Oesophageal motor responses to gastro-oesophageal reflux in healthy controls and reflux patients

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Abstract

Aims—To compare oesophageal motor responses to gastro-oesophageal reflux (GOR) in 16 healthy controls (group 1) and 25 reflux patients, 15 without (group 2) and 10 with (group 3) oesophagitis.

Methods—All subjects underwent 24 hour ambulatory oesophageal pH measurements (5 cm above the lower oesophageal sphincter (LOS)) combined with pressure monitoring (5, 10, and 15 cm above the LOS for oesophageal body motility and 27 cm above the LOS for voluntary swallow detection). Contraction patterns (peristaltic, simultaneous, isolated, mixed type, and non-transmitted swallows) and peristaltic contraction wave characteristics (amplitude, duration, and velocity) during GOR were compared in the three groups.

Results—The average number of motor activities per minute was significantly higher in group 1 ($p < 0.05$). In all groups, the most common motor contraction pattern was peristaltic. The percentage of peristaltic activity per subject was significantly higher in group 1 ($p < 0.05$). There were no significant differences in other contraction patterns among the three groups ($p > 0.05$). Of the peristaltic contraction wave characteristics there were no significant differences in any parameters (amplitude, duration, and velocity) among the three groups ($p > 0.05$). The average pH increment in response to motor activities was significantly higher in group 1 ($p < 0.05$).

Conclusions—Motor responses to GOR were found to be predominantly primary peristaltic in all groups. During GOR, reflux patients have less frequent activity, a smaller proportion of activity is peristaltic, and the average pH increment in response to motor activities is reduced compared with controls.

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Keywords: acid clearance; ambulatory; oesophagus; pH; pressure

Ambulatory long term pressure recording has become possible due to three developments: pressure sensor miniaturisation resulting in a smaller diameter pressure catheter¹; the introduction of portable digital data recorders with an improved data compression technique² or

with a large storage capacity³; and the development and validation of automatic computer analysis which has made it possible to analyse long term oesophageal pressure data quickly, consistently, and objectively.⁴⁻⁶ Combined with pH monitoring, ambulatory pressure recording can be used to study oesophageal motor responses during gastro-oesophageal reflux (GOR) and to elucidate the mechanisms that lead to the restoration of a normal oesophageal pH.

Oesophageal acid clearance after GOR depends on two important mechanisms: effective oesophageal peristalsis to return the displaced gastric contents to the stomach,⁷ and swallowing saliva to neutralise the residual acid coating the oesophageal mucosa.⁸ To evaluate acid clearance, previous studies have used a non-physiological method to simulate GOR by infusing a bolus of 0.1 M hydrochloric acid into the oesophagus. The pH increments in response to swallows, taken on command at a fixed time interval, were monitored.⁹ Using ambulatory combined pH and pressure recording, motor responses during naturally occurring acid GOR have been reported in ambulant non-hospitalised reflux patients^{10, 11} and healthy subjects.¹² This study aimed to investigate reflux induced motor activities in patients with proven pathological reflux, and to compare the findings with those from normal control subjects under ambulant conditions.

Methods

SUBJECTS

Subjects were divided into three groups. Group 1 consisted of 16 healthy controls (12 men, mean (SD) age 34.9 (11.6) years). Exclusion criteria were: a history of heartburn more than once every fortnight, dysphagia or regurgitation, the use of medications that interfere with oesophageal motility or gastric pH, previous chest or upper abdominal surgery, diabetes mellitus, and any connective tissue or neurological disorder. Groups 2 and 3 consisted of 25 consecutive patients with heartburn, regurgitation, dysphagia, or chest pain, and pathological acid reflux on 24 hour ambulatory pH monitoring. Group 2 contained 15 patients (13 men, mean age 53.7 (12.6) years) with a normal oesophagus at endoscopy; group 3 contained 10 patients (nine men, mean age 45.4 (6.3) years) with endoscopic oesophagitis (Savary-Miller grade 1 or 2). H_2 receptor antagonists and prokinetic agents were discontinued for 48

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hours and proton pump inhibitors for seven days prior to the study.

STATIC OESOPHAGEAL MANOMETRY AND 24 HOUR AMBULATORY pH MONITORING

All subjects underwent static manometry to exclude primary or secondary oesophageal motility disorders such as achalasia or scleroderma, followed by 24 hour ambulatory pH monitoring to confirm the presence of pathological GOR. Static manometry and 24 hour ambulatory pH monitoring have been described in our previous study.¹⁰ Briefly, static manometry was performed using a catheter with six surface mounted miniature pressure transducers (Gaeltec, Isle of Skye, UK) and an antimony pH catheter (Synectics Medical, Stockholm, Sweden) was inserted transnasally and positioned 5 cm above the manometrically defined upper margin of the lower oesophageal sphincter (LOS).

A reflux episode was defined as starting when the oesophageal pH fell below 4, and ending when the pH rose to 5. Using commercially available software (Oesophagraph, Synectics Medical, Sweden), the total, upright, and supine reflux times, the number of reflux episodes, the number of reflux episodes longer than five minutes, the longest reflux episode, and the DeMeester score were calculated.¹³ A score greater than 14.7 (based on our estimate of the ninety fifth percentile of normal volunteers) indicated abnormal acid exposure, differentiating pathological from physiological reflux.

AMBULATORY PRESSURE AND pH MONITORING ASSEMBLY

The five pressure sensor catheter (Gaeltec, Isle of Skye, UK) consisted of a 5 cm long sensor to monitor LOS pressure (the Sphinctometer),¹⁴ three surface mounted miniature strain gauge pressure sensors placed 2.5 cm, 7.5 cm, and 12.5 cm above the Sphinctometer to measure oesophageal body pressures, and a fifth pressure sensor 24.5 cm above the Sphinctometer to detect pharyngeal or cricopharyngeal activity associated with voluntary swallows. The Sphinctometer was positioned in a similar manner to the Dent Sleeve¹⁵ and recorded the integrated output of the pressure and length components of the LOS (the maximum length $\times$ pressure value occurring when its middle portion was positioned at the point of maximum LOS pressure). Therefore by positioning the four proximal sensors 2.5 cm, 7.5 cm, 12.5 cm, and 24.5 cm above it, the pressure points measured were 5 cm, 10 cm, 15 cm, and 27 cm above the maximum LOS pressure. LOS data generated by the Sphinctometer can only be used qualitatively and will not be discussed further. An antimony pH catheter was bonded to the pressure catheter so that the pH sensor was 5 cm above the upper margin of the LOS. The pressure and pH catheters were introduced transnasally under local anaesthesia. After correct positioning of the Sphinctometer in the LOS, 10 wet swallows (5 ml boluses) were given to ensure that the recorder was functioning. At the completion of the record-

ing, data were downloaded onto the host computer for semiautomatic analysis.

PRESSURE AND pH RECORDING SYSTEM

All pressure and pH measurements were monitored simultaneously at eight samples per second (the minimum sampling rate for oesophageal peristaltic activity is six samples per second)¹⁶ on a 24 hour ambulatory recording device (7-MPR, Gaeltec, Isle of Skye, UK). With an internal computer to record data in a compressed form, all pressure changes above a preset level of 6 mm Hg were recorded. Baseline data points were only stored at two second intervals when pressure changes were less than 6 mm Hg, reducing stored data by a factor of between four and 20. The resulting 24 hour recording used a maximum of 515 KB of disk space. Data were downloaded onto a 410/1 Acorn Archimedes computer (Acorn Computers, Cambridge).

AMBULATORY PRESSURE AND pH DATA ANALYSIS

Oesophageal motor activity was defined as primary if the contraction waves in the body of the oesophagus were related to a pharyngeal pressure rise of greater than 20 mm Hg or to cricopharyngeal swallowing activity, and secondary if the contraction waves were not related to pharyngeal or cricopharyngeal swallowing activity. Oesophageal motor activities were further classified as:

Peristaltic: defined as a time interval of 0.25–7 seconds between the peaks of contractions in two adjacent levels, 5 cm apart.

Simultaneous: defined as a time interval of less than 0.25 seconds between the peaks of contractions in adjacent levels.

Isolated: defined as a contraction detected at a single site when no appropriate matching contractions could be found at the other levels.

Reverse peristaltic: defined as occurring when the time interval between the peaks of the contractions in two adjacent levels was -0.25 to -1 seconds.

The motor patterns from the three channel pressure recording in the body of the oesophagus were grouped into four main contraction types: peristaltic, simultaneous, isolated, and mixed type (a mixture of peristaltic, simultaneous, and reverse peristaltic). Oesophageal motor responses to acid reflux were analysed as follows:

Automatic analysis of the pressure data was performed to classify the contraction patterns (peristaltic, simultaneous, isolated, or mixed type) and to evaluate the characteristics of the peristaltic contraction wave (amplitude, duration, and velocity).

From the analysis reflux table (containing information on all reflux episodes), the exact time of each reflux episode was identified and the contraction patterns and peristaltic contraction wave characteristics within each reflux period were noted. Manual analysis was used to identify whether contraction patterns in response to reflux were primary, secondary, or non-transmitted.

TABLE 1 Percentage total, upright, and supine reflux times for groups 1, 2, and 3

	Total reflux (%)	Upright reflux (%)	Supine reflux (%)
Group 1 (n=16)	1.35 (0.1–7.5)*	2.05 (0.2–8.6)*	0.25 (0–3.6)*
Group 2 (n=15)	10.70 (4.7–31.6)	11.50 (3.4–31.2)	12.1 (0–31)
Group 3 (n=10)	9.10 (2.7–26.4)	9.45 (0.6–22)	8.75 (0–34)

Values expressed as median percentage time (range).

* $p < 0.05$ group 1 *v* groups 2 and 3.

TABLE 2 Number of reflux episodes, total reflux duration, and associated motor responses during GOR in the three groups

	Reflux episode	Total reflux duration (min)	Associated motor activities ^a	Average number of motor activities/min Median (range)
Group 1 (n=16)	459	465.6	706 (P:625; S:81)	1.72* (0.34–5.38)
Group 2 (n=15)	794	2623.0	1923 (P:1795; S:128)	0.89 (0.25–1.61)
Group 3 (n=10)	579	1482.6	1263 (P:1156; S:107)	0.88 (0.41–1.82)

^aP, primary; S, secondary.

* $p < 0.05$ group 1 *v* groups 2 and 3.

STATISTICAL ANALYSIS

Statistical tests based on a normal distribution were used for most analyses. However, the reflux parameters (total, upright, and supine percentage times) and the average number of motor activities per minute during GOR had skewed distributions and so non-parametric methods (the Kruskal-Wallis one way analysis of variance followed by a Mann-Whitney test) were used to compare the three groups with respect to these variables.

The percentages of each type of contraction were calculated across the three groups for each subject, and the mean percentages of each type of contraction (peristaltic, simultaneous, isolated, mixed type, and non-transmitted swallows) during GOR were compared. A one way analysis of variance followed by Tukey's multiple comparison test was used to compare the mean percentage of each type of contraction per subject across the three groups.

To compare the pH increment in response to motor activities (either all types of contraction together or peristaltic contraction alone) or to peristaltic contraction wave characteristics (amplitude, duration, and velocity) across the

three groups, a repeated measures analysis of variance could not be used because different subjects occurred in different groups with widely varying numbers of repeated samples. A nested analysis of variance¹⁷ was felt to be the more appropriate method. A Tukey test for multiple comparisons was then performed to compare the pH increment in response to motor activities or peristaltic contraction wave characteristics across the three groups.

Results

REFLUX DATA

Table 1 shows the reflux parameters. When total, upright, and supine times for the three groups were compared, there was a significant difference between the groups ($p < 0.01$). For all three periods, groups 2 and 3 had significantly greater reflux than group 1 ($p < 0.01$) and there was no significant difference between groups 2 and 3 ($p > 0.05$).

REFLUX EPISODES AND ASSOCIATED MOTOR RESPONSES DURING GOR

Table 2 shows the number of reflux episodes, duration of reflux, and the associated motor activities. In all groups, the percentage of secondary activity was small (less than 11.5%) compared with primary activity. When the average number of motor activities per minute per group was compared, a significant difference was found ($p < 0.01$). In group 1 the average number of motor activities per minute (1.72) was significantly higher than that in group 2 ($p < 0.01$) and group 3 ($p < 0.05$). No significant difference was found between groups 2 and 3 ($p > 0.05$).

DISTRIBUTION OF CONTRACTION PATTERN TYPES AND PRIMARY AND SECONDARY ACTIVITIES DURING GOR

Figure 1 shows the percentage distribution of motor activities (peristaltic, simultaneous, isolated, mixed type contractions, and non-transmitted swallows) during GOR for the three groups, evaluated in the upright (fig 1A) and supine (fig 1B) periods. These show that peristaltic contraction was the most common motor activity in all groups and in both periods. Group 1 had the highest percentage and group 3 the lowest percentage of peristaltic activity.

Figure 2 shows the percentages of primary (fig 2A) and secondary (fig 2B) activities within different contraction patterns during GOR. Peristaltic activity was the predominant primary motor contraction wave in the three groups. Secondary peristaltic activity was less common than other secondary non-peristaltic activities (simultaneous, isolated, and mixed type contractions); group 3 had the lowest percentage of secondary peristaltic activity but the highest percentage of secondary simultaneous activity. No secondary non-transmitted swallows were detected.

Statistical analysis was not performed for data from figs 1 and 2 individually as the range of percentages was too great and because there were no secondary non-transmitted swallows (fig 2B). Therefore only the percentages of each type of motor activity in each group were

Figure 1: Percentages of different motor activities during GOR in the upright (A) and supine (B) period.

Figure 2: Percentages of different primary (A) and secondary (B) activities during GOR.

Figure 3: Comparison of the mean (SD) percentages of each of the five types of motor activity (peristaltic, simultaneous, isolated, mixed type contractions, and non-transmitted swallow) between the three groups. * $p < 0.05$ group 1 v groups 2 and 3.

calculated. Statistical analysis was performed to compare data between the three groups over the total period. It was inappropriate to analyse the data from the upright and supine periods, as very few data were obtained from the healthy controls (group 1) in the supine period.

Figure 3 shows the percentages of the five types of motor activities for the total period. It was found that the mean percentage of peristaltic activity per subject in group 1 was

TABLE 3 Mean (SD) percentage of peristaltic contractions in the three groups

	Percentage	Comparison	95% CI*	p Value
Group 1	67.15 (12.2)	Group 1-group 2	2.45 to 25.0	$p < 0.05$
Group 2	53.43 (12.4)	Group 1-group 3	2.43 to 27.7	$p < 0.05$
Group 3	52.08 (14.51)	Group 2-group 3	-11.5 to 14.16	$p > 0.05$

*The 95% confidence interval (CI) shows that it is 95% confident that the differences of means between group 1 and group 2, group 1 and group 3, and group 2 and group 3 lie between 2.45 and 25, 2.43 and 27.7, and -11.5 and 14.16, respectively, for the mean percentages of peristaltic activity during the total period.

TABLE 4 Mean (SD) pH increment in response to all motor activities in the total period

	pH (unit)	Comparison	95% CI*	p Value
Group 1	0.89 (0.87)	Group 1-group 2	0.43 to 0.56	$p < 0.05$
Group 2	0.39 (0.58)	Group 1-group 3	0.38 to 0.52	$p < 0.05$
Group 3	0.44 (0.56)	Group 2-group 3	-0.1 to 0.015	$p > 0.05$

*The 95% confidence interval (CI) shows that it is 95% confident that the differences of means between group 1 and group 2, group 1 and group 3, and group 2 and group 3 lie between 0.43 and 0.56, 0.38 and 0.52, and -0.1 and 0.015, respectively, for overall pH increment in response to all motor activities during the total period.

significantly higher than that in groups 2 and 3 ($p < 0.05$) (table 3). No significant difference in the mean percentage of peristaltic activity per subject was found between groups 2 and 3 ($p > 0.05$). For the other four types of motor activity (simultaneous, isolated, mixed type contractions, and non-transmitted swallow) no significant differences were found among the three groups.

pH INCREMENT IN RESPONSE TO MOTOR ACTIVITY
The mean pH increment in response to all motor activities was significantly different for the total period ($p < 0.01$) (table 4). The mean pH increment in group 1 was significantly greater than that in groups 2 and 3 ($p < 0.05$). No significant difference was found between the reflux groups.

Figure 4 shows the pH increments in response to each individual type of motor activity in each group over the total time period. Statistical analysis was performed only on the average pH increments in response to peristaltic activity. For other types of motor activity the proportion was too small when compared with peristaltic activity, and only descriptive statistics were performed. The change in pH in group 1 (table 5) was significantly higher than that in groups 2 and 3 ($p < 0.05$). No significant difference was found between the reflux groups.

COMPARISON OF PERISTALTIC CONTRACTION WAVE CHARACTERISTICS (AMPLITUDE, DURATION, AND VELOCITY)

The mean peristaltic amplitude and duration for each group at each position (5 cm, 10 cm, and 15 cm above the LOS) in the oesophagus, and the mean peristaltic wave velocity (from 15 cm to 5 cm above the LOS) for each group were calculated. No significant differences in any of these parameters, at any position, were found among the three groups.

Discussion

The aim of this study was to investigate the motor responses during GOR in healthy controls (group 1), and reflux patients without oesophagitis (group 2) and with oesophagitis (group 3). Ideally, age matched controls should have been used, but the average age of healthy controls in this study was less than that of the reflux patients. A previous study¹⁸ has shown that there is no change in peristaltic amplitude, duration or LOS pressure in asymptomatic adults from age 15 to 74 years. Another study by Khan *et al*¹⁹ showed that there was only a minor decrease in oesophageal peristaltic amplitude and primary peristalsis when asymptomatic controls over 60 years of age were compared with asymptomatic controls under 40 years of age. The subjects used in this investigation have an average age of below 60 years, therefore the difference in age between controls and reflux patients should not have had a significant effect on the results.

Total, upright, and supine reflux times were significantly higher in the reflux groups (groups 2 and 3) when compared with healthy controls, agreeing with previous studies using 24 hour

Figure 4: Mean (SD) pH increments in response to each type of motor activity during the total period.

TABLE 5 Mean (SD) pH increment in response only to peristaltic activity, and comparison among the three groups

	pH (unit)	Comparison	95% CI*	p Value
Group 1	0.99 (0.88)	Group 1–group 2	0.44 to 0.61	p<0.05
Group 2	0.46 (0.63)	Group 1–group 3	0.41 to 0.59	p<0.05
Group 3	0.49 (0.58)	Group 2–group 3	–0.11 to 0.05	p>0.05

*The 95% confidence interval (CI) shows that it is 95% confidence that the differences of means between group 1 and group 2, group 1 and group 3, and group 2 and group 3 lie between 0.44 and 0.61, 0.41 and 0.59, and –0.11 and 0.05, respectively, for overall pH increment in response to peristaltic activity during the total period.

ambulatory oesophageal pH monitoring.²⁰ There were no significant differences in the percentages of total, upright, and supine reflux between the two reflux groups. This may be a reflection of the relatively subjective nature of endoscopic grading in mild oesophagitis. A contributing factor may be that some patients had received prior acid suppression therapy from their referring specialists, altering the degree of endoscopic oesophagitis. Although it is true to say that the grade of oesophagitis tends to worsen with increasing acid exposure, this is not absolute: some patients have oesophagitis and a relatively short acid exposure time, and others have no oesophagitis and a considerably longer acid exposure time. The extent of oesophageal acid exposure cannot act as a predictor for the presence or absence of oesophagitis.

Although the control group had lower total, upright, and supine reflux times than the reflux groups, the average number of motor activities per subject in response to GOR was significantly higher. The importance of the frequency of oesophageal motor activity in acid clearance was shown by Paterson *et al.*²¹ They used combined ambulatory pH and pressure recording to study the effect of cisapride. They found that the mechanism responsible for the efficacy of cisapride in decreasing oesophageal acid exposure time was an increase in the number of oesophageal contractions, rather than an increase in the amplitude or duration of contractions. In this study we have demonstrated that control subjects have a greater frequency of motor activity in response to GOR compared with reflux patients. Therefore the higher frequency of motor responses to GOR may be one of the major factors leading to acid clearance.

The results of this study showing primary peristalsis to be the predominant contraction type leading to acid clearance are in agreement with those of our earlier study¹⁰ and with other studies.^{11–12, 22} The proposed trigger mecha-

nisms for GOR induced oesophageal motor responses are either primary peristalsis induced by swallowing, or secondary peristalsis induced by oesophageal intraluminal distension. Studies of acid infusion or oesophageal distension have shown that both these events can stimulate secondary peristalsis.²³ Therefore the initiation of secondary peristalsis was suggested to be important in limiting the duration of reflux episodes.²⁴ This study demonstrated that during GOR, secondary activity is uncommon (less than 11.5%) compared with primary activity. Even when secondary activity was stimulated, approximately 80% of this activity was non-peristaltic (simultaneous, isolated, and mixed type contractions) in all groups. This study is consistent with a recent study by Paterson *et al.*²⁵ who demonstrated that more than 70% of the balloon distension induced motor responses were non-peristaltic. The same study also demonstrated that the percentage of secondary peristalsis was much less than previously reported.²⁶ Non-peristaltic activity is known to be ineffective in clearing the volume of the refluxate²⁷; even when the volume of refluxate is cleared by secondary activity, there is no saliva delivered to neutralise the remaining acid coating the oesophageal mucosa. Therefore this study confirms the conclusion drawn in previous studies,^{10–12} that secondary activity does not play an important role in acid clearance.

There was evidence from this study that the mean percentage of peristaltic activity was significantly lower in the reflux groups than in the control group, but the mean percentage of non-peristaltic activity (simultaneous, isolated, mixed type contractions, and non-transmitted swallow) was similar in all groups. This agrees with Bumm *et al.*,²⁸ who reported that the frequency of oesophageal peristalsis during the GOR period was decreased in reflux patients. In this study, however, no clear explanation can be offered for the impairment of GOR induced peristalsis in reflux patients.

When the pH increments in response to all motor activities in the three groups were compared, the pH increment in the control group was significantly higher than that in the reflux groups. No significant difference was found between the reflux groups. The reason for the greater pH increment in response to all motor activities in the control group may be due to the significantly higher percentage of peristaltic activity in the control group when compared with the reflux groups. Peristaltic activity accounted for the greatest proportion of the entire motor activity, and this was then further investigated for its effect on pH increment. The average pH increment in response to peristaltic activity (table 5) was in concordance with the pH increment in response to all motor activities (table 4). In addition, this study shows that non-transmitted swallows can restore oesophageal pH (fig 4)—that is, ineffective motor activity (the amplitude of the non-transmitted swallow was less than 10 mm Hg) was responsible for the pH increment and therefore another factor such as saliva must account for the pH increment. This evidence

that a non-transmitted swallow can restore oesophageal pH supports the acid neutralising effect of saliva as documented by Helm *et al.*⁸

We found no significant differences in peristaltic contraction wave characteristics (amplitude, duration, or velocity) during GOR among the three groups. The magnitude of peristaltic amplitude (>30 mm Hg) was established by Kahrilas⁹ as important in clearing reflux material (volume clearance) from the oesophagus, but in our study we were unable to measure volume changes during GOR. However, it demonstrated that the restoration of oesophageal pH did not depend on the magnitude of peristaltic amplitude, duration, or velocity. One possible explanation for the difference between controls and reflux patients was suggested by Barham *et al.*²⁹ They proposed that in patients with reflux disease further reflux episodes may superimpose on the original reflux episode, appearing to delay acid clearance. These findings are consistent with those of our earlier study³⁰ and those of Allen *et al.*,³¹ who showed no association between the pH increment and the magnitude of the peristaltic contraction amplitude, duration, and velocity. This again reinforces observations made by Paterson *et al.*²¹ in their study of acid clearance on cisapride therapy: the increase in the number of contractions is more important than the augmentation of contraction amplitude or duration in reducing the acid clearance time.

In conclusion, this study confirms that primary peristalsis is the major acid clearance mechanism in both normal subjects and reflux patients. In addition, we have shown that reflux patients have less frequent motor activity, a smaller proportion of which is peristaltic, and the average pH increment in response to motor activities during GOR is reduced, relative to controls.

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