ALIMENTARY TRACT

Reflux patterns and related oesophageal motor activity in gastro-oesophageal reflux disease

S Kruse-Andersen, L Wallin, T Madsen

Abstract

Simultaneous intraoesophageal pH and pressure monitoring were performed for 12 hours in 20 patients with abnormal acid gastro-oesophageal reflux or oesophagitis and in 10 healthy volunteers to determine characteristic reflux patterns with time. Increased acid exposure was not the only factor that characterised patients with oesophagitis. Indeed an overlap existed between patients with and without oesophagitis regarding total acid exposure time. Patients with oesophagitis suffered reflux nearly as much at night and in the morning as during the postprandial period. They also had as much reflux as a result of small and slow changes in pH around the pH limit of 4 as they had due to proper reflux episodes. This did not change over time after the postprandial period. More 12 hour acid exposure was related to more frequent night time reflux. In normal subjects compared with patients reflux triggered increased contractile activity, and contractile activity at a normal pH was greater in patients than in normal subjects.

It is generally agreed that the development of oesophagitis depends upon the amount of contact time between acid and the oesophageal mucosa but there has been less agreement about the importance of the timing of this acid exposure. Some authors have found that the development of oesophagitis is related to increased night-time reflux,¹⁻⁴ partly explained by impaired oesophageal clearance.^{2,4,5} Others have recently found evidence to support the view that postprandial reflux is the most important factor.⁶⁻⁹

Impaired clearance at night may be caused by a prolonged arousal response after reflux⁵ or by a reduced contractile activity. Orr, however,⁵ found a normal contractile response to acid instillation during sleep in patients with oesophagitis compared with normal subjects. Spontaneous contractile activity during periods of low and normal intra-oesophageal pH has received little attention in the investigation of reflux disease.

The purpose of this study was to perform a detailed analysis of postprandial and night-time reflux patterns to determine whether factors in addition to reflux time could be responsible for the development of oesophagitis. We have also recorded contractile activity at the same time

as pH measurements and analysed results separately for periods of low and normal intra-oesophageal pH.

Methods

STUDY POPULATION

Ten healthy subjects and 20 patients with gastro-oesophageal acid reflux or oesophagitis underwent 12 hours of simultaneous monitoring of pH and pressure activity between 8 pm and 8 am. Ten patients (eight men and two women with a median age of 51 years (range, 27-71 years)), consecutively admitted for quantification of acid gastro-oesophageal reflux had endoscopically and histologically confirmed oesophagitis. In all of them the severity of the oesophagitis was grade 1 or 2, and none had oesophageal ulcers or strictures. In five a hiatal hernia had been found on x ray. Antacid medication was stopped the day before the study. None of the patients had been taking H₂ antagonist treatment in the week before monitoring. A second group of 10 patients (nine men and one woman with a median age of 58 years (range, 20-67 years)) had abnormal acid reflux, but normal oesophageal mucosal appearance and histology.¹⁰ The group of normal subjects comprised eight men and two women with a median age of 36 years (range, 30-53 years) who had never experienced chest discomfort or symptoms of gastrointestinal disease. Informed consent was obtained from each volunteer.

APPARATUS

A combined pH and pressure probe was constructed by adding two open tipped polyethylene catheters (Clay Adams PE 160) to a pH probe (Radiometer GK 2801 C-O). After calibration in buffered solutions of pH 7.00, 4.01, and 1.09 the probe was introduced transnasally and the tip advanced to the stomach for measurement of intraluminal pH. The most distal pressure port located 3 cm proximally to the pH probe was used to position the probe 5 cm proximally to the gastro-oesophageal sphincter. The catheters, which were situated 15 cm apart, were connected to microtip transducers (Millar PC-350), a pneumohydraulic capillary flush system (Intraflo R CFS 03), and two battery powered amplification and calibration units (Miller TBC-100). All signals were simultaneously transferred to a frequency modulated tape recorder (Lyrec TR

Oesophagus Laboratory,
Department of Thoracic
and Cardiovascular
Surgery T, Odense
University Hospital,
Odense, Denmark
S Kruse-Andersen
L Wallin
T Madsen

Correspondence to:
Dr S Kruse-Andersen,
Kløvervænget 14 D, DK-5000
Odense C, Denmark.

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47 or 87). After completion of the monitoring, the stomach contents were again checked for acidity and the probe was checked for pH drift. Playback was performed with a 64 fold time compression and the signals were printed out on a mingograph (Siemens Elema 803) with a paper speed of 10 cm/s. This system fulfils the requirements for precise pH and pressure measurements of the oesophagus.¹¹⁻¹³

EXPERIMENTAL CONDITIONS

Monitoring began one hour after a light meal, and was carried out for 12 hours between 8 pm and 8 am. The primary aim of the study was to compare reflux and pressure parameters obtained at different times over a lengthy monitoring period. To enable us to do this the subjects' body position had to remain unchanged for the duration. The subjects were therefore in the recumbent position for the whole of the 12 hour period to prevent body position having any influence on reflux and pressures. In addition, subjects were not allowed to eat, drink, or smoke while they were being monitored.

DATA ANALYSIS

The 12 hour monitoring period was subdivided into four, three hour periods: a postprandial period, early and late night periods, and a morning period. Pressure events were described according to earlier definitions.¹² Briefly, time relations between pressure peaks at the recording sites were used to classify the pressure events into propagating, simultaneous, reverse, and segmentary peristaltic contractions. A relative pressure amplitude change of 8 mmHg and a rise time of 1 mmHg/s were the criteria for a pressure peak to be registered. A propagating peristaltic event was registered, when a distal pressure peak occurred 1-5.8 seconds after a proximal peak.

Simultaneous contractions were characterised by a distance between proximal and distal peaks of less than 1 second. During reverse peristalsis the proximal peak occurred 1-3 seconds after the distal peak. When the distance between proximal and distal peaks exceeded these limits a segmentary contraction was noted. We differentiated between reflux episodes characterised by a sudden and appreciable drop in pH, usually seen in normal subjects, and reflux that was the result of small or slow variations around the generally accepted pH limit of 4. Reflux episodes were defined as reductions in pH greater than 2 pH units and $\text{dpH/dt} > 0.5$ pH units/s to a $\text{pH} \leq 4$. These limits were chosen because they could easily be fulfilled for each of the 53 reflux events recorded in normal subjects. Reflux events that did not fulfil these criteria were classified as pH fluctuations. The end of a reflux episode was defined as a pH value greater than 4 remaining stable for more than 30 seconds.

STATISTICS

Differences between groups were assessed by the Mann-Whitney U test or the Kruskal-Wallis test in cases of two or more groups respectively. In cases of two or more related samples, the Pratt's test or the Friedman's test were employed. When significant differences were present between more than two independent or related samples, a multiple comparison procedure was carried out.¹⁴ Correlation was evaluated by calculation of the Spearman's rank correlation coefficient. The sex distributions were compared using the Fisher's exact probability test. P values less than 0.05 were regarded as significant.

Results

Patients with abnormal acid reflux were older than the normal subjects ($p < 0.05$). There were, however, no significant differences between the patient groups or between normal subjects and patients with oesophagitis. There was no difference in sex distribution between groups. Two normal subjects had no acid reflux.

On average, patients with oesophagitis had more reflux than patients without oesophagitis. The difference was not significant, however. This was due to a much greater interindividual variation in total acid exposure time in the group of patients with oesophagitis than in the group without oesophagitis (Fig 1). Only three patients with oesophagitis had more reflux than patients without oesophagitis, and two refluxed less. Figure 2 shows that acid exposure in normal subjects was close to zero after the postprandial period. Patients with abnormal reflux did not show a noticeable reduction in acid reflux until the latter half of the monitoring period. The group of patients with oesophagitis had less reduction in acid exposure over time than patients without oesophagitis resulting in significant differences late at night ($p < 0.02$) and in the morning ($p < 0.001$). Patients with oesophagitis still had reflux for more than one fifth of the time during the last six hours.

In patients with oesophagitis most reflux events were recorded as small or slow variations

Figure 1: Acid exposure recorded over 12 hours in three subject groups: (N) normal subjects; (PatR) patients with abnormal reflux; (ES) patients with oesophagitis.

Figure 2: Acid exposure (min/hour/subject) during four successive three hour periods in normal subjects (N); in patients with pathological acid reflux but no oesophagitis (PatR); and in patients with oesophagitis (ES). 0–3 h=postprandial interval; 3–6 h=early night interval; 6–9 h=late night interval; 9–12 h=morning interval.

in pH resulting in the pH dropping below 4 without the characteristic sudden and appreciable fall that can usually be seen when reflux occurs in normal subjects. When the duration of proper reflux episodes only was measured, acid exposure time did not differ between patients with and without oesophagitis (Fig 3). Late at night and in the morning pH fluctuations were more frequent in patients with oesophagitis than in those without this disorder ($p<0.05$) (Fig 4). Patients without oesophagitis had a few fluctua-

Figure 3: Total acid exposure over 12 hours due to reflux episodes in normal subjects (N), patients with abnormal reflux (PatR), and patients with oesophagitis (ES). Reflux episodes were defined as a pH drop of >2 pH units and $dpH/dt >0.5$ pH units/sec to $pH \leq 4$.

Figure 4: Number of pH fluctuations recorded during four successive three hour periods in normal subjects (N), patients with abnormal reflux (PatR), and patients with oesophagitis (ES).

tions only and virtually none during the late night period or in the morning. In contrast, the number of reflux episodes were very similar in these two groups.

Normal subjects and patients with abnormal reflux had significantly fewer reflux events during the late night period than postprandially ($p<0.05$ and $p<0.02$, respectively). The total number of episodes of reflux in patients with oesophagitis reached a maximum in the morning and no significant reduction occurred at night (Fig 5). In addition, they had as many reflux events caused by pH fluctuations as by proper reflux episodes. Fluctuations in pH also accounted for a greater proportion of the total acid exposure time in the late night and morning periods than postprandially, although these differences are not significant.

Normal subjects experienced almost 80% of their total reflux during the postprandial period (Fig 6). Among patients with abnormal reflux, less than 60% of the reflux took place postprandially. Patients with oesophagitis had an almost equal distribution throughout the monitoring period. Consequently, relatively less

Figure 5: Number of pH fluctuations (○), number of reflux episodes (■), and total number of reflux events (●) in patients with oesophagitis.

Figure 6: Distribution of recorded reflux during the 12 hour monitoring period. The values plotted for each time period represent the proportion of total reflux that took place in that particular period. ES-7 pt refers to the seven patients with oesophagitis that had reflux within the upper range of abnormal reflux without oesophagitis. (ES=patients with oesophagitis, N=normal subjects, PatR=patients with abnormal reflux.)

reflux took place postprandially in patients with oesophagitis than in normal subjects ($p<0.005$) and patients without oesophagitis ($p<0.05$). Conversely, patients with oesophagitis experienced a greater proportion of their total reflux at night than normal subjects ($p<0.005$). In the morning they still had relatively more reflux than the other groups ($p<0.05$) whereas no difference existed between patients with abnormal reflux and normal subjects. Exclusion of the three patients with reflux greater than the upper range of those with abnormal reflux had no effect on the almost even distribution of reflux throughout the monitoring period in patients with oesophagitis (Fig 6). No patient in the oesophagitis group had reflux throughout the postprandial period, as the mean time without acid reflux was 122 minutes (range, 36–177 minutes).

A significant relation existed between the total duration of acid reflux and the proportion of reflux episodes that took place during the night-time ($p<0.002$). Subjects with more pronounced reflux experienced a greater number of their reflux episodes at night than those with less severe reflux (Fig 7). Approximately three times as much reflux was associated with twice as many reflux episodes occurring at night. In addition, relatively more reflux events occurred as fluctua-

Figure 7: Correlation ($\rho=0.63$) between the relative frequency of reflux episodes at night and total reflux time.

tions in pH correlated to increasing reflux ($p<0.00001$).

Contractile activity was evaluated for a six hour period at night in the patient groups and for 12 hours in normal subjects as two of the patients had no reflux in one of the night intervals and some normal subjects only refluxed in one interval. During acid reflux, a total of 3764 pressure events were recorded. Fourteen hundred and thirty seven (38%) propagated through the whole of the oesophagus, 265 (7%) were simultaneous contractions, and 2062 (55%) were reverse or segmentary contractions. The numbers of the different kinds of pressure events recorded during acid reflux in the groups are presented in the Table. Patients with oesophagitis had relatively fewer contractions that propagated through the whole of the oesophagus during acid reflux, although the difference did not reach statistical significance. The contractile activity triggered by reflux in normal subjects was about twice the activity caused by reflux in patients ($p<0.01$ for contractions/hour during the 12 hours, Fig 8). Patients with abnormal reflux had

Figure 8: Pressure activity during periods of acid reflux for three successive time periods. 0–3 h=three hour postprandial interval, 3–9 h=six hour night interval, and 9–12 h=morning interval. The dashed line represents the level of pressure activity in normal subjects (N), ES=patients with oesophagitis, PatR=patients with abnormal reflux. Calculations in normal subjects are based on the whole 12 hour recording period.

Frequency of pressure events recorded during acid reflux in normal subjects, in patients with abnormal reflux, and in patients with oesophagitis

Group	Propagating contractions	Simultaneous, reverse, and segmentary contractions
Normal subjects		
Median	3	3
Range	0–9	0–23
Abnormal reflux		
Median	54	54
Range	30–186	16–174
Oesophagitis		
Median	69	93
Range	4–135	16–490

significantly greater contractile activity in the morning than those with oesophagitis ($p < 0.05$) (Fig 8). In patients with oesophagitis the contractile activity at night was significantly lower than postprandially and in the morning ($p < 0.05$). In contrast to pressure activity during low pH, patients with oesophagitis had a greater contractile activity during intervals of normal intra-oesophageal pH than normal subjects ($p < 0.05$). However, there was no difference between patients with and without oesophagitis.

Discussion

It has recently been claimed that reflux during the daytime, and especially postprandial reflux, is the most important factor in the development of oesophagitis.⁶⁻⁹ Admittedly, the majority of subjects experience the most pronounced reflux postprandially and significantly less during the night-time. In a previous study of people with abnormal reflux without oesophagitis we also found a significant reduction in the frequency of reflux and duration of acid exposure between the postprandial period and the night-time.¹⁰ In patients with abnormal reflux, however, a greater proportion of the reflux took place at night than in normal subjects. The present study shows that this shift towards comparatively more reflux at night is even more pronounced in patients with oesophagitis. It was present to the same degree in patients with oesophagitis who did not reflux more than patients without oesophagitis. This suggests that patients who are likely to develop oesophagitis might be identified early by studying the time patterns of reflux. Similar proposals have been made by Robertson *et al.*³ Only three of our patients with oesophagitis had more and two had less reflux than patients with abnormal reflux without oesophagitis. Thus, factors other than total reflux time must be important in the development of peptic lesions, and the occurrence of relatively more reflux during the night-time may be one such important factor. It may be that important cellular regeneration takes place at night and persisting reflux at this time is especially harmful. Generally, normal subjects do not reflux after the postprandial period. Patients with abnormal reflux have more reflux in the first half of the night, whereas those with oesophagitis have virtually as much reflux during the second night period and in the morning as they do postprandially and early at night.

Postprandial and upright reflux has been found to correlate more closely with total 24 hour acid exposure than night-time reflux in symptomatic patients.^{9 15} This correlation should not be surprising, however, as long as postprandial and upright reflux constitute a greater proportion of total reflux time than does night-time reflux. This correlation is important if the major aim is to identify a shorter time period that is suitable for the detection of abnormal reflux. It does not, however, prove that postprandial reflux is the most important cause of oesophagitis or that postprandial reflux provides the most clear distinction between patients with oesophagitis and other groups. A substantial reduction in postprandial reflux would presumably be the most

beneficial thing for patients with oesophagitis but in patients as well as normal subjects a reduction in night time and morning reflux always seems to take place before a reduction in postprandial reflux occurs. Patients with oesophagitis, however, were not even able to reduce reflux at times when the other groups had virtually stopped. If they were able to do this their oesophagitis might heal despite substantial postprandial reflux.

The most difficult problem in analysing pH recordings is that in patients with pronounced reflux, the pH may remain close to the detection level for long periods, resulting in frequent wavering of the pH curve above and below the preset limit.¹⁶ These fluctuations in the pH value have little in common with the abrupt and noticeable fall in pH seen in normal subjects. To differentiate between these two phenomena we added a limit as to the rate of pH drop to the definition, using normal subjects as reference. Likewise, it was necessary to define an end point for reflux events, as the pH curve in many patients with oesophagitis made a very slow approach towards the detection limit with small fluctuations around pH 4, often synchronous with respiration. A limit of 18 seconds was chosen by one group¹⁶ but in most cases no definitions have been supplied.

We found pronounced differences between groups with regard to the predominant type of reflux they experienced. In patients with abnormal reflux without oesophagitis, reflux episodes were well-defined. In patients with oesophagitis, however, more than half of the acid exposure was due to slow fluctuations in pH regardless of the monitoring period. This finding does not support the theory that reflux in oesophagitis patients is caused by gastric distention and decreased emptying, as gastric volume can hardly be presumed to increase towards the morning.

The contractile activity after spontaneous reflux was greater in normal subjects than in patients. There was good agreement between an increased pressure activity in those with abnormal reflux during the last period of monitoring and a reduction in acid exposure during the same time. It is also noteworthy that patients with oesophagitis had an insufficient reduction in night-time acid exposure and at the same time a low pressure activity triggered by night-time reflux.

In most previous investigations of reflux patterns, oesophageal motor activity was evaluated by means of short term manometry carried out before pH monitoring and without knowledge of actual intra-oesophageal pH at the time of measurement.^{3 7 8 17 18} Frequent contractions during intervals of normal pH may contribute to frequent relaxation of the gastro-oesophageal sphincter. The high pressure activity during normal pH seen in the patient groups may therefore, to some extent, explain why they had frequent episodes of reflux as well as prolonged reflux.

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