

ALIMENTARY TRACT

Symptomatic gastro-oesophageal reflux, abnormal oesophageal acid exposure, and mucosal acid sensitivity are three separate, though related, aspects of gastro-oesophageal reflux disease

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Abstract

The Bernstein test has been used as a test of oesophageal acid sensitivity for over 30 years but its clinical value has been challenged by the advent of ambulatory pH monitoring. Furthermore, the relation between mucosal acid sensitivity, symptomatic reflux, and abnormal oesophageal acid exposure time is unclear. This study examined the relation between these three parameters in patients referred for pH monitoring with unexplained chest pain or heartburn. Fifty consecutive patients were studied – nine with non-cardiac chest pain and 41 with a history of heartburn. Symptomatic reflux was defined as a $\geq 50\%$ temporal association between pain episodes and reflux events (pH < 4) during pH monitoring. A positive acid perfusion test (in which the patient's usual symptoms were evoked by acid, though not saline) had a 100% sensitivity, 73% specificity, and 81% accuracy for the detection of symptomatic reflux. All 10 patients with symptomatic reflux during pH monitoring had evidence of mucosal acid sensitivity. A negative acid perfusion test made symptomatic reflux unlikely. However, symptomatic reflux or a positive acid perfusion test, or both, were found in some patients with a normal oesophageal acid exposure time during pH monitoring. Mucosal acid sensitivity, abnormal oesophageal acid exposure time, and symptomatic reflux should be regarded as separate, though related aspects of reflux disease. The Bernstein test is simple, safe, and easily performed. A positive test helps to identify an oesophageal cause of symptoms, particularly in patients in whom other aspects of 'gastro-oesophageal reflux disease' are absent, or who do not have symptoms during pH monitoring.

It is now recognised that so-called gastro-oesophageal reflux disease arises when gastric refluxate causes symptoms or oesophageal mucosal damage, or both. Current diagnostic tests evaluate four aspects of reflux disease – the amount of gastro-oesophageal reflux, reflux symptoms, mucosal acid sensitivity, and the presence of mucosal damage. There are now many publications reporting the sensitivities and specificities of the various tests for the diagnosis of reflux disease.¹⁻¹⁴ Nevertheless, many investigators have recognised that varying definitions of reflux disease and the lack of any absolute standard against which the diagnostic tests may be compared render these sensitivity and specificity calculations of doubtful value. In fact, no test available at present can be expected to serve as a gold standard for oesophageal reflux disease, because the disease itself is not a single entity. There has been longstanding recognition that not all patients with oesophagitis have reflux symptoms and not all patients with reflux symptoms have oesophagitis. Consequently, there should be no surprise or disappointment when carefully performed tests of different facets of reflux disease fail to produce agreement. For example, a negative acid perfusion test in a patient with oesophagitis should not be viewed as a false negative result¹² – it is no more than a demonstration that acid sensitivity is absent in that patient. Symptomatic gastro-oesophageal reflux, mucosal acid sensitivity, and abnormal oesophageal exposure to acid are all distinct aspects of gastro-oesophageal reflux disease. The aim of this study was to examine the relations between them in patients referred for investigation of non-cardiac chest pain or heartburn.

Methods

Fifty consecutive patients referred with either non-cardiac chest pain (four men and five women; mean (SD) age 43.2 (12.9) years) or suspected gastro-oesophageal reflux (26 men and 15 women; mean (SD) age 43.2 (11.3) years) were studied. They had all undergone endoscopy before referral. Of the 41 patients referred because of suspected reflux symptoms, two had a Barrett's oesophagus and six had oesophagitis. All nine patients with non-cardiac chest pain had a normal endoscopy appearance. Myocardial

The Bernstein test has been in clinical use for over 30 years as a means of reproducing oesophageal pain.¹ It was originally designed as a test of oesophageal acid sensitivity. It has also been used more recently as a provocative test during oesophageal manometry in patients with non-cardiac chest pain.²⁻⁴ Nevertheless, the role of acid perfusion in the elucidation of oesophageal pain has been challenged by the advent of ambulatory pH monitoring.⁵

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ischaemia was excluded by exercise cardiography and coronary arteriography, as appropriate.

ACID PERFUSION TEST

The acid perfusion test was performed after routine oesophageal manometry. Physiological saline was infused into the oesophagus 7 cm from the lower oesophageal sphincter via an Arndorfer catheter at a rate of 6 ml/minute for seven minutes. If no symptoms were produced, the infusion rate was increased to 14 ml/minute for a further eight minutes by infusing saline at 8 ml/minute through a second port within the proximal oesophagus at approximately 22 cm from the lower sphincter. Next, the infusion was changed without the patient's knowledge to 0.1 N HCl at 6 ml/minute for seven minutes, and at 14 ml/minute for a further eight minutes if no symptoms were evoked. The test was regarded as positive if infusion of acid, but not saline, reproduced the patient's usual chest pain, discomfort, or heartburn. Electrocardiography was performed if symptoms were produced either with saline or acid, or at the completion of the acid infusion, if symptoms were not elicited.

TWENTY THREE HOUR PH MONITORING

Twenty three hour pH monitoring was performed using a combined glass pH electrode with an internal reference electrode (Radiometer, Copenhagen) which was calibrated against two buffers at pH 4 and 7 before each study. The pH probe was passed through the nose and positioned 3 cm above the upper border of the manometrically defined lower oesophageal sphincter. Output from the electrode was recorded onto a battery driven (microchip) recorder.

Ambulatory pH monitoring was performed on an outpatient basis after stopping all medication for at least 48 hours. No restrictions were placed on patients' activities, eating, drinking, or smoking habits. Each patient was provided with a digital watch and a diary card on which to record the time of eating, drinking, and changes of posture and the time of onset of their symptoms. Symptoms were defined as reflux related if their onset was reported during, or up to five minutes after, a reflux episode. (A reflux episode was defined as the time during which pH fell below 4 until it rose again above pH 4).

The pH recordings were analysed by an Apple II computer which measured the distal oesophageal acid exposure times, expressed as a percentage of recording time. A total acid exposure time of >7% recording time is taken as abnormal in our laboratory. Our normal range is based upon pH monitoring in 34 healthy control subjects, performed under identical conditions to those of the present study.¹⁵

DATA ANALYSIS

Ambulatory pH recordings

A symptom-reflux association was defined as the percentage of pain (or heartburn) episodes that occurred during, or up to five minutes after, a

reflux event. 'Symptomatic gastro-oesophageal reflux' was taken as a 50%, or greater, association between pain episodes and reflux events.

Comparisons between acid perfusion test, symptomatic reflux, and abnormal acid exposure time

Ambulatory pH monitoring was used to measure distal oesophageal acid exposure time and to identify patients with symptomatic reflux. The acid perfusion test defined patients with oesophageal acid sensitivity. The sensitivity, specificity, positive and negative predictive values, and accuracy of each of these parameters were calculated, taking each of the other two as arbitrary gold standards. For example, the sensitivity and specificity of oesophageal acid sensitivity (positive acid perfusion test) as a test for symptomatic reflux and abnormal acid exposure time were calculated. Since sensitivity and specificity are related to disease prevalence, however, the positive and negative likelihood ratios were also calculated. The positive and negative likelihood ratios are estimates of the discriminatory power of a test and are independent of disease prevalence.^{16,17} Hence, the higher the positive likelihood ratio the greater the odds in favour of disease if the test is positive. Conversely, the greater the negative likelihood ratio the greater are the odds against disease if the test is negative. In order to clarify the interrelations between acid sensitivity, symptomatic reflux, and abnormal acid exposure time, Venn diagrams were used to express the data for two threshold values of symptom-reflux association – 50% (used to define symptomatic reflux in this paper) and 25% as suggested by Hewson *et al.*⁵

Results

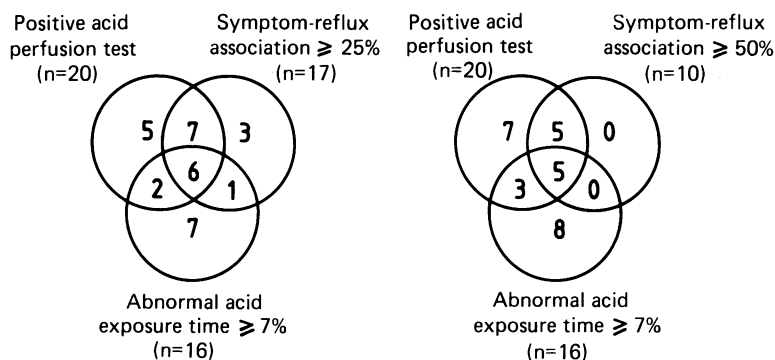
REPORTING OF SYMPTOMS

Two of the 50 patients reported their symptoms as being constantly present during pH monitoring and one patient failed to record the timing of symptoms. Therefore, symptomatic reflux could only be assessed in 47 patients (nine with non-cardiac chest pain and 38 with suspected reflux).

The patients' usual pain or heartburn was reported by six of the nine patients with non-cardiac chest pain and 26 of 38 patients who presented with possible reflux symptoms during ambulatory pH monitoring. The median number of reported pain episodes in both the patients with non-cardiac chest pain and suspected reflux was 2 with ranges of 0 to 20 and 0 to

TABLE I Overall results of acid perfusion test (APT) and pH monitoring in 50 consecutive patients

Test results	pH Monitoring			Reporting uninterpretable
	SRA >50%	SRA <50%	No pain reported	
APT +ve:				
Normal reflux	5	5	2	1
Abnormal reflux	5	1	2	0
APT -ve:				
Normal reflux	0	13	6	1
Abnormal reflux	0	3	5	1



Relation between a positive acid perfusion test (APT), abnormal acid exposure time (AET), and symptomatic reflux (defined as a symptom-reflux association of >25% and <50%.

Not all the patients experienced pain during pH monitoring. Considering the left hand Venn diagram, 2 of 5 patients with +ve APT alone, 5 of 7 with abnormal reflux alone, and both those with abnormal AET and +ve APT did not experience pain.

In the right hand Venn diagram, the corresponding numbers of patients without pain during the pH study were 2 of 7, 5 of 8, and 2 of 3.

11, respectively. None of the patients with non-cardiac chest pain complained of heartburn during pH monitoring or acid perfusion. Therefore data relating to symptomatic reflux and positive acid perfusion test results refer to the patients' usual symptoms in all cases. Two of the nine patients with non-cardiac chest pain experienced their usual pain during the acid perfusion test and both had symptomatic reflux on pH monitoring. Of the 38 patients with suspected reflux symptoms, 19 had their symptoms reproduced by acid perfusion (positive acid perfusion test) and eight of these had symptomatic reflux. There were no electrocardiographic changes during acid perfusion.

INTER-RELATIONS BETWEEN ACID SENSITIVITY, SYMPTOMATIC REFLUX, AND ABNORMAL OESOPHAGEAL ACID EXPOSURE TIME

The overall results in the 50 patients are shown in Table I. The inter-relations between symptom-reflux association, acid exposure time, and a positive acid perfusion test are shown in the Figure (n=47). Table II shows the sensitivities,

TABLE II Relations between abnormal acid exposure time (>7.0% recording time), oesophageal acid sensitivity (+ve acid perfusion test), and symptomatic reflux (symptom-reflux association >50%). The sensitivities, specificities, positive and negative predictive values, and likelihood ratios have been calculated for each of the three parameters using the other two as arbitrary gold standards

	Abnormal acid exposure time	Oesophageal acid sensitivity	Symptomatic reflux
Oesophageal acid sensitivity:			
SENS (%)	40	-	100
SPEC (%)	70	-	73
PPV (%)	50	-	62
NPV (%)	61	-	100
PLR	1.35	-	3.67
NLR	0.85	-	0.00
ACC (%)	57	-	81
Symptomatic reflux:			
SENS (%)	55	62	-
SPEC (%)	78	100	-
PPV (%)	50	100	-
NPV (%)	82	73	-
PLR	2.50	-	-
NLR	0.57	0.38	-
ACC (%)	72	82	-
Abnormal acid exposure time:			
SENS (%)	-	40	50
SPEC (%)	-	70	82
PPV (%)	-	50	55
NPV (%)	-	61	78
PLR	-	1.35	2.75
NLR	-	0.85	0.61
ACC (%)	-	57	72

SENS=Sensitivity; SPEC=specificity; PPV=positive predictive value; NPV=negative predictive value; PLR=positive likelihood ratio; NLR=negative likelihood value; ACC=accuracy.

specificities, positive predictive value, negative predictive value, and likelihood ratios calculated for each of the three parameters using the other two as gold standards, based upon the data in Table I.

The inter-relations between the three parameters are perhaps best understood by reference to the Figure. Using our definition of symptomatic reflux (symptom-reflux association >50%), it can be seen that all 10 patients with symptomatic reflux had an acid sensitive oesophagus and five of these had an abnormal acid exposure time. Ten of 20 patients with a positive acid perfusion test, however, did not have symptomatic reflux on pH monitoring. However, of these 10 positive patients, four did not experience symptoms during pH monitoring. Hence, while symptomatic reflux occurred only in those with acid sensitivity, acid sensitivity was not specific for symptomatic reflux. Eight of 16 patients with abnormal acid exposures had neither acid sensitivity nor symptomatic reflux. (However, five of these eight patients had no pain during ambulatory pH monitoring.) Therefore, all the patients with symptomatic reflux had acid sensitivity and 50% had abnormal acid exposure. Conversely, 50% of those with a positive acid perfusion test had symptomatic reflux (62% considering only those with pain during pH monitoring). Half of the patients with abnormal acid exposure had neither acid sensitivity nor symptomatic reflux. (The corresponding figure was 33% of patients who experienced pain during pH monitoring.) When the data were analysed using a lower threshold to define symptomatic reflux, as suggested by Hewson *et al.*,³ the same overall pattern emerged. The number of patients with symptomatic reflux increased from 10 to 17, as expected. Thirteen of 20 patients with acid sensitivity had symptomatic reflux on pH monitoring (13 of 16 considering only those with pain during pH monitoring). With a symptom-reflux association of >25%, 44% of patients with an abnormal acid exposure time had neither reflux related symptoms nor acid sensitivity (33% after excluding those without pain during pH monitoring).

Table II expresses the relations between symptom-reflux association, acid exposure time, and acid perfusion test numerically. Oesophageal acid sensitivity (positive acid perfusion test) is predictive of symptomatic reflux (sensitivity 100%, specificity 73%, and accuracy of 81%). It is also a good discriminatory test for symptomatic reflux (positive likelihood ratio 3.67). Abnormal acid exposure did not, however, identify patients with either oesophageal acid sensitivity or symptomatic reflux.

Discussion

Gastro-oesophageal reflux disease encompasses a spectrum of disorders in which gastric refluxate causes symptoms or damage to the oesophageal mucosa, or both. Although the term gastro-oesophageal reflux disease has been variously used to describe reflux oesophagitis, reflux-related symptoms, abnormal oesophageal acid exposure, and mucosal acid sensitivity, it is becoming clear that these four aspects of reflux

disease should be regarded as separate, though related entities.

The classic symptoms of gastro-oesophageal reflux are heartburn and acid regurgitation.¹⁸ Patients with reflux disease do not invariably present with typical symptoms, however, and a confident clinical diagnosis is not always possible on the basis of the history alone. Palmer¹⁹ found that only 4.1% of 413 patients with oesophagitis complained of classic reflux symptoms while an additional 14.3% had subxiphoid pain, 18.1% had dysphagia, and 9.4% had dyspepsia. Hence, less than half the patients with oesophagitis had symptoms possibly attributable to reflux. We have previously shown that only 60% of patients with oesophagitis had heartburn, regurgitation, or retrosternal chest pain as major presenting complaints.²⁰ Similar difficulties in diagnosing reflux disease on the basis of the history were encountered by Wienbeck and Berges.¹⁸ In the present study, 84% of patients had an endoscopically normal oesophagus at the time of referral for ambulatory pH studies. Conversely, the proportion of patients thought to have reflux symptoms who have endoscopic evidence of oesophagitis varies from 40% to 80% in published series.²¹⁻²⁴

The relation between reflux symptoms and abnormal acid exposure also raises further difficulties. We²⁵ and others⁵ have recently shown that reflux symptoms can occur in some patients with normal oesophageal acid exposure times.

We therefore examined the relation between mucosal acid sensitivity, as determined by the acid perfusion test, and both distal oesophageal acid exposure time and symptomatic reflux during ambulatory pH monitoring in patients referred for ambulatory pH studies. Of course, this group is probably not representative of reflux patients as a whole. Nevertheless, patients requiring pH monitoring for the diagnosis of their symptoms constitute a clinically important group. We defined 'symptomatic reflux' as a 50%, or greater, association between the patient's usual symptoms of chest pain or heartburn and reflux events. Since there is some disagreement as to threshold value for this temporal association we also used a threshold symptom - reflux association of 25% as recommended by Hewson *et al.* The present study confirms that abnormal acid exposure has a low predictive value for both oesophageal acid sensitivity and symptomatic reflux during pH monitoring, as we defined it. All the patients with symptomatic reflux, however, had evidence of mucosal acid sensitivity during acid perfusion when we used a symptom-reflux association of 50%. (However, four of 17 patients with a symptom-reflux association of >25% did not have acid sensitivity.) Therefore, in this group of patients, symptomatic reflux can be explained on the basis of mucosal sensitivity to acid using a threshold symptom-reflux association of 50%, though not of 25%. Conversely, a negative acid perfusion test makes symptomatic reflux (symptom-reflux association >50%) unlikely as no patient with a negative test had symptomatic reflux during pH monitoring. There were, however, patients with acid sensitivity who did not have symptomatic reflux on subsequent pH

monitoring, even though acid infusion reproduced their usual symptoms. This confirms our previous studies³ and those of Janssens *et al.*²⁶ A possible explanation is that these patients have an 'irritable' oesophagus^{27,28} which can respond to different stimuli by producing the same pattern of symptoms. Experimental support for the concept of the irritable oesophagus comes from the work of Peters *et al.*²⁹ who showed that during combined ambulatory pH and pressure recordings some patients experienced identical symptoms during episodes of either dysmotility, gastro-oesophageal reflux, or both. Heartburn may also occur during belching even when it is not associated with reflux - presumably as a result of acute gaseous distension of the oesophagus.³⁰

In conclusion, the acid perfusion test is safe, simple to perform, and does not require expensive equipment. After 30 years of clinical use, it remains a useful test for elucidating oesophageal chest pain, particularly in patients who do not experience symptoms during prolonged pH monitoring or who have atypical presentations, lack endoscopic evidence of oesophagitis, or have normal acid exposure times. Oesophagitis, abnormal acid exposure, mucosal acid sensitivity, and symptomatic reflux as defined by the temporal relation between symptoms and reflux events, should be regarded as separate, though related, aspects of gastro-oesophageal reflux disease. Identity of results from the various tests of reflux disease should neither be expected nor sought.

- Bernstein LM, Baker LA. A Clinical test for esophagitis. *Gastroenterology* 1958; 34: 760-81.
- De Caestecker JS, Blackwell JN, Brown J, Heading RC. The oesophagus as a cause of recurrent chest pain: which patients should be investigated and which tests used? *Lancet* 1985; ii: 1143-6.
- De Caestecker JS, Pryde A, Heading RC. Comparison of intravenous edrophonium and oesophageal acid perfusion during oesophageal manometry in patients with non-cardiac chest pain. *Gut* 1988; 29: 1029-34.
- Kjellin G, Tibbling L. Oesophageal motility during acid-provoked heartburn and chest pain. *Scand J Gastroenterol* 1985; 20: 937-40.
- Hewson EG, Sinclair JW, Dalton CB, Wu WC, Castell DO, Richter JE. Acid perfusion test: Does it have a role in the assessment of non-cardiac chest pain? *Gut* 1989; 30: 305-10.
- Tuttle SG, Bettarello A, Grossman MI. Esophageal acid perfusion test and a gastroesophageal reflux test in patients with esophagitis. *Gastroenterology* 1960; 38: 861-72.
- Siegel CI, Hendrix TR. Esophageal motor abnormalities induced by acid perfusion in patients with heartburn. *J Clin Invest* 1963; 42: 686-95.
- Bennett JR, Atkinson M. Oesophageal acid perfusion in the diagnosis of precordial pain. *Lancet* 1966; ii: 1150-2.
- Skinner DB, Booth DJ. Assessment of distal esophageal function in patients with hiatal hernia and/or gastroesophageal reflux. *Ann Surg* 1970; 172: 627-37.
- Benz LJ, Hootkin LA, Marguiles S, Donner MW, Cauthorne RT, Hendrix TR. A comparison of clinical measurements of gastroesophageal reflux. *Gastroenterology* 1972; 62: 1-5.
- Sladen GE, Riddell RH, Willoughby JMT. Oesophagoscopy, biopsy, and acid perfusion test in diagnosis of "reflux" oesophagitis. *BMJ* 1975; 1: 71-6.
- Behar J, Biancani P, Sheahan DG. Evaluation of esophageal tests in the diagnosis of reflux esophagitis. *Gastroenterology* 1976; 71: 9-15.
- Breen KJ, Whelan G. The diagnosis of reflux oesophagitis: An evaluation of five investigative procedures. *Aust NZ J Surg* 1978; 49: 156-61.
- Kaul B, Petersen H, Grette K, Myrvold HE, Halvorsen T. The acid perfusion test in gastroesophageal reflux disease. *Scand J Gastroenterol* 1986; 21: 93-6.
- De Caestecker JS. Twenty-four-hour pH monitoring: advances and controversies. *N J Med* 1989; 34: S20-S39.
- Department of Clinical Epidemiology and Biostatistics University Health Centre. How to read clinical journals. II. To learn about a diagnostic test. *Can Med Assoc J* 1981; 124: 703-10.
- Simel DL. Playing the odds. *Lancet* 1985; i: 329-30.
- Wienbeck M, Berges W. Esophageal disorders in the etiology

- and pathophysiology of dyspepsia. *Scand J Gastroenterol* (Suppl 109) 1985; 109: 133-43.
- 19 Palmer ED. The hiatus hernia-esophagitis-esophageal stricture complex. *Am J Med* 1968; 44: 566-79.
 - 20 Heading RC, Blackwell JN, Cameron EWJ. Long term management of reflux patients. In: *Cimetidine in the 80s*. Ed J H Baron. Churchill Livingstone 1981: 172-80.
 - 21 DeMeester TR, Wang CI, Wernley JA, et al. Technique, indications and clinical use of 24 hour esophageal pH monitoring. *J Thorac Cardiovasc Surg* 1980; 79: 656-67.
 - 22 Schindlbeck NE, Heinrich C, Konig A, Dendorfer A, Pace F, Muller-Lissner SA. Optimal thresholds, sensitivity and specificity of long-term pH-metry for the detection of gastroesophageal reflux. *Gastroenterology* 1987; 93: 85-90.
 - 23 Knill-Jones RP, Card WI, Crean GP, James WB, Spiegelhalter DJ. The symptoms of gastro-oesophageal reflux and of oesophagitis. *Scand J Gastroenterology* 1984; 19 (suppl 106): 72-6.
 - 24 Johansson KE, Boeryd B, Johansson K, Tibbling L. Double-blind crossover study of ranitidine and placebo in gastro-oesophageal reflux disease. *Scand J Gastroenterol* 1986; 21: 769-78.
 - 25 Howard PJ, Pryde A, Heading RC. Acid exposure times do not identify patients with symptomatic gastro-oesophageal reflux. *Clinical Science* 1989; 76 (suppl 20); 40P.
 - 26 Janssens J, Vantrappen G, Ghillebert G. 24-hour recording of esophageal pressure and pH in patients with noncardiac chest pain. *Gastroenterology* 1986; 90: 1978-84.
 - 27 Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with oesophageal chest pain. *Gastroenterology* 1986; 91: 845-52.
 - 28 Vantrappen G, Janssens G, Ghillebert G. The irritable oesophagus - a frequent cause of angina-like pain. *Lancet* 1987; i: 1232.
 - 29 Peters LF, Petty DA, Wu WC, Castell DO. Spontaneous non-cardiac chest pain: evaluation by 24-hour ambulatory esophageal motility and pH monitoring. *Gastroenterology* 1988; 94: 878-86.
 - 30 Tuttle SG, Ruffin F, Bettarello A. The physiology of heartburn. *Ann Intern Med* 1961; 55: 292-300.