Gastric Motor Abnormalities in Diabetic and Postvagotomy Gastroparesis: Effect of Metoclopramide and Bethanechol

JUAN-R. MALAGELADA, WYNNE D. W. REES, LAURENCE J. MAZZOTTA, and VAY LIANG W. GO
Gastroenterology Unit, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Gastroparesis is a relatively uncommon but clinically troublesome disorder that develops in some patients with diabetes mellitus or after gastric operations. Its pathogenesis remains obscure. We used a manometric technique to record pressure changes in fasting patients in the gastric fundus, distal stomach, and adjacent small bowel of patients with severe gastroparesis, asymptomatic diabetic patients, asymptomatic postsurgical patients, and healthy controls. Patients with gastroparesis had normal interdigestive motor cycles (phase III) in the intestine but not in the stomach. Sporadic motor activity in the stomach (phase II) also was markedly reduced. Metoclopramide and bethanechol significantly increased gastric motor activity in these patients, often triggering an intense burst of motor activity in the stomach, similar to phase III. These observations suggest that gastroparesis is a potentially reversible disorder and should encourage further attempts for pharmacologic control of the syndrome.

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Material and Methods
A total of 41 subjects were divided into five groups.

Gastroparesis Patients
Gastroparesis was diagnosed when patients fulfilled all of the following criteria: (a) intractable nausea and vomiting, recurrent bezoar formation, and radiologic or endoscopic (or both) evidence of gastric stasis in the absence of mechanical obstruction or mucosal abnormality. However, milder, even asymptomatic, gastroparesis has been recognized. Gastroparesis also may be a feature of the “intestinal pseudo-obstruction syndrome,” a poorly defined group of disorders involving the intestine, bladder, and smooth-muscle organs. These latter types of gastroparesis will not be discussed.

The pathogenesis of diabetic and postsurgical gastroparesis is obscure and may represent a neuropathic disorder. As its name indicates, gastric stasis is believed to be caused by a failure of gastric motility to propel stomach contents into the intestine. Radiologic studies have commented on the relative or total absence of gastric peristalsis in this condition. Drugs, like metoclopramide and bethanechol, which increase gastric motility, are reported to be clinically helpful, although the evidence is inconclusive. Unfortunately, the motor abnormality has not been characterized, in part because of lack of standardized manometric methods for the study of gastric motility. Thus, we do not know whether fundal, antral, or intestinal motor activities are affected differently; whether interdigestive motor cycles are disturbed; or whether motor patterns are different in patients with different underlying diseases (that is, diabetes or postsurgical). In the present study, we tried to answer these questions.
trointestinal series (little or no contrast medium emptied by 30 min and contrast medium present in the stomach after 6 hr); (c) food present in morning gastric aspirate after overnight (more than 12 hr) fasting; and (d) endoscopic verification of a normal configuration of the stomach (other than surgical deformity), absence of mucosal lesions, and no mechanical obstruction. These criteria as sured that only patients with severe, unquestionable gastroparesis were included in the study.

Two groups of patients with gastroparesis were studied. One group (10 patients) had undergone truncal vagotomy with partial gastric resection and gastroenterostomy performed 6 mo to 6 yr before the study (mean 2.2 yr). There were 6 women and 4 men with ages ranging from 33 to 64 yr (mean 50.7). Five patients had evidence of bezoar on radiologic or endoscopic examination. The other group (7 patients) had severe juvenile-onset diabetes. There were 6 women and 1 man with ages ranging from 22 to 61 yr (mean 41.1). The duration of their diabetes ranged from 6 to 38 yr (mean 17.7). All patients were taking insulin, and their blood sugar levels at the time of study ranged between 125 and 280 mg/dl (mean 215). All patients but one had clinical or electromyographic evidence of peripheral neuropathy. In addition, 5 patients had diabetic retinopathy, and 3 had advanced nephropathy.

Disease Controls and Healthy Controls

Two groups of disease controls were studied. One group (5 patients) had truncal vagotomy, partial gastric resection, and gastroenterostomy performed 6 mo to 5 yr previously (mean 2.7). There were 2 women and 3 men with ages ranging from 30 to 58 yr (mean 46.8). The second group (5 patients) had advanced juvenile-onset diabetes. There were 3 women and 2 men with ages ranging from 22 to 52 yr (mean 41.2). The duration of their diabetes ranged from 3 to 14 yr (mean 9.4). All patients were taking insulin, and their blood sugar levels at the time of study ranged from 100 to 250 mg/dl (mean 166). All but one had clinical or electromyographic evidence of peripheral neuropathy. Two patients also had retinopathy, and three had advanced nephropathy. As opposed to patients with gastroparesis, none of these disease controls had significant gastrointestinal symptoms or evidence of gastric stasis on radiologic examination. They were recruited for these studies as they were being investigated for other problems or from the Rochester community where they reside.

Fourteen healthy volunteers, ages 21-74 yr (mean 31) also were studied.

Patients, disease controls, and healthy volunteers fasted for at least 12 hr before study. In addition, all patients were given liquid diets for 48 hr or longer if morning aspirates still revealed retained food particles. All participants gave informed consent, and studies had been previously approved by Mayo Clinic Human Studies Committee.

Transducers

Gastrointestinal motor activity was measured by a highly sensitive transducer assembly previously described.15-18 It consisted of four miniature strain-gauge

Pressure transducers (Millar Instruments, Houston, Tex., model PC 350) attached in series to a polyvinyl intestinal tube that facilitated positioning of the pressure sensors within the lumen of the stomach and the adjacent small bowel. The sensor tips were attached 1, 5, and 20 cm from the tip of the tube, with the 20-cm sensor being enclosed within a 150-ml capacity rubber balloon attached to the polyvinyl tube. The fourth transducer was attached 22 cm from the tip of the tube and served as a marker of tube position throughout each study period (see later). Before each study, the transducers were connected to a four-channel pen recorder (Coulb Instruments, Cleveland, Ohio, model 2400) and calibrated using transducer control units (Millar Instruments, model TC 100).

Procedure

Intact stomach (diabetic patients and healthy controls). The tube was positioned fluoroscopically with its tip and distal transducer within the proximal duodenum, the second transducer within the gastric antrum, and the third transducer enclosed in the 150-ml balloon at the gastric fundus, which was inflated with air (Figure 1). The fourth transducer was located at the lower esophageal sphincter (LES) and enabled the continuous monitoring of the position of the tube throughout each study period. Finally, a 14-F sump tube was positioned in the most dependent part of the stomach.

Post-surgical stomach (patients with truncal vagotomy and partial gastric resection with gastrojejunos tomy). The tip of the tube was maneuvered fluoroscopically until the distal transducer was located within the jejunum, approximately 3 cm distal to the surgical Anastomosis (Figure 2). The second transducer was positioned in the distal part of the gastric remnant approximately 1-2 cm proximal to the anastomosis, and the third and fourth transducers were positioned as described for the intact stomach. In order to accomplish the correct positioning of the transducers as described, the distance between transducers had to be slightly varied from patient to patient, depending on the size of the gastric remnant determined by prior radiologic contrast examination. A 14-F sump tube was then placed with its tip in the most dependent portion of the gastric pouch.
Figure 2. Disposition of manometric assembly in patients with prior partial gastric resection and gastrojejunal anastomosis. Position of two proximal pressure transducers is identical to that in patients without prior gastric surgery. Two distal transducers are located one at each side of gastrojejunal stoma.

All studies began at 0700 hr. Intubation was carried out as described above. Throughout the experimental period, the subjects adopted a semireclining posture (45° to the horizontal), and gastric contents were continually aspirated and discarded.

**Experimental Design**

In patients and disease controls, each study consisted of two parts: first, interdigestive motor activity was recorded for at least 3 hr; and second, 10 mg of metoclopramide (A. H. Robins Co., Richmond, Va.) or saline (placebo) were administered intravenously during a 10-min period in randomized order, and the effect on motor activity was evaluated during the subsequent hour. In some patients, 5 mg of bethanechol (Merck, Sharp and Dohme, Inc., New York, N.Y.) were given subcutaneously, and the motor response was evaluated during the subsequent hour. The use of bethanechol was not randomized because of the uncertainty about its duration of action.

Healthy subjects were similarly studied for at least a 3-hr period, but they did not receive any drugs.

**Analysis of Results**

When present, fasting motor activity consisted of well-defined interdigestive cycles with three phases: phase I (quiescence), phase II (random but persistent contractions), and phase III (terminal burst of high-amplitude and high-frequency contractions that followed phase II and terminated in the subsequent phase I). In healthy persons, it is easy to appreciate the simultaneous occurrence of phase III in fundus and antrum (Figure 3). Duodenal phase III starts either simultaneously or shortly afterward, but usually lasts longer. A phase IV is also recognized by some authors as the transition from phase III to phase I.

Each motor recording was analyzed, and the following parameters were measured:

1. Three-hour motility index for each transducer site (except LES)—area (mm²) occupied by all phase II and III contractile waves during the 3-hr observation period for the fundal, distal stomach, and small-bowel transducers. The frequency of phase III activity, and the number of contractions that exceeded 12 mm Hg in amplitude also were recorded (contraction frequency).
2. Thirty-minute motility index for each transducer site (except LES) after administration of saline metoclopramide or bethanechol—area (mm²) occupied by all contractile waves during the 30 min after infusion for the fundal, distal stomach and small-bowel transducers. The number of contractions that exceeded 12 mm Hg also was recorded.

**Results**

**Postsurgical Gastroparesis**

In postsurgical gastroparesis, intestinal interdigestive motor cycles developed essentially with the same frequency as in healthy controls (Table 1). Only 1 patient failed to show phase III activity in the

![Figure 3](image-url)
intestine. In contrast, interdigestive motor cycles were not recognizable in the stomach of 8 of the 9 patients studied. The postsurgical controls had normal or greater than normal number of phase III activity, both in the stomach and in the duodenum.

The fundic tone (8.0 ± 1 mm Hg, mean ± SE) was similar to healthy (7.0 ± 1) and postsurgical controls (10 ± 2), P > 0.05. Besides absent phase III activity, very little spontaneous motor activity was observed in the fundus (balloon-enclosed pressure transducer) or distal gastric remnant (free transducer). This was reflected in a very small motility index (significantly lower) in this group than in healthy or postsurgical controls (Figure 4). A lesser degree, but statistically significant reduction in small-bowel motility index, was also observed (Figure 4). A parallel decrease in the frequency of contractions (number per 3 hr) in stomach and gut also was observed (data not shown). Postsurgical controls had a significantly lower motility index in the distal stomach (explainable on the basis of prior antrectomy) and a lower (but not significantly so) index in the fundus. The small-bowel motility index in postsurgical controls was normal.

**Diabetic Gastroparesis**

As observed for patients with postsurgical gastroparesis, interdigestive motor cycles occurred with normal frequency (at least one complex every 3 hr) as determined by monitoring intestinal activity (Table 1). In contrast, only in 1 of the 7 patients was phase III activity recognizable in the stomach, coinciding with phase III in the bowel (Figure 5). In asymptomatic diabetic patients, interdigestive motor cycles in the stomach and in the intestine were normal.

The fundic tone in diabetic gastroparesis (11 ± 1 mm Hg) was similar to that of asymptomatic diabetic patients (10 ± 2), but the fundic motility index was greatly reduced in comparison with that of healthy controls or asymptomatic diabetic patients (Figure 6). The antral motility index also was low, but the average percentage of decrease in fundic motility index relative to healthy controls (91.3%) and asymptomatic diabetic patients (82.1%) was greater than for antral motility index (83.3% and 75%, respectively). The small-bowel motility index was similar in healthy controls and diabetic patients, either asymptomatic or with gastroparesis (Figure 6). Measurements of contraction frequency paralleled those of motility index (data not shown).

**Effect of Drugs on Gastrointestinal Motor Activity**

In patients with diabetic gastroparesis, metoclopramide significantly increased fundic, antral, and small-bowel motility index (Figures 7 and 8). However, gastric motility after metoclopramide consisted of random, phasic changes in pressure without evidence of the intense, rhythmic activity of 3/min, which characterizes antral phase III activity, or the elevation of baseline pressure, which characterizes fundic phase III activity (Figure 8). After metoclopramide use, 3 of 6 patients in whom small-bowel recordings were available showed phase III-like activity in the intestine but not in the stomach.

In patients with postsurgical gastroparesis, metoclopramide also had a stimulatory effect on gastric and intestinal motility index (Figure 7). However, because of previous antrectomy, the capacity of the distal gastric remnant to respond to the drug is, in absolute terms, small. In contrast to the findings in diabetic gastroparesis, in 5 of 9 postsurgical patients, phase III activity was noted in the fundus after metoclopramide use, preceding the corresponding phase III activity in the bowel. Further, unlike pa-
patients with diabetic gastroparesis, patients with postsurgical gastroparesis did not show phase III activity in the intestine after metoclopramide use, without a corresponding phase III activity in the fundus.

In 3 patients with diabetic gastroparesis and in 2 patients with postsurgical gastroparesis, the effect of bethanechol was compared with that of metoclopramide and placebo. The increase in fundic motility index effected by bethanechol was significantly greater than placebo and was similar to that of metoclopramide (Figure 9). However, in contrast to metoclopramide, bethanechol did not trigger phase III activity in any patient, either in the stomach or in the small bowel.

Although there were no serious side effects from the metoclopramide infusion, some patients complained of transient tremor, drowsiness, anxiety, or blurred vision, these effects being most pronounced after infusion of the total dose and lasting only 5–10 min. The patients were unaware of the order of metoclopramide and saline infusions and did not notice any effects from the control infusion. Bethanechol caused mild flushing and nausea in 2 of the 5 patients who received the drug.

**Discussion**

In this study, we examined the interdigestive motor patterns in patients with severe diabetic and postvagotomy gastroparesis. Although several radiologic studies have commented on decreased gastrointestinal peristaltic activity in these patients, systematic manometric studies for diagnostic and therapeutic evaluation are not available.

The results of our study must be interpreted in the context of these limitations.
light of current physiologic knowledge on interdigestive motor patterns. Cycles of myoelectrical activity during prolonged fasting were originally described in the canine small bowel by Szurszewski and have since been reported in a number of animal species and in humans. These motor cycles appear to originate in the upper gut (maybe as proximal as in the lower esophageal sphincter) and are propagated distally to the terminal ileum. The mechanisms that regulate cycle periodicity and propagation remain unknown, although intrinsic innervation of the gut appears to be essential for propagation. In the dog, cyclic variation in plasma motilin is closely correlated with antroduodenal phase III activity, but such an association occurs infrequently in humans (Kees, Malagelada, Go, unpublished data).

A key finding of our study is that interdigestive motor cycles were absent in the stomach, whereas they were essentially intact in the small bowel. This suggests that the mechanisms responsible for this cyclic activity continue operating in these patients, yet the stomach is not responsive to the action of these mechanisms. Furthermore, our study shows that the absence of interdigestive motor complexes is not the consequence of diabetes or vagotomy, because the disease control groups (diabetic and postsurgical) also had essentially normal cyclic activity. It is intriguing that postsurgical controls showed a trend toward both increased frequency of interdigestive motor cycles and decreased gastric motility index. The significance of this is unclear for, at least in the dog, truncal vagotomy causes a slight decrease or no effect on the incidence and propagation of a complex. The asymptomatic diabetic controls showed a decrease in gastric motility index, and others have commented on the decreased gastric emptying in such patients, although this finding has not been universal. Because all these subjects were asymptomatic, variations in gastric motor activity may occur without clinical manifestation.

The function of interdigestive cycles is unknown, but the propagated phase III activity may act as an "intestinal housekeeper," periodically sweeping luminal contents, bacteria, and debris into the colon. Perhaps more relevant to patients with gastroparesis is the observation that gastric phase III activity plays a role in the evacuation of nondigestible solids from the stomach. Nondigestible solids can be defined as particulate dietary components which, because of their size and mechanical resistance to antral grinding and to acid-peptic degradation, are selectively discriminated by the distal stomach and not allowed to pass into the duodenum with other components of the meal. Nondigestible solids are evacuated later with the return of the interdigestive motor complex. In light of these concepts, it is intriguing that "bezoars" often found in patients with chronic gastroparesis (as it was true in 5 of 10 of our patients with postsurgical gastroparesis) are composed largely of nondigestible solids such as vegetable fibrous material and other debris. One ex-
planation for the formation of these bezoars could be the absence of gastric interdigestive motor complex leading to their selective accumulation in the stomach.

Metoclopramide significantly increased motor activity in the proximal gastric, distal gastric, and small bowel in both groups of patients with gastroparesis. This observation confirms the results of an earlier study on the antral motor response to metoclopramide in a patient with diabetic gastroparesis. Furthermore, metoclopramide significantly improves gastric emptying of solids and liquids in diabetic and postvagotomy gastroparesis, and this effect is likely to result from the increased gastric motor activity (fundic and distal), as demonstrated in the present study. The precise mechanism of action of metoclopramide remains controversial, but it may involve cholinergic and antidopaminergic actions.

From a pathogenetic standpoint, both metoclopramide and bethanechol temporarily restored gastric motor index to normal. Further, metoclopramide triggered the appearance of gastric phase III in patients with postsurgical gastroparesis. These are encouraging indications that, even in severe gastroparesis, the gastric musculature remains able to contract and generate normal intraluminal pressures. Thus, this is a potentially reversible phenomenon rather than a primary organ failure. Further, subtle but possible revealing differences between postsurgical and diabetic gastroparesis were observed. Only in the former did metoclopramide restore the gastric interdigestive motor complex, perhaps reflecting pathogenetic differences between both types of gastroparesis: vagal interruption being perhaps the main feature of postsurgical gastroparesis and a more diffuse visceral neuropathy present in diabetic gastroparesis. More needs to be known about the physiologic regulation of interdigestive motility before we can fully interpret its pathophysiologic abnormalities. Also, larger scale trials should be undertaken before asserting the clinical value of gastric manometric recordings.

References