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Association between gastric myoelectrical activity and intraluminal nitric oxide

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SUMMARY

Background: We have previously shown that the intraluminal concentration of NO in *H. pylori*-positive patients is significantly reduced compared to that in *H. pylori*-negative patients.

Aim: The aim of this study was to evaluate the effect of *H. pylori* infection on gastric motor activity in relation to the level of NO and nitrite in the stomach in humans.

Methods: Thirty-two *H. pylori*-negative and 32 *H. pylori*-positive patients with dyspepsia were studied. Gastric myoelectrical activity was recorded for 24 h using surface electrogastrography. Intraluminal gas and juice were endoscopically collected from the stomach to determine NO and nitrite and nitrate (NOx) levels using a chemiluminescence system.

Results: The percentage of tachygastria in the morning preprandial state was significantly higher ($P = 0.005$) in *H. pylori*-positive than -negative patients. In *H. pylori*-negative patients, there was a significant positive correlation between NO levels and the percentage of bradygastria ($r = 0.56$, $P = 0.001$) and a significant negative correlation between NOx levels and the percentage of normal electrical activity ($r = -0.57$, $P = 0.001$) in the preprandial state.

Conclusions: Gastric motor activity is associated with NO and NOx levels in the gastric lumen. *H. pylori* infection may play a role in the pathogenesis of abnormal gastric myoelectrical activity.

INTRODUCTION

H. pylori has been recognized as a causative factor for gastritis and peptic ulcer and plays an important role in the pathogenesis of gastric adenocarcinoma and low-grade B cell lymphoma of mucosa-associated-lymphoid tissue (MALT lymphoma).[1–3] However, it is controversial whether *H. pylori* infection is linked to symptoms among patients with non-ulcer dyspepsia (NUD) and which, if any, subgroup of NUD patients is relieved of symptoms following eradication of *H. pylori* infection. There have been a number of studies on the effect of eradication of *H. pylori* infection in NUD.[4–7] Four well-designed, larger trials have reported conflicting results. One, a single-centre, randomized, placebo-controlled study of 318 patients, suggested that one in five patients with NUD will benefit from eradication therapy.[4] In the other three trials, however, the rate of response in the eradication group was more than 24%, but similar to that of the placebo group.[5–7] The inclusion of patients with gastro-oesophageal reflux disease (GERD) may decrease the chance of a positive response by eradication, whereas the inclusion of patients with peptic ulcer disease may increase the chance. Part of the problem is that, despite the evidence suggesting a benefit, there is no definite structural or biochemical explanation for the symptoms of NUD. One possibility is an effect on gastric motility but unfortunately, there is little information regarding the effect of *H. pylori* infection on gastric myoelectrical activity.

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Gastric myoelectrical activity modulates gastric motor activity. It has been shown that abnormal gastric myoelectrical activity is associated with gastric motility disorders and gastrointestinal symptoms such as nausea and vomiting, both of which are common in NUD.[8–12] Electrogastrography (EGG) provides an accurate measurement of the gastric slow waves and is a non-invasive method for assessing gastric myoelectrical activity.

Nitric oxide (NO) is a messenger molecule that plays various roles in diverse physiological, pharmacological and pathological processes.[13] It is known that NO plays dual roles in the regulation of gastric mucosal integrity,[14] and acts as a physiological neurotransmitter of non-adrenergic, noncholinergic neurones in the stomach that regulate gastric emptying. However, only a few papers have been published regarding its role as a centrally acting neurotransmitter modulating gastrointestinal motility.[15–17] It has been recently demonstrated that NO is highly concentrated in the gastric lumen and plays an important role in defending against pathogenic micro-organisms in the stomach.[18–20] Evidence has accumulated suggesting that NO plays an important role in the *H. pylori*-related gastric mucosal lesions.[21–23] We have previously shown that the intraluminal concentration of NO in *H. pylori*-positive patients is significantly reduced compared to that in *H. pylori*-negative patients. In contrast, the concentration of nitrite in gastric juice is significantly and reciprocally elevated in *H. pylori*-positive patients. Further, intraluminal concentration of NO increased to normal levels following the eradication of *H. pylori*.[24] The aim of the present study was to evaluate the effect of *H. pylori* infection on gastric motor activity in relation to NO and NOx levels in the stomach in humans.

METHODS

This single-centre, prospective, interventional study of gastric motor activity in *H. pylori*-negative and -positive patients, was performed at the Wakayama Medical Hospital in Japan between January 1999 and December 2000.

Patients

Patients with symptoms of upper abdominal discomfort, except those related to GERD, who were scheduled for routine diagnostic upper gastrointestinal endoscopy, were invited to participate. Patients were excluded from the study if the initial endoscopy demonstrated ulcer or malignant disease or more than three gastric erosions in the upper gastrointestinal tract. Patients with chronic organic disease such as diabetes mellitus, cardiac, hepatic, renal disease, etc., and or the use of chronic drugs except those for dyspepsia were excluded. Demographic data collected at study entry included age, sex, smoking status, alcohol consumption, and drug treatment. Drinking was defined as regular alcohol consumption of more than 35 g per day. All subjects were instructed not to take medicines during the 2 days before the EGG study. This study was approved by the Wakayama Medical College Ethical Committee, and informed consent was obtained from each patient.

Diagnosis of H. pylori

Gastric mucosal biopsies were taken from the greater curvature of the corpus and antrum for *H. pylori* culture, rapid urease test and histopathological examination by Giemsa staining. Patients were considered to be infected with *H. pylori* if at least two of the three tests were positive, and *H. pylori*-negative if all tests were negative.

Electrogastrography

Surface electrogastrography was used to record gastric myoelectrical activity. Before placement of electrodes, the abdominal skin at each recording site was cleaned with exfoliating skin-prep jelly (Omni Prep; Weaver & Co., Aurora, CO, USA) to reduce electrical impedance between electrodes. The skin was rubbed until pink. A thin layer of electrode gel was then applied to the recording sites. Three silver-chloride electrocardiograph (ECG) electrodes were placed on the abdominal surface over the stomach, one each on the epigastric area bilaterally, just below the lower rib, and a reference electrode was positioned at the midpoint above the umbilicus. The two epigastric electrodes were connected to yield a bipolar EGG signal, which was amplified using a portable EGG recorder (Digitrapper EGG; Synetics Medical Inc., Irving, TX, USA) with low and high cutoff frequencies of 0.5 and 18 cpm, respectively. On-line digitization with a sampling frequency of 1 Hz was performed using an analogue-to-digital converter installed on the recorder, with digitized samples stored in the recorder. The EGG was recorded in each subject for

24 h. At the end of each study the stored data were downloaded to a personal computer (Sharp Mebius MN 390-X26) using a software polygraph (Synetics Medical Inc.). After the deletion of motion artefacts, the recording was divided into three portions: preprandial (for 30 min in the fasting state before each meal); postprandial (30 min after each meal); and supine (in bed at night), and each portion was then subjected to computerized spectral analysis using programs previously reported.[25] The percentage of normal 2- to 4-cpm gastric waves was defined as the percentage of time during which regular 2- to 4-cpm slow waves were present over the entire observation period. This ratio reflects the regularity of gastric myoelectrical activity and was computed using adaptive running spectral analysis methods. If the peak power of 1-min EGG was within the range 0.5–2 cpm, the corresponding EGG was considered to show bradygastria. If the peak power was within the range of 4–18 cpm, that portion was called tachygastria.

Assay for nitric oxide and NOx in the gastric lumen

Five mL of gas in the gastric lumen was endoscopically collected through an Olympus PR-4Q tube without inflation by air, and 1 mL of gastric juice was also endoscopically collected from the stomach. Gastric juice was centrifuged at 12 000 g for 5 min and 100 μL of supernatant was used for assay. The concentrations of NO and NOx were measured using a chemiluminescence system (NO analyser Model-280 NOATM; Sievers, CO, USA). The concentration was calculated automatically by a computer analysis system (NOAAnalysis; Sievers), which displays the signal in real time and provides peak integration and calibration. A sample of known concentration of NO was used for calibration.

Statistical analysis

Values are expressed as mean ± S.D. Statistical analysis for significant differences was performed using the nonparametric Mann–Whitney *U*-test. Mantel–Haenszel chi-square analyses were performed to measure differences in the overall prevalence of outcomes. *P*-values are two-tailed. Correlations between percentage of EGG and NO or NOx were tested using Pearson's correlation coefficient.

RESULTS

Sixty-four individuals were studied, 32 *H. pylori*-positive and 32 *H. pylori*-negative. The two groups were well balanced with respect to demographic and clinical features (Table 1). However, endoscopic findings were significantly different between the two groups, with atrophic gastritis being more common in the *H. pylori*-positive patients (75%) than in the *H. pylori*-negative patients (37%) ($P = 0.006$). There was no difference in clinical symptoms suggesting NUD between *H. pylori*-positive and -negative patients.

The percentage of normal wave recordings was lower (70.9% ± 21.6% vs. 80.7% ± 17.4%, $P = 0.047$) in the *H. pylori*-positive patients than in the negative. Further, the percentage with tachygastria in the preprandial state was higher (22.4% ± 21.7% vs. 11.6% ± 12.8%, $P = 0.042$) in the *H. pylori*-positive patients; the percentage of tachygastria in the morning preprandial state was particularly significant (27.2% ± 26.3% vs. 10.4% ± 12.4%, $P = 0.005$). Percentages in the postprandial and supine states were not significantly different between the two groups (Table 2).

The intraluminal concentration of NO in *H. pylori*-positive patients was not significantly reduced

Table 1. Demographic and clinical characteristics of the patients

Variables	*H. pylori*-positive ($n = 32$)	*H. pylori*-negative ($n = 32$)	*P* value
Age: Mean (S.D.)	43 (16)	45 (15)	0.46*
Range	18–69	22–68	
Gender: (%) Males	41	41	1.0**
Smoking: (%) Yes	25	44	0.19**
Drinking: (%) Yes	25	38	0.42**
Endoscopic finding			0.0095**
Normal	7	16	
Atrophic gastritis	24	12	
Gastric erosion	1	4	

*T-test; **Chi-square.

Table 2. EGG findings in *H. pylori*-positive and -negative patients

	H. pylori-positive	*H. pylori*-negative	*P* value
Preprandial state			
Bradygastria	6.7 ± 8.1	7.9 ± 10.4	0.90
Normal wave	70.9 ± 21.6	80.7 ± 17.4	0.047
Tachygastria	22.4 ± 21.7	11.6 ± 12.8	0.042
Morning preprandial			
Bradygastria	7.7 ± 12.8	8.2 ± 11.8	0.90
Normal wave	65.1 ± 25.7	81.4 ± 15.9	0.042
Tachygastria	27.2 ± 26.3	10.4 ± 12.4	0.005
Postprandial state			
Bradygastria	6.6 ± 5.4	5.6 ± 3.8	0.71
Normal wave	78.4 ± 16.4	81.3 ± 11.47	0.73
Tachygastria	15.0 ± 15.8	13.0 ± 9.4	0.66
Supine			
Bradygastria	6.7 ± 5.0	4.2 ± 3.4	0.39
Normal wave	74.9 ± 18.7	82.2 ± 11.4	0.13
Tachygastria	19.7 ± 18.7	13.5 ± 9.4	0.25

Values are expressed as a percentage of recording (mean ± S.D.).

compared to that in *H. pylori*-negative patients The concentration of NOx in the gastric juice was higher, but was not significantly elevated in *H. pylori*-positive patients (Table 3).

There were significant positive correlations between NO level and the percentage of bradygastria in the preprandial state ($r = 0.56$, $P = 0.001$, Figure 1), and significant negative correlations between NOx level and the percentage of normal electrical activity in the preprandial state ($r = -0.57$, $P = 0.001$, Figure 2) in *H. pylori*-negative patients. However, in *H. pylori*-positive patients, there was no significant relation between NO or NOx levels and EGG data.

DISCUSSION

NUD is subdivided into ulcer-like, dysmotility-like, and nonspecific symptoms based on the combination of several symptoms. Reflux-like dyspepsia is currently considered to be part of the symptom complex of GERD.[26] However, the pathophysiology of NUD is unclear and standard clinical investigation, including laboratory tests and conventional imaging studies, do not detect an apparent cause. Studies of NUD have often been criticized for failing to use validated outcome measures. Most studies support the hypothesis that NUD represents an underlying motility disorder with a probable neuropathic source. Approximately 40–50% of patients with dysmotility-type dyspepsia have delayed solid-phase gastric emptying.[27] Several techniques exist to measure the motor function of the stomach. Some of the early studies used contrast radiographic procedures, especially cinefluoroscopy, to examine both gastric motor activity and emptying. The barium meal

Table 3. NO and NOx levels in *H. pylori*-positive and -negative patients

	H. pylori-positive	*H. pylori*-negative	*P* value
NO	3443 ± 2985	4538 ± 4640	0.56
NOx	12.3 ± 26.1	3.3 ± 9.1	0.16

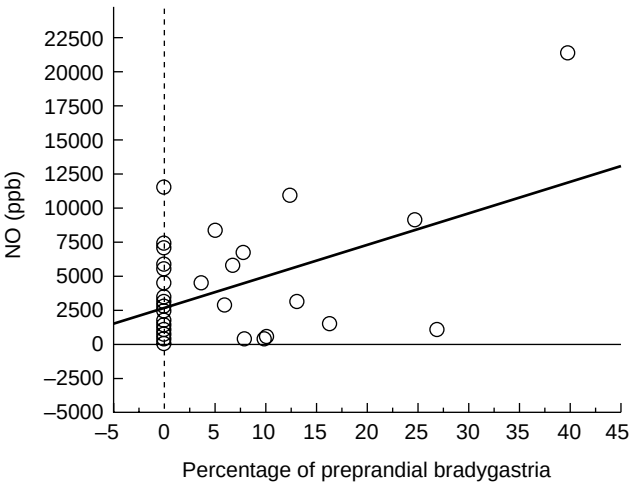

Figure 1. Correlation between NO levels in the gastric lumen and the percentage of preprandial bradygastria. There was significant positive correlation between NO levels and the percentage of bradygastria in the preprandial state ($r = 0.56$, $P = 0.001$) in *H. pylori*-negative patients.

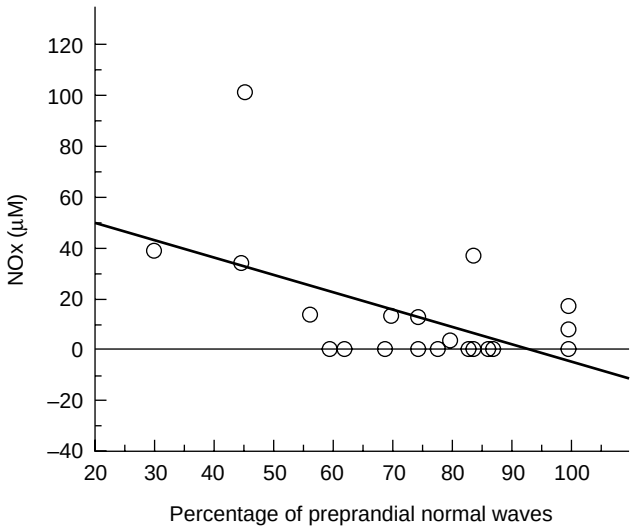

Figure 2. Correlation between NOx levels in the gastric juice and the percentage of preprandial normal electrical activity. There was significant negative correlation between NOx levels and the percentage of normal electrical activity in the preprandial state ($r = -0.57$, $P = 0.001$) in *H. pylori*-negative patients.

technique is both insensitive and crude. The addition of strain-gauge transduction or perfused manometric tubes allows simultaneous study of gastroduodenal motility and gastric emptying, but these are invasive and cause significant discomfort. EGG is an accurate measurement of the gastric slow wave and is a non-invasive method for assessing gastric myoelectrical activity, which modulates gastric motor activity.[28–30] It is known that normal electrical activity of the EGG is not significantly affected by age or sex.[31]

It has been shown that abnormal gastric myoelectrical slow waves (tachydysrhythmias, tachygastrias, and bradygastrias) are associated with gastric motility disorders and gastrointestinal symptoms such as nausea and vomiting, which are common in NUD.[8, 12] It has been also shown that the percentage of time in which normal 2–4 cpm slow waves predominate in the postprandial state differentiates patients with NUD from healthy controls with 100% specificity and 43% sensitivity.[12] On the other hand, it has been reported that a normal EGG does not guarantee normal emptying of the stomach.[9, 29, 32] For example, in a study of diabetic gastroparetic patients, there was no association between the EGG and gastric emptying.[9] Chen *et al.* suggested that cisapride was more effective for the treatment of NUD with abnormal EGG, which was defined as a percentage of normal gastric waves below 70%, or a decrease in postprandial amplitude.[33]

Tachygastria has been related to gastric retention, nausea and vomiting, and motion sickness.[34–36] However, no previous reports suggesting an influence of *H. pylori* on gastric motor activity have appeared to date. One study indicated that *H. pylori* is not a determining factor in the abnormal distension of the proximal and distal stomach to liquid ingestion that is associated with an increased sensation of fullness and bloating in dyspeptic patients.[37] In our study, *H. pylori* infection induced tachygastria in the preprandial state. Therefore, it is possible that *H. pylori* infection causes dyspepsia-inducing tachygastria in some patients whose symptoms might be improved by eradication. Although changes in postprandial EGG amplitude, which reflect a change in slow-wave amplitude, have been frequently observed,[31, 38] *H. pylori* infection did not change EGG data in the postprandial state in our study. Further investigations are needed on gastric motor activity in the postprandial state under conditions of a standardized diet.

NO generated by neuronal structures has been shown both *in vivo* and *in vitro* to be an important mediator of non-adrenergic, noncholinergic (NANC) relaxation in smooth muscle throughout the gastrointestinal tract.[14, 39, 40] NO synthase has been shown to be immunolocalized in nerve fibres and cell bodies of the myenteric plexus.[41] Inhibition of NO formation also blocks the smooth muscle relaxing activity of other putative NANC transmitters, such as vasoactive intestinal polypeptide, adenosine 5-triphosphate and gamma-aminobutyric acid, suggesting that NO is the final mediator of the effects of such agents.[42] NO in the gastric lumen presumably modulates gastric motor activity. On this basis, *H. pylori* infection may modulate gastric motor activity by changing NO levels within the gastric lumen. We found a significant positive correlation between NO levels and the percentage of bradygastria and a negative correlation between NOx levels and the percentage of normal electrical activity in the preprandial state in *H. pylori*-negative patients.

We have previously shown that the intraluminal concentration of NO in *H. pylori*-positive patients is significantly decreased compared to that in *H. pylori*-negative patients.[24] NO is highly concentrated in the gastric lumen and readily diffuses through cell membranes. Almost all NO in the gastric lumen is delivered by extrinsic sources from saliva in the acidic environment of the stomach, and nitrite and nitrate levels

in gastric juice are dependent on local acid production.[18–20] *H. pylori* infection induces hypochlorhydria in patients with pangastritis and decreases the normal secretion of ascorbic acid, which inhibits nitrosation and the production of potentially mutagenic *N*-nitroso compounds into the gastric lumen.[43, 44] It is likely that *H. pylori* infection is responsible for the expression of iNOS, which forms potentially genotoxic nitrating species such as peroxynitrite and nitrosating species. Although *H. pylori* infection increases NO production, we suggest that NO levels in the gastric lumen are decreased because the hypochlorhydria induced by *H. pylori* inhibits the conversion of NOx to NO and infection promotes the conversion of NO to NOx by means of superoxide radicals.[45] *H. pylori* has been reported to generate substantial amounts of superoxide radicals, as measured by the chemiluminescence method.[46] It is predicted that *H. pylori* infection reduces levels of NO and inhibits stomach muscle relaxation. However, in the present study, NO and nitrite levels showed no significant difference between the *H. pylori*-positive and -negative status. This difference from the previous study may be due in part to the small number of subjects and to the exclusion of patients with ulcer or more than three gastric erosions. Subjects in the present study were younger than those in the previous clinical study and eight (25%) of the *H. pylori*-positive patients did not show atrophic gastritis.

It has been proposed that increased inflammation in the enteric mucosa or neural plexi may contribute to symptoms developing as a result of peripheral sensitization, hypermotility activated by induction of mucosal inflammatory cytokines, or both.[47–49] It has been confirmed that intestinal smooth muscle cells respond to interleukin (IL)-1, leading to transcription of the IL-6 gene and secretion of IL-6. IL-1 stimulates substance P synthesis in myenteric nerves and IL-1 and IL-6 synergism results in the suppression of norepinephrine release.[43] IL-1 has also been shown to excite neurones and increase pain perception through the release of mucosal prostanoids.[49] The inflammatory response to *H. pylori* infection of the gastric epithelium is associated with the release of IL-8 and interstitial cell adhesion molecule 1, which leads to the recruitment of neutrophils and additional inflammatory cells, which in turn secrete IL-1, IL-6 and tumour necrosis factor-α into mucosa.[50, 51] As a basis for the production of visceral symptoms therefore, inflammatory cytokines induced by *H. pylori* affecting the gastric mucosa might alter gastric neuromuscular function. In the present study, there were significant correlations between NO or nitrite level and gastric motor activity only in *H. pylori*-negative patients and not in *H. pylori*–positive patients. We suggest that gastric motor activity may be mainly regulated by NO levels in normal *H. pylori*-negative stomach, which are changed by gastric acidity influenced by diet. On the other hand, in *H. pylori*-positive patients, abnormal gastric motor activities might be mediated, at least in part, via reduced NO levels within the gastric lumen associated with *H. pylori* infection and increased formation of inflammatory cytokines. These possibilities are now under investigation in our laboratory.

In conclusion, we found that *H. pylori* infection was associated with tachygastria in the preprandial state. Gastric motor activity was associated with NO and NOx levels in the gastric lumen. We propose the possibility that *H. pylori* infection modulates gastric motor activity and may play a role in the pathogenesis of abnormal gastric myoelectrical activity.

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