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Gastric Electrical Activity and Gastrointestinal Hormones in Dyspeptic Patients

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Key Words

Gastric electrical activity · Electrogastrography · Gastric emptying · *Helicobacter pylori* · Gastrointestinal peptides · Dyspepsia

Abstract

Aims: To explore the patterns of gastric electrical activity, gastric emptying and gastrointestinal hormones in dyspeptic patients and relate them to *Helicobacter pylori* status. ***Methods:*** Twenty-two patients with functional dyspepsia and 29 healthy volunteers underwent cutaneous electrogastrography and dynamic ultrasound before and after a test meal. All dyspeptic patients underwent endoscopy and biopsy; all subjects were examined for the presence of antibodies to *H. pylori,* and the plasma levels of gastrin, neurotensin, cholecystokinin, and pancreatic polypeptide were measured. ***Results:*** The area under the curve (AUC) of the normal slow wave percentage was lower in dyspeptic patients than controls (Kruskal-Wallis p = 0.016; Dunn's test: *H. pylori*-positive patients: 21,235.5 [19,101.0–22,688.8] vs. *H. pylori*-negative controls: 22,532.0 [20,133.0–23,755.0], $p < 0.05$). The AUC of the tachygastria percentage was higher in dyspeptic patients than controls (p = 0.0001; *H. pylori*-positive patients: 2,173.5 [325.8–3,055.3] vs. *H. pylori*-negative controls: 682.0 [118.5–1,902.4], $p < 0.05$; *H. pylori*-negative patients: 1,843.0 [1,107.0–4,277.0] vs. *H. pylori*-negative controls: 682.0 [118.5–1,902.4], $p < 0.05$). The AUC of gastrin was higher in *H. pylori*-positive than *H. pylori*-negative subjects (p = 0.0002; *H. pylori*-positive patients: 16,146.5 [11,368.8–33,141.7] vs. *H. pylori*-negative controls: 11,250.0 [5,674.0–17,448.0], $p < 0.05$; *H. pylori*-positive controls: 20,250.0 [12,070.0–64,430.0] vs. *H. pylori*-negative controls: 11,250.0 [5,674.0–17,448.0], $p < 0.05$). In the total group of dyspeptic patients and in the *H. pylori*-positive patients, a negative correlation was found between the AUC of neurotensin and the total score for postprandial fullness (dyspeptic patients r = –0.51, p = 0.01; *H. pylori*-positive patients r = –0.66, p = 0.02). ***Conclusions:*** In dyspeptic patients, alterations in gastric electrical activity were not related to *H. pylori* infection. Nevertheless, *H. pylori* infection induces higher gastrin levels in both patients and asymptomatic subjects.

Introduction

Nonulcer dyspepsia (NUD) is an ill-defined condition characterized by the presence of heterogeneous dyspeptic symptoms but the absence of mucosal lesions or structural

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abnormalities of the gastrointestinal tract. Several factors, such as impaired gastrointestinal motility, have been considered to contribute to the pathogenesis of functional dyspepsia, while *Helicobacter pylori* infection is thought to play a key role. Up to now, however, no conclusive studies have been published confirming the roles of *H. pylori* infection and altered gastric motor function in the pathogenesis of NUD.

Various neural transmitters and polypeptide hormones are involved in regulating gastrointestinal motility. Motilin and somatostatin play a role in fasting motor activity, whereas cholecystokinin (CCK), gastrin, neurotensin, pancreatic polypeptide and other peptides affect postprandial activity [1]. Some authors have correlated severe dyspeptic symptoms with elevated levels of gastrin, CCK [2], and somatostatin [3]. Others have reported a reduced pancreatic polypeptide response in dyspeptic patients, suggesting an efferent vagal dysfunction [4]. *H. pylori* infection induces increased release of gastrin and CCK and causes somatostatin deficiency in patients with duodenal ulcer and functional dyspepsia [5, 6].

Although the postprandial pattern is induced by hormonal peptides in higher centers, gastrointestinal motility is regulated by the electrical control activity inherent to enteric cells [7] and can be recorded noninvasively by cutaneous electrogastrography (EGG) [8]. EGG can assess motility thanks to its ability to capture the electrical signal from a remote external site, without interfering with the natural activity of the gut. Numerous studies have demonstrated a correlation between EGG patterns and motility events in animals and humans [9, 10]. Myoelectrical abnormalities of the stomach have been recorded in patients with unexplained nausea and vomiting, during pregnancy, in motion sickness, and in patients with anorexia nervosa; this dysrhythmia seems to correlate with antral hypomotility and delayed gastric emptying [11]. Several peptide hormones induce gastric dysrhythmia, including glucagon [12], gastrin, secretin, somatostatin [13], CCK [14], vasopressin [15], and epinephrine [16]. Finally, gastric emptying is usually studied by means of scintigraphy, although ultrasound has been demonstrated to be a reliable, noninvasive method [17].

The aim of this study was to explore the patterns of gastric electrical activity, gastric emptying and gastrointestinal hormones in dyspeptic patients and to relate them to *H. pylori* status.

Patients and Methods

We examined 22 consecutive patients (7 males and 15 females; mean age 37.7 ± 9.4 years) referred by their general practitioners because of dyspeptic symptoms. All patients were recruited in the space of 1 year (from March 12, 1997, to March 11, 1998). We also examined 29 healthy volunteers (11 males and 18 females; mean age 35.2 ± 8.6 years) with no digestive symptoms or systemic diseases. All patients and control subjects gave their written consent to enrolment in the study, which was approved by the ethics committee of our institute.

Dyspeptic Patients

Functional dyspepsia was defined, following the criteria described by an International Working Group, as 'persistent or recurrent abdominal pain or abdominal discomfort, heartburn, nausea, vomiting, or other symptoms considered as being referable to the proximal alimentary tract in absence of anatomical and structural lesions' [18].

Patients were considered eligible if they had no previous history of gastric tumors, gastric or duodenal ulcers or gastric surgery. They were asked to refrain from taking nonsteroidal anti-inflammatory and prokinetic drugs, antibiotics, bismuth, antacids, H_2-receptor antagonists, omeprazole, sucralfate or misoprostol in the 2 months prior to the examination scheduled as a medication-free time period.

The absence of organic lesions was confirmed by gastric endoscopy and ultrasound examination of the liver, gallbladder, and pancreas. In addition, systemic, endocrine, and collagen-related diseases were ruled out by the appropriate hematological and biochemical analyses.

Control Subjects

Asymptomatic subjects were enrolled from the administrative employees of our institute who did not regard themselves as suffering from gastrointestinal diseases and were not taking any medication. However, to rule out the presence of concomitant pathologies (either gastrointestinal or not) which could affect the results of the study, the study questionnaire described below was also administered at the time of enrolment to each control subject.

Questionnaire

A previously described [19], partly modified, validated Italian version of a symptomatic questionnaire was administered to each patient (and control subject) in the study. Patients were asked to consider seven different symptoms (epigastric pain, pyrosis, postprandial fullness, vomiting, regurgitation, early satiety, nausea) and grade their intensity (absent = 0; mild = 1; moderate = 2; severe and interfering with daily activities = 3); frequency (<1 episode/month = 1; 1–3 episodes/month = 2; 1–2 episodes/week = 3; 3–4 episodes/week = 4; almost continuous = 5), and duration (<3 months = 1; 3–6 months = 2; 6 months to 1 year = 3; >1 year = 4). The maximum total score was 12.

Endoscopy and Histology

All dyspeptic patients underwent endoscopy and biopsy performed by a blinded gastroenterologist who described the endoscopic appearance of the stomach. An Olympus GIF 100 endoscope (Olympus Corp., Lake Success, N.Y., USA) was used in all cases. At least two biopsies from the antrum (about 2 cm from the pylorus) and two

from the body (small curve) were obtained from each patient for histology, as well as an antral specimen for determining the intrabiopsy urease activity. Two biopsies from the antrum and two from the body were routinely and blindly assessed for histology using hematoxylin and eosin stain and periodic acid Schiff stain by an independent pathologist, unaware of the clinical history or the endoscopic findings corresponding to each biopsy. The presence and severity of gastritis were assessed using the classification of Correa and Yardley [20]. Other histological changes, such as ulceration, intestinal metaplasia, lymphoid follicle formation and lymphoepithelial lesions were also recorded.

Evaluation of H. pylori *Infection*

In dyspeptic patients, the presence of IgG antibodies against *H. pylori* was detected using the ELISA method (Heloritest, Eurospital, Trieste, Italy). In addition, a biopsy sample from the antrum was used to evaluate urease production by means of an 'in-house' CLO test prepared following the procedure of Hazell et al. [21]. During the histological examination, an additional Warthin-Starry stain was used to confirm *H. pylori* presence on the mucosal stream and/or on the foveolar epithelium. The dyspeptic group was subdivided as follows: 12 *H. pylori*-positive dyspeptic patients (5 males and 7 females; mean age 37.5 ± 9.2 years) and 10 *H. pylori*-negative dyspeptic patients (2 males and 8 females; mean age 38.0 ± 10.1 years).

In control subjects, *H. pylori* infection was investigated by means of IgG antibody detection and the ^{13}C-urea breath test (^{13}C-UBT). ^{13}C-UBT was performed under the following conditions: an 8-hour fast; mouth washing before dosing; orange juice (200 ml) as standard meal followed by the administration of 75 mg ^{13}C-urea (Helicobacter test INFAI, SOFAR, Milan, Italy); sampling at baseline and at 30 min with the subjects in a sitting position; collection of breath samples in two 10-ml glass sample containers. The breath samples were analyzed with a gas chromatography-mass spectrometer (GC-MS, Breath Mat plus Finnigan MAT GmbH, Bremen, Germany). *H. pylori* infection was considered present if the difference between the ^{13}C/^{12}C baseline value and the 30-min value exceeded 4.0‰. Fifteen healthy volunteers (8 males and 7 females; mean age 33.9 ± 6.4 years) were found to be positive for *H. pylori* infection and 14 (3 males and 11 females; mean age 36.5 ± 10.55 years) were negative.

Gastrointestinal Hormones

Blood Withdrawal and Preparation of Plasma. Blood samples were collected in ice-chilled tubes containing aprotinin (Antagosan, 200,000 UICH – Hoechst Marion Roussel SpA, Milan, Italy), 500 kIU/ml blood, and 1.0 mg EDTA/ml blood, and centrifuged at 1,600 *g* for 15 min at 4°C. The separated plasma was stored at –70°C until assayed.

Extraction of Gastrointestinal Hormones from Plasma. One milliliter of plasma was acidified with 1 ml of 1% trifluoracetic acid (HPLC grade) and then centrifuged at 3,000 *g* for 20 min at 4°C. The supernatant was loaded onto the pretreated C_{18} column (200 mg, Sep-Columns, Peninsula Laboratories, Calif., USA). The eluant was evaporated until dry using a centrifugal concentrator and then lyophilized. The plasma levels of CCK, neurotensin and pancreatic polypeptide were measured by radioimmunoassay using commercial kits (Peninsula Laboratories, Belmont, Calif., USA). The plasma levels of gastrin were determined using the RIA kit 'GammaDab Gastrin' (Incstar Corporation, Minn., USA).

Electrogastrographic and Gastric Emptying Recordings

After overnight fasting, the EGG recordings were performed using portable equipment before and 360 min after a meal; all the subjects were free to move around the room. The gastric motor function was evaluated using a standard solid-liquid meal (55% carbohydrates, 30% protein, and 15% fat; calorie content 513 kcal). The meal was consumed within 15 min. Two silver-silver chloride bipolar electrodes (Clear Trace, ConMed, Utica, N.Y., USA) were sonographically placed on the cleaned abdominal surface overlying the antropyloric axis to obtain the best signal-noise ratio. The reference electrode was placed to form an equilateral triangle [22]. EGG was performed using a portable EGG recorder (Synetics Medical AB, Stockholm, Sweden). All recordings were made at a sampling frequency of 1 Hz. The internal high- and low-pass filters were set at 1.8 and 16 cpm, respectively. After recording, the electrogastrogram data were fed into a personal computer (Vectra RS 20 Hewlett Packard Company, Palo Alto, Calif., USA) and analyzed by means of a dedicated software program (ElectroGastroGram Version 6.30, Gastrosoft Inc., Synetics Medical). In addition to the analysis available with the ElectroGastroGram, we used Redtech GiPC software to perform further EGG data filtering and analysis. The following parameters were evaluated for each subject [11].

(1) The mean frequency of the EGG: the frequency of the gastric peak was determined by the absolute peak value, and the mean frequency/power was computed by averaging the individual spectra.

(2) The instability coefficient: this specifies the stability of the gastric electrical peak visible on the running spectra plot. It was calculated as the percentage ratio of the frequency standard deviation to the mean gastric frequency.

(3) The percentage of DF in the ranges defined as normal, bradygastric and tachygastric. A rhythmic gastric electrical activity ranging from 2.0 to 4.0 cpm was considered normal. Tachygastria was considered to be present when the running spectra had a dominant peak in the range of 4.0–9.0 cpm, and bradygastria when the dominant peak was <2.0 cpm.

(4) The power ratio: Since the absolute values of EGG power are influenced by several factors (skin conductance, distance between the electrodes and the wall of the stomach, variable shape of the stomach, etc.), the EGG power can be evaluated only as the relative changes. The power ratio is the ratio of postprandial to fasting EGG power values.

The EGG signal was visually inspected to verify that no artifacts were present in any recording period. Periods containing these motion artifacts were deleted before computer analysis. EGG parameters were obtained by means of running spectral analysis. This is currently the method most commonly used to analyze the EGG, and since Van der Schee et al. [23] introduced running spectral analysis in EGG, it has also been possible to analyze the frequency and amplitude changes over time. With this procedure, using a fast Fourier transform the frequency components of 256-second epochs of EGG signal are calculated, overlapped by 75%, and displayed as a three-dimensional frequency plot. An abnormal EGG was defined as a PR of <1.5 or a postprandial 3-cpm percentage of <70% of the time.

The ultrasound gastric emptying examinations were always performed by the same investigator using a real-time apparatus (Sigma 44, Kontron Instrument) equipped with a 3.5-MHz linear probe. The probe was positioned at the level of the transpyloric plane for simultaneous visualization of the antrum, superior mesenteric vein and the aorta. The antral measurements were always taken from the outer profile of the wall. Since the cross-section of the gastric antrum, cor-

responding to the sagittal plane passing through the superior mesenteric vein, is elliptical in shape, its area can be calculated by measuring the longitudinal and anteroposterior (AP) diameters and applying the formula $\pi L \times AP/4$ [24]. During the same EGG recording session, antral measurements were made before the test meal, and at regular 30-min intervals up to 360 min after. The emptying curve was established by plotting the cross-sectional area of the gastric antrum against time. In addition, the antral area was calculated as the area ratio of postprandial values versus the basal value, and plotted against time. In each patient, the final emptying time, the half emptying time, and the area under the curve (AUC) of the emptying time were calculated. The half-emptying time, i.e. the time when the cross-sectional area of the antrum had an intermediate value with respect to the basal value and the maximum value recorded after a meal, was calculated by linear regression analysis of the linear part of the emptying curve [17].

Statistical Analysis

The total integrated response was calculated as the AUC to obtain overall values for the EGG parameters, gastric emptying and gastrointestinal hormones over time. This parameter was felt to be the most appropriate measure of EGG, gastric emptying and hormone values between groups since the fasting concentrations were widely different. To avoid the assumption of normal distribution, data were expressed as median and 5th and 95th percentiles, and nonparametric tests were performed by means of a specific software package (STATA version 4.0 Statistical Software, Stata Corporation, Tex., USA). The two-sample Wilcoxon rank-sum test was performed to compare dyspeptic patients vs. control subjects and Kruskal-Wallis one-way analysis of variance on ranks was used to compare the 4 groups (dyspeptic *H. pylori*-positive patients, dyspeptic *H. pylori*-negative patients, *H. pylori*-positive controls and *H. pylori*-negative controls). Where a difference was found, nonparametric multiple comparisons were performed (Dunn's test) to determine between which groups there was a significant difference. This multiple comparison on ranks does not include adjustment for the level of significance. Correlations were investigated using the Spearman correlation test. A p value of <0.05 was considered statistically significant.

Table 1. Total symptom score and relative frequency of each symptom

Symptom	Symptom score	Number of patients	%
Nausea	0.0 (0.0–10.0)	8/22	36.3
Vomiting	0.0 (0.0–10.0)	9/22	41.0
Early satiety	7.0 (0.0–11.0)	13/22	59.1
Postprandial fullness	8.0 (0.0–11.0)	17/22	77.3
Epigastric pain	8.0 (0.0–11.0)	17/22	77.3
Pyrosis	0.0 (0.0–11.0)	10/22	45.4
Regurgitation	8.0 (0.0–12.0)	16/22	72.7

Dyspeptic patients were grouped regardless of their *H. pylori* status. Median and 5th and 95th percentiles are presented.

Results

Dyspepsia and Symptoms

Table 1 reports the symptom scores and relative frequency in the total group of dyspeptic patients. The most frequent were epigastric pain and fullness (77.3% of the patients). The median total score was 8 (range [0.0–11]).

Table 2 reports the symptom scores and relative frequency in dyspeptic patients in relation to *H. pylori* infection. The most frequent symptom in *H. pylori*-positive patients was pain (75.0% of the patients) and the median score was 7 (range [0.0–12.0]). The most frequent symp-

Table 2. Total symptom score and relative frequency of each symptom

Symptom	Symptom score (Hp+ patients)	Number of patients	%	Symptom score (Hp– patients)	Number of patients	%
Nausea	0.0 (0.0–10.0)	4/12	33.3	0.0 (0.0–9.0)	4/10	40.0
Vomiting	0.0 (0.0–11.0)	3/12	33.3	6.5 (0.0–10.0)	6/10	60.0
Early satiety	3.0 (0.0–11.0)	6/12	50.0	8.0 (0.0–11.0)	7/10	70.0
Postprandial fullness	7.0 (0.0–12.0)	8/12	66.6	10.0 (0.0–11.0)	9/10	90.0
Epigastric pain	7.0 (0.0–12.0)	9/12	75.0	8.5 (0.0–11.0)	8/10	80.0
Pyrosis	4.0 (0.0–12.0)	6/12	50.0	0.0 (0.0–11.0)	4/10	40.0
Regurgitation	7.0 (0.0–12.0)	8/12	66.6	8.0 (0.0–12.0)	8/10	80.0

Dyspeptic patients were grouped according to their *H. pylori* status. Median and 5th and 95th percentiles are presented. Statistical analysis between the 2 groups by the Wilcoxon rank-sum test: n.s. Comparison of frequency by Fisher's exact test: n.s.

Table 3. Electrogastrographic and gastric emptying parameters calculated as the postprandial area under the curve over the basal value in dyspeptic and control subjects

	Dyspeptic patients	Controls	Wilcoxon rank-sum test
Electrogastrographic parameters			
Dominant frequency	711.7 (616.4–799.6)	700.7 (632.6–749.8)	n.s.
Instability coefficient of dominant frequency	4,825.0 (2,580.0–7,890.0)	4,330.0 (1,980.0–8,290.0)	n.s.
Dominant power	382,622.4 (105,941.7–632,220.4)	126,879.6 (36,083.0–355,989.0)	p = 0.0001
Instability coefficient of dominant power	14,645.0 (13,100.0–18,510.0)	14,190.0 (9,600.0–17,280.0)	n.s.
Normal slow wave, %	21,201.5 (15,066.6–23,065.0)	22,032.0 (20,013.0–23,667.0)	p = 0.003
Bradygastria, %	644.5 (100.0–2,688.0)	590 (72.0–1,415.0)	n.s.
Tachygastria, %	2,168.5 (614.8–3,560.6)	1,026.0 (146.0–2,407.0)	p < 0.001
Gastric emptying parameters			
Antral area	2,901.0 (1,830.-0–4,006.0)	2,831.0 (1,963.0–3,723.0)	n.s.

Dyspeptic patients and control subjects were grouped regardless of their *H. pylori* status. Median and 5th and 95th percentiles are presented.

Table 4. Gastrointestinal (GI) hormones calculated as the postprandial area under the curve over the basal value in dyspeptic and control subjects

GI hormones	Dyspeptic patients	Controls	Wilcoxon rank-sum test
Gastrin	15,365.0 (11,354.0–43,907.2)	13,830.0 (6,370.0–59,030.0)	p = 0.06
Neurotensin	12,220.0 (8,130.0–15,680.0)	10,860.0 (8,430.0–17,700.0)	p = 0.03
Pancreatic polypeptide	26,830.0 (11,610.0–74,320.0)	33,730.0 (8,590.0–78,860.0)	n.s.
Cholecystokinin	27,095.0 (6,420.0–78,317.0)	23,750.0 (11,890.0–50,340.0)	n.s.

Dyspeptic patients and control subjects were grouped regardless of their *H. pylori* status. Median and 5th and 95th percentiles are presented.

tom in *H. pylori*-negative patients was fullness (90% of the patients) with a median score of 10 (range [0.0–11.0]). No difference in the median frequency of symptoms was found between the 2 groups.

Comparison between Dyspeptic Patients and Controls

Table 3 summarizes gastric emptying and EGG data calculated as the AUC for the total group of dyspeptic patients and controls. No differences were found in median gastric frequency or the instability coefficient of the dominant frequency. Dyspeptic patients had a significantly higher dominant power, a lower normal slow wave percentage and a higher tachygastria percentage than healthy controls. Dysrhythmia was found in 45.4% (10/22) of all patients. As to gastric emptying time, no differences were found in the AUC of gastric emptying between dyspeptic patients and controls (table 3). Comparison of the gastric emptying curves in dyspeptic patients and controls showed similar profiles (fig. 1a). Both the final emptying time and the half emptying time were similar in the 2 groups (final emptying time in dyspeptic patients: 270.0 [147.0–360.0] min vs. controls: 270.0 [180–360] min; half emptying time: 119.1 [64.4–189.9] min vs. 118.5 [74.4–180.0] min, respectively).

Table 4 shows the AUC for gastrin, neurotensin, pancreatic polypeptide and CCK. The difference between the AUC of gastrin levels obtained in dyspeptic patients and healthy controls showed a trend toward significance (p = 0.06), while the AUC of neurotensin was significantly higher in dyspeptic patients than controls.

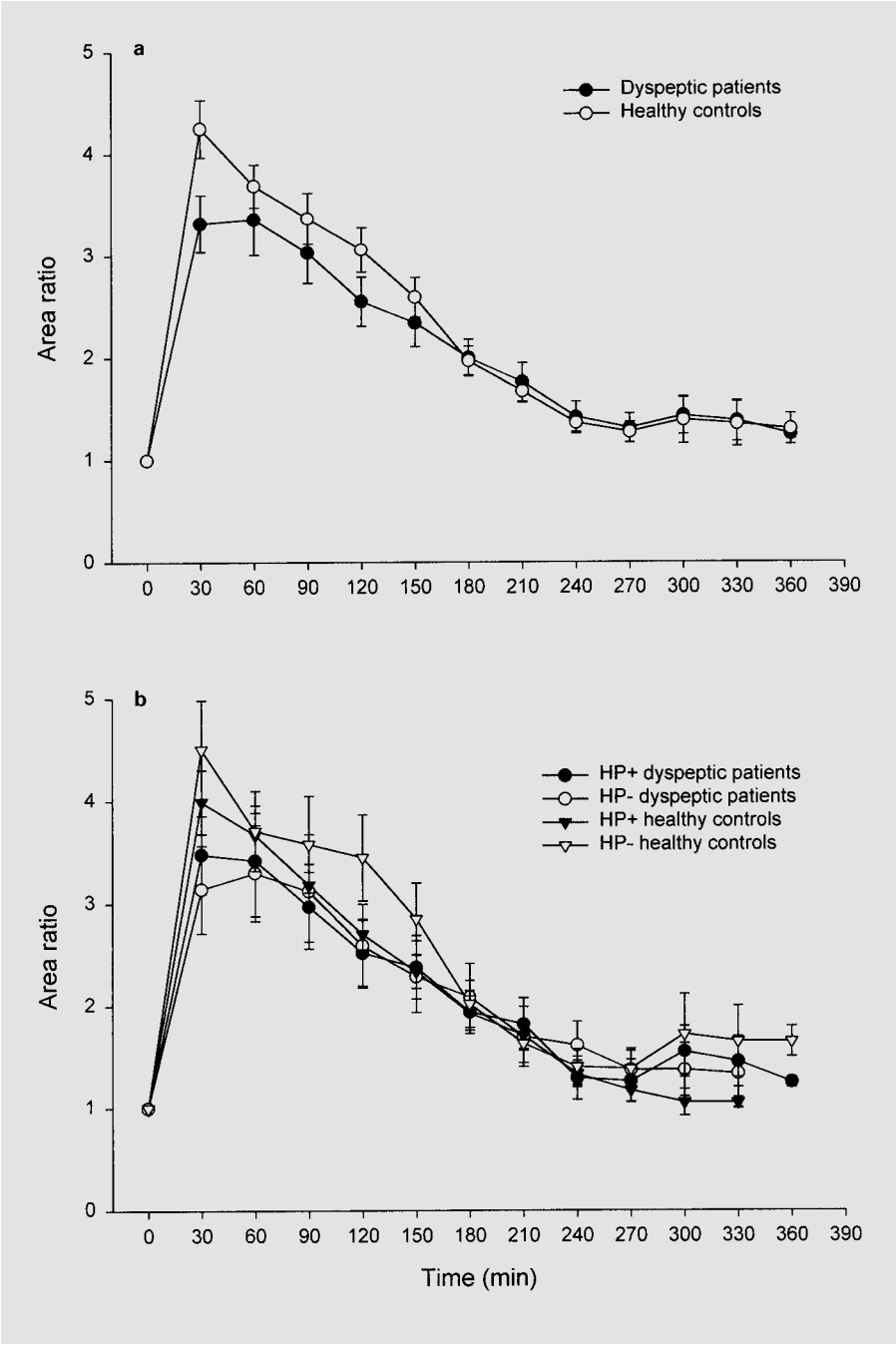

Fig. 1. Comparison of the gastric emptying curves (mean ± SEM) obtained from dyspeptic patients and healthy controls regardless of their Hp status (**a**) and when grouped according to their *H. pylori* status (**b**). No differences in antral dilatation were present postprandially.

Comparison between H. pylori-*Positive Dyspeptic Patients,* H. pylori-*Negative Dyspeptic Patients, and* H. pylori-*Positive and Negative Controls*

Table 5 reports the data on the AUC for gastric electrical activity and gastric emptying after subdividing the dyspeptic group according to *H. pylori* status. No differences were found in the median AUC of gastric frequency and the median instability coefficient of gastric frequency. As to the AUC of gastric power, this was higher in *H. pylori*-positive and negative patients than controls (Kruskal-Wallis p = 0.0005; Dunn's test: *H. pylori*-negative patients vs. *H. pylori*-negative controls $p < 0.05$, *H. pylori*-positive patients vs. *H. pylori*-negative controls $p < 0.05$). The AUC of the instability coefficient of gastric power

Table 5. Electrogastrographic and gastric emptying parameters calculated the postprandial area under the curve over the basal value in dyspeptic and control subjects

	Dyspeptic patients		Control subjects	
	Hp+	Hp–	Hp+	Hp–
EGG parameters				
Dominant frequency	716.2 (611.0–802.0)	708.0 (616.4–773.8)	701.0 (637.0–752.82)	695.0 (620.9–745.4)
IC of dominant frequency	4,825.0 (3,640.0–7,890.0)	4,640.0 (2,150.0–8,130.0)	4,530.0 (1,980.0–8,470.0)	3,555.0 (1,890.0–6,390.0)
Dominant power	326,095.5 (101,937.0–632,220.4)	412,693.0 (187,853.1–855,291.6)	177,036.4 (40,418.0–859,792.0)	79,925.2 (33,683.0–355,989.0)
IC of dominant power	14,330.0 (13,110.0–16,170.0)	16,255.0 (7,280.0–19,270.0)	15,900.0 (10,150.0–17,900.0)	13,135.0 (8,850–17,147)
Normal slow wave percentage	21,235.5 (19,101.0–22,688.8)	20,600.0 (10,839.0–23,454.0)	21,812.0 (18,221.0–23,667.0)	22,532.0 (20,133.0–23,755.0)
Bradygastria percentage	651.0 (59.0–2,688.0)	644.5 (100.0–4,807.0)	639 (148.0–2,031.0)	422.5 (35.0–1,274.0)
Tachygastria percentage	2,173.5 (325.8–3,055.3)	1,843.0 (1,107.0–4,277.0)	1,179.0 (185.0–3,607.0)	682.0 (118.5–1,902.4)
Gastric emptying parameters				
Antral area	3,018.5 (2,280.0–4,275.0)	2,427.5 (913.0–3,398.0)	2,657.0 (1,184.0–4,207.0)	2,867.5 (2,207.0–3,621.0)

Dyspeptic patients and control subjects were grouped according to their *H. pylori* status. Median and 5th and 95th percentiles are presented.

Statistical analysis: Kruskal-Wallis one-way analysis of variance on ranks, and where a difference was found, Dunn's test for nonparametric multiple comparisons was performed.

Dominant power ($p = 0.0005$; dyspeptic Hp+ patients vs. Hp– control subjects and dyspeptic Hp– patients vs. Hp– control subjects, $p < 0.05$); IC of dominant power ($p = 0.007$; Hp+ control subjects vs. Hp– control subjects, $p < 0.05$); normal slow wave percentage ($p = 0.016$; dyspeptic Hp+ patients vs. Hp– control subjects, $p < 0.05$); tachygastria percentage ($p = 0.0001$; dyspeptic Hp+ patients vs. Hp– control subjects and dyspeptic Hp– patients vs. Hp– control subjects, $p < 0.05$).

was higher in *H. pylori*-positive controls than negative controls (Kruskal-Wallis $p = 0.007$; Dunn's test: *H. pylori*-positive vs. negative controls $p < 0.05$). The AUC of the normal slow waves percentage was lower in dyspeptic patients than controls (Kruskal-Wallis $p = 0.016$; Dunn's test: *H. pylori*-positive vs. *H. pylori*-negative controls $p < 0.05$). The AUC of the tachygastria percentage was markedly higher in dyspeptic patients than controls (Kruskal-Wallis $p = 0.0001$; Dunn's test: *H. pylori*-positive patients vs. *H. pylori*-negative controls and *H. pylori*-negative patients vs. *H. pylori*-negative controls $p < 0.05$). EGG dysrhythmia was found in 50.0% (5/10) of *H. pylori*-negative and 41.7% (5/12) of *H. pylori*-positive patients ($p > 0.05$). No differences were found in the AUC of gastric emptying among the 4 groups (table 5). Comparison of the gastric emptying curves among the 4 groups showed similar profiles (fig. 1b). Both the final emptying time and the half emptying time were similar in the 4 groups (final emptying time: *H. pylori*-positive patients: 255.0 [210.0–360.0] min, *H. pylori*-negative patients: 270.0 [120–330] min, *H. pylori*-positive controls: 270.0 [198.0–330.0] min, and *H. pylori*-negative controls: 270 [120.0–330.0] min; half emptying time: *H. pylori*-positive patients: 113.4 [55.0–116.2] min, *H. pylori*-negative patients: 136.3 [72.7–215.6] min, *H. pylori*-positive controls: 114.4 [79.7–178.7] min, and *H. pylori*-negative controls: 122.5 [75.5–175.3]).

Table 6 shows the data on gastrointestinal hormones expressed as the AUC. The AUC of gastrin differed between *H. pylori*-positive and *H. pylori*-negative subjects ($p = 0.0002$; *H. pylori*-positive patients vs. *H. pylori*-negative controls $p < 0.05$, and *H. pylori*-positive controls vs. negative controls $p < 0.05$).

Correlation between Electrogastrographic Data, Gastric Emptying Time, and Gastrointestinal Hormones

No significant correlation was found between EGG and gastric emptying, and EGG data and hormone levels. As to gastric emptying and hormone levels, a negative correlation was found between the AUC of the antral area and the AUC of CCK both in the total group of dyspeptic patients (Spearman test: $r = -0.55$, $p = 0.007$) and in the *H. pylori*-positive patients (Spearman test: $r = -0.78$, $p = 0.0013$).

Table 6. Gastrointestinal (GI) hormones calculated as the postprandial area under the curve over the basal value in dyspeptic and control subjects

GI hormones	Dyspeptic patients		Control subjects	
	Hp+	Hp–	Hp+	Hp–
Gastrin	16,146.5 (11,368.8–33,141.7)	15,370 (11,380.0–59,290.0)	20,250.0 (12,070.0–64,430.0)	11,250.0 (5,674.0–17,448.0)
Neurotensin	12,340.0 (7,390.0–14,010.0)	12,140.0 (8,130.0–18,780)	11,300.0 (9,160.0–22,010.0)	10,015.0 (6,090.0–17,700.0)
Pancreatic polypeptide	26,750.0 (13,170.0–88,690.0)	20,795.0 (6,970.0–46,730.0)	34,220.0 (9,170.0–78,860.0)	23,325.0 (8,410.0–91,220.0)
Cholecystokinin	28,475.0 (3,490.0–78,317.0)	26,365.0 (8,590.0–114,240.0)	30,880.0 (13,550.0–64,350.0)	21,840.0 (11,510.0–46,940.0)

Dyspeptic patients and control subjects were grouped according to their *H. pylori* status. Median and 5th and 95th percentiles are presented.
Kruskal-Wallis one-way analysis of variance on ranks, and where a difference was found.
Dunn's test for nonparametric multiple comparisons was performed.
Gastrin ($p = 0.0002$; dyspeptic Hp+ patients vs. Hp– control subjects, and Hp+ control subjects vs. Hp– control subjects, $p < 0.05$).
Neurotensin ($p = 0.04$; Dunn's test: n.s.).

Correlation between Symptoms and Gastrointestinal Hormones

In the total group of dyspeptic patients (regardless of *H. pylori* status) there was a negative correlation between the AUC of neurotensin and the total score for postprandial fullness (Spearman test: $r = -0.51$, $p = 0.01$). After subdivision of dyspeptic patients according to their *H. pylori* status, *H. pylori*-positive patients were found to have a negative correlation between the AUC of neurotensin and the total score for postprandial fullness (Spearman test: $r = -0.66$, $p = 0.02$). No correlation between symptom scores and gastric emptying data, or between symptom scores and EGG parameters, was found either in the total group or in the 2 patient subgroups.

Discussion

Our study demonstrated impaired gastric electrical activity but normal gastric emptying time in dyspeptic patients as compared to controls. With regard to gastrointestinal hormones, gastrin and neurotensin were higher in dyspeptic patients than controls. After subdivision of patients and controls according to their *H. pylori* status, *H. pylori* infection was found to play a role in altering gastric electrical activity and gastrointestinal hormones, in both patient and control groups.

The study of gastric electrical activity can be seen as an indirect way of evaluating the mechanical activity of the stomach. However, the role of myoelectrical abnormalities, such as gastric dysrhythmias, is uncertain. Some authors have suggested that alterations in gastric electrical activity may be an accidental finding among other abnormalities in gastric electrical and mechanical activity. Others have demonstrated a correlation between tachygastria and the absence of antral motility [25], between tachyarrhythmia and the increased plasma vasopressin, epinephrine and nausea scores [26]. Furthermore, removal of an arrhythmogenic gastric focus led to clinical improvement [27]. Patients with delayed gastric emptying showed significantly more pre- and postprandial tachygastria than patients with normal gastric emptying [28]. Gastric colonization with *H. pylori* did not affect EGG and gastric emptying parameters [29]. Symptomatic functional dyspepsia *H. pylori*-positive patients showed changes in gastric electrical activity in terms of an increased tachygastria percentage and antral hypomotility [30] as evidenced by the absence of phase III of MMC. Our findings showed a higher dominant power in dyspeptic patients, while the normal slow wave percentage was lower and tachygastria higher in dyspeptic patients than controls. When *H. pylori* status was considered, these significant differences persisted in both *H. pylori*-positive and negative dyspeptic patients with respect to *H. pylori*-negative controls. However, in contrast to Thor et al. [30], the percentage of *H. pylori*-positive dyspeptic patients with dysrhythmias was clearly lower, probably due to a different cutoff for the EGG parameters. In addition, *H. pylori*-positive controls showed a higher instability coefficient of the dominant power than *H. pylori*-negative controls. As a result, alterations in gastric electrical activity were found to be present in patients suffering from functional dyspepsia but not to be related to *H. pylori* status. However, the high instability coefficient of the dominant power recorded in *H. pylori*-positive controls could be considered an early index of *H. pylori* infection.

Apart from gastrin, few studies have investigated the role of gastric peptides in patients with dyspepsia. When the AUC of gastrin was considered, our data demonstrate that its levels generally increased in dyspeptic patients with respect to controls – even if only a trend toward significance was found. However, in *H. pylori*-positive patients gastrin levels were significantly higher than in *H. pylori*-negative controls. This evidence is in agreement with data in literature. Gastrin levels increase during *H. pylori* infection [31] and return to normal after eradication of the infection [5]. In addition, our results indicate the presence of specific alterations in the gastrointestinal hormone levels due to the presence of the bacterium. In fact, in *H. pylori*-positive controls, gastrin levels were significantly higher than in *H. pylori*-negative controls. It is possible that *H. pylori* infection and increased gastrinemia may be an early stage of *H. pylori*-related dyspepsia. However, as endoscopy was not performed in healthy controls, the presence of gastritis could not be excluded.

Neurotensin levels were increased in dyspeptic patients with respect to controls, but no significant differences were found among the groups. Watson et al. [32] found no difference between dyspeptic patients and controls, and that circulating levels of neurotensin and other gastrointestinal hormones were not related to symptoms of flatulent dyspepsia. Greydanus et al. [4] found abnormal hormonal levels in functional dyspepsia patients with both normal and slow transit time. Therefore, the role of neurotensin on gastrointestinal motility in functional dyspepsia remains to be elucidated. As regards pancreatic polypeptide and CCK levels, our study did not demonstrate any difference between dyspeptic patients and controls, regardless of the presence or absence of *H. pylori* infection. These findings are in agreement with those in literature. A significant, enhanced pancreatic polypeptide response to the test meal was observed among duodenal ulcer patients, whereas the response pattern in functional dyspepsia patients was very similar to that in healthy subjects [6]. In patients with functional dyspepsia, serum gastrin decreased significantly, but CCK levels did not change when the *H. pylori* infection was eradicated [33]. Therefore, it seems that neither pancreatic polypeptide nor CCK play a crucial role in the pathophysiology of functional dyspepsia.

In our study, an intriguing relationship between hormone levels and gastrointestinal symptoms was found. Neurotensin is known to inhibit postprandial activity. Nevertheless, a negative correlation between this hormone and postprandial fullness was found. The correlation remained after subdivision according to *H. pylori* status. Peptides have recently been found to function as neuromodulators or neuromediators within nociceptive pathways at central and peripheral sites. Among these, neurotensin seems to have a homeostatic bipolar (facilitatory and inhibitory) effect on pain modulation [34]. In functional dyspepsia, the higher levels of neurotensin could disrupt this homeostasis causing a predominance of the antinociceptive effect of neurotensin. This may explain the lower symptom score for dyspeptic patients with high concentrations of neurotensin. Pancreatic polypeptide also has an inhibiting effect on pancreatic secretions and motility. Large doses of pancreatic polypeptide cause inhibition of the gastric pacemaker and the appearance of an ectopic pacemaker distally [35].

Many investigators have tried to identify specific *H. pylori*-related symptoms. There is a suggestion that *H. pylori*-infected patients may have higher ulcer-like dyspepsia scores than *H. pylori*-negative patients [36], and that there is a higher prevalence of *H. pylori* infection in ulcer-like dyspepsia than in dysmotility-like dyspepsia [37]. Despite this, distinct categories of symptoms do not appear to exist between *H. pylori*-positive and -negative patients. In our study, there were no specific symptoms of *H. pylori*-related dyspepsia either in terms of symptom scores or of symptom frequency.

In conclusion, alterations in gastric electrical activity are present in patients suffering from functional dyspepsia, but these alterations are not related to *H. pylori*. However, the presence of the bacterium tends to alter the gastrointestinal hormone pattern, inducing higher gastrin levels. According to accepted guidelines, eradication therapy is now considered advisable in *H. pylori*-positive patients with functional dyspepsia only in specific cases such as those with a family history of gastric cancer, associated therapy (proton pump inhibitor, NSAID), and following gastric surgery. In the light of present evidence, particular attention should be paid to asymptomatic subjects since recommendations for treatment of *H. pylori* in such cases are not categorical. Controlled studies are needed to assess the value of screening programs.

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