

Does *Helicobacter pylori* infection increase gastric sensitivity in functional dyspepsia?

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Abstract

The role of *Helicobacter pylori* infection in the pathogenesis of functional dyspepsia is debated. It is known that a substantial fraction of dyspeptic patients manifest a low discomfort threshold to gastric distension. This study investigated the symptomatic pattern in 27 *H pylori* positive and 23 *H pylori* negative patients with chronic functional dyspepsia, and potential relations between infection and gastric hyperalgesia. Specific symptoms (pain, nausea, vomiting, bloating/fullness, early satiety) were scored from 0 to 3 for severity and frequency (global symptom scores: 0-15). The mechanical and perceptive responses to gastric accommodation were evaluated with an electronic barostat that produced graded isobaric distensions from 0 to 20 mm Hg in 2 mm Hg steps up to 600 ml. Gastric compliance (volume/pressure relation) and perception (rating scale: 0-10) were quantified. Standard gastro-intestinal manometry and recorded phasic pressure activity at eight separate sites during fasting and postprandially were also assessed. *H pylori* positive and *H pylori* negative patients manifested similar severity and frequency of specific symptoms and global symptom scores (mean (SEM)) (severity: 9.5 (2.0) v 9.0 (2.1); frequency: 10.8 (2.0) v 9.7 (2.2)). No differences were seen either in gastric compliance (53 (4) ml/mm Hg v 43 (3) ml/mm Hg) or in gastric perception of distension (slope: 0.50 (0.05) v 0.53 (0.06)). Postprandial antral motility was significantly decreased in *H pylori* positive patients (two hours motility index: 10.4 (0.6) v 12.6 (0.5); $p < 0.05$). It is concluded that *H pylori* infected patients with functional dyspepsia present no distinctive symptoms by comparison with *H pylori* negative counterparts and *H pylori* infection is associated with diminished postprandial antral motility but it does not increase perception of gastric distension.

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Keywords: functional dyspepsia, *Helicobacter pylori*, gastric perception, gastric barostat, gastric compliance, gastrointestinal manometry.

Functional dyspepsia is a highly prevalent clinical syndrome whose aetiology and pathophysiology are poorly understood. Infectious, secretory, motor, psychological, and perceptive

factors have been implicated as possible aetiopathogenic mechanisms.^{1 2} Among these, gastric infection by *Helicobacter pylori* has been incriminated as a cause of functional dyspepsia although published results are controversial. In some therapeutic trials dyspeptic symptoms improved after *H pylori* eradication^{3 4} but in other trials no clinical improvement was detected.^{5 6} Other investigators have proposed an association between *H pylori* positive functional dyspepsia and a specific subgroup of symptoms, mainly abdominal pain.⁷

Pathophysiological abnormalities in functional dyspepsia include motor and sensory disturbances. Antral hypomotility occurs in 25 to 40% of patients and a similar proportion shows delayed gastric emptying.⁸ Possible relations between *H pylori* infection and these motor disturbances in dyspeptic patients have been investigated with conflicting results. For instance some authors have found gastric emptying to be delayed in infected patients⁹ while others have not.^{7 10}

Sensory disturbances in functional dyspepsia are manifested by a diminished perception threshold to gastric distension in the presence of normal intestinal and somatic perception.^{11 12} So far, however, the hypothesis that mucosal inflammation resulting from *H pylori* infection causes gastric hypersensitivity in dyspeptic patients had not been formally explored.

The aim of this study was to investigate whether patients with chronic functional dyspepsia infected by *H pylori* present different clinical, motor, and visceral perception features than non-infected patients.

Methods

Patients and healthy volunteers

Fifty consecutive patients with the diagnosis of chronic functional dyspepsia participated in the study: 27 were *H pylori* positive (seven men and 20 women; mean age: 33 years; age range: 18-55) and 23 were *H pylori* negative (four men and 19 women; mean age: 35; age range: 19-61). Patients were submitted to our hospital, as a referral centre, from general practice and other hospitals for complete evaluation. Twelve healthy volunteers (seven men and five women; mean age: 24; age range: 22-26) served as controls. All participants stopped taking any drugs for at least 72 hours before the study. The protocol for the study had been previously approved by the institutional review board of the Hospital General Vall d'Hebron and informed consent

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was obtained from all participants in the study.

Inclusion criteria for dyspeptic patients were (a) presence of at least two symptoms of a five symptom complex (upper abdominal pain, bloating/fullness, early satiety, nausea, and vomiting); (b) moderate to severe intensity of illness defined by a numerical symptom score that is, a sum score higher than 6 (see clinical evaluation); (c) chronic complaints defined by the presence of the dyspeptic symptoms for at least two years before study; (d) absence of biochemical and morphological evidence of gastrointestinal, biliary, and systemic diseases, as established by negative results of physical examination, laboratory tests, upper gut endoscopy and ultrasonography, or oral cholecystogram; (e) absence of history suggestive of previous peptic ulcer disease; (f) absence of symptoms predominantly suggesting gastro-oesophageal reflux disease or irritable bowel syndrome; and (g) no previous abdominal surgery other than appendicectomy or hernia repair.

Clinical evaluation

Dyspeptic symptoms were evaluated using a questionnaire listing five symptoms: upper abdominal pain, nausea, vomiting, bloating/fullness, and early satiety. Severity and frequency of each symptom were separately evaluated by a defined numerical score. Severity: 0, absent; 1, mild (awareness of symptom but easily tolerated); 2, moderate (interference with normal activities); 3, severe (incapacitating); total severity score: 0–15. Frequency: 0, absent (less than once per month); 1, rarely (less than once per week); 2, occasionally (less than three times per week); 3, often (more than three times per week); total frequency score: 0–15. A global symptom index, for each symptom and for the total score, was also obtained by multiplying severity by frequency.

Detection of *H pylori*

In every patient four antral and four fundic biopsy specimens were obtained by endoscopy. *H pylori* was identified by bacterial culture, direct staining techniques, and in vitro urease production as previously described.¹³ Specimens were processed within two hours after being obtained. Each specimen was smeared into a glass slide, heat fixed, Gram stained, and examined with a $\times 100$ oil immersion lens for a minimum of five minutes. It was

also cultured on a *H pylori* selective medium: brain-heart infusion agar with 7% horse blood, 1% isovitalax, vancomycin (6 mg/l), nalidixic acid (20 mg/l), and amphotericin B (2 mg/l). The plates were incubated at 37°C in a microaerophilic atmosphere for seven days. *H pylori* strains were identified by the following tests: Gram stain, oxidase, catalase, urease, growth at 42°C in microaerophilic atmosphere and cephalothin, and nalidixic acid sensitivity.

A patient was considered infected by *H pylori* if the bacterial culture was positive or, when negative, in the presence of all three following results: positive Gram stain, positive urease test, and visualisation of compatible micro-organisms in the biopsy specimen.

Gastrointestinal manometry

The procedure has been previously described in detail.¹⁴ In brief, an eight lumen orointestinal tube (5 mm OD) was placed under fluoroscopic guidance so that six recording sites (1 cm apart) lay across the gastroduodenal junction and two aboral recording sites (10 cm apart) in the descending and distal duodenum, respectively. The probe was connected to a low compliance manometric perfusion system.¹⁵ Antrointestinal pressure activity was continuously recorded on an eight channel paper polygraph (Dynograph Recorder R611, SensorMedics, Anaheim, CA) for three hours fasting and for two hours after ingestion of a 435 kcal solid liquid meal.

Measurement of perception to gastric distension

We used this test specifically to evaluate the perception elicited by intragastric distension as well as the gastric compliance (volume/pressure relation). The procedure was performed by means of an electronic barostat¹⁶ to produce standardised gastric distension, as described.

After an overnight fast, the bag of the barostat, finely folded, was introduced through the mouth into the stomach. To unfold the intragastric bag, one lumen of the connecting tube was connected to a pressure transducer, and the bag was slowly inflated through the other lumen of the tube with 300 ml of air. The bag was then completely deflated and connected to the barostat. Pressure and volume inside the intragastric bag were continuously recorded on a paper polygraph (model 1600, MFE, Salem, NH).

Participants were placed in a 30° recumbent position and were asked to relax comfortably. Using the pressure selection dial of the barostat, intrabag pressure was gradually increased by 2 mm Hg stepwise increments every three minutes. Graded distension was induced from 0 mm Hg (atmospheric pressure) up to the pressure value that first provided an intrabag volume >600 ml or when the participants reported discomfort (score=8). Perception of gastric distension was scored at each pressure step using a rating scale graded from 0 to 10. We specifically measured perception of upper abdominal

TABLE I Symptom score in chronic functional dyspepsia. Comparison between *H pylori* positive and *H pylori* negative patients

	Severity		Frequency		Global symptom index	
	HP (+)	HP (-)	HP (+)	HP (-)	HP (+)	HP (-)
Abdominal pain	2.2 (0.2)	2.2 (0.2)	2.6 (0.2)	2.4 (0.2)	6.0 (0.5)	5.8 (0.6)
Nausea	1.8 (0.2)	1.8 (0.3)	1.9 (0.2)	1.7 (0.3)	4.3 (0.6)	4.0 (0.7)
Vomiting	1.3 (0.2)	1.1 (0.3)	1.3 (0.2)	1.2 (0.3)	2.9 (0.6)	2.7 (0.7)
Bloating/fullness	2.3 (0.2)	2.3 (0.2)	2.8 (0.1)	2.5 (0.2)	6.7 (0.5)	6.2 (0.6)
Early satiety	2.0 (0.2)	1.7 (0.2)	2.3 (0.2)	1.9 (0.3)	5.1 (0.5)	4.5 (0.8)
Total symptom score	9.5 (0.4)	9.0 (0.4)	10.8 (0.4)	9.7 (0.5)	25.0 (1.2)	23.2 (1.4)

Data presented as mean (SEM). HP (+): *H pylori* positive; HP (-): *H pylori* negative; Global symptom index: severity \times frequency.

TABLE II Gastrointestinal manometric data during the fasting period

	Functional dyspepsia		Healthy controls
	HP (+)	HP (-)	
Duration of duodenal IMMC (min)			
Total	105 (8)	104 (1)	107 (10)
Phase I	58 (8)	60 (7)	61 (10)
Phase II	39 (7)	36 (5)	43 (9)
Phase III	6 (1)	6 (1)	8 (1)
Number of gastric phases III	1.0 (0.1)	1.4 (0.2)	1.2 (0.2)
Number of duodenal phases III	2.2 (0.1)	2.1 (0.2)	2.3 (0.1)
Propagation velocity of duodenal phase III (cm/min)	14 (2)	10 (1)	12 (2)

Data presented as mean (SEM). IMMC: interdigestive migrating motor complex.

sensation. Before the study, participants were informed of the types of potential sensations (upper abdominal pressure, fullness, bloating, and nausea) to be scored. These symptoms were selected as being the more frequent sensorial responses to gut distension, previously established by specific questionnaires in our laboratory.^{5,6} The assessment of perception was performed by means of a manually activated scale as the intensity of upper abdominal sensation. Intensity scores were defined as follows: 0, absent sensation; 1 and 2, faint sensation; 3 and 4, mild sensation; 5 and 6, moderate sensation; 7 and 8, uncomfortable sensation; and 9 and 10, painful sensation. However, as specified, distensions were discontinued if the discomfort level (score 8) was reached.

Data analysis

To measure gastric compliance we averaged intrabag volumes during each pressure step and volumes at each pressure level were corrected for air compressibility using Boyle's law ($P_1V_1=P_2V_2$). A compliance curve (volume *v* pressure) was then constructed. In each subject, we defined the minimal distending pressure as the first pressure level that provided an intragastric volume of ≥ 30 ml; this pressure

level accounted for intra-abdominal pressure. Perception of gastric distension measured by the score system described above was plotted at each pressure level starting from the minimal distending pressure.

Antrointestinal manometric tracings were visually analysed as previously described.¹⁴ During fasting (three hours), we determined the duration of the interdigestive migrating motor complex at the duodenal level and of each of its different phases, the number of episodes of phase III activity in the antrum and in the intestine, and the propagation velocity of duodenal phase III. In the two hour postcibal period, phasic pressure activity in the most distal antral recording site was analysed using a motility index: $MI = \log_e [(no\ of\ waves \times sum\ of\ amplitude) + 1]$. Duodenal motility was analysed qualitatively according to the criteria of Stanghellini *et al.*¹⁷

Results are expressed as the mean (SEM) values for each parameter measured. Statistical comparisons were performed using Student's *t* test with unpaired analysis for intergroup comparisons. A *p* value of <0.05 was chosen as the significance value.

Results

Clinical data

The duration of the disease estimated from onset of clinical symptoms to the time of study was similar in *H pylori* positive and *H pylori* negative patients (5.63 (0.86) years *v* 7.13 (1.15) years, respectively). Both groups of patients were similar with regard to race, social status, and smoking habit (13 and 15 non-smokers in each group respectively); no alcohol abuse was present in any patient. Also, no differences between *H pylori* positive and negative patients were detected in severity or frequency of individual dyspeptic symptoms, in total symptom score or in symptom indexes (Table I).

Gastrointestinal manometric data

No significant differences were found between *H pylori* positive and *H pylori* negative patients with respect to fasting manometric data; results were similar to those obtained in healthy controls (Table II). The two hour postprandial antral motility index was significantly lower, however, in *H pylori* positive patients than in *H pylori* negative patients (10.4 (0.6) *v* 12.6 (0.5); $p < 0.05$). Moreover 12 of 26 *H pylori* positive patients had postcibal antral hypomotility (values lower than the mean (2 SD) of healthy volunteer values) compared with only four of the 24 *H pylori* negative patients (Fig 1). In one *H pylori* positive patient the antral motility index could not be calculated because of technical difficulties.

Only four patients showed evidence of abnormal duodenal motility during the postprandial period: two patients (both *H pylori* positive) showed evident duodenal hypomotility and another two (both *H pylori*

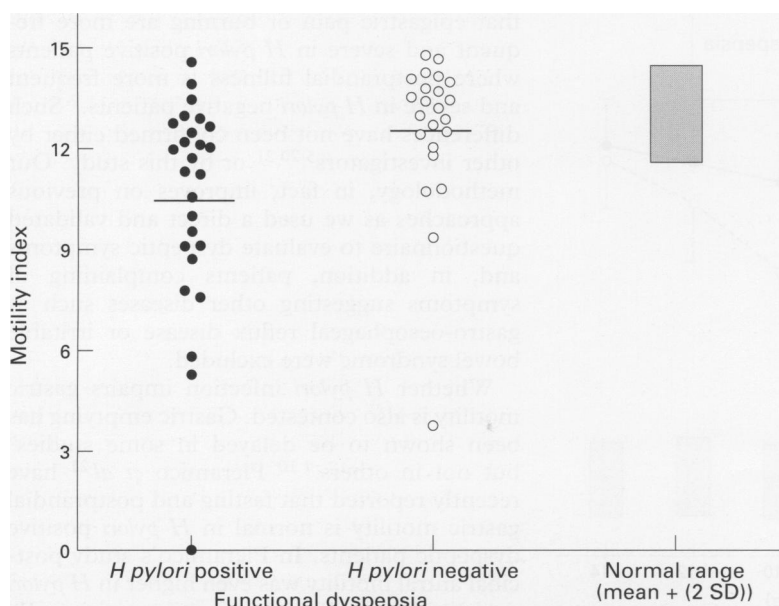


Figure 1: Two hour postprandial motility index. Note that 13 *H pylori* positive patients had hypomotility whereas only four of the *H pylori* negative did. (Values lower than mean (-2 SD) of healthy volunteer values.) ($p < 0.05$ *H pylori* positive patients versus *H pylori* negative patients).

TABLE III Symptom score in chronic functional dyspepsia. Comparison between subgroups of *H pylori* positive patients with normal motility (n=13) and with hypomotility (n=13)

	Severity		Frequency		Global symptom index	
	Normal motility	Hypomotility	Normal motility	Hypomotility	Normal motility	Hypomotility
Abdominal pain	2.3 (0.2)	1.9 (0.2)	2.7 (0.1)	2.5 (0.3)	6.3 (0.7)	5.4 (0.8)
Nausea	1.6 (0.3)	2.0 (0.3)	1.8 (0.3)	2.1 (0.3)	3.8 (0.9)	4.8 (0.9)
Vomiting	1.6 (0.3)	1.2 (0.4)	1.5 (0.3)	1.1 (0.3)	3.5 (0.9)	2.6 (1.0)
Bloating/fullness	2.5 (0.2)	2.0 (0.3)	2.8 (0.1)	2.7 (0.2)	7.1 (0.6)	5.9 (0.9)
Early satiety	2.0 (0.3)	1.8 (0.2)	2.4 (0.3)	2.2 (0.2)	5.5 (0.9)	4.2 (0.6)
Total symptom score	10.0 (0.6)	8.9 (0.5)	11.2 (0.7)	10.5 (0.4)	26.3 (2.1)	23.0 (1.3)

Data presented as mean (SEM). Global symptom index: severity×frequency.

negative) showed bursts of non-propagated phasic pressure activity.

When comparing the clinical data in the subgroup of *H pylori* positive patients who display postprandial antral hypomotility (n=13) with the subgroup with normal motility (n=13) no significant differences were found (Table III). Surprisingly, symptoms suggestive of delayed gastric emptying such as early satiety or postprandial fullness were slightly higher in the subgroup of patients without hypomotility; the same occurred for vomiting and abdominal pain whereas nausea was slightly more prominent in *H pylori* positive patients with postprandial hypomotility.

Perception of gastric distension and gastric compliance

During intubation and basal periods patients reported no symptoms. Stepwise distension of the stomach induced similar abdominal symptoms in dyspeptic *H pylori* positive and *H pylori* negative patients. Both groups experienced significantly more abdominal discomfort than healthy subjects at the same distending levels (Fig 2).

Gastric compliance (volume/pressure relation) was also similar in *H pylori* positive and negative patients, and did not differ from

values obtained in healthy controls (Fig 3).

Discussion

Functional dyspepsia is currently assumed to represent a symptom complex, which includes different pathophysiological mechanisms but produces a stereotyped clinical picture. Diverse abnormalities in motor and sensory upper gut function have been identified. We have shown that, as a group, dyspeptic patients have increased gastric perception to distension, suggesting a change in the afferent sensory pathway.¹¹ As inflammation may enhance both somatic and visceral sensitivity, referred to as hyperalgesia,^{18,19} we investigated whether gastric inflammation caused by *H pylori* infection increases gastric perception to distension. Our results disprove this hypothesis as we found that the perceptive response was similar in *H pylori* positive and *H pylori* negative patients. Confirming our previous results, however,¹¹ we found that in both groups intra-gastric perception was increased when compared with a healthy control group. Thus, gastric inflammatory changes induced by *H pylori* infection do not seem to be responsible for the gastric hyperalgesia seen in functional dyspepsia.

We also investigated whether dyspeptic patients infected by *H pylori* manifested a specific symptom pattern. It has been reported that epigastric pain or burning are more frequent and severe in *H pylori* positive patients where postprandial fullness is more frequent and severe in *H pylori* negative patients.⁷ Such differences have not been confirmed either by other investigators^{5,20,21} or by this study. Our methodology, in fact, improves on previous approaches as we used a direct and validated questionnaire to evaluate dyspeptic symptoms and, in addition, patients complaining of symptoms suggesting other diseases such as gastro-oesophageal reflux disease or irritable bowel syndrome were excluded.

Whether *H pylori* infection impairs gastric motility is also contested. Gastric emptying has been shown to be delayed in some studies⁹ but not in others.^{7,10} Pieramico *et al*²¹ have recently reported that fasting and postprandial gastric motility is normal in *H pylori* positive dyspeptic patients. In Pieramico's study post-cibal antral motility was even higher in *H pylori* positive than in *H pylori* negative patients. By contrast, we have found postprandial antral motor activity to be significantly decreased in dyspeptic patients infected by *H pylori*. This

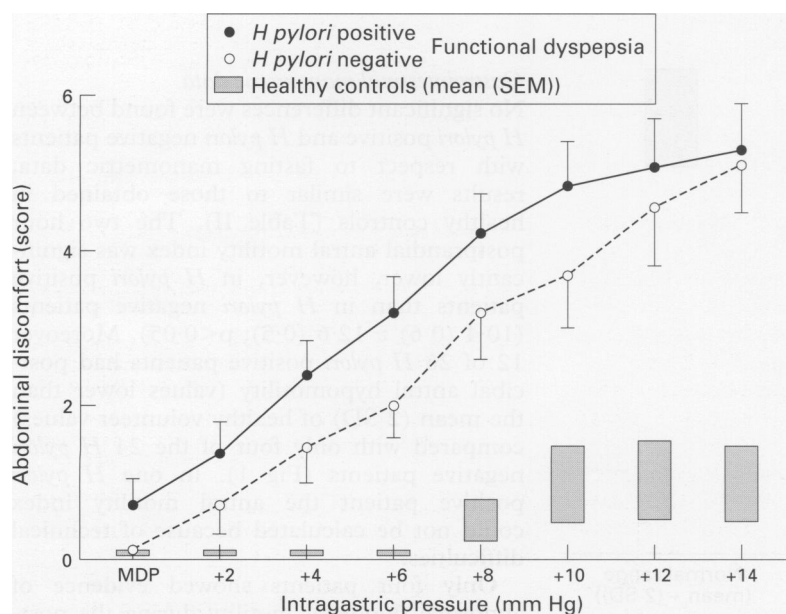


Figure 2: Abdominal discomfort elicited by gastric distension is similar in patients with functional dyspepsia with or without *H pylori* infection. Both groups experienced significantly more abdominal discomfort than healthy subjects. MDP= minimal distending pressure.

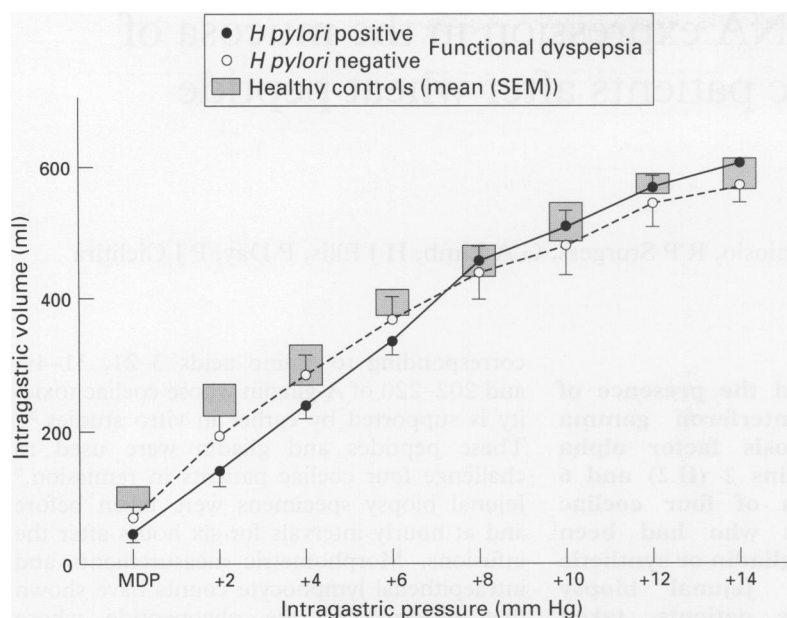


Figure 3: Gastric compliance (volume-pressure relation) is similar in patients with functional dyspepsia with or without *H pylori* infection. Values did not differ from those obtained in healthy subjects.

discrepancy cannot be explained by technical differences as the manometric procedure, the recording period, the type of meal, and the data analysis were almost identical. The difference could be in the selection of the patients with more chronic complaints in our dyspeptic subjects (two years minimum) than in those of Pieramico *et al* (three months minimum). It is conceivable that the motor response to *H pylori* infection could be time dependent as it is for gastric secretion. Nevertheless, the significance of *H pylori* infection in the pathogenesis of gastric hypomotility in functional dyspepsia remains in doubt as none of the upper gut motor abnormalities previously reported seem to correlate strongly with any particular type or intensity of dyspeptic symptoms.^{22 23} In fact, we found no significant differences when comparing the clinical data of *H pylori* positive patients with or without gastric hypomotility. Moreover, prokinetic drugs tend to consistently show pharmacological effectivity in connecting hypomotility and impaired emptying but, such positive motor effects are not invariably associated with symptom improvement.^{24 25} It should also be pointed out that an inverse correlation between gastric mucosal inflammation and postprandial antral motility has been described in peptic ulcer disease,²⁶ but such a correlation is not apparent in patients with chronic functional dyspepsia.²¹

In summary, the symptom complex associated with *H pylori* positive functional dyspepsia is not different from that in *H pylori* negative functional dyspepsia. Moreover, *H pylori* infection cannot be held responsible for the gastric hyperalgesia exhibited by many dyspeptic patients. Although postcibal antral motility is somewhat diminished in *H pylori* positive patients, such a finding may well represent an epiphenomenon as no relation with symptoms could be shown. These findings could have important therapeutic consequences, that is:

(1) eradication is not mandatory for symptom relief in chronic functional dyspepsia, and (2) drugs affecting visceral sensitivity can be effective regardless of *H pylori* status.

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