PAPERS

Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD

K C Trimble, A Pryde, R C Heading

Abstract

Some patients undergoing ambulatory oesophageal pH monitoring to investigate symptoms suggestive of gastro-oesophageal reflux disease (GORD) are found to have oesophageal acid exposure within the physiological range but show a close correlation between their symptoms and individual reflux episodes. It is suggested that these patients might exhibit enhanced oesophageal sensation, akin to the heightened perception of both physiological and provocative stimuli in the gut that has been described in patients with functional gastrointestinal disorders. This study tested the hypothesis by measuring the sensory thresholds for oesophageal balloon distension and discomfort in 20 patients with symptoms of GORD, in whom ambulatory pH monitoring had shown normal acid exposure times, but in whom the symptom index for reflux events was 50% or greater, and compared these with 15 healthy volunteer controls, and with control groups with confirmed excess reflux. The study group showed lower thresholds both for initial perception of oesophageal distension, and for discomfort, compared with healthy controls (median ml (range)); 7·5 (2–19) *v* 12 (6–30) ($p=0·002$) and 10 (5–20) *v* 16 (8–30) ($p<0·0001$), respectively. Sensory thresholds in the study group were also significantly lower than in patients with excess reflux, and than patients with Barrett's oesophagus, who also exhibited significantly higher sensory thresholds than healthy controls. No differences in sensory thresholds for somatic nerve stimulation were found between the study group and healthy controls. The results show a spectrum of visceral sensitivity in GORD, with enhanced oesophageal sensation in patients with symptomatic but not excess gastro-oesophageal reflux, suggesting that their symptoms result from a heightened perception of normal reflux events.

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Keywords: gastro-oesophageal reflux disease, visceral sensation, sensory thresholds, symptom index.

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Ambulatory oesophageal pH monitoring is now a widely accepted technique for the investigation and diagnosis of patients with suspected gastro-oesophageal reflux disease (GORD) by detecting excess oesophageal acid exposure.[1] The additional use of a symptom diary card or event marker permits correlation of symptoms with reflux events generating a symptom index (SI).[2] A positive diagnosis of GORD can be confidently made in patients who have both a high oesophageal acid exposure time and a positive SI, but by no means all patients so studied show both abnormalities.[3] In some, a close correlation between symptoms and episodes of reflux is found, but the total acid exposure is within the normal (or physiological) range.[4–6] These patients comprise 6·7% of those referred to our laboratory for diagnostic pH monitoring. Their symptom pattern, severity, and duration seem to be similar to those with confirmed excess reflux.[7]

The term 'irritable oesophagus' has been used to describe patients in whom oesophageal symptoms are not associated with any one specific stimulus, but may be reproducibly evoked by a variety of stimuli, both physiological and provocative, including acid reflux and motor events.[8] It is suggested that these patients may exhibit changed visceral sensation in the oesophagus. We postulated that patients with symptoms suggestive of GORD who are found to have normal acid exposure time on pH monitoring, but a positive SI for reflux events – that is, symptomatic but not excess

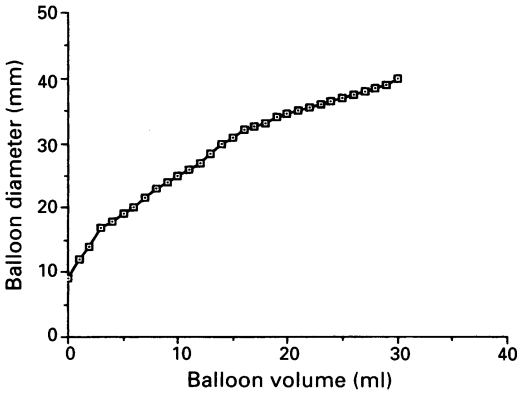

Figure 1: Relation of distending volume to diameter of the balloon used in the studies.

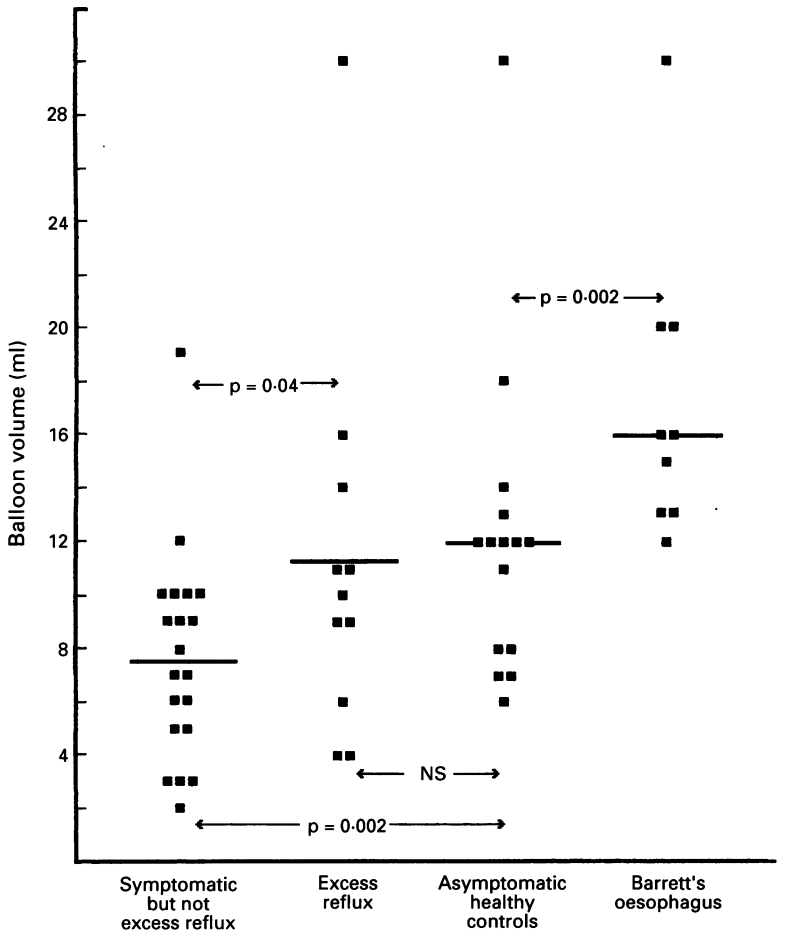

Figure 2: Individual subject data (with medians) for sensory thresholds for perception of oesophageal balloon distension.

gastro-oesophageal reflux – might represent a clearly definable subgroup of patients with the 'irritable oesophagus' in whom abnormalities of oesophageal sensation might be shown, akin to changes in sensory perception shown in the appropriate part of the gut in patients with oesophageal chest pain,[9 10] functional dyspepsia,[11] or irritable bowel syndrome (IBS).[12 13] The aim of this study was to measure the sensory thresholds for perception of balloon distension and discomfort in patients with symptoms of GORD in whom ambulatory pH monitoring had recorded normal acid exposure time but who showed a positive SI for reflux events, and to compare these with those found in other patients with reflux disease and with healthy controls.

Methods

SUBJECTS

Twenty patients for the study group (11 M, 9 F, median age 37·5 years, range 18–64) were recruited on the basis of the results of a routine 23 hour ambulatory pH monitoring study, which had been performed to investigate typical symptoms of GORD. All patients had had upper gastrointestinal endoscopy within the three months before the pH study showing no evidence of oesophagitis, and all had normal static oesophageal manometry. The inclusion parameters from the pH study were a normal total acid exposure time (<6·95% of a 23 hour study)[14] and a SI (based on the formula: SI=(number of symptom episodes associated with a reflux event/number of symptom episodes reported)×100) for heartburn/pain episodes (on the basis of at least three such episodes) of ≥50%. A symptom episode was held to be associated with a reflux event if it coincided with the onset of the reflux event (pH reaching 4) or occurred within the subsequent five minute period.[6] All patients stopped taking GORD drugs both before the original pH monitoring and this study; patients taking psychotropic drugs or other drugs possibly affecting visceral sensation were excluded.

Three groups of control subjects were also studied. Eleven patients (8 M, 3 F, median age 41 years, range 31–72) found to have excess oesophageal acid exposure (≥6·95% of 23 hour study) and a positive SI (≥50%) (four having endoscopic evidence of oesophagitis grade I or II) were recruited from those having routine pH monitoring for investigation of reflux symptoms. Nine patients (5 M, 4 F, median age 60 years, range 36–83) with histologically confirmed Barrett's oesophagus were recruited from the routine endoscopy service. The normal control group comprised 15 healthy volunteers (10 M, 5 F, median age 32 years, range 24–54). pH Studies were not carried out in the normal controls, but none had any history suggestive of reflux or of other gastrointestinal complaints.

Study design

A perfused multilumen manometry catheter (Arndorfer ESM3) was adapted so that a latex balloon 3 cm in length and of unrestricted diameter was positioned around the third of five recording ports (after Richter *et al*).[9] The balloon channel was filled with air and connected to a three way tap to permit measurement of intra-balloon pressure during inflation. Figure 1 shows the volume-diameter characteristics of the balloon used with stepwise air inflation outside subjects. The relation was roughly linear over the range of inflations used in the studies. Balloon length did not change during inflation, and there were no significant differences in vivo balloon pressure-volume characteristics measured between the various subject groups. Although in vivo assessment of possible effects of oesophageal resistance deforming the balloon was not made, previous studies have found little deforming of similar balloons inflated in the oesophagus.[9 15] A new balloon assembly of the same dimensions was required after the first 19 studies because of damage to the apparatus, the volume-diameter and compliance of this balloon were tested and shown to be identical to the first assembly. The physical characteristics of the balloon assembly were tested at intervals during the studies and did not change with time and repeated use.

Studies were performed on fasted subjects. The balloon catheter, connected to a low compliance constant water perfusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) was passed transnasally into

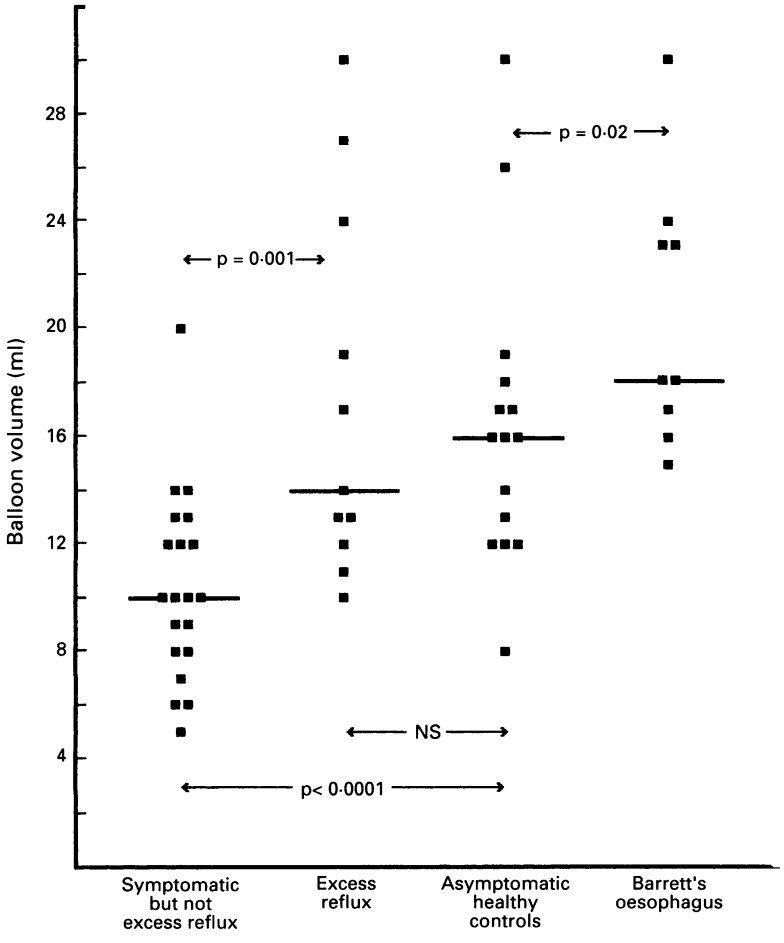

Figure 3: Individual subject data (with medians) for sensory thresholds for discomfort evoked by oesophageal balloon distension.

the oesophagus. The position of the lower oesophageal sphincter in each subject was determined by a station pull through technique and in each case the centre of the balloon was positioned 10 cm proximal to the lower oesophageal sphincter and the catheter fixed in position by taping to the nasal bridge. This position of the balloon relative to the sphincter was chosen partly for reasons of comparison with other similar studies assessing responses to oesophageal distension[9 10 16] and partly to avoid the segment of oesophagus likely to be most affected by reflux. Subjects were positioned in such a way as to ensure they were unaware of the occurrence or timing of balloon inflation. Rapid inflations (within two seconds) of the balloon with air were carried out by hand from a syringe in sequential 1 ml increments for 10 seconds at intervals of about 20 seconds, the balloon being fully deflated between inflations. The interval between balloon inflations was varied from time to time to avoid anticipatory effect. Subjects were asked to report the initial perception of any sensation in the chest, abdomen or back, and to indicate the perception of discomfort, but were given no other instructions or prompting during the study. Studies were stopped when the subject reported discomfort. Reproducibility of balloon distension in respect of sensory threshold reporting was assessed in a sample of patients (n=8) and normal controls (n=7) by repeating the studies five minutes later, and was found to have a coefficient of variation of r=0·97 for both initial perception and discomfort thresholds, according with reproducibility data for this technique reported by ourselves and others.[9 16 17] After the procedure patients were asked in an open ended fashion to volunteer a description of the sensation produced, and to compare it with their GORD symptoms.

Sensory thresholds for initial perception and discomfort evoked by a somatic stimulus in the 20 patients with symptomatic but not excess gastro-oesophageal reflux and in the healthy controls was also measured. This was done to assess if any differences in sensory threshold seen in the oesophagus were specific to visceral sensory function or a reflection of a generally heightened sensitivity to noxious stimuli, and to attempt to control for differences in perception that might occur as a result of possible greater anxiety in the study group. An electrocutaneous stimulus from a constant current generator (Mystro MS25, Medelec, Surrey) was applied to the index finger of the non-dominant hand at 1 pulse/second (100 μs) in increments from 0–100 mA. Subjects were asked to report perception of, and the occurrence of, discomfort evoked by the stimulus. Variability within subject for this technique was again found to be <10% for both thresholds.

Results are expressed as median and ranges, and the statistical significance of differences between study and control subjects assessed using the Mann-Whitney U test. Ethical approval for the study was obtained from the institution's ethics committee.

Results

The mean total acid exposure time of the study group with symptomatic but not excess reflux was 3·4% (range 0·4–6·8). The mean SI for reflux episodes was 73% (range 50–100). Although the median age of the normal control subjects was lower than that of the patient groups, the only statistically significant difference in ages between the groups was in respect of the nine patients with Barrett's oesophagus, who were older than the other three groups of subjects (p<0·02). In none of the groups was there a correlation between sensory thresholds and either age or sex.

The results of the oesophageal sensory thresholds of the study and control groups for perception of balloon distension are shown in Fig 2, and those for discomfort in Fig 3. The patients with symptomatic but not excess reflux exhibited significantly lower thresholds than normal controls both for the perception of oesophageal distension; (median ml (range)); 7·5 (2–19) *v* 12 (6–30) (p=0·002) and for discomfort; 10 (5–20) *v* 16 (8–30) (p<0·0001). In addition, these patients also showed lower sensory thresholds for both perception and discomfort than patients with symptomatic excess reflux (p=0·04 and p=0·001 respectively), whose sensory thresholds were not significantly different from those of healthy controls. Patients with Barrett's oesophagus were found to have significantly higher thresholds for both sensations than any of the other groups, with

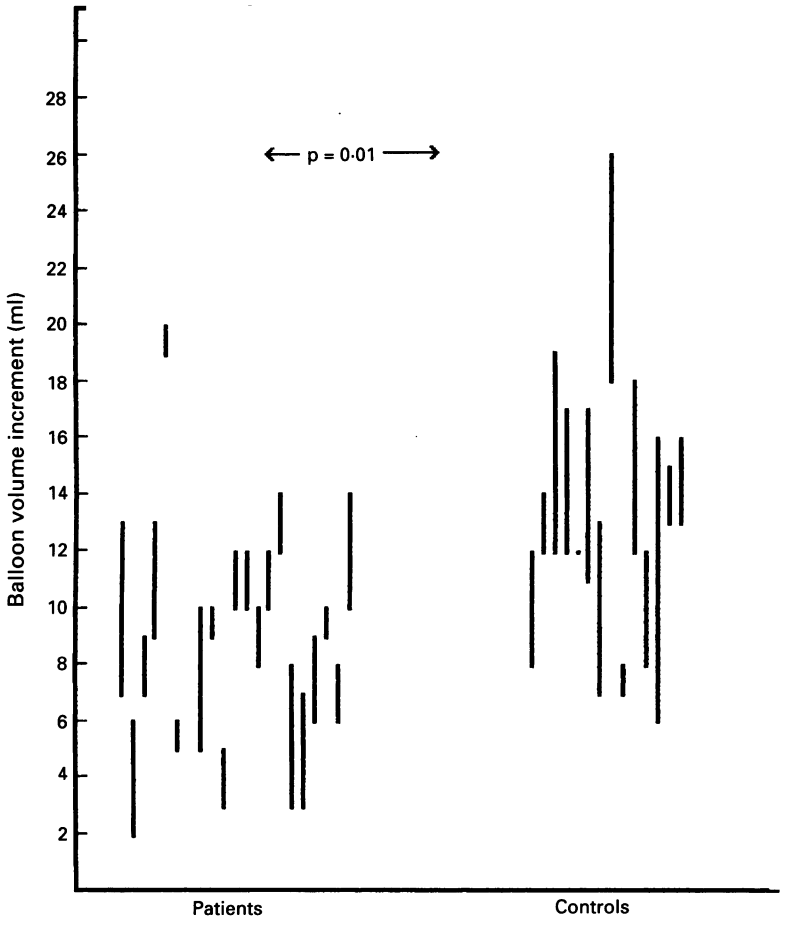

Figure 4: Individual subject data for tolerance of the sensation of oesophageal balloon distension in patients with symptomatic but not excess gastro-oesophageal reflux and normal controls. The lower and upper ends of each vertical line represent the perception and discomfort thresholds for each subject respectively, the length of the line representing the increment in distending volume required to change the sensation from perception to discomfort.

the exception of the thresholds for discomfort in the patients with excess symptomatic reflux, which were similar. One subject in each of the normal control, excess reflux, and Barrett's groups perceived no sensation whatever up to a maximum distending volume of 30 ml, both thresholds for these subjects have been recorded on the figure as 30 ml. Reanalysis of the comparison between the study group with normal acid exposure but a positive SI and the normal control subjects excluding this outlier from the second group still shows statistically significant differences in respect of both thresholds ($p=0·004$ and $p<0·0001$ respectively).

An additional difference between the patients with symptomatic but not excess reflux and the normal control subjects was noted in the respect of the increment in distending volume required to change the sensation evoked from perception to discomfort, the increment being lower in the patient group; 2·0 (1–6) *v* 4·5 (0–10) ($p=0·01$) (Fig 4). Both patient and control groups volunteered a range of descriptions of the sensation produced by oesophageal distension (Table). Eleven of 20 patients in the study group described the sensation as identical to their presenting GORD symptoms.

Figure 5 shows the results of the somatic sensory thresholds. The magnitude of electrocutaneous stimulus required to evoke both perception and discomfort, and the increments between the two sensory thresholds were similar in both the study and normal control groups.

Discussion

The technique of oesophageal balloon distension has been previously used in the investigation of pathophysiological mechanisms in patients with non-cardiac chest pain,[9 16] and similar techniques have been successfully used to investigate enhanced visceral sensitivity in patients with functional disorders affecting other parts of the gastrointestinal tract.[11–13] In addition to these provocative studies, enhanced perception of physiological motor activity occurring in the intestine has been shown in patients with IBS and may contribute to the occurrence of symptoms in these patients.[18] Our findings raised the possibility that similar abnormalities in visceral sensory function might also contribute to symptoms in other gastrointestinal disorders not usually regarded as 'functional'.

A wide range of symptom severity is recognised in patients with GORD and severity is known to correlate imperfectly with other measures of oesophageal reflux.[19 20] Some patients have minimal symptoms despite severe oesophageal mucosal injury, while others may describe severe heartburn yet have no oesophagitis and exhibit oesophageal acid exposure time within or barely above the normal range. It has been suggested that differing degrees of visceral sensitivity for noxious stimuli might contribute to this phenomenon.[21] We hypothesised that patients presenting with heartburn who are found to have ambulatory oesophageal acid exposure within the physiological range but who have a close association between their symptoms and reflux events (a high symptom index) might constitute the more sensitive extremity of a spectrum of visceral sensitivity in GORD patients. If this were so they could provide a valuable insight into variation in oesophageal sensory function. In contrast with the commonly encountered problem of case definition in patients with functional gastrointestinal disorders,[22] these subjects comprise a group that is precisely definable on the basis of the objectively measured variables of total acid exposure time and symptom index.

The results of our study show that patients with symptomatic but not excess gastro-oesophageal reflux as assessed by ambulatory pH monitoring do indeed have lowered

Description of sensation produced by oesophageal distension in patients with symptomatic but not excess reflux and in normal controls

Sensation	*Patients*	*Controls*
Tightness/pressure	7*	6
Heartburn	6†	4
Lump	4	3
Nausea	2	0
Warmth	1	2

*=Five described sensation as identical to reflux symptoms.
†=Six described sensation as identical to reflux symptoms.

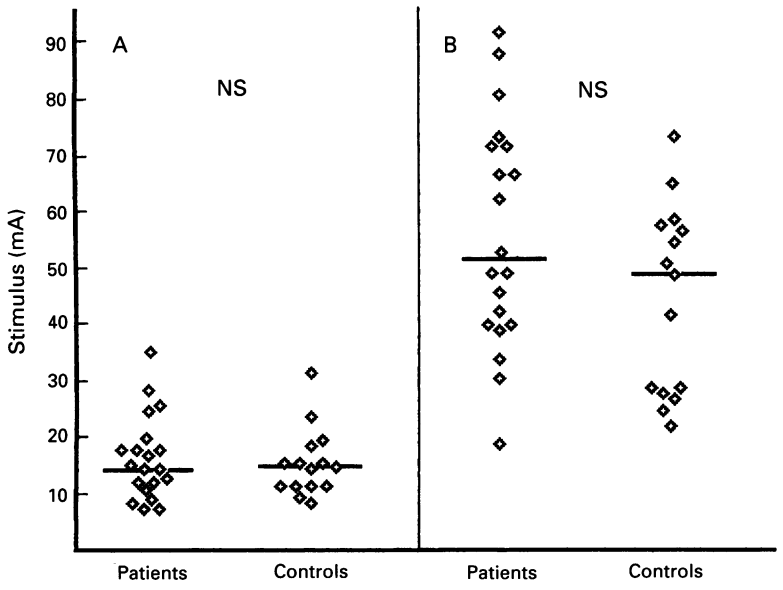

Figure 5: Somatic nerve sensory thresholds (with medians) for perception (A) and discomfort (B) produced by electrocutaneous stimulation in patients with symptomatic but not excess gastro-oesophageal reflux and normal controls.

thresholds for nociception within the oesophagus. Although shown using the non-physiological stimulus of balloon distension it must be borne in mind that these patients were selected on the basis that they already exhibited 'acid sensitivity' by virtue of perceiving low levels of reflux symptomatically – a 'physiologic Bernstein test'.[23] Formal acid perfusion tests were not carried out on these patients, but we have previously shown that acid perfusion tests are consistently positive in patients with a SI $\geq$50%, regardless of the total acid exposure time.[3] Comparison of the sensory thresholds obtained in the study group with the control group of 'genuine' refluxers shows that the enhanced sensitivity seen in patients who have symptoms without excess reflux is probably a primary phenomenon rather than a consequence of reflux disease. The results obtained in the patients with Barrett's oesophagus must be interpreted with caution in view of the older age group of these patients, but nevertheless are intriguing and may lend support to the previously proposed concept of diminished oesophageal sensitivity in this condition.[24 25] Although a change in sensation secondary to the mucosal change occurring in Barrett's cannot be excluded in this group, it is notable that at endoscopy only one of the Barrett's patients had columnar mucosa extending more than 8 cm proximal to the gastro-oesophageal junction.

Overall our results show that a wide range of oesophageal sensitivity exists, and that this may be an important factor in determining the occurrence and severity of GORD symptoms. The apparent perception of normal (physiological) degrees of reflux by patients with symptomatic but not excess gastro-oesophageal reflux may be exactly akin to the heightened perception of intestinal physiological events described in IBS patients.[18]

Two issues regarding the definition of our group of patients with symptomatic but not excess reflux merit further discussion. In view of the evidence regarding the accuracy and reproducibility of ambulatory pH monitoring in the quantification of oesophageal acid exposure,[26 27] it is probable that underestimation of the magnitude of acid reflux accounts for some of our patients falling into this category. Nevertheless the lower sensory thresholds recorded in these patients compared with both healthy controls and patients with excess symptomatic reflux does show that we have identified a 'sensitive' end to a range of visceral sensitivity in GORD, however comprised. Secondly, our choice of the cut off value for total acid exposure time of $<$6·95% of a 23 hour study, was because this is the upper limit of normal acid exposure time used in our laboratory, derived from the 95th percentile of the range of total acid exposure time in 34 control subjects drawn from our population.[14] This mathematical discriminator between physiological and pathological degrees of reflux is higher than that used by some authorities,[28] though consistent with others.[29] Our patient group with a positive SI for reflux episodes, however, encompassed a wide range of acid exposure time values, from negligible reflux right up the limit of 6·95%. The differences in sensory thresholds were still evident when only those patients with total acid exposure time $<$4·0% were assessed.

No differences were seen between patients with positive SI but normal acid exposure and normal controls in respect of sensory thresholds for somatic nerve stimulation showing that the enhanced sensitivity of the oesophagus exhibited by the patient group is not merely a reflection of a reduced pain threshold generally. This finding is consistent with other studies of functional gastrointestinal disorders where somatic sensory thresholds have been found to be normal in patients with functional dyspepsia[11] and normal or even increased in patients with IBS.[12 30] The finding in this study that the patient group required significantly smaller increments in balloon volume to change the sensation from mere perception to discomfort is also an interesting one. The possibility of a generally lower tolerance of noxious stimuli is also refuted by the data for somatic nerve stimulation suggesting that this is a specific visceral (or in this case oesophageal) phenomenon.

The term 'irritable oesophagus' was coined to describe patients in whom it seemed that the mechanism of pain of oesophageal origin related not to any specific stimulus (such as reflux or motility disorder) but rather to irritability of the oesophagus itself.[8] Although originally reported in the context of angina-like pain, we believe that the term also applies to the patients described in this study. In this context, it is significant that over half the subjects in the patient group identified the sensation produced by balloon distension to be the same as the reflux symptoms with which they had presented. The mechanisms that govern changes in visceral nociception are still

poorly understood,[31] but this study clearly identifies a spectrum of oesophageal sensitivity in GORD, and shows that in addition to its proposed role in functional gastrointestinal disease, enhanced visceral sensation is a factor in symptom genesis in some patients with reflux symptoms.

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