

Alkaline gastro-oesophageal reflux: dual probe pH monitoring

S Y Iftikhar, Sally Ledingham, D F Evans, S W Yusuf, R J C Steele, M Atkinson, J D Hardcastle

Abstract

Although the aetiology of Barrett's oesophagus or columnar lined oesophagus (CLO), remains unknown, bile reflux has been implicated as a factor in its pathogenesis. This study aimed to detect alkaline reflux in gastro-oesophageal reflux patients using dual probe pH monitoring. Thirty patients with histologically diagnosed CLO, 15 age and sex matched patients with oesophagitis (grade 1-3), and 15 healthy volunteers were studied by dual probe, 18 hour pH monitoring and analysis of the bile acid content of oesophageal refluxate. Total acid exposure and acid exposure in the upright and supine postures were greater in CLO subjects than in oesophagitis patients and controls. Furthermore, the number of reflux episodes lasting more than five minutes and the duration of the longest reflux episode were significantly greater in the CLO subjects than the oesophagitis and control subjects. Nine subjects with CLO and oesophagitis, however, were not identified as refluxers, although six had a bile acid concentration in their oesophageal aspirate higher than the 95th centile value of the controls. There was no correlation between the oesophageal pH and the bile acid contents of refluxate. It is concluded that dual probe pH monitoring is not useful in detecting alkaline refluxers. pH monitoring, although the only subjective test available to identify acid refluxers, is not a sufficiently sensitive test with which to define alkaline reflux.

(*Gut* 1995; 37: 465-470)

Keywords: Barrett's oesophagus, oesophagitis, pH monitoring.

The pathogenesis of Barrett's oesophagus or columnar lined oesophagus (CLO) is still unclear. It is unquestionably linked with gastro-oesophageal reflux, but although patients with CLO tend to have a greater degree of acid exposure than those with reflux oesophagitis, there does not seem to be any difference between patients with complicated disease and those with uncomplicated disease in this respect.¹ Interestingly, CLO patients are known to have a greater concentration of bile acids in their gastric contents² and oesophageal refluxate³ than patients with simple reflux oesophagitis. Furthermore, CLO can develop after total gastrectomy when no acid is present.⁴ It is therefore probable there are factors other

than acid in the pathological process associated with gastro-oesophageal reflux.

Twenty four hour oesophageal pH monitoring is now considered the 'gold standard' investigation for detecting gastro-oesophageal reflux. It has the advantage of measuring the frequency and duration of acid exposure to the oesophageal mucosa,^{5,6} and it is the most sensitive available method of determining objectively the presence of gastro-oesophageal reflux.⁷ Despite the widely accepted role of 24 hour pH monitoring, however, it is well known that some patients with reflux symptoms may have negative pH studies.⁸ In addition, some patients with severe reflux oesophagitis have little or no demonstrable acid reflux,^{9,10} and asymptomatic volunteers can occasionally have evidence of extensive reflux on pH monitoring.¹¹ This can be explained by the fact that pH monitoring may not identify subjects with alkaline reflux because the pH of the refluxate in these patients may lie within the normal range. The present study was therefore designed to assess duodenogastric reflux and gastro-oesophageal reflux simultaneously in patients with CLO and reflux oesophagitis and in control subjects.

Subjects and methods

The subjects in this study comprised 30 patients with histologically proved CLO, 15 patients with oesophagitis (grades 1-3), and 15 healthy volunteer controls recruited from the Nottingham University staff and student population. All patients with CLO had circumferential columnar epithelial lining of the lower oesophagus extending at least 5 cm from the gastro-oesophageal junction, and the median length of CLO was 7.5 cm (range 5-19 cm). The sex ratio and age range of each group is shown in Table I. Local ethical committee approval was obtained and all subjects gave informed consent in writing before the study began.

BILE COLLECTION

In the week preceding the study all medication that might have affected gastrointestinal

TABLE I The sex ratio and age range of subjects with columnar lined oesophagus (CLO), oesophagitis, and controls

	Men	Women	Mean (SD) (y)	Median (y)	Range (y)
CLO (n=30)	15	15	62.5 (10.2)	65	35-78
Oesophagitis (n=15)	10	5	59.5 (7.3)	61	30-79
Control (n=15)	10	5	20.7 (1.3)	21	19-23

Department of
Surgery, Derbyshire
Royal Infirmary,
London Road, Derby
S Y Iftikhar

Department of
Surgery, University
Hospital, Nottingham
S Ledingham
D F Evans
S W Yusuf
R J C Steele
M Atkinson
J D Hardcastle

Correspondence to:
Mr S Y Iftikhar, Department
of Surgery, Derbyshire Royal
Infirmary, London Road,
Derby DE1 2QY.

Accepted for publication
24 February 1995

TABLE II Oesophageal manometry results

Group	Mean UOSP Median (range)	Mean LOSP segment Median (range)	Peak peristaltic pressure		
			Upper oesophageal segment Median (range)	Middle oesophageal segment Median (range)	Lower oesophageal segment Median (range)
Columnar line oesophagus (n=30)	40 (15-72) NS	0 (0-15) p=0.004	32 (16-64) NS	32 (20-64) NS	32 (16-64) p=0.04
Oesophagitis (n=15)	40 (24-56) NS	7 (0-23) p=0.0007	40 (24-70) NS	40 (16-56) NS	40 (24-72) NS
Control group (n=15)	40 (32-48)	12 (6-20)	46 (26-54)	48 (40-56)	44 (32-56)

UOSP=upper oesophageal sphincter pressure; LOSP=lower oesophageal sphincter pressure.

motility or secretion was stopped, and the subjects fasted for 24 hours before the investigation. On the day of the study the position of the lower oesophageal sphincter (LOS) was determined in each subject by manometry, using the station pull through technique.¹² On the same afternoon oesophageal intubation was performed per nares with a 9 FG paediatric repleg tube so that the end of the tube was 5 cm above the LOS.¹³ Bile was collected from the oesophagus of all the subjects using the technique described by Gotley *et al.*¹⁴ Oesophageal secretion was collected by continuous aspiration at -40 mm Hg and was stored as two hourly aliquots for analysis of bile acid concentration by high performance liquid chromatography as previously described.³

The study began at 4.00 pm after a rest period of 45-60 minutes to allow for the effects of the intubation to subside. Any oesophageal aspirate collected thus far was discarded. At 6.00 pm a high fat test meal was eaten and at 10.00 pm the subject retired to bed, being allowed to sleep with their normal arrangement of pillows. The subject was woken at approximately 7.00 am and from then on sat upright. A high fat breakfast was eaten at 8.00 am and the study ended at 10.00 am.

pH MONITORING

At the same time as oesophageal intubation, two pH sensitive electrodes were passed per nares and positioned so that one lay 5 cm above the LOS, and the other in the stomach 5 cm below the LOS. The gastric pH electrode was a glass combination type LOT 440M4 (Ingold, Switzerland) which has an integral reference electrode. This model is 4 mm diameter at its tip with a 3 mm glass electrode and cable. The electrode's effective length is 95 cm with an inbuilt Ag-AgCl reference electrode and a liquid junction at 2 cm from its tip. The electrolyte, FriscoLyte, is supplied from the inside of the 95 cm long plastic cable. The oesophageal pH electrode was a 1.5 mm diameter non-combination miniature glass electrode, M1.5 (Ingold, Switzerland) with a rigid portion of 20 mm and total length of 1.5 m. In this study a two channel pH data recorder (Proxima Electronics, Italy) was used.¹⁵ The recorder features variable pH sampling times, automatic detection of the subject's postures, and subject response keys which can be programmed specifically to record particular events (for example, pain symptoms) that occur during the monitoring period.

pH electrodes were prepared by soaking overnight in pH 9 buffer and calibrating in buffers at pH 9 and pH 4. The pH sampling rate was set to six seconds and recording time to 18 hours. During the study subjects were asked to record symptoms and meal times. No drinks, other than water, were allowed. The pH meter was kept vertical when the subject was upright and horizontal during the supine period to allow automatic recording of posture.

ANALYSIS OF pH DATA

The data stored after each study were transferred from the pH recorder on to computer disc using the *Proxima Light* pH meter analysis program. The percentage of time spent the pH was below 4, the number of reflux episodes, reflux episodes lasting more than five minutes, and longest reflux episode were analysed for upright, horizontal, and total monitoring periods and these were compared between groups. In addition, DeMeester's composite reflux score¹⁶ which takes into account six variables (percentage acid exposure for the upright, supine, and total study period along with the number of reflux episodes, those lasting more than five minutes or more, and the single longest reflux episode) was calculated for each subject and the groups were compared.

Using the Event Computing Function available on the analysis program, the mean (SD) of gastric and oesophageal pH were determined in CLO, control subjects, and oesophagitis patients for each study period, preprandial, postprandial period, total upright, and total horizontal study periods.

STATISTICAL ANALYSIS

Because of the variable distribution of the data, a non-parametric test, the Mann-Whitney U test was used. All the analysis for p values were two tailed and corrected for ties. Correlation analysis was performed using Pearson's rank correlation test.

Results

PRESSURE STUDIES

The mean lower oesophageal sphincter pressure in the CLO group (median 0, range 0-15 cm of H₂O) was significantly lower than that in the oesophagitis (median 7, range 0-23 cm of H₂O) or control groups (median 12, range 6-20 cm H₂O) and the oesophagitis

TABLE III pH Monitoring results in the 18 hour study period

	Total time % pH<4 Median (range)	Total no of reflux episodes Median (range)	No of reflux episodes lasting >5 min Median (range)	Largest reflux episode (min) Median (range)	Reflux score Median (range)
Columnar lined oesophagus (CLO) (n=30)	11 (0-74)	27 (5-344)	5 (0-41)	25 (0-402)	70 (1-396)
Oesophagitis (OES) (n=15)	6 (1-29)	26 (5-164)	3 (0-14)	20 (1-332)	36 (4-179)
Control (n=15)	1 (0-94)	7 (0-58)	0 (0-15)	2 (0-150)	3 (0-393)
CLO v OES	p=0.03	NS	NS	NS	p=0.06 NS
CLO v Control	p=0.0002	p=0.0003	p=0.0001	p=0.0008	p=0.0002
OES v Control	p=0.007	p=0.003	p=0.009	p=0.008	p=0.001

patients had significantly lower LOS pressures than the controls (Table II). There were no statistically significant differences in the upper oesophageal sphincter pressures between the three groups. Similarly, no differences were observed between the peak peristaltic pressures of upper and mid oesophageal segments of the CLO, oesophagitis, and control subjects. The peak peristaltic pressure of the columnar lined oesophageal segment of the CLO group (median 32, range 16-64 cm H₂O) was significantly lower, however, than that seen in the oesophagitis group (median 40, range 15-56 cm H₂O) and the control group (median 44, range 32-56 cm H₂O) (Table II). No difference was found in the peak peristaltic pressure of the lower oesophageal segment in oesophagitis group when compared with that in control group.

OESOPHAGEAL pH MONITORING RESULTS

The total percentage time the pH was less than 4 (median 11%, range 0-74) was significantly higher in CLO patients than in oesophagitis patients (median 6%, range 1-29) and controls (median 1%, range 0-94) (Table III). There was no significant difference found in the total number of reflux episodes over the total monitoring period when CLO patients were compared with oesophagitis patients. Both CLO (median 27, range 5-344) and oesophagitis (median 26, range 5-164) groups, however, had significantly higher numbers of reflux episodes than the control group (median 7, range 0-58) (Table III).

When the numbers of reflux episodes lasting more than five minutes were compared in the three groups, the CLO (median 5, range 0-41) and oesophagitis (median 3, range 0-14) groups were again comparable but both had a significantly higher number of these episodes than the control group (median 0, range 0-15) (Table III). The duration of the longest reflux

episode was also similar in the CLO (median 25 minutes, range 0-402) and oesophagitis groups (median 20 minutes, range 1-332) but both had significantly longer episodes when compared with the control subjects (median 2.0 minutes, range 0-150) (Table III). DeMeester's reflux score in the CLO group (median 70.0, range 1-396) was significantly higher than that in the oesophagitis group (median 36.0, range 4-179) and the control group (median 3.0, range 0-393). Furthermore, oesophagitis patients had a significantly higher reflux score than the control group) (Table III).

The total percentage of time pH >7 was comparable between the CLO (median 4.8, range 0-16.6) and oesophagitis group (median 2.8, range 0-11.5).

OESOPHAGEAL pH PROFILE IN VERTICAL AND HORIZONTAL POSTURES

In the vertical posture, the total percentage time the pH was less than 4, the number of reflux episodes, the number of reflux episodes lasting more than 5 minutes, and the duration of the longest reflux episode were comparable between CLO and oesophagitis groups. They were, however, all significantly greater when compared with controls for both the CLO and oesophagitis groups (Table IV). Furthermore, no differences were observed in the percentage of time the pH was >7 in the upright posture between the CLO (median 9.2, 0-34.2) and oesophagitis groups (median 6.7, range 0-23.8). Similarly, no difference was observed in the supine posture between CLO (median 0, range 0-7.4) and oesophagitis patients (median 0, range 0-3.78).

In the horizontal posture, the percentage of time that the pH was <4 in the CLO group (median 15.5%, range 0-98) was significantly greater than that in the oesophagitis (median 2.0%, range 0-35) and control groups (median

TABLE IV pH Monitoring results in the upright posture

	Total time % pH<4 Median (range)	Total no of reflux episodes Median (range)	No of reflux episodes lasting >5 min Median (range)	Largest reflux episode (min) Median (range)
Columnar line oesophagus (CLO) (n=30)	13.5 (0-72)	17 (2-113)	3 (0-18)	14.5 (0-275)
Oesophagitis (OES) (n=15)	4 (1-22)	21 (2-83)	1 (0-9)	15 (1-332)
Control (n=15)	1 (0-87)	5 (0-37)	0 (0-6)	2 (0-95)
CLO v OES	NS	NS	NS	NS
CLO v Control	p=0.001	p=0.0005	p=0.0003	p=0.001
OES v Control	p=0.007	p=0.002	p=0.01	p=0.007

TABLE V *pH Monitoring results in the supine posture*

	Total time % pH<4 Median (range)	Total no of reflux episodes Median (range)	No of reflux episodes lasting >5 min Median (range)	Largest reflux episode (min) Median (range)
Columnar lined oesophagus (CLO) (n=30)	15.5 (0-98)	7 (0-231)	2 (0-23)	20.5 (0-402)
Oesophagitis (OES) (n=15)	2 (0-35)	5 (0-121)	0 (0-9)	1 (0-151)
Control (n=15)	0 (0-99)	1 (0-32)	0 (0-9)	2 (0-150)
CLO v OES	p=0.02	CLO v OES NS	CLO v OES p=0.05	CLO v OES p=0.02
CLO v Control	p=0.0006	CLO v Control p=0.001	CLO v Control p=0.005	CLO v Control p=0.007
OES v Control	NS	OES v Control p=0.05	OES v Control NS	OES v Control NS

0%, range 0-99) (Table V). The number of reflux episodes were comparable in the CLO (median 7, range 0-231) and oesophagitis (median 5, range 0-121) groups but both had a significantly larger number of reflux episodes than the controls (median 1.0, range 0-32) (Table V). Both the number of reflux episodes lasting more than five minutes and the duration of the longest reflux episode, however, were greater in CLO patients (median 2.0 and 20.5) than in the oesophagitis subjects (median and 1.0) and controls (median 0 and 2.0). No such difference was observed between oesophagitis and control subjects (Table V). Furthermore the percentage of time the pH was >7 was comparable in the CLO (median 0, range 0-7.4) and oesophagitis groups (median 0, range 0-3.8), and they were both comparable with the controls (median 0, range 0-2.3).

PREPRANDIAL AND POSTPRANDIAL OESOPHAGEAL pH

There were no significant differences in the preprandial oesophageal pH of CLO (median pH 6.5, range 3.7-8.3), oesophagitis (median pH 6.4, range 5.5-8.2), and control (median pH 6.2, range 4.7-7.9) groups. Significant differences were found, however, between the CLO group (median pH 6.1, range 2.9-8.1) and controls (median pH 5.9, range 4.7-8.3) ($p=0.01$) and the oesophagitis group (median pH 6.6, range 2.9-8.1) and controls ($p=0.05$) in the postprandial study period.

GASTRIC pH RESULTS

Gastric pH in 18 hour study period

There was no difference in the pH profile of the CLO, oesophagitis, and control groups in the 18 hour study period. Similarly, the preprandial gastric pH was comparable in the CLO, oesophagitis, and control subjects. In the postprandial study period, CLO patients (median 2.8) were comparable with the

controls (median 3.2) but had a significantly lower gastric pH than the oesophagitis subjects (median 4.2) (Table VI).

Gastric pH in the upright and supine study periods

There was no significant difference in the gastric pH of CLO, oesophagitis, and control groups in the upright posture. In the supine posture, however, the mean gastric pH of the CLO group (median 1.6) was significantly lower than that of the oesophagitis group (median 2.1), but comparable with that of controls (median 1.7) (Table VI).

CORRELATION BETWEEN OESOPHAGEAL pH AND OESOPHAGEAL BILE ACID CONCENTRATION

The total bile acid concentration in CLO group (median 1351 $\mu\text{M/l}$, range 0-14011 $\mu\text{M/l}$) was comparable with that of the oesophagitis group (median 817 $\mu\text{M/l}$, range 123-5721 $\mu\text{M/l}$) but significantly higher than that in controls (median 465 $\mu\text{M/l}$, range 20-2300 $\mu\text{M/l}$). Fifteen patients with CLO and three patients with oesophagitis had oesophageal bile acid concentrations higher than the 95th centile value of controls (1105 $\mu\text{M/l}$). There was no significant correlation between the median gastric pH of each study period and the bile acid concentrations found in the oesophageal aspirate samples (Pearson's correlation coefficient = -0.1) (Fig 1). Similarly, no correlation was found between the bile acid concentrations and the median oesophageal pH of each study period (Fig 2). Furthermore, there was no significant difference in the total bile acid concentration between complicated (median 1275 $\mu\text{M/l}$ range 0-5745 $\mu\text{M/l}$) and uncomplicated CLO (median 1340 $\mu\text{M/l}$ range 0-14011.5 $\mu\text{M/l}$).

SENSITIVITY OF OESOPHAGEAL pH MONITORING

The 95th centile value of the total percentage of time the pH was <4 in control subjects was 3%, which was considered to be the cut off point for acid refluxers in the two patient populations. Five subjects in the CLO group and four subjects in the oesophagitis group had overall values below the 95 centile value of controls. Therefore, the overall sensitivities of this measure for the CLO and oesophagitis group were 83.3% and 73.3%. Four subjects in CLO group and four in oesophagitis group had values less than 95th centile value for the

TABLE VI *Gastric pH monitoring results*

	pH in 18 h study period Median (range)	pH in upright posture Median (range)	pH in supine posture Median (range)	
Columnar lined oesophagus (CLO) (n=30)	2.03 (0.7-6.4)	2.4 (0.8-9.1)	1.6 (0.5-6.4)	NS
Oesophagitis (n=15)	2.2 (1.3-4.1)	3 (1.6-6.0)	1.7 (1.4-4.1)	NS
Control (n=15)	2.3 (1.4-5.5)	3.4 (1.5-6.0)	2.1 (1.3-5.6)	
			CLO v Control p=0.05	

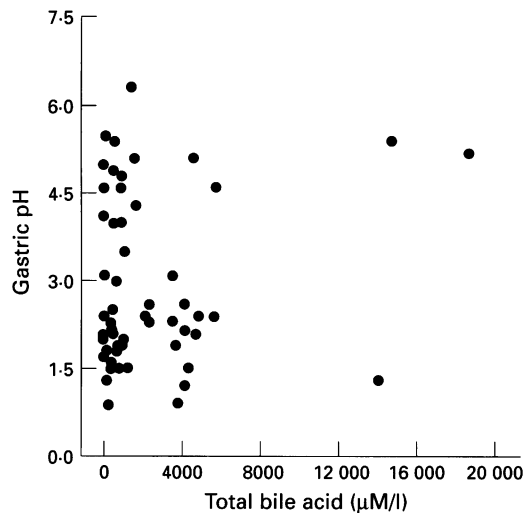


Figure 1: Correlation between the median gastric pH and total bile acid concentration in the oesophageal aspirate of columnar lined oesophagus and oesophagitis patients and controls. (Pearson's rank correlation coefficient=0.1, NS.)

composite DeMeester score (score <18) in the control population. Therefore, the overall sensitivities of pH monitoring for the composite score in the CLO and oesophagitis groups were 86.6% and 73.3%. Six of the nine patients who were identified as non-refluxers by pH monitoring had oesophageal bile acid concentrations higher than the 95th centile value of the controls. The other three also had bile present in their oesophageal aspirates, but in concentrations similar to those of the controls.

Discussion

In his study it was necessary to perform oesophageal manometry in all the subjects in order to allow accurate placement of the pH electrode and repleg tube above the LOS. This provided an opportunity to confirm the findings of our previous study,¹⁷ and, indeed, the CLO patients were again found to have significantly lower LOS pressures than the oesophagitis patients, who in turn had lower

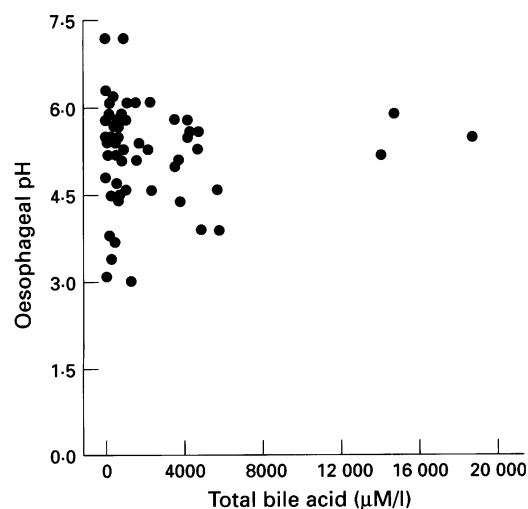


Figure 2: Correlation between the median oesophageal pH and bile acid concentration in columnar lined oesophagus and oesophagitis patients and controls. (Pearson's rank correlation coefficient=0.1, NS.)

pressures than the normal controls. In addition, the finding of significantly reduced peak peristaltic pressures in the lower oesophageal segment of the patients with CLO was reproduced.

Although it has been argued that motility disorders may be a result of oesophagitis,¹⁸ it is equally possible that they may contribute to the severity of the reflux either as a primary or secondary phenomenon. In any event, it is well established that CLO is associated with severe acid reflux as measured by 24 hour pH monitoring.¹ In the present study, using an 18 hour pH monitoring period, both CLO and oesophagitis subjects had higher numbers of reflux episodes than normal healthy volunteers, but the CLO subjects had comparable numbers of reflux episodes to the oesophagitis patients.

CLO patients, however, had more prolonged acid exposure and higher reflux scores compared with oesophagitis patients. This finding lends support to Iacone *et al*¹⁹ who have suggested that CLO is an end stage of reflux oesophagitis, and is in concordance with Gillen *et al*¹ who also showed longer acid exposure in CLO patients.

It is of interest that the CLO subjects showed a greater percentage time of when the pH was <4 in the total study period, but only in the supine study period were the number of reflux episodes lasting >5 minutes and the longest reflux episodes greater than these found in the oesophagitis group. This finding highlights the fact that CLO subjects seem to have a poor capacity for emptying the oesophagus, especially in the supine posture, and is in keeping with our finding of reduced peristaltic pressure in the lower oesophageal segment.

Gastric pH monitoring was performed in order to correlate it with non-acid reflux, and the pH probe was positioned 5 cm below the LOS in order to determine pH in the proximal stomach. This was done to try to obtain a true index of alkaline reflux, as duodenogastric reflux is not necessarily transmitted to the fundus.²⁰ Furthermore, in a recent study Attwood *et al* showed a relationship between oesophageal and gastric alkalisation in a significant proportions of patients with CLO.²¹ Alkalinisation of the proximal stomach for a significant length of time was not evident in our study. Indeed, the median gastric pH in the CLO patients remained significantly lower than that of the oesophagitis and control groups in the postprandial period and in the supine position. In addition, the percentage time the pH was >5 in the upper stomach was comparable in the CLO, oesophagitis and control groups. These findings suggest that gastric pH monitoring is not a true index of alkaline reflux, as both CLO and oesophagitis patients had significantly higher concentrations of bile acid in their oesophageal aspirate than the controls. Thus, even when the pH below the cardia is >5, oesophageal pH changes must be interpreted with care; other workers have shown that some fundic pH changes are not related to duodenogastric

reflux as they are not preceded by antral alkalisation.¹³

In the present study oesophageal alkalisation (pH >7) was found more in the upright posture, but the percentage of time the oesophageal pH was >7 was comparable in all groups studied. This is indicative of increased saliva production during the day, and this finding is consistent with those of Singh *et al.*²² Furthermore, it suggests that there does not have to be true monitorable alkalisation for alkaline gastro-oesophageal reflux.

Altogether, nine patients with CLO and oesophagitis could not be identified as refluxers using the total percentage of time the pH was <4 as an index. Furthermore, eight patients in the CLO and oesophagitis group had a composite score less than 95th centile value of the controls. Six of these patients were identified as bile refluxers, and it is likely that in these patients in the reflux was masked by its alkaline nature.

Zaninotto *et al.*¹³ showed that CLO patients had shorter periods of gastric alkalisation than normal subjects and oesophagitis patients when gastric and oesophageal pH were monitored simultaneously. This and other evidence²³ questions whether gastric alkaline pH is a true indicator of the level of bile reflux in the stomach, which is probably more important than simply identifying its occurrence. Certainly in the present study there was no correlation between gastric or oesophageal pH, and the oesophageal aspirate concentration of bile acid in the nine study periods. Significant gastro-oesophageal bile reflux can mask acid reflux and yet not be detected as alkaline reflux by the oesophageal pH probe. It therefore seems that gastric pH measurements do not add any useful information over and above oesophageal pH, and oesophageal pH monitoring cannot attain 100% sensitivity because of its inability to identify alkaline refluxers.

- 1 Gillen P, Keeling P, Byrne PJ, Hennessy TPJ. Barrett's oesophagus: pH profile. *Br J Surg* 1987; 74: 774-6.
- 2 Gillen P, Keeling P, Byrne PJ, Healy M, O'Moore RR, Hennessy TPJ. Implications of duodenogastric reflux in the pathogenesis of Barrett's oesophagus. *Br J Surg* 1988; 75: 540-3.
- 3 Iftikhar SY, Evans DF, Steele RJC, Ledingham S, Atkinson M, Hardcastle JD. Bile reflux in columnar lined

- Barrett's oesophagus. *Ann R Coll Surg Engl* 1993; 75: 411-16.
- 4 Meyer W, Vollmar F, Bar W. Barrett oesophagus following total gastrectomy. *Endoscopy* 1979; 11: 121-6.
- 5 De Meester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB. Patterns of gastro-oesophageal reflux in health and disease. *Ann Surg* 1976; 184: 459-70.
- 6 Moosa AR, Skinner DB. Gastro-oesophageal reflux and hiatal hernia. A re-evaluation of current data and dogma. *Ann Roy Coll Surg Engl* 1976; 58 (2): 126-132.
- 7 De Meester TR, Wang Ching I, Wernley JA, Pellegrini CA, Little AG, Klementchitsch P, *et al.* Techniques, indications and clinical use of 24 hour oesophageal pH monitoring. *J Thorac Cardiovasc Surg* 1980; 79 (5): 656-70.
- 8 Bancewicz J. Benign oesophageal disorders. In Irving M, Bert RW, eds. *Gastroenterological surgery* London, Boston, Durban, Singapore, Toronto, Wellington: Butterworths International Medical Series, 1983; 1-32.
- 9 Pelligrini CA, De Meester TR, Wernley JA, Johnson LF, Skinner DB. Alkaline gastro-oesophageal reflux. *Am J Surg* 1978; 135: 177-84.
- 10 Ritchie WP. Bile acids, the 'barrier' and reflux-related clinical disorders of the gastric mucosa. *Surgery* 1977; 82: 192-200.
- 11 Willen L, Marsden T. 12-hour simultaneous registration of acid reflux and peristaltic activity in the oesophagus. A study in normal subjects. *Scand J Gastroenterol* 1979; 14: 561-6.
- 12 Dodds WJ. Instrumentation and methods for intraluminal oesophageal manometry. *Arch Intern Med* 1976; 136: 515-23.
- 13 Zanninotto G, Merigilano S, Lostantini M, Anselmino A, Beghi A, Juliani M, Bonavina I, Ancona E. Twenty four hour monitoring of oesophageal and gastric pH; Normal values in asymptomatic volunteers and in patients with oesophagitis. In: Dal Pal C, Pessina Ac eds. *Proceedings of the fifth international congress on ambulatory monitoring*, Isam 1985. Pardore: Cleup Editore 557-61.
- 14 Gotley DC, Morgan AP, Cooper MJ. Bile acid concentrations in the refluxate of patients with reflux oesophagitis. *Br J Surg* 1988; 75: 587-90.
- 15 Evans DF. Ambulatory pH system. Product review. *Journal of Ambulatory Monitoring* 1988; 1 (2): 127-38.
- 16 Johnson F, De Meester TR. Development of the 24 hour intraoesophageal pH monitoring composite scoring system. In: De Meester TR, Skinner DB, eds. *Oesophageal disorders: pathophysiology and therapy*. New York: Raven Press, 1985.
- 17 Iftikhar SY, Hardy JG, Evans DF, Ledingham S, Atkinson M. Dysphagia and dysmotility in columnar lined Barrett's oesophagus. *Eur J Gastroenterol and Hepatol* 1992; 4: 111-4.
- 18 Sinar DR, Fletcher JR, Cordova CC, Eastwood GL, Castell DO. Acute acid induced esophagitis impairs esophageal peristalsis in baboons. *Gastroenterology* 1981; 80: A1286.
- 19 Iascone C, De Meester TR, Little AG, Skinner DB. Barrett's oesophagus. Functioning assessment, proposed pathogenesis and surgical therapy. *Arch Surg* 1983; 118: 543-9.
- 20 Mattioli S, Pillotti V, Zannoli P, Felice V, Castellini A, Conci A, Gozzetti G. Three probe 24 hour home oesophago-gastric pH monitoring: a new method for the study of gastro-oesophageal and duodeno-gastric reflux. *Gastroenterology* 1986; 95 (5): 1539.
- 21 Attwood SEA, Ball CS, Barlow AP, Jenkinson L, Norris TL, Watson A. Role of intragastric and intraoesophageal alkalisation in the genesis of complications in Barrett's columnar lined lower oesophagus. *Gut* 1993; 34: 11-15.
- 22 Singh S, Bradley LA, Richter JE. Determination of oesophageal 'alkaline' pH environment in controls and patients with gastro-oesophageal reflux. *Gut* 1993; 34: 309-16.
- 23 Gotley DC, Morgan AP, Cooper MJ. Prolonged intragastric pH monitoring in the diagnosis of duodeno-gastro bile reflux. *Gut* 1988; 29: A1451.