMC, and written consent forms were obtained from all subjects before the study.

This study consisted of 1) a baseline evaluation of medical history and upper gastrointestinal (GI) symptoms, GE test, HQOL, assessment of nutritional status, pregnancy testing, and blood chemistries to determine qualification for enrollment; 2) surgical placement of the GES system by laparotomy, removal of any parenteral nutrition, gastric decompression or feeding tubes, and gastric-jejunal feeding devices, and in some cases placement of a feeding jejunostomy tube if not already in place; and 3) follow-up at 6 and 12 months after implantation to repeat baseline measurements. In addition, adverse events, including hospitalizations, were monitored throughout the follow-up period.

Implantation of electrodes and neurostimulator and programming

The GES system used in this study was Enterra Therapy, which consists of three components: an implantable neurostimulator (Medtronic Model 7425G), two intramuscular leads (Medtronic Model 4301) (see Fig. 1A), and an external programmer (Medtronic Model 7432). During surgery, one pair of electrodes was inserted into the muscularis propria of the greater curvature of the stomach at 9.5 and 10.5 cm proximal to the pylorus. The electrodes were secured to the serosa of the stomach using 5-0 silk sutures and a plastic disc. Intraoperative endoscopy ensured there was no penetration of the electrodes into the gastric lumen. The

other end of each 35-cm length lead was connected to the pulse generator, which was secured in a subcutaneous pocket in the abdominal wall to the right of the umbilicus, as previously described (15) (see Fig. 1B). The pocket was generously irrigated with an antibiotic-containing solution, and the patient received intravenous antibiotics both before and for 2 days after surgery. The load impedance was tested using the programmer to verify electrical integrity of the implant system with both an open and closed neurostimulator pocket. The pulse generator was initially programmed to standardized parameters: pulse width, 330 μ s; (current) amplitude, 5 mA; frequency, 14 Hz; cycle ON, 0.1 s; and cycle OFF, 5.0 s. GES was initiated in the operating room or within 48 h after surgery.

Assessment of symptoms

Each patient completed a Symptoms Interview Form at baseline and 6 and 12 months postsurgery to assess the vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain during the last 2 weeks before the interview. The severity of each symptom was graded 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). The frequency of each symptom was graded as 0 = absent, 1 = rare (once/week), 2 = occasional (two to three times/week), 3 = frequent (four to six times/week), and 4 = extremely frequent (more than seven times/week). The sum of the six symptom subscores was used as an overall total symptom score (TSS) of severity or frequency.

Measurement of GE

GE scintigraphy was performed in the morning after an overnight fast, as previously described (19), with prokinetics stopped for at least 3 days. This standardized method for GE consists of a scrambled egg substitute (120 g of Free Cholesterol & Fat Free Egg; Sunny Fresh Foods, Monticello, MN; 60 kcal) labeled with ^{99m}Tc sulfur-colloid (1 mCi), two slices of whole wheat bread (120 kcal), 30 g jelly (75 kcal), and 120 ml of water (19). The meal has a total caloric value of 255 kcal (nutritional composition: 72% carbohydrate, 24% protein, 2% fat, and 2% fiber). Anterior and posterior images

Table 1—Summary of results of upper GI symptom severity and frequency, HQOL, and GE

	Baseline	6 months of GES	12 months of GES
Severity score (0–4)			
<i>n</i>	48	37	28
Vomiting	3.3 ± 0.1	1.5 ± 0.2*	1.3 ± 0.3*
Nausea	3.6 ± 0.1	1.9 ± 0.2*	1.7 ± 0.3*
Early satiety	2.9 ± 0.1	1.4 ± 0.2*	1.2 ± 0.3*
Bloating	2.7 ± 0.2	1.3 ± 0.2*	1.1 ± 0.2*
Postprandial fullness	2.8 ± 0.2	1.0 ± 0.2*	1.4 ± 0.2*
Epigastric pain	2.6 ± 0.2	1.4 ± 0.2*	1.1 ± 0.2*
TSS of severity (0–24)	17.6 ± 0.6	8.5 ± 0.9*	7.9 ± 1.3*
Frequency score (0–4)			
<i>n</i>	48	37	28
Vomiting	3.4 ± 0.1	1.5 ± 0.2*	1.4 ± 0.3*
Nausea	3.6 ± 0.1	1.9 ± 0.2*	1.9 ± 0.3*
Early satiety	3.1 ± 0.2	1.6 ± 0.2*	1.6 ± 0.3*
Bloating	2.8 ± 0.2	1.4 ± 0.2*	1.4 ± 0.3*
Postprandial fullness	3.0 ± 0.2	1.3 ± 0.2*	1.6 ± 0.3*
Epigastric pain	2.8 ± 0.2	1.4 ± 0.2*	1.1 ± 0.3*
TSS of frequency (0–24)	18.5 ± 0.6	8.9 ± 1.0*	8.9 ± 1.4*
HQOL			
<i>n</i>	47	37	28
PCS	23.8 ± 1.3	30.8 ± 1.9*	33.5 ± 2.2*
MCS	36.9 ± 1.8	47.4 ± 2.3*	46.0 ± 2.0*
Gastric retention (%)			
<i>n</i>	44	34	24
At 2 h	76.0 (60.8–86.3)	65.5 (55.0–83.5)*	74.5 (54.5–85.3)
At 4 h	50.0 (26.5–74.5)	38.5 (17.0–51.0)*	38.0 (15.8–64.3)

Data are means ± SE, except GE results (percentage retention), which are reported as median (interquartile range). **P* < 0.05 vs. baseline.

of the stomach were taken immediately after eating and then hourly for 4 h. Gastric retention of gamma counts was calculated by the Department of Nuclear Medicine using geometric and decay correction. Blood glucose was measured before the GE and the test was cancelled if glucose levels were <75 or >275 mg/dl.

Delayed GE was defined as the percentage of gastric retention >60% at 2 h, >10% at 4 h, or both (19).

Assessment of HQOL

The HQOL was assessed by using the previously validated SF-36 Health Status Survey Questionnaire (20). Two summary scores were derived and reported as the Physical Composite Score (PCS) and the Mental Composite Score (MCS). The PCS and MCS are norm-based measures in which the means ± SD for the general U.S. population is 50 ± 10 (21).

Evaluation of nutritional status and HbA_{1c}

BMI was derived from the standard calculation. The need for either enteral or par-

enteral nutritional support was noted at baseline and at 6- and 12-month follow-up. In addition, HbA_{1c} was measured in a fasting blood sample (normal range 3.5–6.0%) (6).

Statistical analysis

The symptom subscores, TSS, BMI, HbA_{1c}, PCS, MCS, and nutritional status, reported as means ± SE at baseline and after 6 and 12 months of GES were compared by ANOVA, paired *t* test, and χ^2 analysis. The Wilcoxon's signed-rank test was used for paired comparison of GE. Results of GE are reported as median and interquartile range. Statistical significance was assigned at *P* < 0.05.

RESULTS

Baseline demographics

All 48 patients (33 female and 15 male, mean age 38 years, range 21–65 years, 45 Caucasian) evaluated in this report were insulin dependent. Their duration of diabetes averaged 18.9 years (range 1–39 years). The mean duration of gastropa-

retic symptoms was 5.9 years (range 1–20 years). Other specific diabetes complications were retinopathy (*n* = 22), peripheral neuropathy (*n* = 21), renal insufficiency/nephropathy (*n* = 18), cardiovascular disease (*n* = 8), history of heart transplantation (*n* = 1), kidney transplantation (*n* = 5), pancreas transplant (*n* = 4), and hemodialysis (*n* = 3). On average, the subjects had lost 9.5 kg (range 0–45.4 kg) and had been hospitalized for a mean of 75 days (range 0–252 days) in the year before the GES. At the time of the study, 13 patients were enterally supplemented through a variety of feeding tubes and 9 were receiving total parenteral nutrition (TPN). Of the 48, 44 had delayed solid GE at baseline (Table 1); the remaining 4 could not complete the GE study because of vomiting, but were included in this study on the basis of their clinical history and prior abnormal GE results from outside medical centers.

Upper GI symptoms

The results of upper GI symptoms are summarized in Table 1. In comparison with baseline, four of six symptom severity subscores (vomiting, early satiety, bloating, and postprandial fullness) decreased >50% at 6 months of GES and were sustained at 12 months. The mean severity of the two other symptoms (nausea and epigastric pain) also decreased >50% at 12 months compared with baseline. Both total symptom severity and frequency were significantly reduced at 6 months of GES and sustained at 12 months compared with baseline. Excluding patients who died (*n* = 4), had devices removed (*n* = 4), or were lost to follow-up (*n* = 12), 28 patients completed their Symptom Interview Form at the 12-month follow-up. Among the 28, 59% had a >50% decrease in TSS and only 2 patients (7%) had no change. Of the 12 patients lost to follow-up, 5 refused further participation because of personal financial reasons, 2 could not travel because of limitations (partial leg amputation and severe depression), 4 did not respond or were impossible to reach because of new addresses, and 1 came for follow-up after the 12-month visit deadline and was not counted.

HQOL

At baseline, mean PCS and MCS scores (23.8 and 36.9, respectively) (Table 1) were substantially below the U.S. norm

(50 ± 10) (21); both scores significantly improved at 6 and 12 months postsurgery. The majority of the improvement was observed within the first 6 months. Specifically, the MCS increased to 47.4 at 6 months, approaching normal. Hospitalization averaged 75 ± 11 days (range 0–252 days) for the year before receiving GES therapy. This average significantly decreased to 23 ± 4 days (range 0–75 days; $P < 0.05$) during the 1st year of GES; nine patients had no hospital admissions.

GE

Median gastric retention at 12 months was not significantly changed from baseline: 76.0% (range 60.8–86.3%) to 74.5% (range 54.4–85.3%) at 2 h, and 50.0% (range 26.5–74.5%) to 38.0% (range 15.8–64.3%) at 4 h. Although numerically less, neither the mean 2- nor the mean 4-h gastric retention at 12 months was statistically different from that at baseline or 6 months (see Table 1). Of the 24 patients who completed the GE test at 12 months, 5 (21%) normalized their GE, whereas all others continued to have delayed emptying, including 9 (38%) whose gastric retention worsened.

Nutritional status and glucose control

In all, 22 patients with a 12-month follow-up were receiving nutritional support at the time of surgery, either by enteral feeding tubes ($n = 13$) or TPN ($n = 9$). After 1 year of GES, no one was receiving TPN. Of the 13 patients with jejunal feeding at baseline, only 5 required any supplemental feeding at 12 months ($P < 0.05$, χ^2 analysis). Average body weight increased over baseline by >2 kg at 6 months and continued to increase by 12 months (64.3 ± 1.8 vs. 66.5 ± 2.1 vs. 67.3 ± 2.4 kg; $P < 0.05$ vs. baseline). There was a reduction in mean HbA_{1c} levels from 9.4% at baseline to 8.7% at 6 months and 8.4% at 12 months. This reduction was statistically significant at 12 months compared with baseline ($P < 0.05$).

Adverse events related to GES therapy

The implanted GES system was removed in four patients at 3, 10, 12, and 16 months postsurgery; in two the GES was removed solely due to a postoperative infection at the pulse generator site (3 and 10 months postsurgery), and in one case,

the pulse generator was pushing against the skin in a thin patient, eventually causing skin penetration and infection that did not respond to antibiotics (12 months postsurgery). The fourth patient presented with volvulus about the wires and required surgery to resect part of the small bowel and remove the GES system (16 months postsurgery).

Additional long-term medical problems

Only two patients died before 6 months of follow-up: one in the immediate postsurgery period from a pulmonary embolus and one at 3 months from her own decision to stop hemodialysis. Another two patients died after 9 months of GES: one from a myocardial infarction and one from aspiration pneumonia. An additional five patients died at 12–63 months postsurgery, all deaths being unrelated to GES therapy: a brain stem hemorrhage (13 months), complications of diabetes (14 and 19 months), sepsis related to end-stage renal failure (43 months), and myocardial infarct (63 months).

CONCLUSIONS— The patients in this series were a selected group of diabetic patients who had medically refractory gastroparesis and had the GES system implanted for at least 12 months (April 1998 to June 2002). The most common cause of gastroparesis is diabetes, although several conditions can contribute to impaired gastric motility (18,22). There are ~18 million persons with diabetes in the U.S. (22), and 10% have type 1 diabetes. Gastroparesis has been found in up to 50% of patients with type 1 diabetes and 30% with type 2 diabetes (6,22,23). Therefore, DGP constitutes the largest group of gastroparetic patients with a common pathophysiology of motility disorder. Previous studies have shown that high-frequency GES by an implantable system offers an effective alternative for treatment of refractory gastroparesis (14–17). However, the patients' gastroparesis included in those previous studies had multiple etiologies, with <20 patients having DGP. Moreover, only a few had long-term follow-up data. Therefore, the present study was the first to evaluate the effects of high-frequency GES in a large group of patients with DGP who also had rigorous follow-up.

In this study, we confirmed that GES

by a permanently implantable system (Enterra Therapy) significantly reduced severity and frequency of all upper GI symptoms assessed, including vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain. This finding is in agreement with previous studies on GES in gastroparesis (14–17). The chronic effect of high-frequency GES on six upper GI symptoms and TSS as assessed in the present study was reported in 33 gastroparetic patients (17 diabetic gastroparesis and 16 idiopathic gastroparesis) (17). Similar to the present study, that report showed that TSS was significantly improved ($P < 0.05$) at 6 and 12 months compared with baseline for the combined group and for both etiologies. For the symptom subscores, only the severity of nausea and vomiting were significantly improved in the diabetic subgroup at 6 ($n = 13$; $P < 0.05$) and 12 months ($n = 11$; $P < 0.05$). However, all six symptom subscores assessed in the present study were significantly reduced at 6 and 12 months of GES ($P < 0.05$). One obvious explanation of these difference in the results of symptom subscores is the larger database available for analysis in our study.

Accompanying the symptom improvement was a significant improvement in the HQOL, as evaluated using the previously validated SF-36 questionnaire (20). These findings are consistent with a previous report (17). Although it does not correct other comorbidities of underlying diabetes, GES clearly makes life more functional on both mental (MCS) and physical (PCS) levels for the majority of patients.

The significant reduction in HbA_{1c} levels combined with the decrease in hospitalization days were major findings. By controlling nausea and vomiting and hence stabilizing food intake and maximizing the glucose/insulin relation, better diabetes control was achieved. Along with this goal comes the attendant nutritional stability and increase in weight. Although there has been a rare report of chronic prokinetic therapy (e.g., levosulpiride) helping glycemic control in type 1 diabetes—related DGP (24), GES in the current setting was used to treat DGP refractory to all standard medical therapy and was still able to induce better HbA_{1c} levels with the attendant positive long-term implications. Also, the lack of nausea and vomiting could allow those

patients to be candidates for renal and pancreas transplantation because they could absorb the oral immunosuppressant agents and thereby prevent organ rejection. In addition, the economics of fewer hospitalizations and the accompanying substantial savings emphasize another parameter of measuring long-term outcome and quality of life (18).

The median gastric retention measured by a standardized 4-h scintigraph of a solid meal was not significantly reduced at 12 months. The 4-h gastric retention at 6 and 12 months was still four times more than the normal value (i.e., markedly delayed). This observation is in agreement with previous reports (15,17), indicating no association between changes in symptoms and GE in gastroparetic patients treated with high-frequency GES (17). Individually, only 20% patients evaluated at 12 months of GES had their 2- or 4-h gastric retention reduced to a normal value. In contrast, McCallum et al. (11) showed that low-frequency, high-energy GES for 1–3 months significantly improved GE and returned the majority of gastroparetic patients (67%) to normal levels as well as reversing gastric dysrhythmia with enhancement of the gastric slow waves (11,12). The major difference between these two studies was the stimulation parameters used. This suggests in the future that different stimulation parameters will be needed to reverse dysmotility in DGP.

The major adverse event related to GES therapy was infection. Patients with long-term diabetes have a higher risk for postoperative infection (25). In addition, once the implantable GES system is infected, it may be impossible to eradicate the infection without removing the device. In the present study, of four patients (8%) who had their GES system removed, three did so because of infection at the implant site. This result is consistent with that of another long-term study (17) in which 9% of 33 patients had their GES system removed due to infection of the pulse generator pocket.

We reviewed the literature to better understand the long-term mortality in DGP. In a recent study of the natural history of diabetic gastroparesis, 24% of patients died at 9 years of follow-up, with the major causes of death being cardiovascular or renal (23). There was a significant relation between the risk of death and duration of diabetes ($P = 0.02$). The

mean duration of diabetes for the four patients who died in our present study was 25.3 years, substantially higher than in the survivors (12 years) or the deceased in the study discussed above (18 years) (23). This may give some perspective to the mortality rate of 8% at 1 year in our present study.

The exact mechanisms of action of GES remain to be elucidated. In a recent study in patients who had both a GES system and recording electrodes implanted, we found that high-frequency GES did not normalize dysrhythmias while still achieving symptom reduction (26). Other mechanisms of action that could be hypothesized for high-frequency GES include gastric fundic relaxation, the autonomic nervous system, and release of GI hormones, including ghrelin (10,18). Activation of central control mechanisms for nausea and vomiting in the brain stem and central nervous system by stimulating afferent pathways is the most unifying theory, but as yet there are no supporting data.

This study was not placebo controlled. A recent double-blind study (17) did show that 1 month of GES was significantly better than 1 month of sham stimulation. Recently published long-term data indicate that the symptomatic improvement with GES is sustained in the majority of initial responders (27). It is highly unlikely that a placebo effect in our study could explain 1 year of sustained clinical improvement in a group of gastroparetic patients who had failed months and years of medical therapy.

In conclusion, high-frequency GES by a permanently implantable system is safe and significantly improves upper GI symptoms, quality-of-life measures, glycemic control, and nutritional status while reducing hospitalization days in diabetic patients with medically refractory gastroparesis. This advance in therapy offers new hope and better outcomes than achieved by traditional medical therapy for this challenging group of patients.

Acknowledgment—This work was supported in part by Medtronic, Inc. (Minneapolis, MN). Z.L. is partially supported by an endowment honoring Dr. Arthur P. Klotz at University of Kansas School of Medicine.

The authors would like to acknowledge the following individuals for their contributions: Sara Durham, Suzanne Denton, and Katherine Roesser; the faculty, fellows, and nursing staff

in the Division of Gastroenterology; and Janet Kelly and the operating room staff as well as surgical residents. We also wish to acknowledge Dr. Joseph Kyner and the staff of the Cray Diabetic Center at the University of Kansas Hospital and Dr. Twillman in Psychology and Pain Management for their role in the care of these patients, and the faculty of the Nuclear Medicine Department. We also especially thank Warren Starkebaum, PhD, at Medtronic for his critical review and suggestions as well as the Medtronic Gastroenterology Group.

Parts of this study were presented in abstract form at the 103rd Annual Meeting of the American Gastroenterological Association, 19–22 May 2002, San Francisco, California.

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