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ALIMENTARY TRACT

Evaluation of the magnitude of gastro-oesophageal reflux in Barrett's oesophagus

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Abstract

A manometric study to determine the role of gastro-oesophageal reflux in Barrett's oesophagus was performed on 20 patients with Barrett's oesophagus and 53 patients with reflux oesophagitis without Barrett's oesophagus (25 with mild oesophagitis and 28 with severe oesophagitis). For the same reason, the 20 patients with Barrett's oesophagus also underwent 24 hour continuous oesophageal pH monitoring, and the results obtained were compared with those of 20 oesophagitis patients without Barrett's oesophagus (10 with mild oesophagitis and 10 with severe oesophagitis). The manometric results show that the motor changes found in the Barrett's group are specific but similar to the motor dysfunction associated with reflux oesophagitis. Motor anomalies are probably related more to the inflammatory process in the oesophageal wall than to the metaplastic changes themselves. The pH monitoring results show that while reflux in the Barrett's oesophagus patients was greater overall than in the oesophagitis group without Barrett's oesophagus, the changes are similar when the results are compared with the severe oesophagitis group. In conclusion there are other factors besides gastro-oesophageal reflux involved in the pathogenesis of Barrett's oesophagus.

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The pathogenesis of Barrett's oesophagus has been controversial since Barrett first described it in 1950.[1] There are two general theories – those of congenital and acquired pathogenesis. The invariable association of Barrett's epithelium with gastro-oesophageal reflux supports the view that the condition is acquired.[2-20] On the other hand, reflux may exist in the absence of Barrett's epithelium and give rise to the changes of oesophagitis only. Why Barrett's epithelium develops in some patients with gastro-oesophageal reflux and not in others is unknown, although some authors[21-23] suggest that the magnitude of reflux is a very important factor. To examine this hypothesis we assessed pH profiles and manometric studies of the lower oesophageal sphincter and the lower third of the oesophagus in two separate groups of patients – one with Barrett's oesophagus and one with oesophagitis without Barrett's oesophagus – and compared reflux between the groups.

TABLE I *Characteristics of the patient and the control groups*

	Barrett's oesophagus (n=20)	*Control group (n=20)*	*Mild oesophagitis (n=25)*	*Severe oesophagitis (n=28)*
Age (yrs)				
Mean (SD)	43·8 (15·6)	42·1 (13)	49·3 (14·5)	59·2 (11·6)
Median (Q_1–Q_3)	49·5 (37·5–64·5)	45·5 (28·5–59·5)	49 (40–59)	59 (56–68)
Sex (M/W)	14/6	10/10	11/14	17/11

Q_1–Q_3 = interquartile range.

Methods

PATIENTS

The study was performed in 73 patients divided into three groups – patients with mild oesophagitis without Barrett's oesophagus (n=25), those with severe oesophagitis without Barrett's oesophagus (n=28), and patients with Barrett's oesophagus (n=20). Oesophagitis was considered mild when endoscopy showed non-confluent erosions appearing as red spots or stripes which may have been coated with fibrin. It was considered severe when there were circumferential confluent longitudinal erosions that bled easily. Barrett's oesophagus was confirmed when the endoscopy showed circumferential columnar metaplasia in the distal oesophagus over a length of 3 cm or more in continuation with the cardia. The diagnosis was confirmed in all patients by anatomicopathological study. Oesophagitis was also present in 10 of the 20 Barrett's patients.

Patients with columnar metaplasia of less than 3 cm in length or those in whom this metaplasia appeared in the form of tongues or isolated islands were excluded from the study. We also excluded patients with strictures secondary to gastro-oesophageal reflux, as we considered that these could determine oesophageal motor anomalies per se, and patients with oesophagitis secondary to generalised diseases (collagenopathies, etc) and previous Heller's myotomy.

The control group comprised 20 asymptomatic subjects with normal endoscopy and biopsy appearances.

The age and sex characteristics of each group are shown in Table I.

The study protocol was approved by the Human Research Committee of this hospital (a regional teaching hospital) and informed written consent was obtained from each subject before oesophageal endoscopy, manometry, and 24 hour pH monitoring.

MANOMETRIC STUDY

Manometry was performed in 73 patients and 20 control group subjects using a probe with three microtransducers (Gaeltec Ltd, Microtransducers Pressure) located at the distal end, 120° radially to one another and spaced 5 cm apart. The electrical signals of these sensors were picked up by the amplifiers of a Hewlett-Packard 7754 B System polygraph and recorded on heat sensitive paper. The method for intraluminal oesophageal manometry, described in previous reports,[24] was as follows. After the patient had fasted for at least 12 hours and had not received medication for a minimum of 48 hours, the recording probe was passed through the nostrils into the stomach. The patient was then placed in the supine position and three rapid pull-throughs were performed through the lower oesophageal sphincter with the recording sensors. Discontinuous pull-throughs were made in the oesophageal body every 2 cm, and at least six dry deglutitions were recorded in each position. These discontinuous pull-throughs were performed until the upper oesophageal sphincter was reached. To calculate the lower oesophageal sphincter pressure in each subject, the mean was taken of the nine measurements obtained, taking the gastric expiratory pressure as zero reference. Pressure of the deglutition waves of the lower third of the oesophageal body was calculated as the mean of all the pressure peaks recorded, taking the basal oesophageal pressure as zero reference. The time interval between the onset of peristaltic waves at each pair of adjacent recording sites was measured. The 5 cm covered, divided by the time of wave travel, gives the propagation velocity. The contraction waves were considered tertiary when they began simultaneously at two or three adjacent recording sites. Finally, deglutition without response was considered when no contraction wave was seen after the deglutition. In short, the parameters studied were the following: the mean basal pressure of the lower oesophageal sphincter (expressed in mmHg) the mean amplitude of the contractile waves of the distal third of the oesophageal body (mmHg), the mean propagation velocity of the waves of the distal third of the oesophageal body (cm/second), and the mean percentages of tertiary waves and of deglutitions without response in the distal third of the oesophageal body.

pH METRIC STUDY

Measurement of pH was performed in the 20 control group subjects, the 20 Barrett's patients, and in 20 oesophagitis patients without Barrett's oesophagus – 10 with mild oesophagitis and 10 with severe oesophagitis.

The pH recording system comprised: (a) a GK 2801 C pH electrode (Radiometer, Copenhagen); (b) aPHM 62 Standard pH meter (Radiometer, Copenhagen); and (c) a Hewlett-Packard 7754 B System polygraph with a bioelectrical amplifier (Medium Gain DC-Preamplifier 8802 A).

The oesophageal pH monitoring procedure was similar to that described by Johnson and De Meester.[25] After the patient had fasted for 12 hours and not received medication for 48 hours, the recording electrode was passed through the nose into the oesophagus and positioned 5 cm above the upper portion of the lower oesophageal sphincter, previously located by the manometric study. Continuous pH recording was performed for 24 hours. During this time the patient was allowed to stand, sit, walk around the polygraph, or lie down, and a standard diet was served. A reflux episode was considered to have occurred when the pH in the oesophagus dropped below 4. The following parameters were evaluated in all patients and control subjects: total number of reflux episodes associated with a pH<4, the number of reflux episodes with pH<4 and duration of more than five minutes, duration of the longest episode, the total time during which the pH was <4, and the percentage of total time that the oesophageal pH was <4.

STATISTICAL METHODS

For each of the parameters studied, the mean (SD) were calculated, as well as the medians and interquartile ranges. To compare the different groups we used Student's combined *t* test with previous log transformation of data, given the asymmetry of distribution found in some cases. The parameters that underwent this transformation were related to the pH metric study, and were the following: longest episode pH<4 (minutes), total time pH<4 (minutes), and percentage time pH<4.

TABLE II *Manometric evaluation of the lower oesophageal sphincter and the distal third of the oesophageal body*

	Barrett's oesophagus (n=20)	*Control group (n=20)*	*Mild oesophagitis (n=25)*	*Severe oesophagitis (n=28)*
Mean basal pressure (LOS) (mmHg)				
Mean (SD)	10 (6·1)	17·2 (6·5)**	14·7 (5·2)**	9·1 (4·1)
Median (Q_1–Q_3)	10 (4·5–12)	16 (12·8–20·3)	14·7 (10·2–18·7)	10·2 (6–13)
Mean amplitude of the contractile waves (mmHg)				
Mean (SD)	32·8 (22·8)	25·5 (8·9)	30·6 (23·5)	22·3 (9·4)
Median (Q_1–Q_3)	27·7 (17·6–40)	27·1 (18·7–30·5)	20·8 (16–30·2)	19 (13·7–30·6)
Propagation rate of the contractile waves (cm/sec)				
Mean (SD)	3·6 (1·1)	3·9 (1·3)	3·7 (1·3)	3 (0·7)
Median (Q_1–Q_3)	3·5 (2·5–4·1)	3·6 (2·9–4·6)	3·5 (3·1–5)	3·2 (2·6–4·1)
Percentage of tertiary waves				
Mean (SD)	34·8 (37·3)	7·4 (12·2)*	36·7 (32·8)	64·9 (41·5)*
Median (Q_1–Q_3)	22 (0–60)	0 (0–15)	33 (0–50)	100 (40–100)
Percentage of deglutitions without motor response				
Mean	14·3 (22)	0**	4 (18·1)**	17·1 (30·1)
Median (Q_1–Q_3)	0 (0–20)	0 (0–0)	0 (0–0)	0 (0–30)

*p<0·05 compared with Barrett's oesophagus group; **p<0·01 compared with Barrett's oesophagus group.
Q_1–Q_3=interquartile range. LOS=lower oesophageal sphincter.

TABLE III *Comparison of the manometric evaluation between Barrett's oesophagus without oesophagitis and Barrett's oesophagus with oesophagitis groups*

	Barrett's oesophagus without oesophagitis (n=10)	*Barrett's oesophagus with oesophagitis (n=10)*
Mean basal pressure (LOS) (mmHg)		
Mean (SD)	13·4 (5·8)	6·4 (4·4)**
Median (Q_1–Q_3)	11·6 (9·7–17·1)	4·5 (3·7–11·1)
Mean amplitude of contractile waves (mmHg)		
Mean (SD)	33·7 (17·3)	32·5 (27·7)
Median (Q_1–Q_3)	37 (18·2–47·5)	27·7 (17·6–36·3)
Propagation rate of contractile waves (cm/sec)		
Mean (SD)	4 (1·3)	3 (0·7)
Median (Q_1–Q_3)	3·7 (3·1–5)	3·1 (2·5–3·7)
Percentage of tertiary waves		
Mean (SD)	29 (37·5)	40 (38·6)
Median (Q_1–Q_3)	11 (0–55)	40 (12–50)
Percentage of deglutitions without motor response		
Mean (SD)	1·7 (4·9)	23·2 (29·9)*
Median (Q_1–Q_3)	0 (0–7)	0 (0–55)

*p<0·05; **p<0·01.
LOS=lower oesophageal sphincter. Q_1–Q_3=interquartile range.

Results

MANOMETRIC STUDY

(1) Comparison of the Barrett's group with the remaining study groups (Table II). The lower oesophageal sphincter pressure in the Barrett's group was significantly lower than that of the control and the mild oesophagitis groups. There were no differences compared with the severe oesophagitis group.

The mean amplitude and propagation rate of the contractile waves in the distal third of the oesophageal body in the Barrett's group were similar to those found in the control, mild, and severe oesophagitis groups.

The percentage of tertiary waves in the distal oesophagus in the Barrett's group was significantly higher than that found in the control group and significantly lower than that reached in the severe oesophagitis group.

The percentage of deglutitions without motor response in the distal oesophagus in the Barrett's group was significantly higher than that observed in the control and mild oesophagitis groups, with no differences between the Barrett's and severe oesophagitis groups.

(2) Comparison of the Barrett's oesophagus without oesophagitis group and the Barrett's oesophagus with oesophagitis group. As can be seen in Table III, the presence of oesophagitis and Barrett's oesophagus did not imply changes in the mean amplitude and propagation rate of the contractile waves in the distal third of the oesophagus. Both the percentage of tertiary waves and deglutitions without response increased, however, in the presence of oesophagitis, although this increase was only significant for the deglutitions without response. It must also be noted that the presence of oesophagitis in the Barrett's group was associated with a significant decrease in the lower oesophageal sphincter pressure.

pH METRIC STUDY

As can be seen in Table IV, the Barrett's group patients had appreciably higher reflux rates than those of the control group, with a high statistical significance for all the parameters studied. When comparing Barrett's group with the global oesophagitis group, the reflux rates were higher in the former, reaching statistical significance for all parameters except for the total number of episodes with pH<4. When oesophagitis patients were subgrouped into mild and severe, however, the differences with the Barrett's group were maintained in the mild oesophagitis subgroup but not in the severe oesophagitis subgroup.

Discussion

The association of Barrett's oesophagus with gastro-oesophageal reflux has been established by a number of authors,[2-20] and the 'congenital' theory of pathogenesis is presently considered valid in certain cases only. In this respect our results support the 'acquired' theory – the 20 patients with Barrett's oesophagus were shown to have gastro-oesophageal reflux by 24 hour continuous pH monitoring, although two of them were asymptomatic. Why Barrett's epithelium develops in some patients with gastro-oesophageal reflux and not in others remains unknown. Some authors[21-23] have found that gastro-oesophageal reflux is greater in patients with Barrett's oesophagus than in those with oesophagitis without Barrett's oesophagus. Our data coincided with this theory when we compared the Barrett's group with the global oesophagitis group. When we divided the oesophagitis group into two subgroups, mild and

TABLE IV *24 Hour pH monitoring results for each group of patients*

	Barrett's oesophagus (n=20)	*Control group (n=20)*	*Oesophagitis group (n=20)*	*Mild oesophagitis (n=10)*	*Severe oesophagitis (n=10)*
No of reflux episodes pH<4					
Mean (SD)	81·4 (49·7)	13·3 (13·7)***	73·1 (38·3)	71·2 (30·7)	74·7 (45·1)
Median (Q_1–Q_3)	83·5 (35·5–107)	7·5 (2·5–15·5)	77 (50–98)	86·5 (59–100)	72 (42–81)
No of reflux episodes pH<4 of >5 min in duration					
Mean (SD)	13·8 (5·9)	0·25 (0·4)***	9·3 (8)*	4·6 (3·4)***	13·2 (8·7)
Median (Q_1–Q_3)	12 (10–17·5)	0 (0–0·5)	6·5 (3–10·5)	3 (2–4)	10 (7–18)
(L) Longest episode pH<4 (min)					
Mean (SD)	100·5 (173)	3·4 (2·1)***	47 (85·5)**	19·7 (8·5)***	68·8 (112)
Median (Q_1–Q_3)	40 (29–87)	3 (2–4·5)	22 (14–31)	14 (14–22)	31 (22–38)
(L) Total time pH<4 (min)					
Mean (SD)	357 (271·6)	10·8 (7·4)***	215 (252)***	97 (44·4)***	310 (310)
Median (Q_1–Q_3)	310·5 (181·5–414)	10·5 (5–15)	99 (68·5–174·5)	73 (62–130)	157 (98–498)
(L) % Time pH<4					
Mean (SD)	26·7 (20·1)	0·8 (0·5)***	15·4 (18·3)***	6·8 (2·8)***	22·4 (22·4)
Median (Q_1–Q_3)	21·3 (13·7–33·5)	0·8 (0·3–1·1)	7·1 (5–13)	5 (4·5–8·9)	12·5 (6·7–35·6)

*p<0·05 compared with Barrett's oesophagus group; **p<0·01 compared with Barrett's oesophagus group; ***p<0·001 compared with Barrett's oesophagus group.
(L)=statistical comparison made using log transformation of the data.

severe oesophagitis, however, and compared these with the Barrett's group, we observed that the reflux parameter values were greater in the Barrett's group than in the mild oesophagitis group, but there was no difference in these values between the Barrett's oesophagus and severe oesophagitis groups. This means that the development of Barrett's oesophagus is not due to a greater quantity of reflux.

Our manometric findings in patients with Barrett's oesophagus are in agreement with some authors.[8 26 27] In patients with Barrett's oesophagus, the manometric oesophageal pattern was no different from that found in patients with reflux oesophagitis. The hypotensive lower oesophageal sphincter and the other manometric findings in the lower third of the oesophagus (tertiary waves, deglutitions without response) are not specific for Barrett's oesophagus and they can occur in patients with reflux oesophagitis. These facts suggest that changes in the oesophageal motility depend on the inflammation of the oesophageal wall and not on epithelium replacement.

This concept is supported by the finding that the grade of hypotensive lower oesophageal sphincter and the percentage of deglutitions without motor response were greater than in Barrett's patients without oesophagitis than in those with oesophagitis.

These results suggest that other factors besides gastro-oesophageal reflux are implicated in the pathogenesis of Barrett's oesophagus. It is still not known which constituents of the refluxed material are important in the development of the columnar epithelium. Acid and pepsin have received the most attention, but Barrett's mucosa has been observed to develop after total gastrectomy with oesophagojejunostomy.[12] This observation indicates that acid and pepsin are not the only pathogenetic factors and suggests a role for bile acids or for small intestinal and pancreatic secretions. In addition to gastro-oesophageal reflux, genetic factors seem to play a part in the development of Barrett's oesophagus, as indicated by reports of families with a high prevalence of Barrett's oesophagus.[28 29]

An undefined pathogenic role for cigarette smoking and alcohol ingestion has also been suggested, because of the frequent association of these habits with Barrett's oesophagus.[30] The influence of these and other factors in the development of Barrett's oesophagus and elucidation of the main factor in its pathogenetic mechanism remain, however, to be determined.

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