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Compliance of the Proximal Stomach and Dyspeptic Symptoms in Patients with Type I Diabetes Mellitus

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In the present study the function of the proximal stomach and its role in eliciting dyspeptic symptoms were evaluated in patients with diabetes mellitus. Eight type I diabetics with cardiovascular autonomic neuropathy and dyspeptic symptoms, and 10 healthy volunteers were studied using an electronic barostat device connected to a intragastric bag. The intragastric bag was inflated and deflated by stepwise pressure increments, creating pressure–volume curves. During the experiment the blood glucose concentrations were maintained within the euglycemic range in the diabetics. The volume–pressure curves showed a larger volume during the pressure increase in the diabetics than in the controls ($P < 0.01$). This resulted in a significant difference in compliance (dV/dP), 57.2 ± 4.2 ml/mm Hg in diabetics and 43.7 ± 3.5 ml/MM Hg in controls ($P < 0.014$). The volume–pressure curves during deflation of the intragastric balloon were different from the curves during inflation, creating a hysteresis loop. The area between the inflation and deflation curves was 827 ml/mm Hg in diabetics and 627 ml/mm Hg in the controls ($P = 0.21$). Gastric distension induced more upper gastrointestinal sensations in the patients than in the volunteers: nausea ($P < 0.002$), bloating ($P < 0.003$), upper abdominal pain ($P < 0.001$). In conclusion: this study showed that the compliance of the proximal stomach is increased in diabetic patients with autonomic neuropathy and gastrointestinal symptoms. This abnormality, probably due to autonomic neuropathy, is associated with increased symptom generation during gastric distension.

KEY WORDS: stomach; dyspepsia; diabetes mellitus.

Gastrointestinal motor abnormalities are frequently seen in patients with type I diabetes mellitus. Several studies showed delayed gastric emptying for solid and liquid meals in up to 50% of these patients (1, 2). Manometric studies showed abnormal antroduodenal motility in both the postprandial and interdigestive periods (3–8). Although abnormal gastric emptying for liquid meals and abnormal distribution of meals in the stomach suggests impaired function of the proximal stomach, information about the function of this part of the stomach in diabetics is very limited (9, 10). Upper gastrointestinal symptoms are frequently reported by patients with diabetes mellitus. However, the relation between the antroduodenal motor abnormalities and upper gastrointestinal symptoms is poor. A possible explanation for this is that symptoms originate from other parts of the gastrointestinal tract, for instance the proximal part of the stomach.

In the present study we hypothesized that in patients with diabetes mellitus vagal neuropathy leads to alteration of the compliance of the proximal stomach

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and that this part of the stomach plays a role in generating dyspeptic symptoms. In order to study the tone of the proximal stomach and the perception of distension of this part of the stomach, we used an electronic barostat device as described by Azpiroz and Malagelada (11). In order to distinguish the effects of autonomic neuropathy and hyperglycemia, proximal gastric function was evaluated in patients with evidence of cardiac autonomic neuropathy during euglycemia. The blood glucose concentrations were kept within the euglycemic range, using the modified glucose clamp technique (12).

MATERIALS AND METHODS

Eight patients (two male and six female, age 47.0 ± 9.6 years, body weight 71.3 ± 11.0 kg) with type I diabetes mellitus and 10 healthy volunteers (five male and five female, age 30.5 ± 4.0 years, body weight 69.6 ± 14.8 kg) participated in this study. The duration of their known diabetes was 10.4 ± 12.1 years. The patients were selected on the basis of upper gastrointestinal symptoms and cardiovascular autonomic neuropathy. None of the patients showed abnormal anatomy of the upper gastrointestinal tract as verified endoscopically. All diabetic patients suffered from one or more complications of diabetes mellitus, such as neuropathy, nephropathy, or retinopathy. The creatinine concentration was 126 ± 74.3 mmol/liter. The glycated hemoglobin (Hbal) concentration, measured in the week before the study, was 8.3 ± 2.0%, (range 5.6–10.5%, normal 4–7%). Metabolic control was considered poor (Hbal > 10%) in three patients, moderate (Hbal 7–10%) in three patients, and good in two patients.

All medication that is known to influence gastrointestinal motility, apart from insulin, was discontinued 48 hr before the experiment. Four of the diabetic patients and all healthy volunteers were naive to oral intubation. Written informed consent was obtained from each subject. The protocol was approved by the Human Ethical Committee of the University Hospital Utrecht.

Assessment of Cardiovascular Autonomic Neuropathy. Autonomic nerve function was assessed by standardized cardiovascular reflex tests (13): (1) variation in systolic blood pressure in response to upright position, (2) heart rate variation in response to upright position with calculation of the ratio between the heart rate response that occurs at the 15 and 30th beat after standing, (3) beat-to-beat rate variation during deep breathing, (4) calculation of the quotient of the heart rate during and after Valsalva maneuver, and (5) blood pressure response to sustained handgrip. All tests were scored as normal (0 points), borderline (0.5 points), or abnormal (1 point). From the total score (0–5 points) the degree of involvement was obtained (normal 0–0.5, early involvement 1–2, definite involvement 2.5–3.5, severe involvement 4–5 points). Four patients showed early autonomic neuropathy, three patients definite autonomic neuropathy, and one severe autonomic neuropathy.

Gastric Barostat. The barostat consists of an air injection–aspiration system and an electronic feedback mechanism that keeps the pressure in the system constant. The system was designed to measure the volume of air within an (intragastric) bag maintained at a preselected pressure level (14). The barostat was connected with a single-lumen catheter (F12) to an polyethylene bag with a capacity of 750 ml that was introduced into the stomach transorally.

Assessment of Gastrointestinal Sensations. During the barostat study, sensations were scored at the end of every 3-min period at each pressure level. The symptoms scored were nausea, pain, and bloating. These sensations were scored using three separate visual analog scales varying from no symptoms (0 points) to symptoms as bad as can be (100 points) (15).

Glucose Clamp Technique. During the test the glucose concentration was maintained within the euglycemic range in patients with type I diabetes mellitus. This was achieved by a modified glucose clamp technique as describe by DeFronzo et al (12). Before the start of the study, two cannulas were inserted into the anticubital veins, one in each arm. One cannula was used to infuse insulin (Actrapid, Novo Nordisk Farma BV, Zoeterwoude, The Netherlands) and glucose 20%. The rate of glucose 20% infusion was adjusted to maintain a glucose concentration of 5–8 mmol/liter. Blood samples were drawn from the cannula that was not used for glucose and insulin infusion. Glucose concentration was measured every 10 min with Glukotest 1-44R strips (Boehringer Mannheim) and a portable glucose meter (Reflolux S, Boehringer Mannheim).

Experimental Design. The study was performed after an overnight fast. The subjects were placed in a 30° recumbent position. The barostat experiment was started when two successive the blood glucose levels (taken 10 min apart) were within the euglycemic range. The barostat bag was introduced through the mouth into the stomach. First, the intragastric bag was insufflated with 100 ml air in order to unfold the bag. After aspiration of the 100 ml air, the catheter was connected to the barostat. Then the minimal intragastric distending pressure (MDP), defined as the first pressure level that provides an intragastric bag volume of more than 30 ml, was determined. This pressure is needed to overcome the intraabdominal pressure (16). After determination of the MDP, the pressure was increased in a stepwise fashion using 2 mm Hg increments every 3 min. This was continued until the intragastric bag volume exceeded 600 ml or until unacceptable symptoms were induced. Perception of gastric distension was scored at the end of every three-minute period at each pressure level using visual analog scales. After the maximum pressure was reached, the pressure was decreased stepwise at 3-min intervals until the minimum distending pressure was reached.

Analysis. The volumes during every pressure step were averaged over the last minute before the next pressure step. Boyle's law was used to correct the volume at each pressure level of the closed barostat; the relation between dV and dP was linear with the regression coefficient −5.76 ml/mm Hg. The volume–pressure curves starting at MDP up to the maximum level volume (600 ml) and the calculated compliance, being dV/dP), were compared using ANOVA. The results of the sensation scores in patients and healthy volunteers were compared using ANOVA. Correlation coefficients were calculated using Pearson's test.

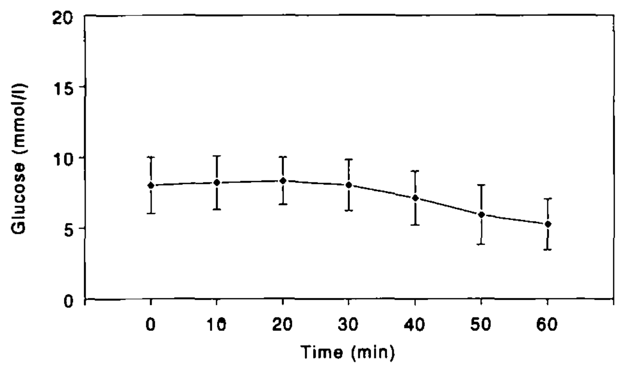

Fig 1. Plasma glucose concentrations (mean ± SD) during barostat experiment.

RESULTS

Oral intubation and the intragastric bag were well tolerated by all patients and healthy volunteers. During the study, the glucose concentrations were within the euglycemic range, as shown in Figure 1.

Compliance of Proximal Stomach. The minimal distension pressure (MDP) in the patients with type I diabetes mellitus and healthy controls showed no difference: 7.1 ± 2.3 mm Hg and 6.23 ± 0.4 mm Hg, respectively. The pressure–volume curve in response to the stepwise pressure increase showed a larger volume at each pressure in the diabetes patients, resulting in a significant difference between the pressure–volume curves ($P < 0.01$, ANOVA) (Figure 2). In six patients the pressure was not increased after 8 mm Hg above MDP, because this would lead to an intragastric bag pressure more than 600 ml. Therefore, 8 mm Hg was used as upper limit for the calculation of the compliance (dV/dP). The compliance was greater in diabetics, 57.2 ± 4.4 ml/mm Hg, than in the controls, 43.7 ± 3.5 ml/mm Hg ($P < 0.01$).

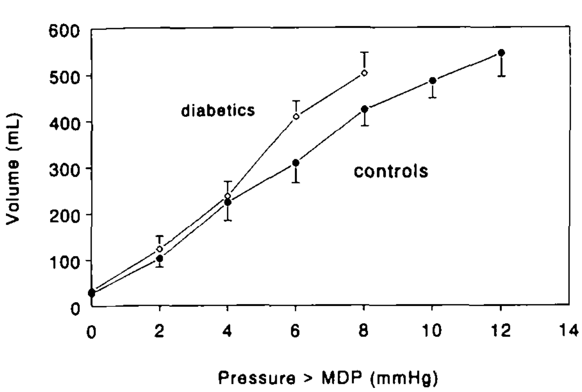

Fig 2. Volume–pressure curve during inflation of the intragastric bag in diabetic patients (open diamonds) and healthy volunteers

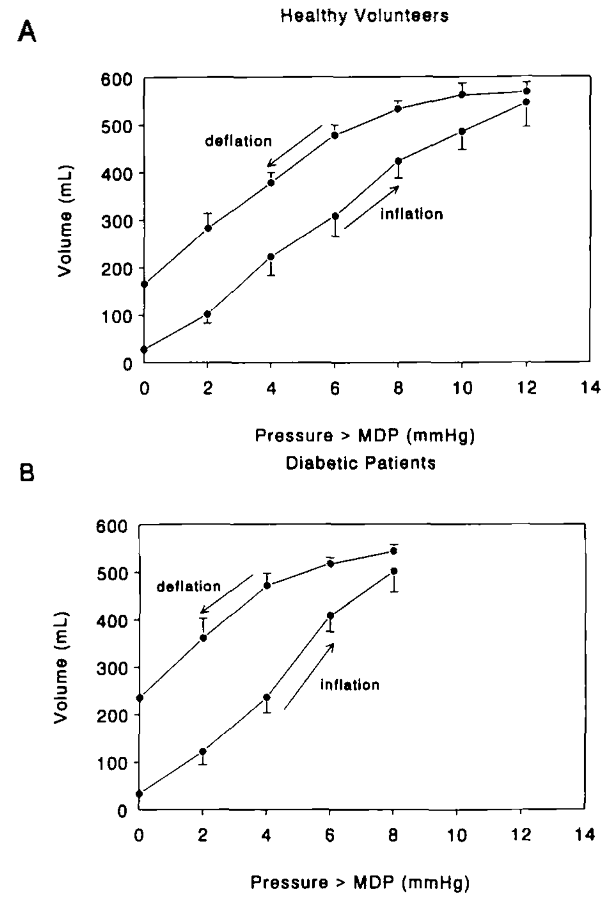

Fig 3. Volume–pressure curves during inflation and deflation of the intragastric bag in healthy volunteers (A), and in diabetes patients (B), showing a difference in curves during inflation and deflation in both the healthy volunteers ($P < 0.0001$) and diabetic patients ($P < 0.0001$).

The pressure–volume curve during stepwise deflation of the intragastric bag was different from the pressure–volume curve during stepwise inflation of the intragastric bag in both the diabetic patients ($P < 0.001$) and the healthy volunteers ($P < 0.0001$) (Figures 3 and 4). The area between the volume curves created by inflation and deflation of the intragastric bag showed no significant difference between the diabetic patients (827 ml/mm Hg) and healthy volunteers (627 ml/mm Hg). There was no difference in the residual volume at MDP after deflation of the intragastric bag between the patients (235.4 ± 50.1 ml) and the controls (165.5 ± 34.1 ml) ($P = 0.23$).

Sensations in Response to Gastric Distension. The stepwise pressure increase resulted in an increase in upper gastrointestinal sensations in the diabetic patients (nausea: $P < 0.05$, bloating: $P < 0.001$, pain: P

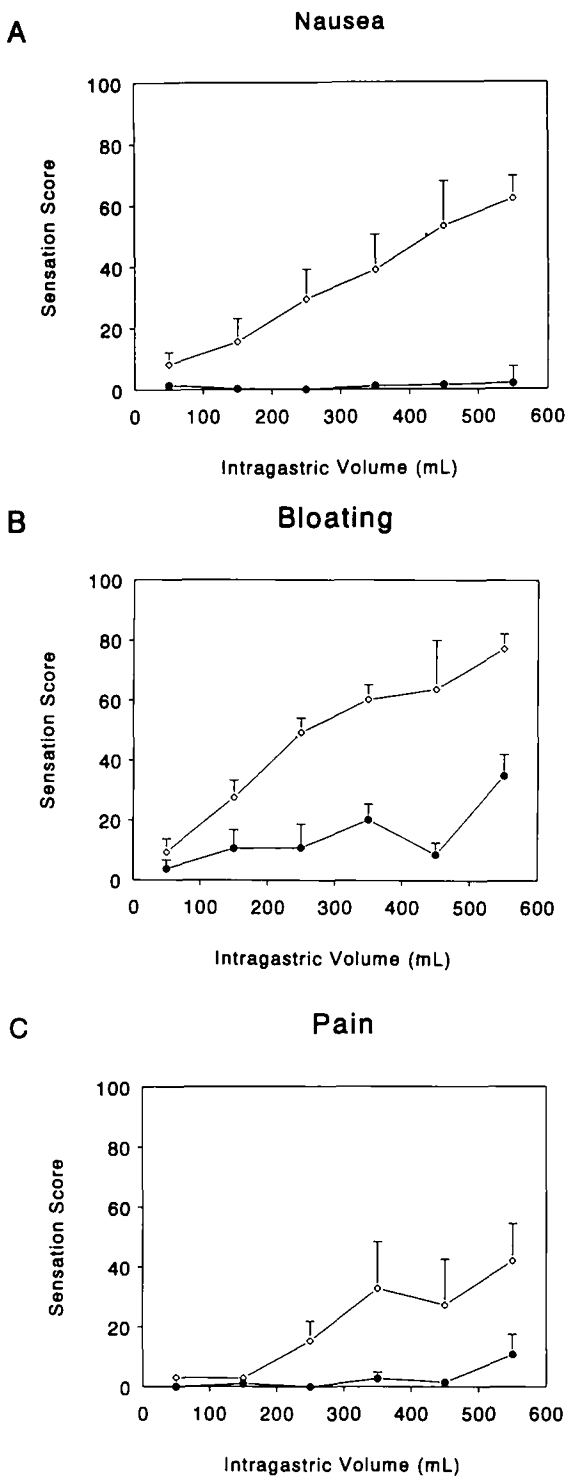

Fig 4. Sensation scores for nausea (A), bloating (B), and upper abdominal pain (C) during distension of the proximal stomach in diabetic patients (open diamonds) and healthy volunteers (solid dots), showing higher sensation scores for nausea ($P < 0.002$), bloating ($P < 0.003$), and abdominal pain ($P < 0.001$) in the diabetes patients than in the healthy volunteers.

teers. The sensation scores in the diabetic patients at the same pressure were significantly higher in the diabetics than in the healthy controls (nausea: $P < 0.05$, bloating, $P < 0.001$, and pain: $P < 0.01$).

The difference in compliance in different intragastric bag volumes in the diabetics and healthy volunteers at each pressure level. Therefore, we also compared the sensation scores at the same intragastric volumes. As compared to the controls, the patients had higher scores of nausea ($P < 0.002$), bloating ($P < 0.003$), and upper abdominal pain ($P < 0.001$) at the different intragastric bag volumes (Figure 4). There was a significant correlation between nausea and bloating ($r = 0.80$, $P < 0.001$) and abdominal pain ($r = 0.55$, $P < 0.001$). No relation was observed between the sensation scores before intragastric bag inflation and the maximum sensation scores, nausea ($r = 0.22, P = 0.59$), bloating ($r = 0.29, P = 0.48$), and pain ($r = 0.55$, $P = 0.16$).

DISCUSSION

Studies concerning gastric emptying in unselected patients with type I diabetes mellitus showed delayed gastric emptying for solid and liquid in up to 50% (1, 2). Although gastric emptying is dependent on the integration of the motor activity of the proximal stomach, antrum, and the proximal small intestine, little is known about the function of the proximal stomach in diabetes mellitus.

In the present study the function of the proximal stomach was evaluated using an electronic barostat. In the diabetic patients the intragastric bag volume at each pressure step was greater than in healthy volunteers, resulting in an increased compliance of the proximal stomach in the diabetic patients. The viscoelastic properties of the stomach are responsible for the compliance. The viscoelasticity of the stomach is created by connective tissue and smooth muscles of the stomach wall. The myogenic component is influenced by cholinergic innervation and is regulated both through vagovagal pathways and by intramural plexuses. Azpiroz and Malagelada showed that in dogs vagal blockade by cooling produces reversible gastric relaxation (11), and in patients after vagotomy a larger intragastric volume at low pressure has been shown, suggesting alteration of gastric tone after vagotomy (17). Several studies have shown the influence of elevated plasma glucose levels on the gastrointestinal tract and recently it has been shown that hyperglycemia (>15 mmol/liter) increases gastric compliance (18–21). In this study the glucose concentrations were kept within the euglycemic range, with the exception of slightly elevated glucose concentrations for short periods of time. All patients in this study suffered from autonomic neuropathy, a well-known complication of diabetes mellitus (22, 23). Therefore, the increased compliance observed in the diabetic patients is most likely due to autonomic neuropathy. Although studies concerning the smooth muscle function in diabetes mellitus are inconsistent, smooth muscle dysfunction cannot be ruled out (24–26).

In both patients and healthy volunteers, the pressure–volume curve during inflation was different from the curve during deflation of the intragastric bag. This phenomenon is called hysteresis and is caused by the delay of the stomach wall to return to its original shape. This delay is influenced by both myogenic and neurogenic factors.

Patients with diabetes mellitus frequently complain of dyspeptic symptoms. A survey in diabetic outpatients showed that 75% had one or more gastrointestinal symptoms (27). In the present study one of the inclusion criteria was upper gastrointestinal symptoms. During the gastric distension, all individual upper gastrointestinal sensations increased significantly at the same intragastric pressure as well as at the same intragastric volumes. These results suggest that the sensitivity of the proximal stomach is increased in diabetic patients with gastrointestinal symptoms and autonomic neuropathy. The increased sensitivity of the proximal stomach may be responsible for dyspeptic symptoms in the postprandial period, in which the proximal stomach is distended by a meal.

In conclusion, this study provides evidence of an abnormal compliance of the proximal stomach in patients with type I diabetes mellitus. Furthermore, it shows an increase of sensitivity of the proximal stomach in diabetic patients with autonomic neuropathy and upper gastrointestinal symptoms. Autonomic neuropathy is very likely to be a major factor in these abnormalities.

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