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Gastric manometric abnormalities in patients with dyspeptic symptoms after fundoplication

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SUMMARY We describe six patients in whom severe dyspeptic symptoms developed after fundoplication. The symptoms began immediately after operation (three patients) or shortly thereafter (three and eight months). There were no other known predisposing factors to gastroparesis. Seven, age-matched, healthy volunteers served as controls. Pressure activity from antrum (two sites), duodenum (two sites), and jejunum (one site) was recorded by a low compliance perfusion system connected to external strain gauge transducers. Activity was recorded for three hours during fasting and for two hours after the ingestion of a solid and a liquid meal. To determine whether an inadvertent vagotomy had been performed, basal acid output and the response to insulin (Hollander's test) were measured on a separate day. Manometric studies revealed postprandial hypomotility in these patients, whereas fasting antral and intestinal activities were normal. Acid output increased in all patients during insulin induced hypoglycaemia. In three patients, an antrectomy was subsequently performed, and they were relieved of their symptoms. We conclude that, after fundoplication, symptoms associated with postprandial antral hypomotility may develop in some patients. The pathophysiologic mechanism is unknown, but a positive acid response to insulin induced hypoglycaemia does not support the occurrence of incidental vagotomy. We do not know the prevalence of this motor abnormality among asymptomatic patients with prior fundoplication. A favourable symptomatic response to antrectomy in several of our patients, however, suggests that the symptoms were related to antral motor dysfunction.

Postprandial epigastric fullness and discomfort, abdominal distension, belching, nausea, and vomiting are common gastroenterologic symptoms in patients with otherwise negative clinical, radiologic, or endoscopic evaluations. These patients have been considered traditionally as being afflicted with 'functional dyspepsia', which is a poorly defined diagnosis of exclusion without an established pathophysiologic base. It has been long suspected, however (largely on an empiric basis), that these so-called functional symptoms are caused by abnormal gut motility.

Patients with somatic or visceral (or both) neuromuscular diseases may present similar symptoms, often in association with delayed gastric emptying. Such may be seen in myotonic dystrophy,[1] demyelinating diseases,[2 3] or chronic intestinal pseudo-obstruction[4] (a degenerative disorder of the myenteric plexus[5] and/or smooth muscle of the gut[6]) and in acquired visceral neuropathies such as those associated with diabetes mellitus or after vagotomy.[7–10] More recently, gastric electrophysiologic disturbances (tachygastria and tachyarrythmia[11]), or gastric stasis, or both[12–15] have been found in patients who have similar symptoms but who were without a predisposing cause or evidence of a neuromuscular disorder elsewhere.

The conditions listed above probably represent a small fraction of the large number of patients with functional dyspepsia attending any gastroenterologic clinic, suggesting that much work remains to be done to elucidate possible 'organic' basis for most patients with this entity. During the last two years, we have observed a group of patients in whom severe dyspeptic manifestations developed immediately or shortly after undergoing surgical repair of a hiatal hernia with fundoplication for chronic gastro-oesophageal reflux. In this report, we describe their clinical features, document their antral manometric abnormalities, and report their

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Table 1 *Clinical data on six patients with dyspepsia after fundoplication*

Patient	*Sex and age (yr)*	*Present symptoms*	*Type of operation*	*Symptoms before fundo-plication*	*Time elapsed since fundo-plication (mth)*	*Onset of present symptoms after fundo-plication*	*Radiology/ endoscopy*	*Medical therapy*	*Surgical therapy*
1	F 20	Postprandial nausea, vomiting, pain	Nissen fundo-plication (subsequently taken down)	Reflux oesophagitis, 2 yr. Severe endoscopic changes	5	Immediately	Small hiatal hernia, retained food	Meto-clopramide, bethanechol	None
2	F 49	Postprandial fullness, abdominal distension, mild dysphagia	Nissen fundo-plication	Reflux oesophagitis, 3 yr. Hiatal hernia	36	Immediately	Neg	Meto-clopramide, bethanechol (ineffective)	Antrectomy, Billroth I anastomosis
3	F 51	Postprandial easy satiety, nausea, abdominal cramping	Nissen fundo-plication	Reflux oesophagitis, 10 yr. Hiatal hernia	36	2–3 wk	Neg	Meto-clopramide bethanechol	None
4	M 39	Postprandial bloating, fullness, nausea, regurgitation	Nissen fundo-plication + proximal gastric vagotomy	Reflux oesophagitis, 5 yr. Large hiatal hernia	72	8 mth	Neg	Meto-clopramide (ineffective)	Antrectomy, Billroth I anastomosis
5	M 40	Postprandial pain, fullness, bloating	Nissen fundo-plication	Reflux oesophagitis, 20 yr. Severe endoscopic changes. Hiatal hernia	5	Immediately	Neg	Meto-clopramide	None
6	F 59	Postprandial fullness, nausea, epigastric discomfort	Nissen fundo-plication + pyloro-myotomy	Reflux symptoms, 10 yr. Dysphagia. Large hiatal hernia. Mild oesophagitis by endoscopy	96	Immediately	Retained food	Meto-clopramide (ineffective)	Antrectomy, Billroth I anastomosis

responses to subsequent antrectomy performed on several of these patients.

Methods

SUBJECTS

Six patients (two men and four women; ages 20 to 59 years, mean 43·0 years) experienced symptoms referable to a motor disturbance of their upper gastrointestinal tract after undergoing surgical repair of a hiatal hernia by fundoplication (Table 1). Their average height was 170 cm (range 158–189 cm) and their average weight 74 kg (range 52–91 kg). Four of the patients (cases 2, 3, 5 and 6) had a conventional Nissen fundoplication. One patient (case 1) had symptoms immediately after the fundoplication was taken down because it had induced severe dysphagia and she had been unable to eat normal meals. In case 4, a proximal gastric vagotomy had been performed in addition to the fundoplication. In case 6 a pyloromyotomy but no vagotomy had also been performed as her preoperative acid output was low (basal acid output 0·2 mmol/h; maximal acid output 10·5 mmol/h). Before the operation, all patients had experienced symptoms consistent with gastro-oesophageal reflux (which were corrected by the operation) but had no symptoms referable to gastroparesis. None had evidence of any systemic disease known to be associated with abnormal gastrointestinal motility.

Seven healthy volunteers (four men and three

women; ages 21 to 46 years, mean 30·4 years) served as controls for the manometric studies. Their average height was 176 cm (range 165–190 cm) and their average weight 77 kg (range 61–93 kg).

All participants gave informed consent, and studies had been previously approved by Mayo Clinic Human Studies Committee.

UPPER GASTROINTESTINAL MANOMETRY

Pressure activity in the stomach and proximal intestine was recorded by a low compliance perfusion system originally described by Arndorfer *et al*[16] and modified by us.[17] After an overnight fast, each subject swallowed a radiopaque, five lumen polyvinylchloride tube. The tube was carefully positioned under fluoroscopic control, so that one of the recording sites was in the proximal jejunum, one at the angle of Treitz, one in the descending duodenum, and two in the antrum. The recording sites in the antrum were 3·5 cm apart and the intestinal sites were located 10, 30, and 50 cm distal to pylorus (Fig. 1). The tubes were perfused with distilled water *via* a pneumohydraulic pump (perfusion rate 0·1 ml/min). Intraluminal pressure changes were recorded continuously using strain gauge transducers attached to each tube. Permanent graphic images of the changes in the output of each transducer were drawn by means of a paper chart recorder. Throughout the study, subjects were in a semireclining posture (45° to the horizontal).

Fasting gastrointestinal motility was recorded for three hours or until two migrating motor complexes[18 19] were detected, whichever came first. One volunteer was fed after two and a half hours of fasting recording. After completion of the fasting recordings, each subject ate a solid liquid mixed meal consisting of 70 g of chicken meat, 135 g of potato, 25 g of butter, 0·1 g of salt, and 145 g of tapioca pudding. This meal induces a good antral contractile response.[20] The meal was always ingested during phase II of the interdigestive motor complex (irregular activity). Motility after feeding was recorded for two hours in all but one subject. In this patient, the test was terminated at 90 minutes at his request.

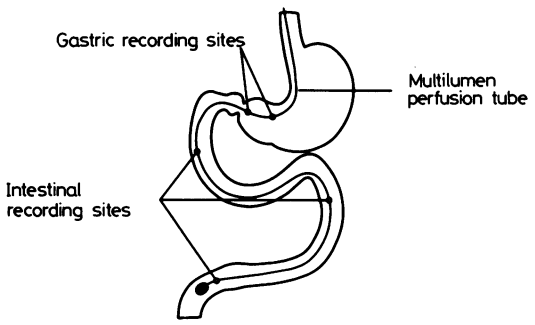

Fig. 1 *Method for recording upper gastrointestinal pressure activity. A five lumen, open tipped tube, connected to external strain gauge transducers and perfused with distilled water, was positioned with three recording sites in the proximal small bowel (20 cm apart) and two in the distal antrum (3·5 cm apart).*

GASTRIC SECRETORY RESPONSE TO INSULIN HYPOGLYCAEMIA

Within one week after the manometric study, we performed a conventional Hollander's test in all six patients. After an overnight fast, each patient swallowed a nasogastric tube (Salem Sump 18 F). Under fluoroscopic control, the tip of the tube was positioned in the most dependent portion of the stomach. A fasting sample of gastric juice was hand aspirated, the tube was connected to an automatic suction pump, and aspiration was started for one hour of basal collection. Insulin (0·25 U/kg) was given intravenously, and the gastric aspirate was continuously collected for a total of two hours (eight periods of 15 minutes each). During the basal hour and 30 and 60 minutes after insulin was given, blood samples were drawn for glucose determinations.

ANALYSIS OF MOTILITY DATA

The total number of interdigestive migrating motor complexes was determined from the number of phase III episodes (bursts of regular contractions migrating aborally on at least two recording intestinal sites). The numbers of phase III episodes beginning in the stomach and of those beginning in the intestine also were noted.

The total number of pressure waves, sum of their amplitudes, mean amplitude, and motility index (number of waves multiplied by the sum of amplitudes) were determined separately during the fasting and feeding periods. Feeding pressure activity was computed in four separate 30-minute intervals. As the fed observation period of patient 3 lasted only 90 minutes, the missing data during the 90- to 120-minute period was estimated, for purposes of analysis only (see Statistical Analysis), by using the mean values for the five remaining patients during the period.[21]

ANALYSIS OF HOLLANDER'S TEST RESULTS

Acid concentration and pH during the basal hour, acid concentration of each 15-minute interval of postinsulin periods, and blood glucose concentrations at 30 and 60 minutes after the insulinergic stimulus were used to evaluate the results of the Hollander test. A decrease in blood glucose concen-

tration to 50 mg/dl or less was considered indicative of a valid stimulation. An increase of 20 mmol/l in acidity during the two hours after insulin stimulation (if the fasting pH was less than 3·5) or an increase of 10 mmol/l (if the fasting pH was greater than 3·5) was considered evidence for the presence of functioning efferent vagal fibres. The test was suspended when increases in acidity indicating functioning efferent fibres were achieved.

STATISTICAL ANALYSIS

Because fasting motility data were not normally distributed, the Wilcoxon's rank sum test was used to compare data from patient and control groups. Cumulative pressure activity during the fed period was approximately normally distributed and was analysed by means of the two tailed Student's *t* test. The motility index data for patients and controls did not show equal variances, even when variance stabilising transformations were attempted, and therefore they were analysed by the Wilcoxon's rank sum test.

In comparing motility data of patients with controls during the fed period, Student's *t* distribution with 10 (rather than 11) degrees of freedom was used to assess statistical significance of the computed test statistics in order to take into consideration the missing values during the 90- to 120-minute period in case 3 of the patient group.

Results

FASTING MOTILITY

All seven control subjects and five of the six patients had at least one interdigestive migrating motor complex (Table 2). This complex started in the stomach in only one of the six patients, whereas it did so in five of the seven controls (this difference being borderline significant p=0·05, by Wilcoxon's rank sum test). The total numbers of gastric pressure waves, their mean amplitude, and their motility index were similar in patients and controls (Table 2). Thus, no abnormalities in fasting motility were observed in the patients, other than a possible decrease in the number of gastric phase III activity.

FED MOTILITY

During the two-hour feeding period, patients had a significantly lower total number of antral pressure waves ($p<0·01$, by Student's *t* test), sum of amplitudes ($p<0·01$, by Student's *t* test), mean wave amplitude ($p<0·05$, by Student's *t* test) (Table 3). Time analysis of cumulative antral number of pressure waves and motility index pooled at 30-minute intervals (Table 3, Fig. 2) showed that antral hypomotility was a consistent feature in the patient's group. The intestinal fed pattern appeared grossly normal, but no detailed quantification of waves was attempted. An example of the different fed motor

Table 2 *Motor variables recorded during fasting periods (180 minutes)*

Subject	*Total migrating motor complexes*	*Complex beginning in:* *Stomach*	*Duodenum*	*Total no. of pressure waves*	*Sum of pressure wave amplitude*	*Mean amplitude**	*Total motility index* ($\times 10^3$)†
Patient group							
1	2	0	2	108	4370	40·5	472·0
2	2	1	1	35	1760	50·3	61·6
3	1	0	1	51	670	13·1	34·2
4	2	0	2	52	3770	72·5	196·0
5	0	0	0	225	3270	14·5	735·8
6	2	0	2	57	2580	45·3	147·1
Mean	1·5	0·2	1·3	88	2737	39·4	274·5
SE	0·3	0·2	0·3	29·2	556	9·2	112·1
Control group							
7	3	1	2	51	1200	23·5	61·2
8	2	1	1	57	2230	39·1	127·1
9	1	1	0	70	2000	28·6	140·0
10	2	1	1	87	2920	33·6	254·0
11	1	0	1	60	2700	45·0	162·0
12	1	0	1	33	1870	56·7	61·7
13	2	1	1	116	4320	37·2	501·1
Mean	1·7	0·7	1·0	67·7	2463	37·7	186·7
SE	0·3	0·2	0·2	10·2	375	4·1	58·0

* Equals sum of pressure wave amplitudes ÷ no. of pressure waves.
† Equals no. of pressure waves × sum of pressure wave amplitude.

Table 3 *Motor variables recorded during fed periods (120 minutes)*

Subject	Total no. of pressure waves	Sum of pressure wave amplitude	Mean amplitude*	Cumulative motility index ($\times 10^3$)†
Patient group				
1	167	5120	30·7	232·6
2	118	2110	17·9	70·8
3	170·2	4098	24·1	193·7
4	46	580	12·6	7·2
5	81	1240	15·3	385·9
6	171·5	7010	40·9	52·0
Mean	125·6‡	3360‡	23·6§	157·0§
SE	21·8	1012	4·4	57·8
Control group				
7	280	9660	34·5	678·2
8	195	6630	34·0	386·4
9	173	4260	24·6	211·9
10	174	5440	31·3	248·9
11	251	11 160	44·5	719·9
12	279	11 680	41·9	819·0
13	330	12 860	39·0	1 058·9
Mean	240·3	8813	36·7	589·0
SE	23	1270	2·7	119·3

* Equals sum of pressure wave amplitude ÷ no. of pressure waves.
† Equals cumulative no. of pressure waves × sum of pressure wave amplitude pooled at 30-minute intervals.
Significantly different from control group values: ‡ $p<0·01$; § $p<0·05$.

patterns presented by a healthy control and by a patient after surgical hiatal hernia repair is shown in Figure 3.

case 6 could not be interpreted as subsequently it was determined that this patient had achlorhydria, as documented by lack of response to pentagastrin, 6 μg/kg, given intravenously. Patient 1 probably had functioning vagal fibres, but the results were inconclusive as the test had to be prematurely interrupted when the patient developed signs of hypoglycaemic shock, from which she recovered uneventfully.

RESPONSE TO THERAPY

Three patients (cases 1, 3, and 5) improved symptomatically when treated with metoclopramide, bethanechol, or both drugs in combination. The three remaining patients failed to respond to this treatment and subsequently underwent an antrectomy with Billroth I anastomosis. Postoperatively their symptoms disappeared and they have remained subjectively well for up to one year since surgery.

Discussion

We have described six patients who experienced severe, although non-specific, dyspeptic symptoms after a fundoplication for gastro-oesophageal reflux associated with hiatal hernia. Manometric studies showed that their antrum contracted powerfully during fasting, and yet it appeared unable to organise its motor activity into a normal fed pattern after a *solid* meal. Antral hypomotility after feeding was characterised by a decrease in the frequency of

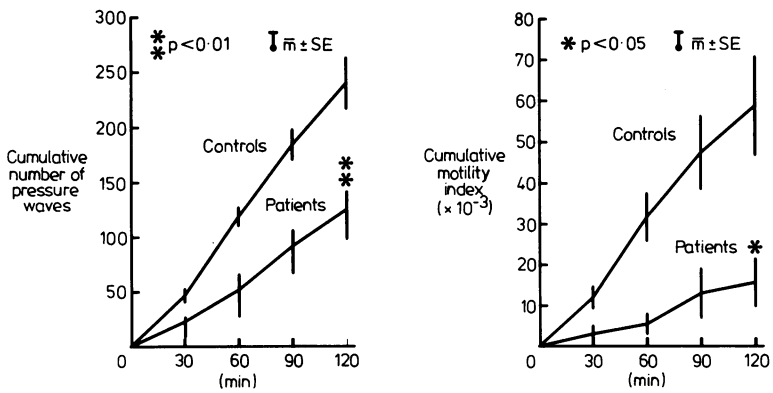

Fig. 2 *Cumulative antral motor activity during feeding in seven healthy controls and in six patients after fundoplication. Number of pressure waves and motility index were pooled at 30-minute intervals during the 2-hour postprandial period.*

GASTRIC SECRETORY RESPONSE TO INSULIN HYPOGLYCAEMIA

The results of the Hollander's test in patients 2, 3, 4, and 5 suggested the presence of functional vagal fibres (note that patient 4 had supposedly a proximal gastric vagotomy performed at the time of her fundoplication). The results of the insulin test in

antral contractions and a milder but definite decrease in the mean amplitude. The apparently intact electromechanical ability of the antrum during fasting suggests that the observed feeding abnormalities are due to a dysfunction in the extrinsic neurohormonal control of gastric motility rather than to a myenteric or myogenic disorder. The

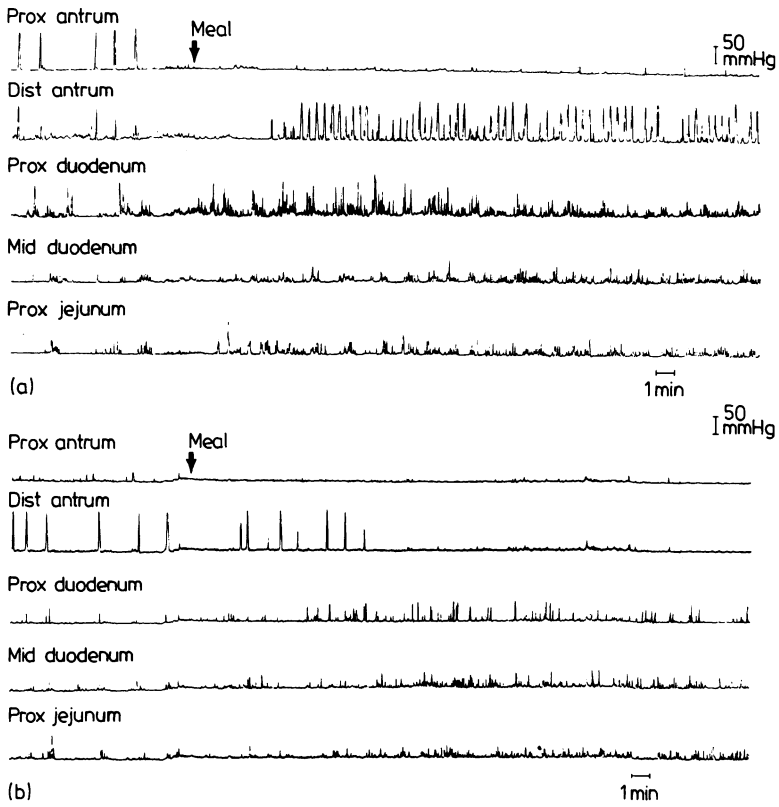

Fig. 3 *Antral and intestinal motility in a healthy control (top panel) and in a patient after fundoplication (lower panel). Pressure recording sites are positioned as indicated in Fig. 1. The different effects induced by the ingestion of a mixed solid-liquid meal during a Phase II (phase of irregular activity of the fasting motility pattern) are shown.*

temporal relationship between the fundoplication and the appearance of new symptoms raises the possibility that surgical manipulation of the gastric fundus somehow interfered with the mechanism controlling antral feeding activity. It is worth noting that symptoms in one patient became apparent after the fundoplication, which had resulted in severe dysphagia and inability to eat, was taken down.

In considering possible explanations for the observed abnormalities it should be noted that gastric surgery has been long recognised as a potential cause of gastric motility disturbances.[9] Specifically, vagotomy has been shown by experimental[22–24] and clinical studies[25 26] to induce antral hypomotility and stasis. The physiologic importance of vagal innervation in the development and maintenance of feeding activity is further suggested by the experimental observations of Miolan and Roman,[27] who reported spontaneous discharges in vagal preganglionic fibres during feeding, and by Diamant *et al*[28], who observed an interruption of feeding activity after vagal blockade was obtained by cooling the cervical vagus trunks.

Inadvertent vagotomy at the time of fundoplication causing the manometric abnormalities is a plausible mechanism to explain the observed abnormalities. The results of the insulin test, however (in four of our patients in whom it can be reliably interpreted, cases 2, 3, 4, and 5), suggest the presence of intact vagal fibres to the gastric secretory area. Still, the inadvertent sectioning or trauma to some vagal fibres might have impaired antral function without totally abolishing the secretory response to insulin. Further, it has been reported that non-operated patients with hiatal hernia[29] or reflux oesophagitis[30] or both exhibit delayed gastric emptying. These patients, therefore, might represent a 'high-risk' group for the development of postoperative motor abnormalities. An alternative hypothesis is that surgical trauma to the proximal part of the stomach primarily impaired the afferent autonomic pathways connecting gastric receptors to vagal centres reducing vagovagal and gastrogastric neural reflexes[31] while sparing the efferent vagal fibres (which largely mediate the response to insulin hypoglycaemia).

A causal relationship between the patient's symptoms and the antral motor disturbances

evidenced manometrically is even more difficult to establish because we could not study gastric motility in our patients before surgery, and neither have we studied asymptomatic patients who underwent a similar operation. Circumstantial evidence, however, would seem to link the clinical and motility disturbances. First, the patient's symptoms are similar to those observed in other patients with well characterised motor disorders of the gut. Second, the manometric abnormalities were limited to the antrum (the intestinal fed motor pattern exhibiting a grossly normal appearance), thus making it less likely that the gut motility abnormality is non-specific. Third, antral contractions after solid meals may have an important role in the grinding and propulsion of solid particles, and thus antral hypomotility can be expected to have significant functional repercussions and cause gastric stasis of solids.[32] Fourth, three patients in whom an antrectomy was performed experienced a remission in their symptoms, although admittedly the follow-up period is still relatively short (less than 1 year).

Caution should be exerted in interpreting manometric evidence of antral hypomotility in individual cases. Although patients postfundoplication had significantly lower motility indices than controls there is moderate interindividual variability and overlap between both groups. Further, Stanghellini and colleagues have recently shown that feeding antral hypomotility can be induced in healthy persons by acute stressful stimuli acting *via* the central nervous system.[33] Thus, an alternative explanation for our findings may be that the observed manometric abnormalities are not the cause but the result of symptoms that in turn induce a stress-related inhibition of antral motor activity after feeding. Further studies will be needed to clarify this matter.

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