Gut 1995; 37: 457–464

PAPERS

Reflux related symptoms in patients with normal oesophageal exposure to acid

G Shi, S Bruley des Varannes, C Scarpignato, M Le Rhun, J-P Galmiche

Abstract

Several studies, using pH monitoring with event markers, have identified patients with normal oesophageal exposure to acid despite an apparent relation between symptoms and reflux episodes. In this series of 771 consecutive patients referred for 24 hour oesophageal pH monitoring, a probability calculation was used to evaluate the relation between symptoms and reflux episodes. Oesophageal exposure to acid was normal in 462 of 771 recordings (59·9%); despite this, 70·8% (327 of 462) of these patients used at least once the event marker. In 96 patients (12·5% of total patients) with normal oesophageal exposure to acid, there was a statistically significant association between symptoms and reflux episodes. The symptom cluster of such patients was similar to that usually seen in patients with gastro-oesophageal reflux disease, but symptoms like belching, bloating, and nausea were common thus overlapping with the symptom pattern of functional dyspepsia. In these patients both the duration and the minimum pH of reflux episodes (either symptom related or asymptomatic) were significantly shorter and higher, respectively, when compared with those of patients with gastro-oesophageal reflux disease. These results are consistent with the idea that oesophageal hypersensitivity to acid is the underlying pathophysiological feature of this syndrome.

(*Gut* 1995; 37: 457–464)

Keywords: pH monitoring, gastro-oesophageal reflux, symptom reflux relations, visceral perception.

Department of Gastroenterology and Hepatology, University of Nantes, France
G Shi
S Bruley des Varannes
M Le Rhun
J-P Galmiche

Institute of Pharmacology, School of Medicine and Dentistry, University of Parma, Italy
C Scarpignato

Correspondence to:
Professor J-P Galmiche, Laboratoire Fonctions Digestives et Nutrition, CHU Nord, 44035 Nantes Cedex, France.

Accepted for publication 16 February 1995

Ambulatory oesophageal pH monitoring is currently regarded as the most objective means for detecting and quantifying gastro-oesophageal reflux. It also represents the most sensitive diagnostic investigation for gastro-oesophageal reflux disease.[1] The availability of modern portable data loggers with one or more event markers has permitted a better understanding of the relations between symptoms and reflux episodes occurring during 24 hour oesophageal pH monitoring. When the relation of oesophageal exposure to acid with symptoms is considered, four possibilities exist – that is, abnormal oesophageal exposure to acid with or without temporal relation between symptoms and reflux episodes and normal oesophageal exposure to acid without or with temporal relation between symptoms and reflux episodes.

Patients with both normal oesophageal exposure to acid and apparent temporal relation between symptoms and reflux episodes have been identified in several studies, including ours.[2–10] Some indices have been proposed to assess the strength of this relation, including symptom specificity index[10–13] and symptom sensitivity index.[13] Unfortunately, cut off values of these indices have been chosen arbitrarily and often differ from one study to another. In addition, it should be considered that some symptoms may occur simultaneously with reflux episodes only by chance. To overcome these limitations, Ghillebert *et al*[14] recently proposed the evaluation of the relation between symptoms and reflux episodes by using a probability calculation based on the binomial law. Although not perfect in theory, this method has the advantage of describing that strength of the association without any previous arbitrary choice. In fact, the association can be regarded as significant if the p value is less than the generally accepted value of 5%.

We have recently adopted this method to calculate the probability that symptoms and reflux episodes occur simultaneously only by chance in a large series of consecutive patients referred to our laboratory for 24 hour oesophageal pH monitoring. Among this large number of subjects, we identified a subset of patients characterised by normal oesophageal exposure to acid and a significant association between symptoms and reflux episodes who seem to have an 'acid hypersensitive oesophagus'. In this study we therefore tried to define the frequency of the acid hypersensitive oesophagus syndrome and its main clinical picture, and to compare – in patients with both normal and abnormal oesophageal exposure to acid – the results obtained with probability calculation with those derived from previously described symptom indices. During these studies, the reproducibility of pH monitoring in the evaluation of symptom reflux relations was also assessed.

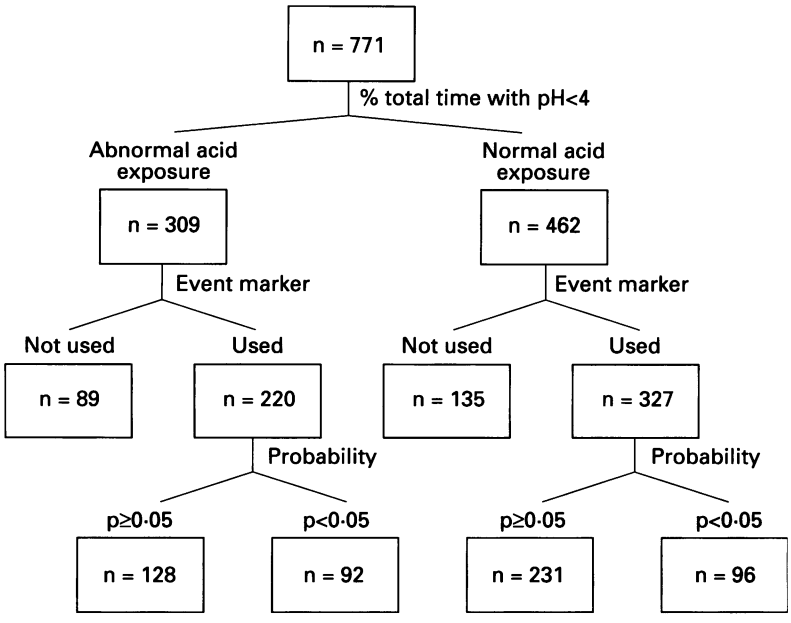

Figure 1: Frequency of patients with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring among a series of 771 consecutive patients referred for 24 hour pH monitoring. Some patients were investigated on several occasions. (n=number of patients.)

Methods

Patients

A total of 771 consecutive patients (392 men and 379 women, age 50·4 (14·8), mean (SD)) were submitted to 24 hour pH monitoring because of symptoms suggestive of gastro-oesophageal reflux disease or non-cardiac chest pain, or both, during the period January 1989–June 1993 (Fig 1). Some patients were studied on several occasions to evaluate the reproducibility of each proposed parameter for assessing the symptom reflux relations.

Endoscopy

Upper digestive endoscopy was performed on an outpatient basis on subjects fasted overnight. A complete examination of the oesophagus, stomach, and duodenum was achieved. Oesophagitis was graded as follows: grade 1 isolated erosions, grade 2 confluent erosions or ulcerations (not circumferential), and grade 3 circumferential lesions. Patients with stricture or Barrett's oesophagus were not included in the study.

Twenty four hour pH monitoring

Twenty four hour oesophageal pH recording was performed using a combined glass pH electrode (440M4, Ingold, Urdorf, Switzerland) and a digital data logger (Digitrapper MKII, Synectics, Stockholm, Sweden). The system was calibrated at pH 1 and pH 7 before each study. The patients fasted for at least 12 hours and had stopped taking any antireflux treatment (that is, antisecretory or prokinetic drugs, or both), which can interfere with the results. The probe was passed through the nose and positioned 5 cm above the upper border of the gastro-oesophageal junction, which was determined either by previous manometry or by the pH step up method.[1] During early studies, pH monitoring was performed in the hospital setting under standardised conditions. More recently (the last 82 cases), studies were performed on an outpatient basis in fully ambulatory conditions – that is, without any dietary restriction except for food and beverages with a pH <5. Periods of eating, drinking, and supine position were specified by patients on a diary card. At the start of the recording, patients were carefully instructed to press the event marker button if they had a symptom. This recommendation was also emphasised on the diary card.

After the 24 hour pH monitoring, the data were downloaded from the digital data logger to an IBM computer and the recorded data were analysed by using a dedicated software (EsopHogram 5.5) written by Gastrosoft (Dallas, USA). Apart from the usual reflux parameters (% time below pH 4 and characteristics of reflux episodes), three indices were calculated to measure the strength of the relation between symptoms and reflux episodes: the probability that symptoms and reflux episodes occurred simultaneously by chance,[14] the symptom specificity index,[10 12] and the symptom sensitivity index.[13] For the evaluation of the temporal relation between symptoms and reflux episodes, pH tracings were reviewed and a symptom and a reflux episode were considered causally related if a symptom occurred during the reflux episode itself or within two minutes after it finished.

The probability (p) that symptoms and reflux episodes occurred simultaneously by chance was obtained by summing a number of partial probabilities, each of which was obtained by using the binomial formula, described later[14]:

$$\frac{n!}{r!\,(n-r)!}\,p^{r}\,(1-p)^{n-r}$$

where n is the total number of symptom episodes signalled by the patient; r ranges from the actual number of symptom episodes that occur during or within two minutes of the end of a fall in pH below 4 to n; p is the probability that one symptom episode occurs during or within two minutes of the end of a fall in pH below 4 only by chance and is calculated from the formula:

$$p=\frac{\text{total time (min) pH below 4}+(2\text{ min}\times\text{number of pH drops below 4})}{\text{Total time (min) of recording}}$$

The symptom specificity index, which determines the percentage of reflux related symptom episodes, was calculated as described by Wiener *et al*[10] whereas the symptom sensitivity index, which calculates the percentage of symptom related reflux episodes was quantified according to Breumelhof and Smout.[13]

Statistical evaluation of data

The pH data are presented as median values with interquartile ranges. Student's *t* test was used to compare the mean duration and minimal pH between the symptom related reflux episodes and the asymptomatic reflux

TABLE I *Clinical characteristics of 96 patients with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring*

Age (mean and range, years)	48·8 (18–73)
Sex (male/female)	45/51
Predominant symptoms (%)	
Digestive symptoms	74·4
NCCP	4·7
Respiratory symptoms	14·0
ENT	6·9
Duration of symptoms (median and range, months)	24·0 (0·5–204)
Endoscopy (n=74)	
Normal mucosa (%)	81·1
Oesophagitis (%)	
Grade 1	14·9
Grade 2	2·7
Grade 3	1·4
Hiatal hernia (%)	37·8

NCCP=non-cardiac chest pain; ENT=ear, nose, and throat.

episodes. Least squares regression analysis was used to calculate the correlation between the probability (-log) that symptoms and reflux episodes occurred simultaneously by chance, the symptom specificity index, and the symptom sensitivity index. A p value $<0·05$ was considered significant.

Results

Frequency and clinical characteristics

Oesophageal exposure to acid was normal (total fraction time of pH below 4<4·2%) in 462 patients (59·9% of the whole patient's population); despite this, 70·8% (327 of 462) of these patients used at least once the event marker (Fig 1). The symptoms reported by patients during 24 hour pH monitoring included heartburn, regurgitation, epigastric pain, epigastric burning, discomfort or non-cardiac chest pain, or all of these. In 96 patients (12·5% of total patients) with normal oesophageal exposure to acid, there was a statistically significant association between symptoms and reflux episodes as previously defined (Fig 1). Five patients had two and one had three pH recordings with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes. Patients with normal oesophageal exposure to acid used more frequently the event marker when they were investigated outside rather than in the hospital setting (87% *v* 67%, p=0·005). Accordingly, the frequency of the acid hypersensitive oesophagus syndrome was slightly but significantly higher when pH monitoring was performed in an outpatient basis (20·7% *v* 10·9%, p<0·01). Table I summarises the clinical characteristics of these patients. Seventy four of these patients also had upper gastrointestinal endoscopy within one month prior to pH monitoring.

The sex ratio (male/female) was not statistically different from that of the whole patient population (45 and 51 *v* 392 and 379, NS) and from that of patients with normal oesophageal exposure to acid (45 and 51 *v* 209 and 253, NS). Age of patients ranged from 18 to 73 years with mean value of 48·8 years, a figure virtually identical to that seen in the whole patient population (48·8 (14·3) *v* 50·4 (14·8) years, NS) and to that seen in patients with normal oesophageal exposure to acid (48·8 (14·3) *v* 50·8 (14·9), NS).

Figure 2 shows the frequency of the different symptoms experienced by these 96 patients. With regard to typical symptoms of reflux, heartburn, regurgitation, and epigastric burning were reported by 76%, 57%, and 50% of patients, respectively. Many patients also complained of belching (68%), or dyspeptic symptoms (for example, bloating, nausea, vomiting, early satiety, loss of appetite), or both (Fig 2). Otherwise, non-cardiac chest pain, ear, nose, and throat symptoms, and respiratory symptoms were seen in 27·8%, 47·8%, and 33·3% patients, respectively. The predominant symptoms (that is, the symptoms leading the patients to seek medical care) were digestive symptoms (74·4%), respiratory symptoms (14·0%), ear, nose, and throat symptoms (6·9%), or non-cardiac chest pain (4·7%). The duration of symptoms ranged from 0·5 month to 17 years (median: 24 months). In those patients in whom endoscopy was performed, it mostly showed a normal oesophageal mucosa and a mild oesophagitis in most of the other patients (Table I).

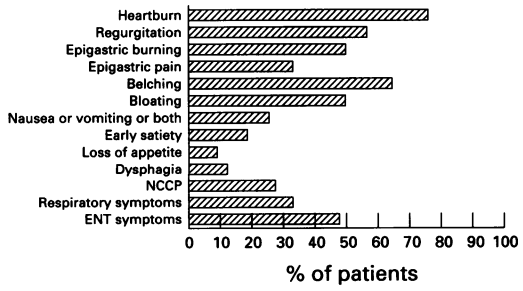

Figure 2: Frequency of the different symptoms seen in 96 patients with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring. (NCCP=non-cardiac chest pain; ENT=ear, nose, and throat).

Frequency of symptom episodes, reflux episodes, and reflux related symptom episodes

In the 96 patients, 1161 symptom episodes and 3306 reflux episodes were registered during the 24 hour pH monitoring. Five hundred and three of 1161 symptom episodes (43·3%) were reflux related as previously defined. Forty three patients (44·8%) had more than four reflux related symptom episodes. Table II shows the results of pH monitoring in the 96 patients.

Probability, symptom specificity index, and symptom sensitivity index

Figure 3 shows the distributions of probability (-log), symptom specificity index, and symptom sensitivity index in patients with acid hypersensitive oesophagus syndrome. The probability was <0·01 in 71 patients and <0·001 in 41 patients (Fig 3A). Nine patients had a symptom specificity index lower than 25%, 48 patients equal or greater than 50%,

TABLE II *Results of 24 hour pH monitoring in 96 patients with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring*

	Median values	*Interquartile range*	*Upper limit of reference values of our laboratory*
% Total	2·0	1·1–3·1	4·2
% Upright	2·6	1·6–4·5	8·0
% Supine	0·3	0·0–1·4	3·0
Total episodes (n)	28	20–41	50
Episodes >5 min (n)	1·0	0–1·0	3
Longest episodes (min)	5·0	3·0–7·5	20

and 23 patients equal or greater than 75% (Fig 3B). The symptom sensitivity index was ≥10% in 70 patients and ≥20% in 38 patients (Fig 3C). When symptom specificity index and symptom sensitivity index were considered together, it was found that 33 (34·4%) patients had a symptom specificity index ≥50% with a symptom sensitivity index ≥10%. No patient had a symptom specificity index <25% and a symptom sensitivity index <10%.

There was a poor albeit significant ($p<0·05$) correlation between probability (-log) and symptom specificity index in both patients with acid hypersensitive oesophagus syndrome and with gastro-oesophageal reflux disease (Fig 4A and Fig 5A). In contrast, a strong and significant ($p<0·0001$) correlation was seen between probability (-log) and symptom sensitivity index (Fig 4B and Fig 5B). As expected, symptom specificity index and symptom sensitivity index were inversely related to each other (Fig 4C), but the correlation in patients with gastro-oesophageal reflux disease (Fig 5C) fell short off statistical significance.

Characteristics of reflux episodes

Table III shows mean duration and minimum pH of symptom related reflux episodes and asymptomatic reflux episodes in patients with acid hypersensitive oesophagus syndrome and those with gastro-oesophageal reflux disease. Symptom related reflux episodes had significantly longer duration ($p<0·001$) than the asymptomatic ones in total time and upright position, but not in supine position ($p>0·05$). Similarly, the minimum pH of symptom related reflux episodes was lower than that of asymptomatic ones in total time and upright position ($p<0·001$), but not in supine position ($p>0·05$). When the characteristics of symptom related (as well as asymptomatic) reflux episodes of patients with acid hypersensitive oesophagus syndrome were compared with those of patients with true gastro-oesophageal reflux disease, both the duration and minimum pH of the first group were significantly shorter and higher than those of the second, respectively.

Reproducibility of pH monitoring in the assessment of symptom reflux relations

During the study period, 13 of 96 patients were studied on at least two occasions by 24 hour pH monitoring. The median interval between the two pH recordings was 12 months (range 1–47 months). Despite this sometimes long interval between assessments, these patients always experienced nearly the same symptoms and used at least once the event marker during each of the 26 pH monitoring. In six of these 13 patients, the diagnosis of acid hypersensitive oesophagus syndrome – that is, patients with normal oesophageal exposure to acid and symptom related reflux episodes – was consistently made. In seven other patients, only one recording showed the pattern of acid hypersensitive oesophagus syndrome (Table IV). Nine patients had normal oesophageal exposure to acid during the two pH recordings. Ten patients had a significant relation between symptoms and reflux episodes on both recordings but four of them had a discrepancy for oesophageal acid exposure between the two pH recordings (Table IV). Oesophageal exposure to acid never exceeded 6·7% of the total time, however, and, albeit abnormal, it always remained very close to the upper limit of normality (4·2%).

Discussion

Although traditional pH metric variables (total reflux time, the total number of refluxes, and the number of refluxes longer than five

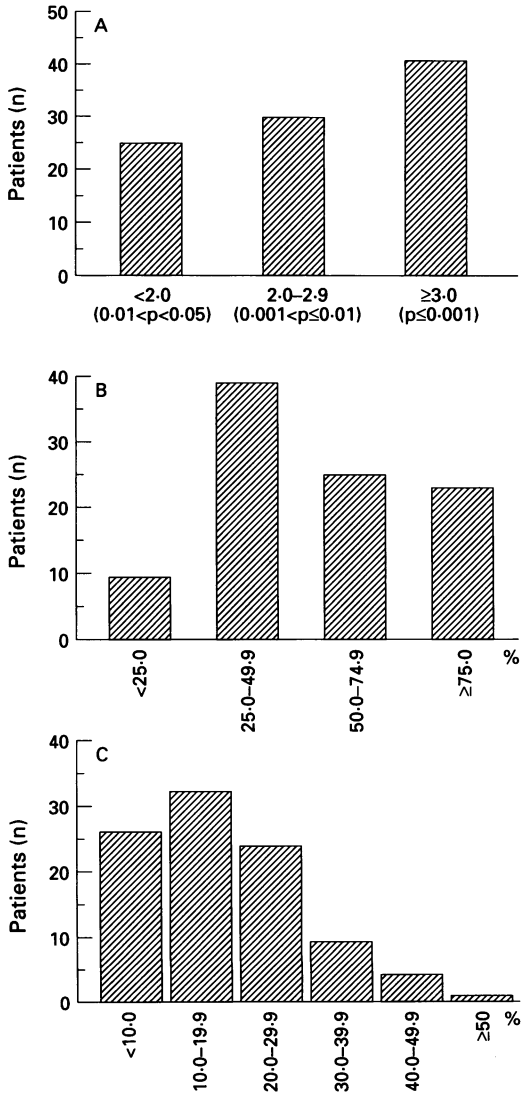

Figure 3: Distribution of probability (-log) (A), symptom specificity index (B), and symptom sensitivity index (C) in 96 patients with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring.

minutes) still remain useful parameters to discriminate between patients with gastro-oesophageal reflux disease and asymptomatic healthy subjects, they do not help in establishing any responsibility for acid reflux in the patient's complaints. The use of the event marker(s) or diary card, or both, is mandatory to show a temporal relation between symptoms and reflux episodes. However, not only could symptoms be unrelated to reflux episodes in the presence of abnormal oesophageal exposure to acid, but also, conversely, a symptomatology that apparently reflux related can be seen in patients whose oesophageal exposure to acid is normal. Although several studies have been able to identify patients with normal oesophageal exposure to acid and acid related symptoms,[2-10] the exact frequency of this acid hypersensitive oesophagus syndrome and its symptom pattern have not been established, as yet.

While analysing symptom reflux relations, two important limitations should be taken into account. Firstly, according to our own experience[2] only half of the patients used the event marker and in only 50% of the cases are symptoms perceived by the patients reflux related. Performing 24 hour pH monitoring outside the hospital setting could improve the diagnostic yield of the technique as shown in this study. Secondly, there is no uniform agreement on how to measure the strength of association between symptoms and reflux episodes. Indeed, although some indices are currently used, different cut off values are used by different groups of investigators. As symptoms may occur simultaneously with reflux episodes only by chance, a more scientifically sound approach could be the one recently described by Ghillebert *et al*,[14] which is based on probability calculation. In our investigation we have therefore adopted this approach to

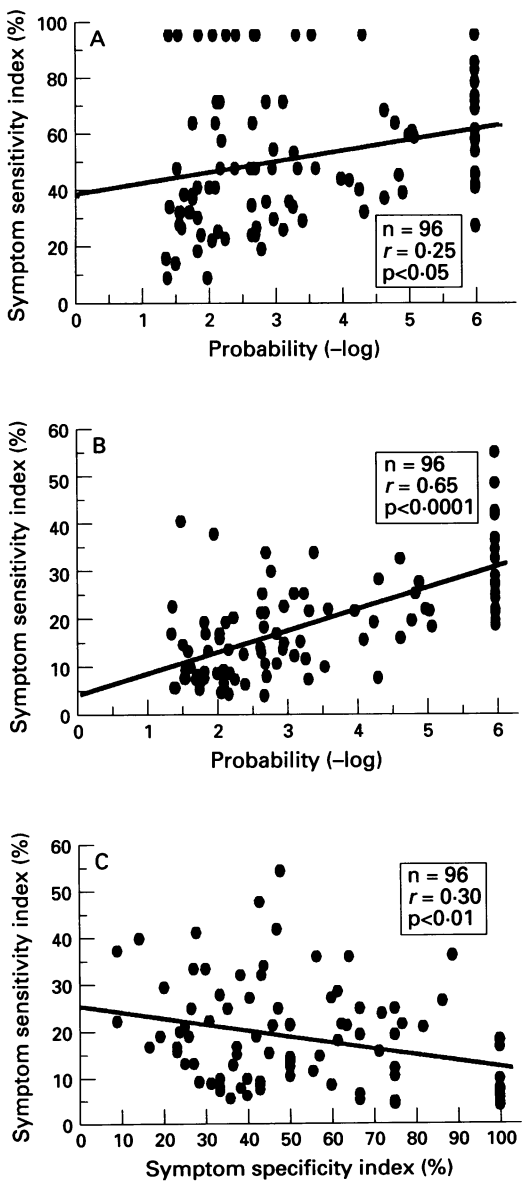

Figure 4: Correlations between probability (-log) and symptom specificity index (A), probability (-log) and symptom sensitivity index (B), and symptom specificity index and symptom sensitivity index (C) in 96 patients with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring.

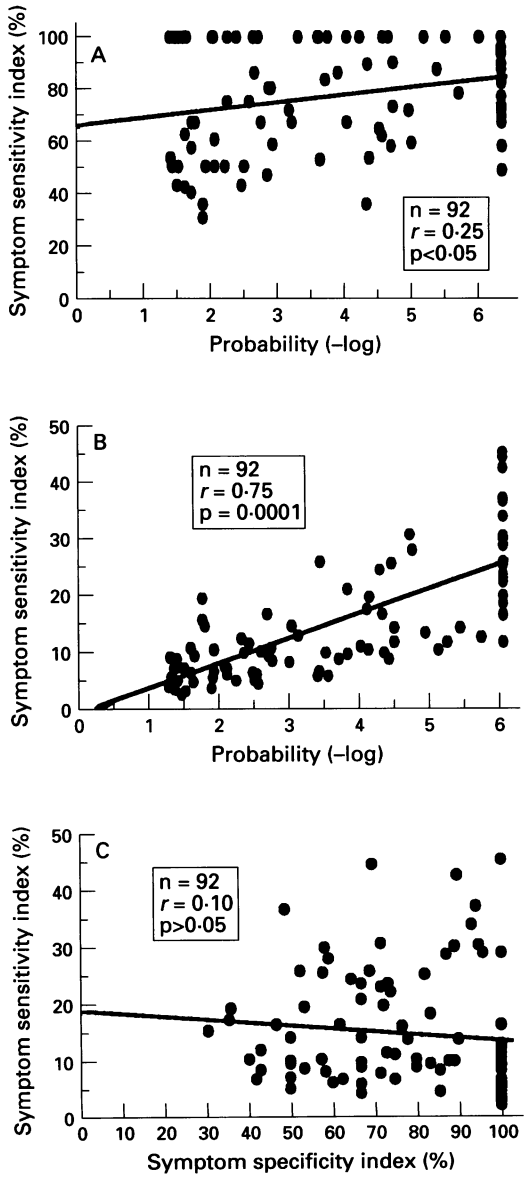

Figure 5: Correlations between probability (-log) and symptom specificity index (A), probability (-log) and symptom sensitivity index (B), and symptom specificity index and symptom sensitivity index (C) in 92 patients with abnormal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring (that is, with gastro-oesophageal reflux disease).

TABLE III *Duration and minimum pH (mean (SEM)) of symptom related reflux episodes and asymptomatic reflux episodes in patients with normal (n=96) or abnormal (n=92) oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes during 24 hour pH monitoring (that is, acid hypersensitive oesophagus (AHO) and gastro-oesophageal reflux disease (GORD), respectively)*

	Symptom related reflux episodes			*Asymptomatic reflux episodes*		
	Patients with AHO (n=504)	*Patients with GORD (n=783)*	*p Value**	*Patients with AHO (n=2502)*	*Patients with GORD (n=4721)*	*p Value**
Duration (min)						
Total	1·28 (0·08)	3·44 (0·23)	<0·0001	0·88 (0·03)	1·76 (0·07)	<0·0001
Upright	1·24 (0·08)	3·26 (0·22)	<0·0001	0·79 (0·03)	1·27 (0·04)	<0·0001
Supine	1·76 (0·38)	5·80 (1·13)	<0·05	1·43 (0·15)	4·56 (0·38)	<0·0001
Minimum pH						
Total	2·76 (0·03)	2·32 (0·03)	<0·0001	2·89 (0·02)	2·77 (0·01)	<0·0001
Upright	2·77 (0·04)	2·33 (0·03)	<0·0001	2·93 (0·02)	2·81 (0·01)	<0·0001
Supine	2·65 (0·14)	2·12 (0·10)	<0·01	2·64 (0·04)	2·51 (0·03)	<0·05

NS=not significant; *Student's *t* test.

identify – among a large series of unselected patients – those with normal oesophageal exposure to acid and a statistically significant association between symptoms and reflux episodes. We also used symptom time window, which was recently demonstrated to be optimal for symptom analysis in 24 hour oesophageal pH and pressure monitoring.[15] Ninety six of 771 patients studied were found to have reflux related symptoms despite a normal oesophageal exposure to acid. They represent the 12·5% of the general patient population and the 20·8% (96 of 462) of those whose oesophageal exposure to acid fell within the normal range.

Frequency of the acid hypersensitive oesophagus syndrome should, however, be considered in the light of methodology to assess symptom reflux relations and of the reproducibility of the technique. An additional aim of our study was therefore to compare results obtained with the probability calculation, considered as the gold standard, with those derived from previously described reflux indices. By using a cut off value of 50%,[9 12 16] only half patients would have been classified as having an acid hypersensitive oesophagus syndrome on the basis of symptom specificity index while, by using the symptom sensitivity index and a cut off value of 10%,[13] 70 of 96 patients would have been included in this group. As a consequence, symptom sensitivity index correlated with the probability value (-log p) in a better way than symptom specificity index.

Although several studies (for review see reference 1) have shown 24 hour pH monitoring to be a reproducible technique to discriminate between patients with normal and abnormal reflux, no one has investigated its reproducibility in patients with normal oesophageal exposure to acid and reflux related symptoms. In this study, we assessed for the first time the reproducibility of pH monitoring in the evaluation of symptom reflux relations and found a concordance (reflux related/reflux unrelated) of 77% between two consecutive recordings. The concordance (normal/abnormal) for oesophageal exposure to acid in the same patient group was not significantly different (69%). Therefore the 'true' frequency of the acid hypersensitive oesophagus syndrome is probably lower than the previously reported estimate. Indeed, some patients (about one third) may be classified as gastro-oesophageal reflux disease because of the failure of the first pH recording to detect a borderline, albeit, abnormal oesophageal exposure to acid. Moreover reproducibility of pH monitoring in the diagnosis of gastro-oesophageal reflux disease was shown to be low in patients with borderline values of oesophageal exposure to acid.[17] Despite the fairly long interval between the two pH monitorings, the diagnosis of acid hypersensitive oesophagus syndrome can be consistently made in about half of the patients, because of the reproducibility of both oesophageal exposure to acid and symptom reflux assessment.

TABLE IV *Results of 24 hour pH monitoring in 13 patients having two separate recordings, at least one of them with normal oesophageal exposure to acid and statistically significant association between symptoms and reflux episodes*

Interval (months)	*pH recording*		*OEA (%)*		*p<0·05*		*SSpI*		*SSeI*	
	First	*Second*	*First*	*Second*	*First*	*Second*	*First*	*Second*	*First*	*Second*
47	In	In	2·0	3·2	Yes	Yes	45·0	41·7	15·5	18·5
13	In	Out	1·2	1·7	Yes	Yes	30·8	50·0	22·2	46·2
1	In	In	3·7	6·2	Yes	Yes	71·9	78·3	24·0	27·3
15	Out	In	1·6	0·9	Yes	No	57·0	0·0	19·4	0·0
12	In	In	1·9	1·2	Yes	No	35·7	0·0	5·5	0·0
9	In	In	4·1	4·0	Yes	Yes	41·2	40·6	20·7	27·1
12	In	In	1·4	2·8	Yes	No	14·3	8·3	40·0	7·7
10	In	In	2·3	5·8	Yes	Yes	75·0	100·0	12·0	4·8
3	In	Out	1·5	6·7	Yes	Yes	100·0	100·0	5·6	10·9
24	In	In	2·5	4·7	Yes	Yes	40·0	50·0	10·0	6·1
42	In	In	2·4	1·2	Yes	Yes	46·2	55·0	21·4	30·6
5	Out	Out	2·7	4·1	Yes	Yes	66·7	73·3	5·4	28·2
7	In	Out	0·6	1·6	Yes	Yes	60·0	30·8	27·3	9·1
Coefficient of variation (%)			42·1		76·9		35·9		61·6	
Concordance (%)			69·2				61·5		38·5	

In=inpatient; Out=outpatient; OEA=oesophageal exposure to acid; p=the probability that the association between symptoms and reflux episodes occur by chance; SSpI=symptom specificity index; SSeI=symptom sensitivity index; first=first 24 hour pH monitoring; second=second 24 hour pH monitoring.

The symptom cluster of patients with acid hypersensitive oesophagus syndrome is similar to that usually seen in patients with gastro-oesophageal reflux disease, but symptoms like belching, bloating, and nausea are common thus overlapping with the symptom pattern of functional dyspepsia. As most patients with reflux related symptoms but with normal oesophageal exposure to acid had a normal oesophageal mucosa at endoscopy (and the remaining only a mild oesophagitis), they should represent the patients with true reflux like dyspepsia. What indeed has been classified as reflux like dyspepsia[18] is actually gastro-oesophageal reflux disease, which encompasses reflux oesophagitis, that is gastro-oesophageal reflux with unequivocal changes within the oesophagus and non-erosive gastro-oesophageal reflux disease – that is, symptomatic reflux proved by objective means, without changes being demonstrated.

The exact mechanisms by which reflux causes oesophageal symptoms are still poorly understood and it is unknown whether symptoms arise directly through activation of chemoreceptors[19] or, indirectly, as a result of motility disturbances or mechanical distension of the oesophagus secondary to reflux. It is now well established, however, that, in patients with gastro-oesophageal reflux disease, about 80% of reflux episodes are symptom free, regardless of the severity of oesophageal lesions.[20] Why some reflux episodes are perceived by the patient and some others are not is also unknown. In agreement with Baldi *et al*[20] and Smith *et al*[21] who studied small series of patients with reflux oesophagitis, we found that symptom related reflux episodes lasted longer than those not perceived by the patient. In addition, both the duration and the minimum pH of reflux episodes (either symptom related or asymptomatic) were significantly shorter and higher, respectively, in patients with acid hypersensitive oesophagus syndrome when compared with those of patients with 'classic' gastro-oesophageal reflux disease. These data clearly suggest the presence of 'hypersensitivity' to acid in the first group of patients.

Results of our investigation are consistent with the idea that acid contact time is one important contributing factor to oesophageal sensitivity. The pH of refluxate also seems to be a critical factor in the perception process. Indeed, we were able to show that when reflux episodes were perceived, pH dropped to a value that was significantly ($p<0.001$) lower than that seen with asymptomatic reflux episodes. And this is true for both acid hypersensitive oesophagus and gastro-oesophageal reflux disease patients. Why the comparatively short lasting (1·28 (0·08) min) and less acidic reflux episodes occurring in the subset of patients with normal oesophageal exposure to acid are perceived still remains unclear. Factors other than acidity can result in an increased pain perception, including volume of the refluxate and non-acidic components. Whether an increased sensitivity to mechanical stimuli is an additional pathophysiological feature of these patients, as described by Janssens and Vantrappen[22] in non-cardiac chest pain patients with the so called 'irritable oesophagus syndrome,' is presently unknown.

If the assumption is accepted that, despite lack of mucosal injury, patients with acid hypersensitive oesophagus syndrome have an increased oesophageal perception as underlying cause, therapeutic effort should be directed to reduce such increased sensitivity. Unfortunately, not all available drugs (namely 5-HT_3 antagonists and opioids), capable of reducing visceral perception in the lower gastrointestinal tract, seem to be effective in the upper gastrointestinal tract.[23] Therefore, reduction of the stimulus intensity remains at present the only alternative in clinical practice. Provided that the acid is the major stimulus, antisecretory compounds should be the drugs of choice. The reported finding of a reduction of oesophageal sensitivity by famotidine in gastro-oesophageal reflux disease patients[24] suggests that H_2 blockers, besides reducing acid secretion, might interfere with the neural pathways controlling visceral perception and give a further rationale for the use of this class of drugs in such a subset of patients.

We are grateful to M F Courjal and B Beignet for their expert technical assistance. This work was partially supported by a grant from the Centre Hospitalier Universitaire of Nantes.

Preliminary data of the present investigation have been presented at the American Gastroenterological Association (San Francisco) and appeared in abstract form (*Gastroenterology* 1992; **102:** A45).

1 Galmiche JP. Scarpignato C. Esophageal pH monitoring. In: Scarpignato C, Galmiche JP. *Functional investigation in esophageal disease. Front Gastrointest Res.* Basel: Karger, 1994; **22:** 71–108.
2 Barré P, Bruley des Varannes S, Masliah C, Cloarec D, Le Bodic L, Galmiche JP. Le marqueur d'événements: un progrès dans l'interprétation de la pH-métrie oesophagienne. *Gastroenterol Clin Biol* 1989; **13:** 32–7.
3 Bruley des Varannes S, Le Rhun M, Simon J, Galmiche JP. The acid hypersensitive esophagus: a frequent cause of symptoms in patients with normal esophageal acid exposure (EAO)? *Gastroenterology* 1992; **102:** A45.
4 Eriksen CA, Cullen PT, Sutton D, Kennedy N, Cuschieri A. Abnormal esophageal transit in patients with typical reflux symptoms but normal endoscopic and pH profiles. *Am J Surg* 1991; **161:** 657–61.
5 Hewson EG, Sinclair JW, Dalton CB, Wu WC, Castell DO, Richter JE. Acid perfusion test: does it have a role in the assessment of noncardiac chest pain? *Gut* 1989; **30:** 305–10.
6 Hewson EG, Dalton CB, Richter JE. Comparison of esophageal manometry, provocative testing and ambulatory monitoring in patients with unexplained chest pain. *Dig Dis Sci* 1990; **35:** 302–9.
7 Howard PJ, Pryde A, Heading RC. Relationship between gastroesophageal reflux and symptoms in patients referred for ambulatory pH monitoring. *Journal of Gastrointestinal Motility* 1990; **2:** 231–9.
8 Johnston BT, McFarland RJ, Collins JSA, Love AHG. Symptom index as a marker of gastro-oesophageal reflux disease. *Br J Surg* 1992; **79:** 1054–5.
9 Singh S, Richter JE, Bradley LA, Haile JM. The symptom index. Differential usefulness in suspected acid-related complaints of heartburn and chest pain. *Dig Dis Sci* 1993; **38:** 1402–8.
10 Wiener GJ, Richter JE, Copper JB, Wu WC, Castell DO. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol* 1988; **83:** 358–61.
11 Ward BW, Wu WC, Richter JE, Lui KW, Castell DO. Ambulatory 24-hour oesophageal pH monitoring: technology searching for a clinical application. *J Clin Gastroenterol* 1986; **8** (suppl 1): 59–67.
12 Richter JE, Hewson EG, Sinclair JW, Dalton CB. Acid perfusion test and 24-hour esophageal pH monitoring with symptom index. Comparison of tests for esophageal acid sensitivity. *Dig Dis Sci* 1991; **36:** 565–71.
13 Breumelhof R, Smout AJPM. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. *Am J Gastroenterol* 1991; **86:** 160–4.
14 Ghillebert G, Janssens J, Vantrappen G, Nevens F, Piessens J. Ambulatory 24 hour intraoesophageal pH and pressure recordings v provocation tests in the diagnosis of chest pain of oesophageal origin. *Gut* 1990; **31:** 738–44.

15 Lam HGT, Breumelhof R, Roelofs JMM, Van Berge Henegouwen GP, Smout AJPM. What is the optimal time window in symptom analysis of 24-hour esophageal pressure and pH data? *Dig Dis Sci* 1994; **39:** 402–9.
16 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.
17 Wiener GJ, Morgan TM, Copper JB, Wu WC, Castell DO, Sinclair JW, *et al.* Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. *Dig Dis Sci* 1988; **33:** 1127–33.
18 Colin-Jones DG, Bloom B, Bodemar G, Crean GP, Freston J, Gulger R, *et al.* Management of dyspepsia: report of a working party. *Lancet* 1988; i: 576–9.
19 Bruley des Varannes S, Galmiche JP. Evaluation of esophageal sensitivity. In: Scarpignato C, Galmiche JP, eds. *Functional investigation in esophageal disease. Front Gastrointest Res.* Basel: Karger, 1994; **22:** 344–65.
20 Baldi F, Ferrarini F, Longanesi A, Ragazzini M, Barbara L. Acid gastroesophageal reflux and symptom occurrence: analysis of some factors influencing their association. *Dig Dis Sci* 1989; **34:** 1890–3.
21 Smith JL, Opekun AR, Larkai E, Graham DY. Sensitivity of the esophageal mucosa to pH in gastroesophageal reflux disease. *Gastroenterology* 1989; **96:** 683–9.
22 Janssens JPF, Vantrappen G. Irritable esophagus. *Am J Med* 1992; **92** (suppl 5A): 27–32S.
23 Zerbib F, Bruley des Varannes S, Oriola RC, McDonald J, Isal JP, Galmiche JP. Alosetron does not affect the visceral perception of gastric distension in healthy subjects. *Aliment Pharmacol Ther* 1994; **8:** 403–7.
24 Marrero JM, de Caestecker JS, Maxwell JD. Effect of famotidine on oesophageal sensitivity in gastro-oesophageal reflux disease. *Gut* 1994; **35:** 447–50.