Alimentary Pharmacology & Therapeutics

Oesophageal hypersensitivity is associated with features of psychiatric disorders and the irritable bowel syndrome

J. H. RUBENSTEIN*, B. NOJKOV*, S. KORSNES*, S. A. ADLIS†, M. J. SHAW†, B. WEINMAN*, J. M. INADOMI‡, R. SAAD* & W. D. CHEY*

*Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, MI, USA; †Health Research Center, Institute for Research and Education, Park Nicollet Clinic, Health System Minnesota, MN, USA; ‡Gastroenterology Division, University of California, San Francisco, CA, USA

Correspondence to:
Dr J. H. Rubenstein, Division of Gastroenterology, University of Michigan Medical School, 3912 Taubman Center, Ann Arbor, MI 48109-0362, USA.
E-mail: jhr@umich.edu

Publication data
Submitted 23 April 2007
First decision 30 April 2007
Resubmitted 29 May 2007
Accepted 30 May 2007

SUMMARY

Background
Twenty per cent of patients with heartburn do not respond to proton pump inhibitors (PPIs). Many have normal oesophageal acid exposure. We hypothesized that such PPI non-responders have heightened oesophageal sensation, and that oesophageal hypersensitivity is associated with psychiatric features including somatization and anxiety.

Aim
To compare oesophageal sensation in subjects with heartburn categorized by response to PPI, and to correlate oesophageal sensation with psychiatric features.

Methods
Twenty-one PPI responders, nine PPI non-responders and 20 healthy volunteers completed questionnaires of psychiatric disorders and gastrointestinal symptoms. Subjects underwent oesophageal sensory testing with acid perfusion and balloon distension.

Results
Healthy volunteers displayed higher thresholds for sensation and discomfort from balloon distension than heartburn subjects (sensation $P = 0.04$, discomfort $P = 0.14$). Psychiatric disorders were associated with increased intensity of sensation ($P = 0.02$) and discomfort from acid ($P = 0.01$). Somatization was associated with increased discomfort from balloon distension ($P = 0.006$). Features of irritable bowel syndrome were associated with increased sensation and discomfort.

Conclusions
Heartburn subjects tend to have heightened oesophageal sensation, suggesting that oesophageal hypersensitivity may persist despite therapy with PPI. Oesophageal hypersensitivity is associated with features of psychiatric disease and with the irritable bowel syndrome, which might partly explain the aetiology of heartburn symptoms that are refractory to PPI.

doi:10.1111/j.1365-2036.2007.03393.x

INTRODUCTION

Up to 20% of Western populations suffer from heartburn on a weekly basis.[1] In the majority of these patients, the symptoms are due to acidic gastro-oesophageal reflux disease (GERD), including those with erosive oesophagitis and non-erosive reflux disease (NERD). However, 30–50% of NERD patients have normal acid exposure time in the oesophagus.[2, 3] These patients have been labelled as having functional heartburn. The response of heartburn symptoms to therapy with proton pump inhibitors (PPI) varies depending on findings from endoscopy and ambulatory pH studies. Patients with either erosive oesophagitis or NERD report 80% symptomatic response to PPI, while patients with functional heartburn have been reported to have approximately 50% symptomatic response.[4–6] Limited evidence suggests that functional heartburn may be associated with oesophageal hypersensitivity to physiologic stimuli or with psychiatric features such as anxiety.[7–11] However, many of these studies were performed in patients labelled with non-cardiac chest pain, a heterogeneous syndrome that likely includes GERD, functional heartburn, oesophageal dysmotility and other disorders. While many patients with GERD do not report heartburn, but instead another type of chest pain, other pain characteristics are less specific for GERD, and so it would be useful to compare patients with functional heartburn, *per se*, to those with true acid reflux. In the clinical setting, heartburn patients are typically treated with potent acid suppressing therapy, and endoscopy and pH studies are reserved for treatment failures. Therefore, it would be useful to examine the relationship between oesophageal sensitivity and psychiatric features, and to characterize oesophageal sensitivity among patients with heartburn who are categorized into the clinically recognizable groups of PPI responders and PPI non-responders (defined as heartburn that has been unresponsive to PPI despite normalization of oesophageal acid exposure time).

The intensity of a sensation, and the associated affective level of discomfort are two distinct components of the experience of pain that are represented in different areas of the cerebral cortex.[12–14] Two people may rate the intensity of sensation from a stimulus the same (for example, 'moderate'), but have differing emotional responses to that sensation (for example 'annoying' vs. 'intolerable'). We hypothesized that features of psychiatric disorders are particularly associated with the affective level of discomfort due to physical and chemical stimuli. We also hypothesized that PPI non-responders have increased oesophageal sensation to chemical and physical stimuli compared to PPI responders or healthy volunteers. To answer these questions, we aimed to compare psychiatric profiles as well as sensation and discomfort from oesophageal acid perfusion and balloon distension among PPI non-responders, PPI responders and healthy volunteers.

METHODS

Study subjects

Subjects with and without heartburn were recruited from the Gastroenterology Clinics and Medical Procedure Unit of the University of Michigan, and from community postings. Subjects were classified into three groups: (i) PPI responders, (ii) PPI non-responders and (iii) healthy controls. All subjects with a prior history of heartburn (defined as a burning sensation beginning in the upper abdomen or lower chest, and rising toward the neck) had experienced symptoms at least three times weekly without the use of PPI or histamine-2 receptor antagonists, and were using a PPI at least daily for a minimum of 6 weeks at the time of enrolment. Subjects with heartburn that was responsive to therapy with a PPI (PPI responders) were defined as those who had complete resolution of heartburn over the 7 days prior to assessment. PPI non-responders were defined as those who had heartburn at least twice in the 7 days prior to assessment despite the use of PPI twice daily for a minimum of 6 weeks prior to assessment. PPI non-responders also were evaluated with 24 h ambulatory oesophageal pH monitoring prior to enrolment; those with a distal oesophageal acid exposure time of greater than 4.2% were excluded. Defined in this way, we expect that all PPI non-responders have functional heartburn. Patients with non-cardiac chest pain would not be included in this group if their pain is not described as a burning sensation, or if they have refractory acid reflux. Subjects were classified as normal controls if they denied any heartburn, or experienced it less than once per week, and denied the use of antacids, histamine receptor antagonists or PPIs.

For all three groups, potential subjects were excluded if they had taken antidepressants, benzodiazepines or gabapentin within 1 week of oesophageal sensation testing; reported any recent history of exertional chest pain, dyspnoea, weight loss, melena or hematochezia; had a history of Barrett's oesophagus, infectious or radiation-induced oesophagitis, oesophageal stricture, Zencker's diverticulum, head and neck surgery, oesophageal surgery, gastric surgery, peptic ulcer disease, malignancy, coronary artery disease, diabetes mellitus, New York Heart Association Class IV congestive heart failure, renal disease requiring haemodialysis, pulmonary disease on home oxygen or with a forced expiratory volume in 1 s of less than 1.0 L, or liver disease with coagulopathy, encephalopathy, ascites, or varices; platelets less than 100 000 per cubic millimetre; international normalized ratio greater than 1.5; were pregnant, younger than 18 years of age; or were unable or unwilling to provide informed consent. Subjects were offered a stipend of $150 for their participation. The study protocol was approved by the Institutional Review Board of University of Michigan Health System.

Questionnaires

Prior to oesophageal sensation testing, subjects completed validated instruments of gastrointestinal symptoms (Digestive Health Status Instrument, DHSI),[15, 16] psychiatric disorders (Brief Symptom Inventory, BSI),[17] and generic health-related quality of life (Medical Outcomes Study Short Form-12, SF-12).[18] Subjects also rated the severity of heartburn experienced in the previous 4 weeks on a 6-point Likert scale from none to severe.

Catheter mounting and placement

The protocol was similar to the one used by Fass *et al.*[19] After an overnight fast, subjects swallowed a 10 French custom dual-lumen catheter (Dentsleeve, Adelaide, Australia). The distal end had an opening for acid perfusion. A separate lumen had three openings for inflation of a balloon mounted on stainless steel rings 5.5 cm apart with the distal opening located 1.5 cm proximal to the end of the catheter. Disposable custom-made polyvinyl spherical balloons with a circumference of 9 cm (Mak-La, Thousand Oaks, CA, USA) were attached to the stainless steel mounts using suture ties and paraffin. Prior to each use, the entire assembly was immersed in water to check for leaks.

While seated, subjects swallowed the lubricated catheter assembly with the aid of a stiffening guidewire. The lower oesophageal sphincter (LOS) was identified by inflating the balloon in the stomach, then withdrawing until tension was appreciated. The balloon was then deflated, and the distal end of the catheter was placed 10 cm proximal to the LOS. Sensation testing with both acid perfusion and balloon distension was then performed, as detailed below. The order of the testing was randomized using a block design with concealed allocation until the time of testing. Sensation testing was performed in subjects with heartburn while taking PPI for at least 6 weeks, and in healthy volunteers while not taking PPI.

Acid perfusion testing

With the catheter tip located 10 cm proximal to the LOS, 0.1 N hydrochloric acid was perfused at 10 mL/min for 10 min or until symptoms were rated 'intolerable,' which ever came first. Subjects were instructed to alert the investigators when they first had any sensation in the chest, upper abdomen or back, and any time remaining was noted. At the conclusion of the perfusion, subjects were asked to rate their sensation on a 20 cm scale that has previously been validated.[12, 13, 19, 20] The scale is a vertical column with descriptors adjacent to it ranging from 'no sensation, faint, very weak, weak…' up to 'extremely intense.' The subjects marked the intensity of the sensation with an 'X', and the distance in centimetres from 'no sensation' was subsequently measured. In addition, subjects were also asked to rate the level of discomfort associated with the sensation. A similarly validated 20 cm scale was used that had adjacent affective descriptors ranging from 'not unpleasant, distracting, annoying, uncomfortable…' up to 'intolerable, excruciating.'[12, 13] Prior to the sensation studies, each subject were instructed on the difference between these two scales using a script. An analogy was made to the sensation someone might feel when stubbing their toe, and that the level of discomfort associated with that sensation might differ if the person was sober or intoxicated. Another analogy was made to a soldier who is shot, but does not have as much discomfort as might be expected because of the 'adrenaline' of the moment. Following the acid perfusion, subjects drank 10 mL of an alginate antacid and sips of water until any sensation resolved.

Balloon distension testing

With the catheter located in the same position (balloon centred at 14.25 cm proximal to the LOS), a computer-driven barostat (G&J Electronics, Toronto, Canada) inflated the balloon using phasic distension to a set of 10 predetermined pressures in an ascending methods of limits paradigm with 4 mmHg increments. The balloon was infinitely compliant within its maximal volume. Each distension lasted 45 s, and there was a 90 s rest between distensions. In each distension, the computer sounded a bell when 15 s remained. At that time, subjects marked copies of the sensation and discomfort scales described above. Threshold pressures for 'weak' sensation (2.9 cm on the sensation scale) were recorded for each subject. Likewise, threshold pressures for discomfort were recorded as identified by the descriptor 'uncomfortable' on the discomfort scale (5.8 cm). If subjects rated the distension 'intolerable,' the sequence was discontinued.

Statistical analysis

The primary outcomes for acid perfusion were the sensation and discomfort in each group. For oesophageal distension, the primary outcomes were the threshold pressure for weak sensation and threshold pressure for discomfort in each group. The threshold was censored if subjects never reported a weak sensation despite completing all distensions; this occurred in 2 healthy volunteers. Likewise, the threshold was censored if discomfort was not induced despite completing all distensions; this occurred in two healthy volunteers and one PPI responder. Secondary outcomes were the correlation between sensation from acid, discomfort from acid, threshold pressure for weak sensation and threshold pressure for discomfort with the components of the SF-12, BSI and DHSI. Results from the BSI were standardized to gender and age.

Parametric comparisons of continuous data were made using *t*-test and ANOVA; chi-square was used for categorical data. Nonparametric comparisons were made using the Mann–Whitney or Kruskal–Wallis rank-sum tests. Linear regression modelling of acid sensation and acid discomfort was performed, controlling for age and gender. In addition to comparing the thresholds pressures for weak sensation and discomfort with balloon distension, general linear mixed models of the longitudinal data were created, allowing for the simultaneous control of subject level characteristics (i.e., subject group, age, gender) as well as the balloon pressure in predicting the level of sensation and discomfort. Correlations between psychiatric symptoms and sensation or discomfort were measured using Pearson correlation coefficients. Analysis was performed using SAS 9.1 statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Subject characteristics

Fifty subjects were enrolled (21 PPI responders, nine PPI non-responders and 20 healthy volunteers). All subjects completed the questionnaires. Five subjects could not tolerate placement of the dual-lumen catheter (all PPI responders); these subjects' responses to the questionnaires were included in the analyses. All PPI non-responders completed pH testing prior to enrolment; one PPI non-responder did not have heartburn during recording, and among the others, only one had a symptom index of at least 50%. The healthy volunteers were younger than the heartburn subjects (Table 1). The healthy volunteers had better physical quality of life than the other groups, as measured by the SF-12 (54.8 healthy volunteers, 51.1 PPI responders, 46.0 PPI non-responders, $P < 0.05$ for comparisons of healthy volunteers to either heartburn group); there was no difference in mental quality of life (53.4, 54.2 and 54.6 for healthy volunteers, PPI responders and PPI non-responders, respectively). The healthy volunteers exhibited less functional symptoms of GERD, dyspepsia and irritable bowel syndrome (IBS) than the heartburn subjects (Figure 1). PPI non-responders experienced a greater impact of their pain on their daily lives than either PPI responders or healthy volunteers (Figure 1). The Global Severity Index from the BSI indicated that there was no overall difference in psychiatric symptoms between the groups (Figure 2).

Acid perfusion testing

Overall, and in each group, the order of testing (acid or balloon first) was not associated with level of sensation or discomfort. Healthy volunteers had a numerical trend toward lower sensation and discomfort with acid perfusion than the heartburn subjects (Figure 3). There was no difference in either sensation or discomfort between PPI responders and PPI non-responders.

Table 1. Demographics and heartburn characteristics

	PPI responders (n = 21)	PPI non-responders (n = 9)	Healthy volunteers (n = 20)	P-value
Age (mean ± s.d.)	40.4 ± 11.2	44.9 ± 13.4	25.4 ± 8.2	<0.0001 (Healthy volunteers vs. other groups < 0.0001)
Male %	66.7%	55.6%	55.0%	0.74
Heartburn severity in prior 4 weeks (proportion greater than 'very mild')	42.9%	88.9%	5%	<0.0001 (Non-responders vs. responders = 0.04, non-responders vs. healthy volunteers < 0.0001, responders vs. healthy volunteers = 0.009)

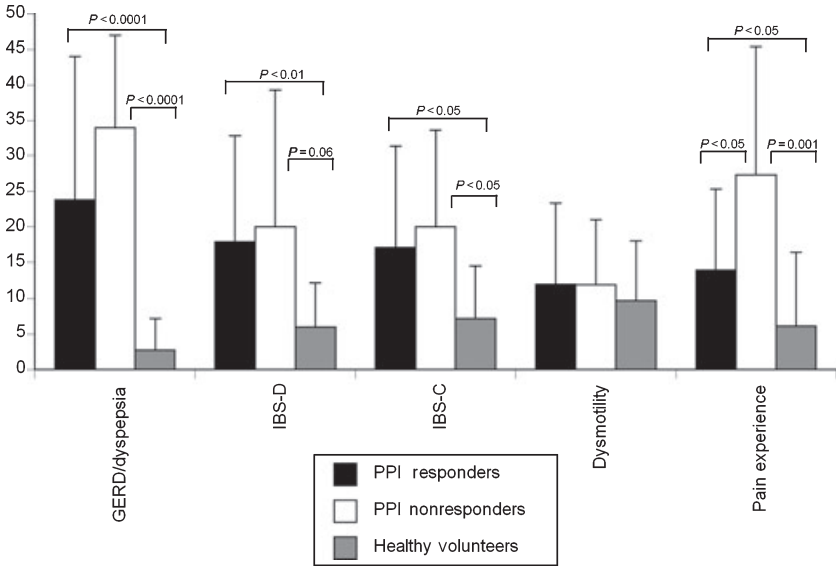

Figure 1. Gastrointestinal symptoms from digestive health status instrument. Healthy volunteers had fewer gastrointestinal symptoms than either heartburn group. PPI non-responders experienced a greater impact of their pain on their daily lives than either PPI responders or healthy volunteers. Columns represent means, and the whiskers are standard deviations.

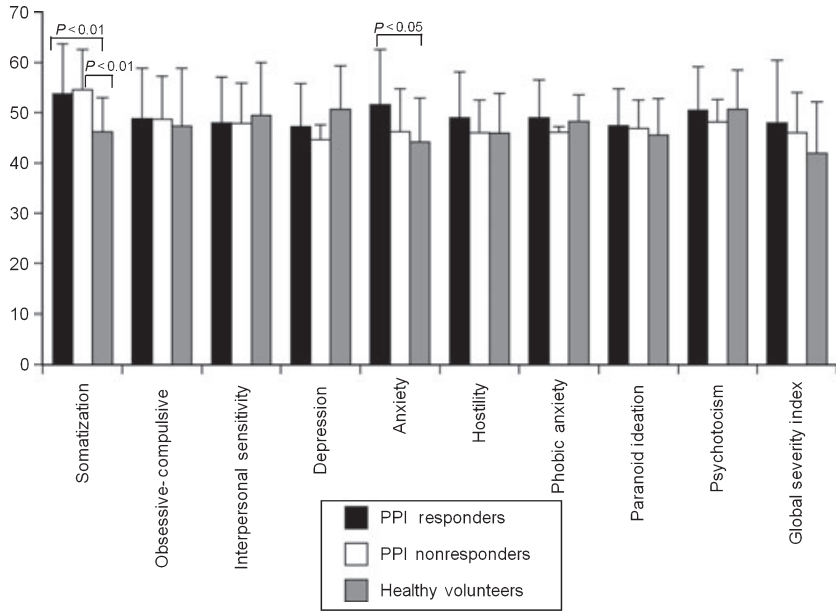

Figure 2. Psychiatric features from brief symptom inventory. In general, there were no differences in features of psychiatric disorders between groups. However, healthy volunteers had fewer symptoms of somatization than either heartburn group, and less anxiety than PPI responders. Columns represent means, and the whiskers are standard deviations.

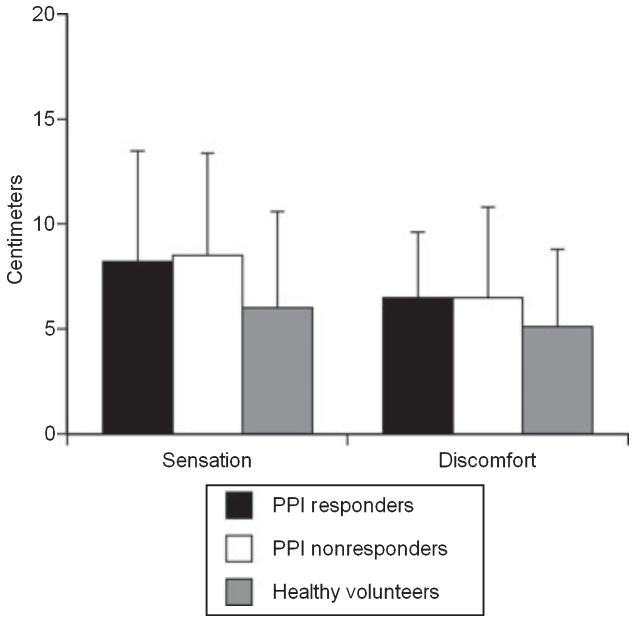

Figure 3. Sensation and discomfort from acid perfusion. No statistically significant differences were observed in sensation or discomfort from acid perfusion between groups. Columns represent means, and the whiskers are standard deviations.

Regardless of the subject grouping, comorbid psychiatric symptoms were associated with increased sensation and discomfort from oesophageal acid perfusion (Table 2). For instance, linear regression modelling, controlling for gender and age, revealed that for each 20 unit increase in the Global Severity Index of the BSI (approximately two standard deviations), there was a 3.9 cm increase in sensation ($P = 0.02$), a difference equivalent to that between 'very weak' and 'moderate' on the scale. Similarly a 20 unit increase in the Global Severity Index was associated with a 2.9 cm increase in discomfort ($P = 0.01$), a difference equivalent to that between 'distressing' and 'dreadful' on the scale. Supporting these associations, the mental component of the SF-12 was inversely correlated with sensation (rho = −0.28, $P = 0.07$) and discomfort (rho = −0.25, $P = 0.10$), although not reaching statistical significance. Interestingly, somatization, anxiety and paranoid ideation were associated with increased affective discomfort, but not with the intensity of sensation (Table 2). In addition, features of constipation predominant IBS were associated with increased sensation (rho = 0.34, $P = 0.02$) and discomfort (rho = 0.30, $P = 0.05$) from acid perfusion. Diarrhoea predominant IBS was also associated, but the correlation did not reach statistical significance.

Balloon Distension Testing

Once again, the order of testing (acid or balloon first) did not affect the threshold pressure for weak sensation or for discomfort. PPI responders had lower threshold pressures for inducing a weak sensation with balloon distension than healthy volunteers (Figure 4). However, no difference in sensation or discomfort was detected compared to PPI non-responders. Once again, features of psychiatric disorders were associated with decreased threshold for discomfort, but not with threshold for weak sensation (Table 2).

Features of IBS were associated with lower threshold pressures for discomfort (rho = −0.40, $P = 0.01$ for

Table 2. Correlations between psychiatric symptoms with sensation and discomfort of acid perfusion and balloon distension

	Acid sensation	Acid discomfort	Balloon sensation threshold	Balloon discomfort threshold
Somatization	NS	0.30 (0.05)	NS	NS
Obsessive-compulsive	0.37 (0.02)	0.44 (0.004)	NS	−0.33 (0.04)
Interpersonal sensitivity	NS	NS	NS	NS
Depression	NS	NS	NS	NS
Anxiety	NS	0.42 (0.005)	NS	−0.43 (0.005)
Hostility	0.37 (0.01)	0.46 (0.001)	NS	−0.39 (0.01)
Phobic anxiety	NS	NS	NS	NS
Paranoid ideation	NS	0.42 (0.005)	NS	−0.33 (0.04)
Psychoticism	NS	NS	NS	NS
Global Severity Index	**0.39 (0.01)**	**0.39 (0.01)**	**NS**	**−0.32 (0.05)**

Results expressed: Pearson correlation coefficient (*P*-value). NS, not significant.

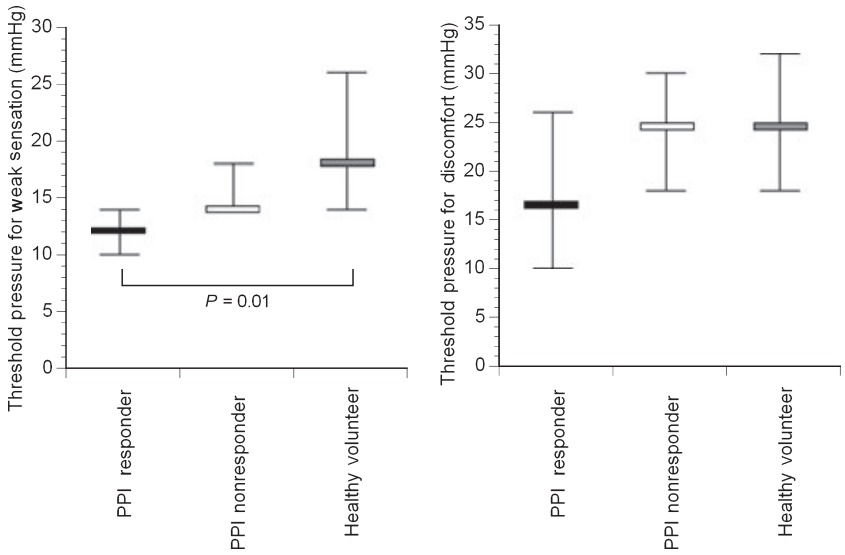

Figure 4. Threshold pressures for inducing weak sensation or discomfort. PPI responders had a statistically significant lower threshold for inducing a weak sensation than among healthy volunteers. Results are shown as median with interquartile range.

diarrhoea predominant, and rho = −0.37, $P = 0.02$ for constipation predominant), but not with threshold pressures for initial weak sensation.

General linear mixed models were performed to analyse the sensation and discomfort with each inflation, rather than simply the threshold values, while controlling for potential confounders. This revealed that PPI responders had greater sensation (+3.1 cm, $P = 0.02$) and discomfort (+2.9 cm, $P = 0.009$) at each balloon distension than healthy volunteers, controlling for age and gender, but there was no detectable difference from PPI non-responders. Controlling for subject group, age and gender, increasing features of somatization were also associated with greater discomfort with each distension (for each 20 point increase in somatization, +2.6 cm, $P = 0.006$); this association remained significant when controlling for features of IBS (+1.9 cm, $P = 0.05$). The association of somatization with sensation was not statistically significant. A similar association with discomfort was found for features of obsessive-compulsive disorder (+1.8 cm, $P = 0.03$), controlling for group, age and gender.

DISCUSSION

We compared the psychiatric profiles and visceral sensation among heartburn subjects that had responded to PPI, those who had not responded to PPI, and healthy volunteers. Our PPI non-responders exhibited similar levels of psychiatric distress and visceral sensation as the comparison groups. However, regardless of their grouping, oesophageal sensation to both acid perfusion and mechanical distension were associated with increased levels of psychiatric distress and with the IBS. The associations appeared stronger with the reported affective levels of discomfort from the stimuli, than with the intensity of sensation. The results suggest that the conscious awareness of, and in particular, the emotional response to physiologic or pathologic oesophageal stimuli may be mediated by psychiatric processes such as anxiety, somatization and paranoia. In the extreme setting, patients requiring in-patient psychiatric admission are more likely to report heartburn than non-psychiatric patients, controlling for medication use.[21] Our results suggest that in the more typical clinical setting, more subtle psychiatric features may in part determine which people with heartburn seek medical care, and may also influence response to therapy.

Visceral afferent sensation is a complex process that may be modulated by factors at the neural receptors or synapses at the local viscera, at the level of the dorsal horn of the spinal cord, and within the brain, including the cerebral cortex. Positron emission tomography has indicated that painful distension of the oesophagus is associated with increased activity in the anterior insula and the anterior cingulate cortex, areas that may represent the sensory-discriminative and affective components, respectively, of pain experience.[14] Visceral hypersensitivity has been more thoroughly studied within the setting of IBS.[14, 20, 22] Evidence suggests that psychological factors influence pain perception in IBS, as patients with the disorder rate even sham rectal distensions as more painful, and

as stress alters pain thresholds.[23] Psychiatric disorders, including somatization, have been associated with IBS, associated with illness coping behaviour among IBS patients, and influence the effect of IBS on quality of life.[24–26] Our finding that oesophageal hypersensitivity is associated with IBS corroborates an earlier report,[27] and suggests that such visceral afferent hypersensitivity is a global phenomenon rather than one limited to a particular segment of the gastrointestinal tract. However, results from this cross-sectional observational study cannot determine the direction of any causal relationship between psychiatric disorders and oesophageal hypersensitivity (the hypersensitivity may induce the psychiatric disturbance rather than vice versa).

As mentioned, we found no statistically significant difference in oesophageal sensation to acid or mechanical distension between PPI non-responders and PPI responders. A recent study found increased chemosensation in NERD patients compared to patients with functional heartburn, leading the authors to conclude that visceral hypersensitivity is not a major phenomenon of functional heartburn.[28] Despite the findings in comparison with either PPI responders or NERD patients, we found non-statistically significant trends toward increased sensation and discomfort in PPI non-responders compared to healthy volunteers. This suggests that visceral hypersensitivity might yet be a phenomenon associated with functional heartburn, and the current study may suffer from limited power to detect such a difference. Other potential aetiologies of functional heartburn might include abnormal oesophageal motor events and non-acidic reflux.[2, 29–31]

Our results may not be generalizable to the clinical setting as we excluded patients using psychotropic medications due to the potential for altering oesophageal sensation.[32–34] We found it difficult to identify large numbers of PPI non-responders who were not already prescribed such medications. In a different study that did not include ambulatory pH monitoring or oesophageal sensation testing, we found that unselected PPI non-responders had more features of psychiatric disorders than PPI responders.[35] Our results may have also been biased toward the null hypothesis by the recruitment process. The majority of people with heartburn symptoms do not seek medical care.[7] Those who do so may be more likely to exhibit psychiatric features such as anxiety or somatization. As we have found that these psychiatric features mediate the perceived severity of chemical and mechanical stimuli in the oesophagus, the findings of little difference between PPI responders and non-responders in terms of sensation or psychiatric profiles may reflect the selection of PPI responders from among patients (as they were almost exclusively receiving prescription PPIs). Likewise, the findings of increased sensation among PPI responders compared to healthy volunteers (largely recruited from the general community) may be explained by these selection processes.

Untreated GERD is associated with hypersensitivity to oesophageal acid perfusion.[36] While therapy with PPI has been found to decrease this hypersensitivity, it does not entirely normalize.[19, 37] We are unaware of any similar studies evaluating the response of sensation of mechanical stimuli to acid-suppressive therapy. We found that patients with heartburn that had been eradicated by PPI still had increased oesophageal sensation to balloon distension, compared to healthy volunteers, and trended toward having hypersensitivity to acid perfusion. These findings could be explained by a durable sensitization induced by prior injurious acid reflux. It could also be due to unmeasured differences in populations (patients vs. community volunteers), or could be explained if our PPI responders had inadequate acid control (which was not uniformly assessed in all responders).

In summary, we found that oesophageal hypersensitivity is associated with features of psychiatric disease and with the IBS. While we did not detect hypersensitivity in our selected sample of patients with heartburn that was unresponsive to PPIs, psychiatric disease and central sensitization may mediate symptoms in unselected patients with refractory heartburn.

ACKNOWLEDGEMENTS

Authors' declaration of personal interests: We thank Daniel Clauw, M.D. and Kimberly Groner, R.N. for the use of their barostat. We also appreciate the methodological advice of Ronnie Fass, M.D. and the statistical advice of Jack Kalbfleisch, Ph.D. We are indebted to Drs. Luke Evans, Laurel Fisher, Timothy Nostrant, Andrea Todisco, Ali Yazdani, Hellan Kang, and the other faculty and fellows of the Gastroenterology Division of the University of Michigan for their assistance in recruiting subjects. Dr. Chey has served as an advisory board member and received research funding from OrthoMcNeil; none of the other authors have personal interests with OrthoMcNeil. *Declaration*

of funding interests: The study was primarily funded by support from Eisai Inc. and PriCara, Unit of Ortho-McNeil, Inc. Additional support was provided by the General Clinical Research Center of the University of Michigan (#1933). Dr. Rubenstein was funded by National Institutes of Health training grants 2 T32 DK07367 and DK062708. Dr. Inadomi was funded by a Faculty Development Award from the American College of Gastroenterology, and a grant from the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service (IIR 99-238-2). The authors had complete control of the study design, collection, analysis, interpretation of the data and writing of the manuscript.

REFERENCES

1 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**: 710–7.
2 Zerbib F, Roman S, Ropert A, *et al.* Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol* 2006; **101**: 1956–63.
3 Fass R. Focussed clinical review: non-erosive reflux disease. *Medscape Gastroenterology*. 2001; **3**: http://www.medscape.com/viewarticle/407966, posted 26 February 2001.
4 Watson RGP, Tham TCK, Johnston BT, McDougall NI. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux - the ''sensitive oesophagus''. *Gut* 1997; **40**: 587–90.
5 Lind T, Havelund T, Carlsson R, *et al.* Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997; **32**: 974–9.
6 Richter J, Peura D, Benjamin S, Joelsson B, Whipple J. Efficacy of omeprazole for the treatment of symptomatic acid reflux disease without esophagitis. *Arch Intern Med* 2000; **160**: 1810–6.
7 Clouse RE, Richter JE, Heading RC, Janssens J, Wilson JA. Functional esophageal disorders. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders*, 2nd edn. Lawrence, KS: Allen Press, 2000: 247–98.
8 Rodriguez-Stanley S, Robinson M, Earnest DL, Greenwood-Van Meerveld B, Miner PB, Jr. Esophageal hypersensitivity may be a major cause of heartburn. *Am J Gastroenterol* 1999; **94**: 628–31.
9 Trimble KC, Pryde A, Heading RC. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. *Gut* 1995; **37**: 7–12.
10 Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986; **91**: 845–52.
11 Howard PJ, Maher L, Pryde A, Heading RC. Symptomatic gastro-oesophageal reflux, abnormal oesophageal acid exposure, and mucosal acid sensitivity are three separate, though related, aspects of gastro-oesophageal reflux disease. *Gut* 1991; **32**: 128–32.
12 Gracely RH, McGrath P, Dubner R. Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptiors: manipulation of affect by diazepam. *Pain* 1978a; **5**: 19–29.
13 Gracely RH, McGrath P, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. *Pain* 1978b; **5**: 5–18.
14 Ladabaum U, Minoshima S, Owyang C. Pathobiology of visceral pain: molecular mechanisms and therapeutic implications V. Central nervous system processing of somatic and visceral sensory signals. *Am J Physiol Gastrointest Liver Physiol* 2000; **279**: G1–6.
15 Shaw M, Talley NJ, Adlis S, Beebe T, Tomshine P, Healey M. Development of a digestive health status instrument: tests of scaling assumptions, structure and reliability in a primary care population. *Aliment Pharmacol Ther* 1998; **12**: 1067–78.
16 Shaw MJ, Beebe TJ, Adlis SA, Talley NJ. Reliability and validity of the digestive health status instrument in samples of community, primary care, and gastroenterology patients. *Aliment Pharmacol Ther* 2001; **15**: 981–7.
17 Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med* 1983; **13**: 595–605.
18 Gandek B, Ware JE, Aaronson NK, *et al.* Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998; **51**: 1171–8.
19 Fass R, Naliboff B, Higa L, *et al.* Differential effect of long-term esophageal acid exposure on mechanosensitivity and chemosensitivity in humans. *Gastroenterology* 1998; **115**: 1363–73.
20 Silverman DHS, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology* 1997; **112**: 64–72.
21 Avidan B, Sonnenberg A, Giblovich H, Sontag SJ. Reflux symptoms are associated with psychiatric disease. *Aliment Pharmacol Ther* 2001; **15**: 1907–12.
22 Mertz H, Morgan V, Tanner G, *et al.* Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000; **118**: 842–8.
23 Whitehead WE, Palsson OS. Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychological influences on pain perception. *Gastroenterology* 1998; **115**: 1263–71.
24 North CS, Downs D, Clouse RE, *et al.* The presentation of irritable bowel syndrome in the context of somatization disorder. *Clin Gastroenterol Hepatol* 2004; **2**: 787–95.
25 Miller AR, North CS, Clouse RE, Wetzel RD, Spitznagel EL, Alpers DH. The association of irritable bowel syndrome and somatization disorder. *Ann Clin Psychiatry* 2001; **13**: 25–30.
26 Halder SL, Locke GR 3rd, Talley NJ, *et al.* Impact of functional gastrointestinal disorders on health-related quality of life: a population-based case-control study. *Aliment Pharmacol Ther* 2004; **19**: 233–42.

27 Trimble KC, Farouk R, Pryde A, Douglas S, Heading RC. Heightened visceral sensation in functional gastrointestinal disease is not site-specific. Evidence for a generalized disorder of gut sensitivity. *Dig Dis Sci* 1995; **40**: 1607–13.
28 Shapiro M, Green C, Bautista JM, *et al.* Functional heartburn patients demonstrate traits of functional bowel disorder but lack a uniform increase of chemoreceptor sensitivity to acid. *Am J Gastroenterol* 2006; **101**: 1084–91.
29 Bhalla V, Liu J, Puckett JL, Mittal RK. Symptom hypersensitivity to acid infusion is associated with hypersensitivity of esophageal contractility. *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G65–71.
30 Rao SS, Gregersen H, Hayek B, Summers RW, Christensen J. Unexplained chest pain: the hypersensitive, hyperreactive, and poorly compliant esophagus. *Ann Intern Med* 1996; **124**: 950–8.
31 Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001; **120**: 1599–606.
32 Peghini PL, Katz PO, Castell DO. Imipramine decreases oesophageal pain perception in human male volunteers. *Gut* 1998; **42**: 807–13.
33 Prakash C, Clouse RE. Long-term outcome from tricyclic antidepressant treatment of functional chest pain. *Dig Dis Sci* 1999; **44**: 2373–9.
34 Varia I, Logue E, O'Connor C, *et al.* Randomized trial of sertraline in patients with unexplained chest pain of noncardiac origin. *Am Heart J* 2000; **140**: 367–72.
35 Chey WD, Nojkov B, Saad R, Rai J, Adlis SA, Shaw MJ. Does the absence of erosive esophagitis really predict a worse response to Proton Pump Inhibitor (PPI) therapy in patients with Gastroesophageal Reflux Disease? *Gastroenterology* 2006; **130**(Suppl. 2): A-179 [Abstract].
36 Bernstein LM, Baker LA. A clinical test for esophagitis. *Gastroenterology* 1958; **34**: 760–81.
37 Sarkar S, Thompson DG, Woolf CJ, Hobson AR, Millane T, Aziz Q. Patients with chest pain and occult gastroesophageal reflux demonstrate visceral pain hypersensitivity which may be partially responsive to acid suppression. *Am J Gastroenterol* 2004; **99**: 1998–2006.