Simultaneous two level oesophageal pH monitoring in healthy controls and patients with oesophagitis: comparison between two positions

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Abstract

For oesophageal pH monitoring, the pH probe is usually positioned 5 cm above the lower oesophageal sphincter (LOS). This is by convention, and has not been compared with other positions in its ability to discriminate between physiological and abnormal acid reflux. Using simultaneous two level 24 hour pH monitoring (5 and 10 cm above manometrically determined LOS) in 31 controls and 51 patients with reflux oesophagitis, the significance of the precise position of the probe in the oesophagus was examined. Secondly, this study compared the discrimination between the two groups achieved at the two levels. Patients had greater acid exposure than controls at both levels. In controls, acid exposure was greater at distal than at the proximal level except the supine acid exposure, which was similar at both levels. In patients, acid exposure was greater at the distal level for all variables (median % of total time pH <4=11.7 v 7.6; $p=0.001$). There was excellent correlation between the two levels for all variables in controls ($r=0.883$, 0.935, 0.813, and $p<0.001$ for percentage of time pH <4 for total, supine, and upright times) as well as in patients ($r=0.848$, 0.848, 0.779, and $p<0.001$). On discriminant and receiver operating characteristic analysis, pH threshold 4 seemed as good as or better than other pH thresholds in discriminating between controls and patients. The percentage of total time pH below 4 seemed to discriminate as well or better than other variables at both levels. The distal level (5 cm above LOS) provided slightly better discrimination than proximal level (10 cm) (percentage of subjects correctly classified=81.7 v 75.6). The critical factor for the reliability of the test is not the precise position of the pH probe relative to the LOS, but that the same position is consistently used in patients and controls.

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pH probe is usually positioned 5 cm above the upper level of the manometrically defined lower oesophageal sphincter (LOS). This is, however, simply by convention and has not been systematically compared with other levels in the oesophagus. Walker *et al.*,⁶ based on their small study on 10 patients and five controls, reported that there was no significant difference between the values obtained from 5 and 10 cm above the LOS and they claimed that the exact position of the probe in the oesophagus was not of crucial importance – a view supported by others.⁷ If this were to be true, pH monitoring would become a much simpler affair in that it would avoid the need for oesophageal manometry, which is not always available and requires considerable investment in time, money, and expertise. A number of other studies, however, using multiple site oesophageal pH monitoring have shown that the degree of acid reflux progressively decreases along the length of the oesophagus in the oral direction in healthy volunteers⁸ and patients.^{9,10} This would indicate that the precise position of the probe may be critically important and that it would be inappropriate to use the reference values for the definition of abnormal reflux from volunteer studies that have used a different position for the probe in their controls. The level of 5 cm above the LOS, however, has been chosen arbitrarily and has not been tested in comparison with other levels in the oesophagus using control and patient groups. It is conceivable that positioning the probe closer to the LOS might detect more acid reflux and improve sensitivity, but it could be argued that it may increase the chances of the probe slipping into the stomach and measure gastric pH particularly in patients with a large hiatus hernia and in the supine position. Positioning the probe higher up in the oesophagus would definitely be associated with a much reduced chance of such an occurrence, but may well be less sensitive. This issue has not been systematically studied so far.

This study was designed to consider a number of issues relating to 24 hour ambulatory oesophageal pH monitoring. Firstly, using simultaneous two level pH monitoring in controls and patients with reflux oesophagitis, the significance of the exact position of the probe in the oesophagus was examined. Secondly, it was proposed to compare the discrimination between the two groups achieved by the pH probes at two levels (5 and 10 cm above LOS) in the oesophagus. A number of variables of acid reflux at different pH thresholds at both levels in the oesophagus were examined to determine the variable and the cut off point for

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Oesophageal pH monitoring was first used by Tuttle and Grossman in 1958.¹ The technology has since improved a great deal and longterm pH monitoring is now a standard component of oesophageal function testing. It is widely regarded as the standard test for the diagnosis of gastro-oesophageal acid reflux.

Despite the popularity of oesophageal pH monitoring, there is still considerable confusion about many aspects of the test particularly regarding the positioning of the pH probe.^{2–5} The

that variable that provided the highest discrimination between the controls and patients.

Methods

PATIENTS
Sixty three patients with endoscopically proved oesophagitis were approached to take part in this study. Seven of them could not tolerate the pH probes, in one patient the distal probe was accidentally disconnected, four patients had only distal pH monitoring (two of them could not tolerate the passage of two probes, and in the other two, there was malfunction of the proximal probe with considerable drift found on calibration after monitoring). Satisfactory two level oesophageal pH monitoring results were available in 51 patients (39 men) who formed the basis of this study. The median age of the patients was 51 years (range 21–77).
The severity of oesophagitis was graded endoscopically according to a modification of the original Savary and Miller classification.¹¹ The distribution of grades of oesophagitis was: grade 1=10; grade 2=32; grade 3=7; and grade 4=2. Barrett's metaplasia was present in nine patients.

CONTROLS
Thirty three healthy volunteers took part in the study. They were totally asymptomatic and had no history of oesophageal, gastric or duodenal

disease. Data from two volunteers had to be excluded because of considerable drift of the pH probes on calibration after the pH monitoring. Satisfactory two level pH monitoring was possible in 31 volunteers (20 men) on whom the results of this study are based. The median age of the volunteers was 33 years (range 22–51).

pH MONITORING
We have described the methodology of this test in a previous paper.¹² In summary, all subjects in this study had two separate antimony pH probes positioned in the oesophagus at 5 and 10 cm above the manometrically determined upper border of the lower oesophageal sphincter. No drugs were permitted for 48 hours before and during the test. The data were analysed using Esophogram software (Synectics Ltd). The reflux variables used in this study were the percentage of total, supine, and upright times below pH thresholds of 5, 4, 3, and 2. The number of reflux episodes lasting longer than five minutes at each of these pH thresholds were also used.

STATISTICAL ANALYSIS
For the analysis of discrimination between the controls and the patients, two separate methods were used. Firstly, linear discriminant analysis was done for each reflux variable after square root transformation of the data. This was necessary because the data were not normally distributed. Square root transformation was preferred over log transformation because the values in a significant proportion of controls and some patients were so low that they approached zero after log transformation and the computer programme (Minitab, USA) tended to exclude these subjects from the analysis. Cross validation was used to compensate for an optimistic apparent error rate.

Secondly, the data were analysed by generating receiver operating characteristic curves^{13 14} for each of the variables of acid reflux. For this, each observed value of a variable was consecutively regarded as a threshold and the percentage of true positive (sensitivity) and false positive (100% specificity) for all of these thresholds were then calculated individually and plotted with the percentage of true positive on the vertical axis and the percentage of false positive on the horizontal axis. This gave the receiver operating characteristic curve for that particular variable. One way of objectively measuring the diagnostic value of a test is to calculate the area under the receiver operating characteristic curve for that test as a fraction of the total area.¹³ The greater the area under the curve, the better is the discriminatory value of the test. The area under the curve was measured for each variable using the trapezoid rule. The cut off points for each variable providing the best discrimination between the two groups were obtained by determining the tangential point with a gradient of 1:1. There was no need for correcting for the difference in the numbers between the two groups as the data (true positive and false positive) were represented in percent-

Figure 1: Comparison of oesophageal acid exposure between controls (n=31) and patients (n=51) at 5 cm above the lower oesophageal sphincter. The difference between controls and patients was highly significant (p<0.001 for all variables). Horizontal line represents the median.

Figure 2: Comparison of oesophageal acid exposure between controls (n=31) and patients (n=51) at 10 cm above the lower oesophageal sphincter. The difference between controls and patients was highly significant (p<0.001 for all variables). Horizontal line represents median.

ages. Once the cut off point for a particular variable was determined, the sensitivity and specificity for that variable was easily read off its receiver operating characteristic curve. The differences in various values between and within the groups were analysed using standard two tailed non-parametric tests (Mann-Whitney and Wilcoxon's signed rank tests). Linear regression was used to analyse correlation between various reflux variables.

TABLE I Comparison of variables of acid reflux between the distal and proximal probes

Variable	Distal	Proximal	p (95% CI)*
Controls			
% Of time pH<4			
Total	1.6 (0.1-11.7)	1.8 (0.0-11.0)	0.018 (0.0 to 0.6)
Supine	0.3 (0.0-25.1)	0.4 (0.0-24.7)	0.279 (-0.13 to 0.03)
Upright	2.2 (0.1-12.1)	1.7 (0.0-5.0)	<0.001 (0.2 to 1.1)
No of episodes >5 minutes	0 (0-5)	1 (0-3)	0.648 (0 to 0)
Patients			
% of time pH<4			
Total	11.7 (1.1-86.2)	7.6 (0.0-60.1)	<0.001 (1.8 to 4.8)
Supine	7.6 (0.0-97.9)	7.9 (0.0-86.3)	<0.001 (0.6 to 3.0)
Upright	10.9 (1.4-85.0)	6.1 (0.1-51.0)	<0.001 (2.6 to 7.2)
No of episodes >5 minutes	6 (0-41)	3 (0-27)	<0.001 (1 to 4)

*95% Confidence intervals for the median difference in values obtained from the distal and proximal probes. All values are median, ranges are given in parentheses.

TABLE II Ratios of acid exposure at 5 v 10 cm above lower oesophageal sphincter: comparison between supine and upright postures

	Ratio of distal v proximal % of time pH<4	
	Upright	Supine
Controls (n=31)	1.5 (0.3-5.2)	0.3 (0-13)
Patients (n=51)	1.83 (0.31-14)	1.3 (0-51)
		p (95% CI)* (upright v supine)
		<0.001 (0.6 to 1.62)
		<0.001 (0.31 to 1.08)

*95% Confidence intervals for the median difference in the ratios of acid exposure (distal v proximal) between upright and supine postures. All values are median, ranges are given in parentheses.

Results

As would be expected, the patients had significantly higher values than controls for all reflux variables measured at both distal and proximal levels. Figures 1 and 2 show the differences between the two groups at pH threshold 4.

The values at the distal level were significantly higher than at the proximal level for all variables in the patients (Table I). In volunteers, however, there was no statistically significant difference for acid exposure in supine posture and the number of reflux episodes longer than five minutes (Table I). Interestingly, the median ratio for acid exposure at 5 v 10 cm above LOS was significantly lower in supine than in upright posture in controls as well as the patients (Table II). In both groups, there was a strong correlation between the corresponding values at the distal and the proximal levels (Fig 3).

The discriminant analysis showed that overall the simple measurement of percentage of total time (compared with the percentage of supine or upright times, or the number of reflux episodes lasting longer than five minutes) provided better or as good discrimination between the two groups at all pH thresholds as the other variables at both distal and proximal levels. Generally the threshold of pH 4 was superior to other pH thresholds at the distal level although the differences between the pH thresholds were comparatively small. At the proximal level, the threshold of pH 5 was marginally superior to pH 4 for the percentage of total time (percentage of subjects correctly classified=78 v 75.6). Tables III and IV show the results of the discriminant analysis for both levels at all pH thresholds.

Similar results were obtained on receiver operating characteristic analysis. Using area under the curve measurement, the percentage of total time pH below 4 emerged as the single best discriminator between the controls and the patients except at the proximal level where percentage of total time pH <5 seemed slightly better (Table V). When the cut off points from each of these curves were obtained using a gradient of 1:1, and the sensitivity and specificity figures were calculated, again the simple measurement of percentage of total time pH <4 emerged as at least as good if not a better single discriminator than other measurements at both distal and proximal levels.

With both methods of analysis (discriminant and receiver operating characteristic analyses), it seemed that the distal level provided slightly better discrimination than the proximal level. The difference was, however, small.

Discussion

Several studies using 24 hour oesophageal pH monitoring have claimed very high sensitivity and specificity rates for this test in the detection of gastro-oesophageal reflux disease (96 and 96% by Fuchs *et al*¹⁵; 100 and 100% by Fink and McCallum¹⁶; 87 and 97% by Johnsson *et al*¹⁷). All of these studies showed very low levels of acid reflux in healthy volunteers. A number of more recent studies have, however, found much higher levels of acid reflux in controls and therefore, lower levels of discrimination. Shaker

Figure 3: Comparison between oesophageal acid exposure at 5 and 10 cm above the lower oesophageal sphincter (LOS) in controls and patients. The data at 10 cm above LOS (proximal level) are represented as solid circles while the hollow squares represent figures at 5 cm above LOS (distal level). There was excellent correlation between the two levels for all variables in controls ($r=0.883, 0.935, 0.813$, and $p<0.001$ for % of time pH <4 for total, supine, and upright times) as well as in patients ($r=0.848, 0.848, 0.779$, and $p<0.001$). The corresponding values for the number of reflux episodes longer than five minutes were $r=0.467$ and $p<0.001$ in controls and $r=0.642$ and $p<0.001$ in patients. Horizontal line represents median.

*et al*¹⁸ found surprisingly high levels of acid reflux in their healthy volunteers, which reduced the sensitivity and specificity of the test to 75 and 79% respectively. Cheadle *et al*¹⁹ reported that

TABLE III Summary of the results of discriminant analysis of 24 hour oesophageal pH data (distal probe)

Variable	% Of total no of subjects correctly classified	% Of total no of patients correctly classified	% Of total no of controls correctly classified
pH <5			
Total	78.0	80.0	74.0
Supine	76.8	78.0	74.0
Upright	75.6	76.0	74.0
No of episodes >5 minutes	81.7	82.0	81.0
pH <4			
Total	81.7	84.0	77.0
Supine	76.8	76.0	77.0
Upright	76.8	80.0	71.0
No of episodes >5 minutes	78.0	80.0	74.0
pH <3			
Total	76.8	82.0	68.0
Supine	81.7	86.0	74.0
Upright	75.6	84.0	61.0
No of episodes >5 minutes	62.2	100.0	0
pH <2			
Total	78.0	98.0	45.0
Supine	53.7	86.0	0
Upright	73.2	94.0	39.0
No of episodes >5 minutes	62.2	100.0	0

TABLE IV Summary of the results of discriminant analysis of 24 hour oesophageal pH data (proximal probe)

Variable	% Of total no of subjects correctly classified	% Of total no of patients correctly classified	% Of total no of controls correctly classified
pH <5			
Total	78.0	82.0	71.0
Supine	65.9	71.0	58.0
Upright	70.7	78.0	58.0
No of episodes >5 minutes	72.0	80.0	58.0
pH <4			
Total	75.6	80.0	68.0
Supine	68.3	75.0	58.0
Upright	72.0	76.0	65.0
No of episodes >5 minutes	72.0	88.0	45.0
pH <3			
Total	73.2	84.0	55.0
Supine	74.4	86.0	55.0
Upright	70.7	82.0	52.0
No of episodes >5 minutes	62.2	100.0	0
pH <2			
Total	69.5	90.0	35.0
Supine	62.2	100.0	0
Upright	65.9	84.0	35.0
No of episodes >5 minutes	62.2	100.0	0

the percentage of total time pH <4 was greater than mean+2 SD in up to 18% of their healthy volunteers. Similarly, Schlesinger *et al*²⁰ reported sensitivity and specificity figures of 73 and 80% respectively.

In this study, the degree of 'physiological reflux' in healthy controls was much higher than that reported by some of the previous workers^{15 17 21} and closer to the values recently reported by Masclee *et al*²² and Shaker *et al*¹⁸ who reported substantial acid reflux in some of their controls. In this study, the fractional acid exposure for the total period was as high as 11.7% in one volunteer. In contrast with the traditionally held view, almost all of this reflux occurred during one prolonged episode of acid reflux lasting nearly two hours while he was asleep at night (fractional supine acid exposure=25.1%). This was certainly not an artifact as the same long reflux episode was also picked up by the proximal probe with its corresponding fractional supine acid exposure being 24.7%.

The much lower levels of acid reflux detected

TABLE V Area under the curve for reflux variables at 5 and 10 cm above lower oesophageal sphincter (LOS)

Variable	Area under the curve	
	5 cm above LOS	10 cm above LOS
pH <5		
Total	0.882	0.856
Supine	0.859	0.781
Upright	0.841	0.817
No of episodes >5 minutes	0.887	0.823
pH <4		
Total	0.906	0.821
Supine	0.880	0.816
Upright	0.880	0.829
No of episodes >5 minutes	0.880	0.821
pH <3		
Total	0.889	0.826
Supine	0.853	0.781
Upright	0.870	0.805
No of episodes >5 minutes	0.832	0.764
pH <2		
Total	0.871	0.765
Supine	0.807	0.743
Upright	0.849	0.786
No of episodes >5 minutes	0.690	0.602

in controls in the earlier studies may have been because of a number of factors such as the use of endoscopy¹⁷ and barium meal¹⁵ to exclude control subjects with asymptomatic oesophagitis or reflux, rigid standardisation of diet,^{8,16} and small sample size.^{8,16}

It has been shown that at both levels, the simple measurement of the percentage of total time pH below 4 provides at least as good or better discrimination than any other variable.

In controls as well as in the patients, the degree of acid reflux was higher at 5 cm than at 10 cm above the LOS. One notable exception to this, however, was the supine reflux in controls, which was not significantly different at the two levels. There are two plausible explanations for this. Firstly the level of supine reflux in volunteers was so low at both levels (median values for percentage of supine time pH <4=0.3 and 0.4 for 5 and 10 cm above the LOS respectively), that it would have been difficult to detect any differences simply for that reason. The second, and an attractive alternative explanation would be that in supine posture, in the absence of the factor of gravity, the refluxate may have travelled higher in the oesophagus than in the upright posture. This impression is reinforced by the fact that the median ratio of acid exposure at 5 v 10 cm above the LOS was significantly lower for the supine posture than for the upright posture in controls as well as the patients. Interestingly Shaker *et al*¹⁸ in their short term pH monitoring study in seven controls and seven patients noted that while the total acid exposure was four to fivefold higher in the distal oesophagus than in the proximal oesophagus, the regional differences were more pronounced in the upright than in the supine posture.

The results of this study are consistent with previous smaller studies, which have also shown a gradient of acid reflux along the length of the oesophagus in volunteers⁸ and patients.^{9,10}

The discrimination between controls and patients was slightly better with the probe at 5 cm above the LOS compared with 10 cm above the LOS. The difference, however, was small and it seems that the critical factor for the reliability of the test is probably not the exact position of the probe relative to the LOS, but that the same position is consistently used for the patients and the controls.

This is the first reported large study on this subject that has compared two different pH probe positions in the oesophagus in their ability to discriminate between controls and patients with reflux disease. It would be interesting now to compare the standard position of 5 cm above the LOS with a second probe closer to the LOS.

It is obvious from this study that there are significant limitations to oesophageal pH monitoring as a diagnostic tool in gastro-oesophageal reflux disease. Even at a modest specificity level of 87%, pH monitoring failed to identify up to 20% of patients with confirmed endoscopic oesophagitis. This is obviously not good enough for a standard test. Equally, however, it must be admitted that other workers have shown that ambulatory pH monitoring is capable of detecting abnormal acid reflux in up to 60% of patients with reflux symptoms and normal endo-

scopy.²² The role of oesophageal pH monitoring in the diagnosis of gastro-oesophageal reflux disease is, therefore, complementary to endoscopy and is best used in patients with normal endoscopy. Because of its ability to permit temporal correlation of symptoms with acid reflux, pH monitoring also has an important part to play in the assessment of atypical symptoms such as chest pain or respiratory symptoms – that is, nocturnal wheezing, hoarseness, etc.,^{23,24} where reflux is suspected to be the cause of these symptoms.

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