OESOPHAGUS

Role of intragastric and intraoesophageal alkalinisation in the genesis of complications in Barrett's columnar lined lower oesophagus

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Abstract

Patients with Barrett's columnar lined lower oesophagus have severe acid gastro-oesophageal reflux and may develop complications, including ulceration, stricture, and carcinoma. The aim of this study was to establish if a relationship exists between the pH profile in the oesophagus and stomach and the development of complications in patients with Barrett's columnar lined lower oesophagus. Twenty four hour ambulatory oesophageal pH monitoring was performed in 26 patients with Barrett's columnar lined lower oesophagus and combined with 24 hour ambulatory gastric pH monitoring in 16. Ten of the 26 with Barrett's columnar lined lower oesophagus had complications including stricture (eight), deep ulceration (one), and carcinoma (one). Oesophageal acid exposure (% time <pH 4) was similar in patients with or without complications (19·2% *v* 19·3% p>0·05). Oesophageal alkaline exposure (% time>pH 7) was greater in patients with complications (24·2% *v* 8·4% p>0·05). Of the 16 patients who underwent gastric pH monitoring there was a clear relationship between gastric and oesophageal alkalinisation in 13. These results support the hypothesis that complications in Barrett's columnar lined lower oesophagus develop in association with increased exposure of the oesophagus to an alkaline environment which appears to be secondary to duodenogastric reflux. The routine use of 24 hour ambulatory gastric pH monitoring in conjunction with oesophageal pH monitoring can help identify those patients at risk.

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Since the original description of a columnarised lower esophagus by Barrett in 1950[1] and Allison and Johnson in 1953[2] it has been recognised that this abnormal lining has a marked propensity to develop serious complications. These include stricture, ulceration, haemorrhage, perforation, and malignant degeneration.[3–6] Such complications occur in approximately 50% of patients with Barrett's columnar lined lower oesophagus.[4 5] It is well recognised that patients with Barrett's columnar lined lower oesophagus represent the worst end of the reflux spectrum with the most severe forms of lower oesophageal sphincter and pump failure and consequently greater degrees of acid exposure.[7] It is unclear, however, why the columnarisation is prone to complications in some patients while remaining quiescent in others.

Bremner has proposed that the columnar lining in Barrett's oesophagus, being gastric in character, is acid resistant, but not bile resistant.[5 8] DuPlessis[9] and Lawson[10] have both shown damage to gastric columnar epithelium by exposure to duodenal contents. Van der Veen *et al* have shown that previous gastric surgery represents an increased risk factor for the development of adenocarcinoma in Barrett's columnar lined lower oesophagus[11] and Gillen *et al* have demonstrated increased bile acid concentrations in the stomach of patients who develop complications.[12] Increased oesophageal alkaline exposure has been previously demonstrated in patients with Barrett's columnar lined lower oesophagus and it has been suggested that this might be secondary to increased duodenogastric reflux using discriminant analysis in a small number of patients.[7]

The aim of this study was, first, to measure the pH profile in the lower oesophagus of patients with Barrett's oesophagus and by simultaneous ambulatory oesophageal and gastric pH monitoring, to correlate any alterations with changes in gastric pH. The second aim was to relate the effects of acid and alkaline exposure to the development of complications in Barrett's oesophagus.

Methods

PATIENTS

Patients were entered into the study after their first upper gastro-intestinal endoscopy showed Barrett's oesophagus. Oesophageal manometry and ambulatory gastric and oesophageal pH monitoring were performed within seven to 14 days of the first endoscopy. The results of pH monitoring (presence of abnormal acid and alkaline exposure in the oesophagus and stomach) and manometric findings (presence of defective lower oesophageal sphincter and defective oesophageal peristaltic pressure) were compared

TABLE I *Characteristics of patients with Barrett's columnar lined lower oesophagus comparing simple Barrett's with the complications of ulceration, stricture or malignant change*

	Simple n=16	*Complicated n=10*
Male:female ratio	8:8	6:4
Age*	59 (15)	67 (11)
Extent of Barrett's columnar epithelium* (cm)	5·9 (2·4)	5·7 (2·9)

*Values are means (standard deviation).

in patients with and without complicated Barrett's oesophagus (ulcer, stricture, or carcinoma).

Twenty six patients with Barrett's columnar lined lower oesophagus were diagnosed by endoscopic documentation of the squamocolumnar junction being circumferentially more than 3 cm above the endoscopically determined anatomical oesophagogastric junction. The demonstration of glandular epithelium (fundic, junctional, or intestinal metaplastic) in biopsy specimens from the lower oesophagus confirmed the diagnosis in all cases. Patients with previous oesophageal or gastric surgery were excluded from the study. The presence of complications was defined by the endoscopic demonstration of ulceration within the columnar lined segment (one), oesophageal adenocarcinoma (one), or oesophageal stricture (eight), the latter defined by a narrowing which prevented the smooth passage of a standard (11 mm) endoscope. The age and sex distribution of patients with and without complications in their Barrett's oesophagus is shown in Table I.

NORMAL VALUES

The range of normal values for the oesophageal pH environment has been derived from previous study of 30 asymptomatic control subjects in this laboratory.[13] Similarly the range of normal values for gastric pH monitoring has been derived from studies in 10 asymptomatic control subjects who had simultaneous ambulatory oesophageal and gastric pH monitoring.[14]

MANOMETRY

Oesophageal manometry was performed using a catheter containing five solid state transducers located at 5 cm intervals along its length and oriented radially around the circumference of the catheter (Gaeltec Ltd, UK). This was attached to a multichannel pen recorder (Lectromed, UK). All procedures were performed in fasted patients. With the patient in the supine position the manometry catheter was passed transnasally into the stomach. The lower oesophageal sphincter was assessed by the station pull through method of Winans and Harris,[15] measuring the lower border of the high pressure zone (defined by a rise in the end-expiratory pressure of 2 mm Hg or more above gastric baseline) and the upper border (return of the end expiratory pressure to within 2 mm Hg of the thoracic baseline) as well as the respiratory inversion point and the end expiratory pressure at each station.

Oesophageal body peristalsis was measured by placing the catheter in the oesophageal body at representative levels and asking the patient to swallow a 5 ml water bolus, or dry swallow alternately for 10 swallows. Oesophageal peristaltic amplitude was measued at each of six representative levels along the length of the oesophagus. The mean amplitude at each level was then plotted on charts where the 90th and 10th percentiles of pressure at these levels in our previously defined normal volunteers were represented by horizontal boxes[16] (Fig 1). Impaired peristalsis was defined as a mean pressure outside the lower limit of normal for that level. These lower limits of normality correspond well with the pressures of ineffective peristalsis as defined by Kahrilas and Dodds.[17]

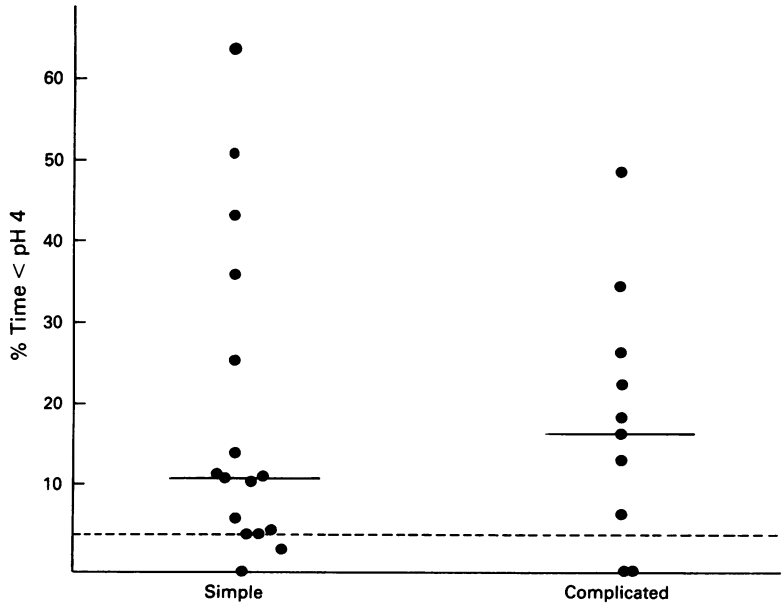

Figure 1: Median peristaltic amplitude during wet swallows at each level of the oesophageal body illustrating the poor motility in patients with Barrett's oesophagus with and without complications, compared with the normal range (10th and 90th percentiles outlined by boxes).

pH MONITORING

All 26 patients underwent 24 hour ambulatory oesophageal pH monitoring. Sixteen patients underwent simultaneous ambulatory oesophageal and gastric pH monitoring. All strictures were dilated at the time of diagnosis (and before pH monitoring when found at presentation). Patients were asked to withhold acid reducing medication for 48 hours before the study. H_2 receptor blockers and Gaviscon were the only acid suppressing agents taken by this group of patients and no patients were taking proton pump blockers.

Two antimony pH probes (Monocrystant Mod 0011, Synectics Medical, Sweden) were calibrated at Ph 1 and 7 at 35°C before the study and then passed transnasally so that the upper probe lay 5 cm proximal to the upper border of the manometrically determined lower oesophageal sphincter and the lower probe 10 cm distal to its lower border. A silver-silver chloride reference electrode was attached to the skin on the chest wall. The probes were connected to a portable recorder (Digitrapper – Synectics

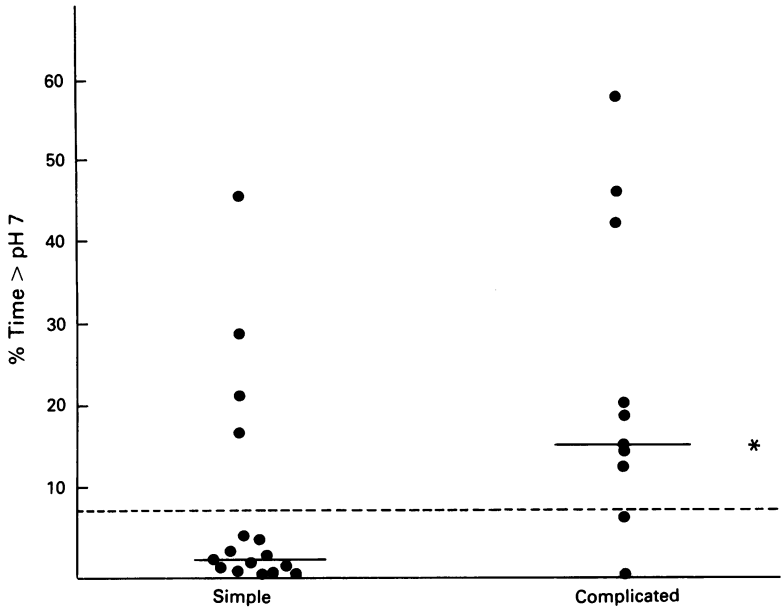

Figure 2: Percentage time that the lower oesophagus was exposed to acid (pH <4) in patients with simple or complicated Barrett's oesophagus. NS=no significant difference, p>0·05, Wilcoxon's rank sum test. ....=upper limit of normal, __=median acid exposure (median=10·8%, interquartile range 5–18% for simple Barrett's versus 6·6–26% for complicated Barrett's oesophagus).

Medical, Sweden) capable of holding data from two channels over a period of 24 hours. Sampling frequency was once every four seconds. During the study the patients were asked to consume a standard diet[18] and to record their meal and sleep periods and any symptoms in a diary. The data were off loaded to a computer (Amstrad PC1640, IBM-compatible) and processed using the Esophagram software (Gastrosoft Ltd, USA). For the purposes of this study the percentage of the time that the intraoesophageal pH was below 4 and above 7 was calculated, as was the percentage of time that the intragastric pH was above 4 as well as documentation of individual alkalinisation episodes. The normal upper limits of oesophageal acid and alkaline exposure as defined by the 90 percentile in our normal volunteers was 5·1% and 8·4% respectively. The corresponding values for percentage of the time the gastric pH was above 4 was 12·2%.

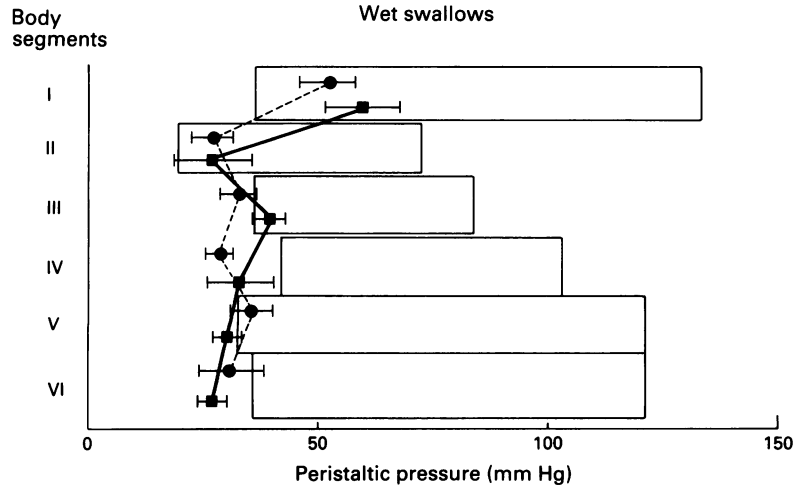

*Figure 3: Percentage time that the lower oesophagus was exposed to alkali (pH>7) in patients with simple or complicated Barrett's oesophagus. *=significant difference, p<0·05, Wilcoxon's rank-sum test. ....=upper limit of normal, __=median alkaline exposure (median=2·1%, interquartile range 0·8%, for simple Barrett's versus 15% interquartile range 11–25% for complicated Barrett's oesophagus).*

STATISTICAL ANALYSIS

The percentage time spent in each pH category for each group was expressed as the median ± interquartile range. For intergroup comparison the data were assumed to be non-parametric and the Wilcoxon's rank-sum comparison was used. To compare the number of patients with normal and abnormal gastric pH profiles the Fisher's exact test was applied. In each case the probability of a $p<0·05$ was regarded as statistically significant.

Results

The duration of exposure of the lower oesophagus to acid in patients with Barrett's columnar lined lower oesophagus is illustrated in Figure 2, and shows that both groups had markedly increased acid exposure (% total time pH <4= 19·2 (5·1)% *v* 19·3 (4·9)%), in comparison with asymptomatic controls. There was, however, no significant difference between the uncomplicated Barrett's patients and those with complications. In contrast, patients with complications of Barrett's columnar lined lower oesophagus had a significantly greater oesophageal alkaline exposure than those without complications (% total time pH >7=24·2 (6·0)% *v* 8·4% (3·4), Wilcoxon's rank-test $p<0·05$, Figure 3). Alkaline exposure in uncomplicated patients was similar to that in our control subjects.

Oesophageal motility studies showed that 16 of the 26 patients with Barrett's columnar lined lower oesophagus had a defective lower oesophageal sphincter as defined by Zaninotto *et al*[19] and a similar proportion of each group had weak or ineffective lower oesophageal peristaltic amplitude. The mean peristaltic amplitude in each group is illustrated by the box diagram in Figure 1. In addition 28% of swallows in the complicated group and 32% in the uncomplicated group showed non-propagated simultaneous contraction in the distal levels of the oesophageal body.

Sixteen patients underwent simultaneous gastric and oesophageal pH monitoring. Table II shows that of the seven patients with increased gastric alkaline exposure, five had increased oesophageal alkaline exposure, illustrating a temporal relationship between gastric and oesophageal alkalinisation. In the nine patients with normal gastric pH patterns eight had a normal oesophageal alkaline profile. This relationship was statistically significant using the Fisher's exact test ($p<0·05$).

Discussion

This study confirms that patients with Barrett's columnar lined lower oesophagus have a marked degree of acid gastrooesophageal reflux, considerably exceeding that seen in the majority of patients with erosive oesophagitis without columnarisation.[7] The finding of a greater degree of alkaline exposure in the lower oesophagus of patients with complications of their Barrett's

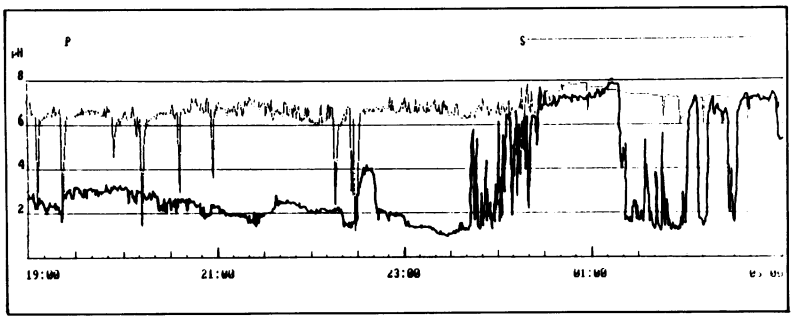

Figure 4: Example of a pH profile printed by the Gastrosoft computer programme from simultaneous oesophageal and gastric monitoring in a patient with Barrett's oesophagus which illustrates abnormal alkalinity in both the oesophagus (with pH>7) and the stomach (pH>4). Upper tracing is oesophageal and the lower tracing (in heavy print) is the gastric pH, which is normal between 2 and 4 initially and then illustrates an alkaline trend which is associated with oesophageal alkalinisation from 00.30 to 01.30 hours.

oesophagus distinguishes them from those without complications and poses the question as to the origin of this distinction.

The data from patients who had undergone simultaneous ambulatory oesophageal and gastric pH monitoring show a correlation between normal and abnormal gastric and oesophageal alkalinisation. In only three of the 16 patients did the gastric and oesophageal findings disagree. This supports the findings of a previous study which described increased oesophageal alkaline exposure in patients with Barrett's oesophagus.[7] In order to obviate the criticism of increasing intraoesophageal pH being related to salivation, however, the present study has extended the application of simultaneous ambulatory oesophageal and gastric pH monitoring and enabled a valid correlation to be made between oesophageal and gastric alkalinisation. The data from pH monitoring do not give direct information on the constituents or origin of the body fluids being measured. The relationship between the gastric and oesophageal pH profiles, however, suggests the probability of duodenogastrooesophageal reflux. Several authors have shown a relationship between the degree of gastric alkalinity and the concentration of bile salts in gastric juice over prolonged periods. Robles *et al* found a correlation of high gastric pH and bile concentrations in controls and in patients who had undergone vagotomy and pyloroplasty.[20] Lendrum *et al* took samples from the oseophagus of both normal volunteers and patients with Barrett's oesophagus and found a significant correlation between rising pH and increasing concentrations of bile salts.[21]

Because of the low resting pH of the stomach, episodes of duodenogastric reflux show relative alkalinity. The per cent time that gastric pH is >4 has been widely used in estimating abnormal increases in gastric pH.[20 22] Brown *et al* used this threshold in normal subjects and in patients after cholecystectomy.[22] It is interesting to note that their normal values were similar to ours, which shows a degree of reproducibility in the normal range. An alternative method of assessing the possibility of duodenogastric reflux is the Fuchs discriminative score.[23]

pH >7 was used to define abnormal alkalinity in the oesophagus because in normal volunteers the pH of the oesophagus is between 4 and 7 for 96% of the time.[7] Time spent outside this range for longer than the 90th percentile in normal subjects implies an abnormal pH exposure. This does not imply that when the pH is between 4 and 7 – that is, within the normal range – that there is no reflux. Indeed it is quite possible that at this pH range there is a mixture of gastric acid and duodenal alkaline juices which may be damaging (with toxic synergism) to the oesophageal mucosa, but this cannot be assessed using the parameter of pH. Qualitative and quantitative assessment of the refluxate during these times of normal pH awaits developments in new biotechnology.

The association of complications in Barrett's oesophagus with the presence of increased duodenogastric reflux is supported by the presence of increased concentrations of bile salts in gastric aspirates of such patients.[12] In view of the fact that there is virtually no resistance to gastro-oesophageal reflux in patients with Barrett's oesophagus,[11 24] this increased duodenogastric reflux is likely to result in significant exposure of the oesophageal mucosa to duodenal juices.

Other possible explanations for increased oesophageal alkaline exposure in patients with complicated Barrett's oesophagus include bacterial alkalinisation of saliva either because of pooling in the oesophagus or because of dental infection. The pooling of saliva in this study was minimised by dilatation of the oesophagus before the pH monitoring period and motility studies showed that a similar proportion of patients in both groups had ineffective peristalsis.

The temporal relationship between oesophageal alkalinisation and abnormal gastric pH patterns lends support to the belief that the difference in pH profiles in Barrett's patients is not the result of salivary pooling or excessive salivation. A conclusive argument will only become available, however, when prolonged in vivo measurements of oesophageal bile concentrations or duodenal enzymes can be achieved. Attempts to measure bile salts directly by continuous aspiration have produced conflicting results.[25-30] Indeed, despite their arguments that bile had little role in the pathogenesis of oesophagitis the data of Gotley *et al*[28] show that 75% of patients with gastrooesophageal reflux disease do have bile in their reflux aspirates at concentrations >30 μmol/l and that higher concentrations of bile were more common at night, at which time our gastric pH profiles show greatest alkalinity. Further support for this concept has recently come from the work of Iftikhar *et al* who showed higher concentrations of bile in oesophageal aspirates from patients with Barrett's columnar lined lower oesophagus.[30] In considering this, Stoker and Williams conclude that

TABLE II *Relationship of oesophageal and gastric alkalinisation in patients with Barrett's oesophagus*

	Oesophageal alkalinisation	
	*Normal**	*Increased*
Gastric alkalinisation		
Normal*	8	1
Increased	2	5

*Normal values for oesophageal alkalinisation are <8·4% of the time above pH 7, and for gastric alkalinisation <12·0% of the time above pH 4. Significant at p<0·05, Fisher's exact test.

when gastric and duodenal secretions mix there may be a toxic synergism between the two that leads to mucosal disruption and intracellular damage to oesophageal cells.[29]

The contribution of duodenogastrooesophageal reflux may be just one of a number of damaging influences in the lower oseophagus of patients with Barrett's oesophagus. From Table I it can be seen that the patients with complications of their Barrett's oesophagus are older (albeit not statistically significant) than patients without complications. It is possible, and indeed would be logical, that increased duration of exposure to gastrooesophageal reflux, independent of the nature of the refluxate, may be a factor in the development of complications in Barrett's oesophagus. This study has clearly shown, however, a correlation between increased alkaline exposure of the stomach and the oesophagus with the development of complications.

These results suggest, first, that simultaneous 24 hour ambulatory oesophageal and gastric pH monitoring is helpful in patients with Barrett's columnar lined lower oesophagus to help identify those patients at greater risk of developing complications. Patients with increased oesophageal alkalinisation require careful surveillance because of their increased likelihood of developing complications. Second, such findings may have therapeutic implications, as optimal therapy for patients with oesophageal alkaline exposure as well as acid exposure may need to be different from those with acid exposure alone. The role of the individual constituents of duodenal juice in the genesis of complications and of surgical procedures such as antireflux surgery and duodenal diversion in their prevention merits further investigation.

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