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Gastrointestinal Transit and Gastric Acid Secretion in Patients with Achalasia

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Previous studies suggest that patients with achalasia exhibit degenerative changes of extraesophageal nerve fibers. We investigated whether these morphological alterations are associated with functional abnormalities of the gastrointestinal tract. Patients with achalasia had a normal acid secretory response (5.5 ± 1.5 mmol/hr) to vagal stimulation when compared to controls (6.0 ± 5.3 mmol/hr). However, the half time of gastric emptying of liquids was significantly shorter in patients with achalasia (10.4 ± 1.8 min) than in control subjects (19.3 ± 11.3 min) (P < 0.01). Although there was a tendency towards a more rapid gastrointestinal transit in patients with achalasia, these changes failed to reach statistical significance. It is concluded that patients with achalasia have a gastric emptying disorder that could either be explained by a selective defect of extraesophageal vagal inhibitory nerve fibers or as an epiphenomenon occurring as a consequence of impaired esophageal emptying.

KEY WORDS: achalasia; gastric emptying; gastric acid secretion; sham feeding; gastrointestinal transit; breath hydrogen excretion; ultrasound; denervation disorders; vagal function.

Although it is generally agreed that achalasia is associated with denervation of the smooth muscle esophagus, the precise etiology of this rare motility disorder remains unknown. It was first suggested by Sir Arthur Hurst (1) that achalasia may be caused by a destruction of the normal esophageal neuroanatomy, a view that was later substantiated by Rake's morphological descriptions of two autopsy cases in which ganglion cells of Auerbach's plexus were either reduced or completely absent (2). Since then, several studies have been published confirming the presence of degenerative changes within the esophageal myenteric plexus of patients with achalasia (3–8).

More recently, morphological data have accumulated suggesting that the neurogenic defect may involve not only the myenteric plexus but also extraesophageal nerve fibers and even the dorsal vagal nucleus of the brain stem. For example, conventional histological as well as electron microscopic studies have revealed abnormalities of extraesophageal parasympathetic nerve fibers consisting of fragmentation of axons and Wallerian degeneration (9–11). In addition, Kimura (12) and Cassella et al (13) described a reduction in the number of cells and degenerative changes in the dorsal motor nuclei of the vagus nerve in a small number of necropsy cases of achalasia. However, pharmacological studies designed to elucidate the site of denervation in achalasia have produced variable results. In one of these studies it was concluded that the neurogenic defect occurs at the preganglionic level (14), while two others produced evidence of postganglionic denervation (7, 15).

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Thus, at present it still remains unclear whether the loss of myenteric ganglion cells and the concomitant functional changes in the achalasic esophagus are a primary and single phenomenon or the consequence of a more centrally located neuronal degeneration.

If the neuronal defect of achalasia is primarily extraesophageal, it should be assumed that the functional abnormalities not only involve the esophagus but also more distal locations of the gastrointestinal tract. The present investigation was therefore performed to answer the following questions: (1) Do patients with achalasia exhibit abnormalities in gastrointestinal transit that are consistent with vagal denervation? (2) Does vagal stimulation lead to a diminished acid secretory response in these subjects?

MATERIALS AND METHODS

Subjects. Studies were performed in 18 patients with achalasia and in 20 healthy volunteers. All patients with achalasia had a long history of esophageal symptoms, ranging from 1.5 to 35 years (mean: 7.42 ± 1.8 years). In each case, the diagnosis of achalasia was confirmed by radiographic, manometric, and endoscopic investigations. All patients had previously undergone at least one pneumatic dilatation. However, there was a mean interval of 1.3 ± 0.3 years between the last treatment and the performance of investigational procedures. None of the control subjects complained of symptoms referrable to the gastrointestinal tract or chest. In addition, all of them had normal esophageal motor function as determined by manometric studies.

Patients with achalasia ranged in age from 18 to 71 years (mean: 42.6 ± 3.1 years), while the mean age of control subjects was 31.0 ± 2.2 years (range: 21 to 53 years). The body surface areas and weights were comparable in patients and controls. Patients had a mean body surface area of 1.79 ± 0.6 m^2 and a mean weight of 66.9 ± 2.4 kg, which was similar to that of controls (mean body surface area: 1.86 ± 0.6 m^2; mean weight: 69.2 ± 3.9 kg). Informed consent was obtained from all subjects, and the research was carried out according to the Declaration of Helsinki.

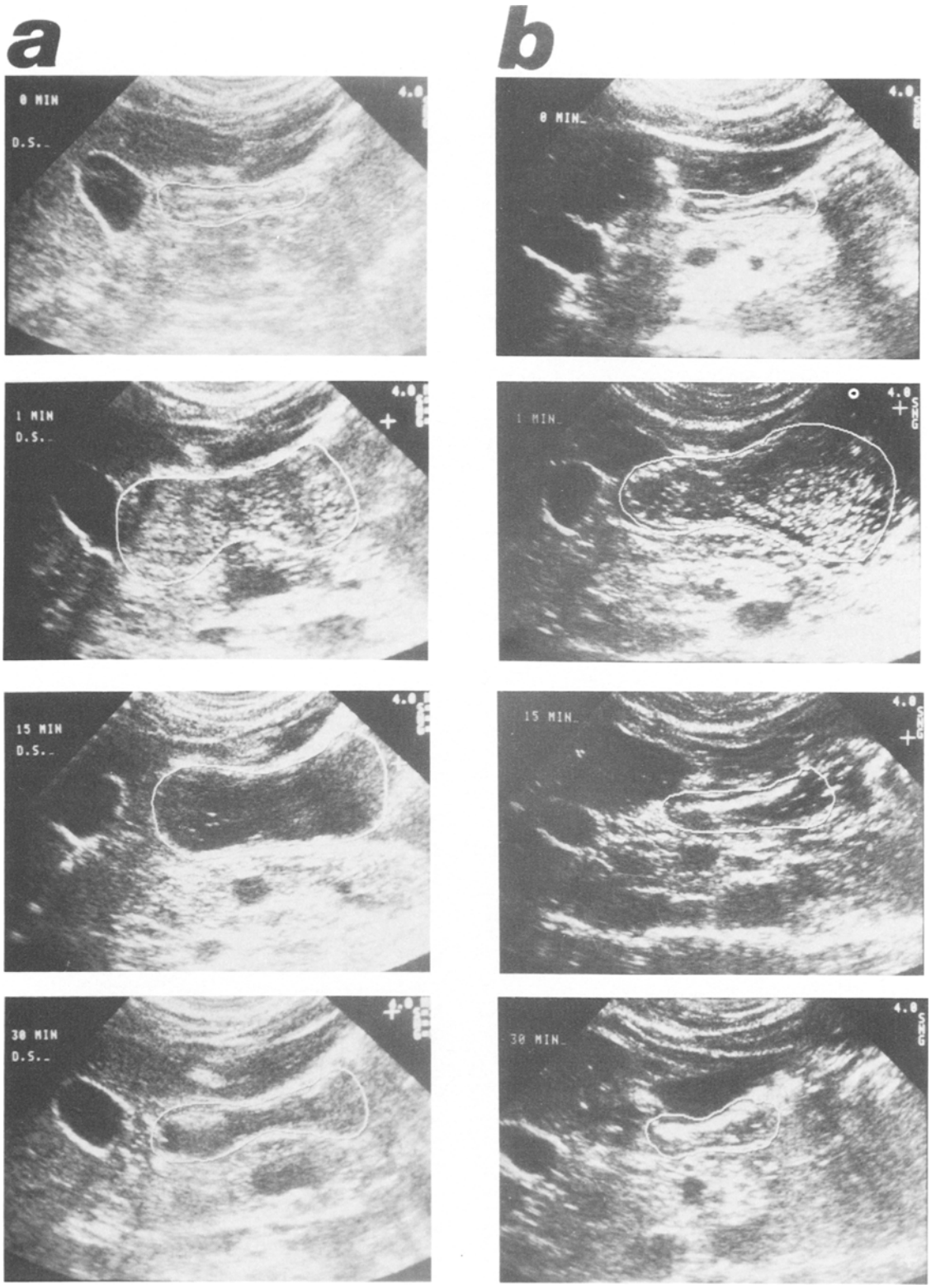
Gastric Emptying Studies. Gastric emptying of liquids was assessed by a real time ultrasound method. After an overnight fasting period of at least 12 hr, a four-lumen manometric catheter was introduced by mouth into the stomach. The assembly consisted of three side-hole catheters for manometric measurements and an additional large-bore catheter for intragastric instillation of the liquid. Following manometric localization of the lower esophageal sphincter (LES) by a stepwise withdrawal method (16), the distal opening of the large-bore catheter was placed immediately distal to the LES and the test solution, consisting of 400 ml of water containing 25 g of lactulose, was instilled into the stomach at a constant rate of 100 ml/min.

Ultrasonographic imaging of the gastric antrum was performed immediately prior to the instillation of the test solution, 1 min thereafter, and for an additional 90 min in 15-min intervals (Figure 1). A high-resolution real-time sector scanner (Kretz-Combison 320; Zipf, Austria) with a rotating 4.0-MHz transducer was used for all examinations. Antral volume determinations were performed by obtaining measurements of the antral length and of multiple longitudinal and anteroposterior diameters of cross sections through the gastric antrum. Antral volumes were calculated using a formula described by Bolondi et al (17), and the rate of gastric emptying was determined from the estimated volume changes occurring after instillation of the test solution. One hundred percent emptying was assumed if the antral volume had returned to its fasting level.

Studies of Gastrointestinal Transit. The stomach-to-cecum transit of the intragastrically instilled lactulose solution was determined simultaneously with gastric emptying by breath hydrogen measurements. The procedure involved collections of end-expiratory air at 15-min intervals before and for 4 hr after instillation of the test sugar solution. Samples were tested for hydrogen concentrations by means of an electrochemical cell consisting of three electrodes and a liquid electrolyte (GMI Medical Ltd., Inchinnan Estate, Renfrew, Scotland). The accuracy of this method has been estimated as ±2 ppm, which is comparable to that of gas chromatographic methods (18, 19). The time at which hydrogen excretion exceeded 20 ppm above baseline was taken as the stomach-to-cecum transit time for each individual. In addition, the time at which breath hydrogen reached its maximum was determined to estimate the time at which the bulk instead of the head of the lactulose column reached the cecum.

Acid Secretory Studies. Gastric acid secretory studies were performed after a 12-hr fasting period. On the morning of the study day, patients and controls were intubated with a 14 FG nasogastric tube to which a smaller manometric catheter had been attached. The open tip of the manometric catheter was located 10 cm proximal to the side holes used for aspiration of gastric contents. To avoid exposure of the subjects to radiation, a combined manometric and ultrasonographic method was used for positioning of the tube. Following manometric localization of the LES, the tube was advanced a further 2 cm into the stomach, resulting in an intragastric localization of its most distal 20 cm. Ultrasonography was then used to confirm that the tip of the tube assembly had reached the gastric antrum.

Prior to the gastric secretory studies, residual contents of the stomach were aspirated, its pH checked, and then discarded. Gastric secretions were then collected for 2 hr by manual aspiration. Samples of gastric juice were collected in 15-min portions. The volume of each sample was immediately read and its acidity was measured by titration to pH 7 against 0.1 N NaOH (pH meter, Knick, Berlin, F.R.G.) using a glass electrode (Ingold, Zürich, Switzerland). Acid secretion was measured for 1 hr prior and an additional hour following modified sham feeding (MSF). After the first hour, a steak meal consisting of a fried and seasoned 200 g sirloin steak was served. The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meal was cooked and prepared in a separate area. Subjects were carefully instructed to chew the food but to avoid swallowing. A basin was provided into which food could be spat out. Sham feeding-stimulated gastric acid secretion was measured for 30 min during and for an additional 30 min after sham feeding.

Statistical Analysis. Results are expressed in mean ± 1 SE. The Wilcoxon rank test was used to detect differences. A P value of less than 0.05 was considered significant.

RESULTS

Gastric Emptying of Liquids. Fifteen patients and 13 control subjects consented to the performance of gastric emptying studies. In eight of them (five patients with achalasia and three controls) intraabdominal gas interfered with sonographic imaging, making accurate volume determinations impossible. Therefore, a total of 10 patients and an equal number of volunteers were available for the analysis of gastric emptying studies.

As illustrated in Figure 2 in patients and controls, the emptying curve for the liquid was nonlinear with a slope that decreased with time in an approximately monoexponential pattern. In patients with achalasia, this curve was shifted to the left, indicating a more rapid initial gastric emptying. The estimated half time for gastric emptying was significantly shorter ($P < 0.01$) in patients with achalasia (10.4 ± 1.8 min) than in control subjects (19.3 ± 11.3 min). Up to 30 min following instillation of liquids, patients with achalasia had higher emptying rates than controls. These changes were highly significant at 15 min (patients: 76.6 ± 4.0%, controls: 44.8 ± 7.8%; $P < 0.01$) and came close to statistical significance at 30 min (patients: 87.7 ± 1.9%; controls, 72.1 ± 7.8%; $P = 0.06$). The rate of gastric emptying in patients with achalasia was related neither to the severity and duration of the disease nor to the length of the time interval between pneumatic dilatation and the investigational procedures.

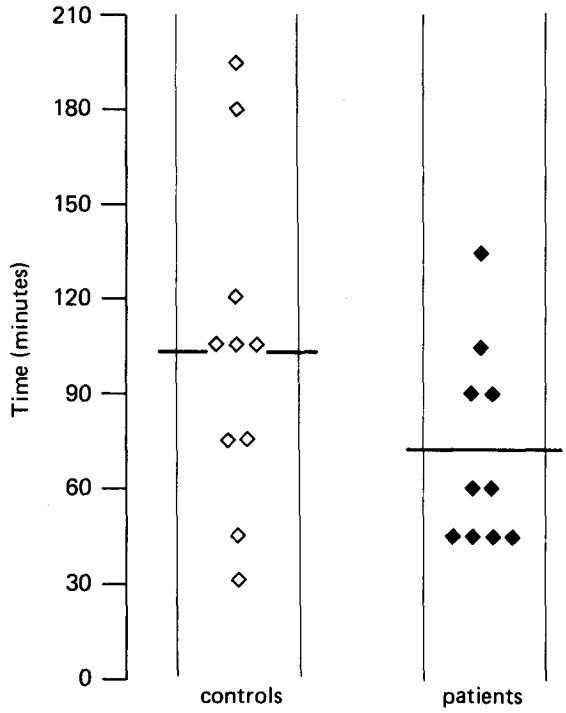

Fig. 3. Gastrointestinal transit time as calculated from the first sustained increase in breath hydrogen excretion in patients with achalasia and controls.

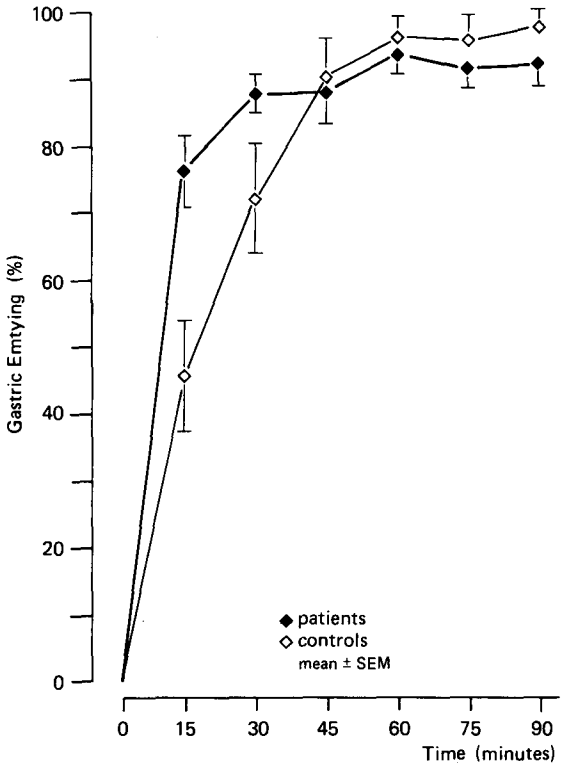

Fig. 2. Gastric emptying of liquids in patients with achalasia and control subjects. The curves indicate the mean percentage of emptying for each different time interval.

Stomach-to-Cecum Transit. Gastrointestinal transit studies were performed in 15 patients with achalasia and in 13 healthy controls: 33.3% of the patients with achalasia and 23% of the control subjects failed to excrete hydrogen as described above and were excluded from the analysis of data. Thus, the stomach-to-cecum transit time could be determined in 10 patients and 10 controls.

The time that elapsed between the ingestion of lactulose and the first significant increase in hydrogen excretion was not significantly different in patients (mean: 72.0 ± 9.8 min) and controls (mean: 103.0 ± 16.5 min) (Figure 3). Maximal hydrogen excretion occurred earlier in patients with achalasia (120.0 ± 17.1 min) when compared to healthy volunteers (169.5 ± 16.3 min), suggesting that the bulk of lactulose transversed the small bowel more rapidly. However, these changes failed to reach statistical significance ($P = 0.05$). As indicated by similar areas under the curve for the 4-hr period, there was no significant differences in total hydrogen excretion between patients and controls ($P > 0.1$).

Gastric Acid Secretion in Response to Sham Feeding. Ten patients and 10 control subjects agreed to have acid secretory studies performed. All of them had a fasting pH of less than 4 and were therefore considered eligible for further investigation. In each instance, an increase in acid secretion was observed following sham feeding, which ranged from 0.6 to 19.7 mmol/hr in control subjects and from 0.7 to 15.5 mmol/hr in patients with achalasia. Following MSF, both groups of subjects showed a statistically significant increase ($P < 0.02$) in mean acid secretion (controls: 6.0 ± 5.3 mmol/hr; patients: 5.5 ± 1.5 mmol/hr) and no difference was observed between the two groups. As indicated in Figure 4, in both groups the rise in acid secretion began immediately after the initiation of sham feeding, reached its maximum after 30 min, and then slowly declined.

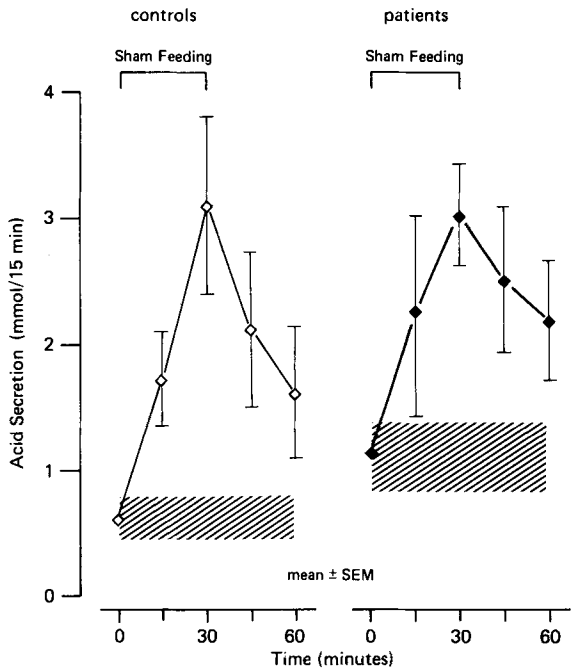

Fig. 4. Gastric acid secretion in response to sham feeding in patients with achalasia and controls. The shaded area represents the average control secretion rates ±1 SE during the hour before sham feeding.

DISCUSSION

Studies investigating the etiology of achalasia have been focused mainly on the neuroanatomy of this disease. The most consistent finding in these investigations is a neuronal destruction of the esophageal myenteric plexus. However, some studies have shown that similar changes occur in the esophageal extrinsic innervation (9–13). At present, it remains unclear whether such extraesophageal vagal degeneration is reflected by functional abnormalities of the vagus nerve.

The hypothesis of extraesophageal vagal dysfunction in achalasia is supported by the observation that some of these patients exhibit an impaired gastric secretory response to insulin stimulation (20–22). In addition, it has also been shown that sham feeding fails to stimulate acid secretion in some patients with achalasia (23). In contrast, however, a more recent investigation failed to show an impaired acid secretory response in patients with achalasia when the insulin test was used for vagal stimulation (24). Some of the conflicting data can possibly be explained on the basis of methodological difficulties. First, the uncontrolled nature of earlier investigations (20) does not allow the conclusion that the alterations observed are specific for patients with achalasia. Second, since insulin-induced hypoglycemia also stimulates acid secretion via nonvagal mechanisms (25, 26), a positive test may not exclude vagal dysfunction. Third, sham feeding has been shown to produce an impaired acid secretion only in those patients with achalasia who exhibit a low or zero basal acid secretion. It remains questionable whether the acid secretory response to MSF in such patients can be used to investigate the functional integrity of the vagus nerve. The current study circumvents some of these pitfalls by using simultaneously studied healthy subjects as controls and by testing the acid secretory response to MSF in unselected patients with achalasia who had a normal rate of basal acid secretion. All of these patients demonstrated some increase in acid secretion following MSF which did not differ significantly from the response of the

controls. Therefore, at least in the majority of patients with achalasia, the vagal pathways controlling acid secretion appear to be intact.

Whereas this study failed to show abnormalities in vagal innervation of the gastric parietal cell, it provided evidence for a disturbance of gastric emptying. The observed more rapid emptying of liquids indicates a decreased distensibility of the gastric fundus (27). Such alterations could either reflect a primary defect in gastric innervation or merely represent an epiphenomenon. For example, it has been shown that an inverse correlation exists between the rate of gastric emptying and body size (28) in that undernourished persons may empty their gastric contents more rapidly. However, such an explanation for enhanced gastric emptying would not be applicable to our findings since the weights and body sizes of the achalasia patients studied by us were comparable to those of controls. An alternative explanation may be given by the fact that rapid filling of the stomach through intragastric instillation of liquids is an unphysiological event for patients with achalasia. Achalasia patients who usually have impaired esophageal emptying may not be able to adapt to rapid gastric filling immediately. Although the patients studied by us had well-compensated disease and did not complain about significant dysphagia, this explanation for the observed emptying abnormality cannot be totally dismissed. Furthermore, since fundic relaxation is also induced by esophageal distension (29–31), it is tempting to speculate that patients with achalasia have a diminished or absent afferent vagal discharge to initiate this reflex. In both instances, the gastric emptying abnormality would have to be considered as an epiphenomenon to the esophageal disease.

A second theory that would explain the gastric motor abnormality in patients with achalasia is vagal denervation of the stomach. Receptive relaxation of the proximal stomach which controls the emptying of liquids is largely impaired after vagotomy (32–34). Although the gastric secretory response to vagal stimulation is normal in patients with achalasia, this observation does not exclude an impairment in vagal function. In contrast to acid secretion, which is mediated through cholinergic nerves, receptive relaxation of the stomach is attributed to the action of nonadrenergic noncholinergic nerve fibers (34–37). Thus, the possibility must be considered that patients with achalasia have a selective defect in the inhibitory vagal innervation of the stomach. Such a hypothesis would be supported by the recent observation that smooth muscle from the esophagogastric junction of patients with achalasia contains diminished concentrations of vasoactive intestinal polypeptide (8), which has been considered a candidate neurotransmitter for inhibitory nonadrenergic, noncholinergic nerves (38).

Stimulated by the observation that some patients with achalasia have abnormalities of the migrating motor complex transversing the small bowel (39), we also investigated whether a disturbance in gastrointestinal transit may occur. Although a tendency towards a more rapid transit was observed in patients with achalasia, these data failed to reach statistical significance. Furthermore, we cannot rule out the possibility that the shorter duration of stomach-to-cecum transit in some patients with achalasia is solely a consequence of more rapid gastric emptying.

In conclusion, the current study shows an enhanced gastric emptying of liquids but a normal gastric secretory response to vagal stimulation in patients with achalasia. Whether these changes represent an epiphenomenon or reflect a selective defect of nonadrenergic, noncholinergic nerve fibers supplying the proximal stomach remains to be determined by future investigations.

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