Oesophageal motor response to reflux is not impaired in reflux oesophagitis

R Timmer, R Breumelhof, J H S M Nadorp, A J P M Smout

Abstract

Whether the oesophageal motor response to reflux, as recorded over 24 hours, is impaired in patients with reflux oesophagitis was investigated. Twenty three patients with oesophagitis (Savary-Miller grades I-IV) and 23 control subjects matched for age and sex underwent 24 hour ambulatory pH and pressure monitoring. All contractions occurring in the 2 minute period after the onset of each reflux episode were analysed automatically using dedicated computer algorithms. A total of 2085 reflux episodes occurred – 1513 in patients and 572 in controls. Oesophageal acid exposure was greater ($p<0.01$) in patients than in controls (mean (SEM) % time pH<4 13·3 (1·7) and 5·3 (0·9)%, respectively). The mean duration of the supine reflux episodes was longer ($p<0.01$) in patients (11·2 (2·8) minutes) than in controls (5·1 (1·8) minutes). In the upright period, no significant differences in the motor response to reflux were found. In the supine period, the patients showed a higher number of reflux induced contractions (4·40 (0·61) *v* 1·62 (0·31), $p<0.01$), a higher contraction amplitude (4·55 (0·42) *v* 2·99 (0·71) kPa, $p<0.02$) and longer contractions (1·86 (0·19) *v* 1·32 (0·29) seconds, $p<0.05$). The percentages of peristaltic and simultaneous contractions that occurred in response to supine reflux did not differ between the two groups. In patients with reflux oeosphagitis the motor response of the oesophagus to reflux is not impaired. During the supine period the response is even stronger than in healthy controls.

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Gastro-oesophageal reflux disease has a multifactorial origin. Dysfunction of the lower oesophageal sphincter and impaired oesophageal acid clearance are thought to be the two most important factors in its pathogenesis. Both neutralisation by saliva and oesophageal motor function determine the oesophageal acid clearance. In previous manometric studies, oesophageal motility and acid clearance were found to be impaired in many patients with oesophagitis.[1-4] The techniques used in these studies were not, however, very physiological. To evaluate the oesophageal acid clearance time a bolus of 15 ml 0·1 N HCl was injected into the oesophagus and pressures and pH were monitored.

The recent development of 24 hour ambulatory pH and pressure monitoring techniques allows us to study oesophageal motility under more physiological conditions and for prolonged times. Computer assisted techniques make it possible to analyse large quantities of data.[5-7]

The primary aim of this study was to investigate the reflux induced oesophageal motor activity in patients with oesophagitis compared with normal control subjects using a 24 hour ambulatory monitoring technique.

Patients and methods

Twenty three patients, 18 men and 5 women (mean (SD) age 55·7 (17·0) years), with endoscopically proved reflux oesophagitis (Savary-Miller grades I-IV) and 23 healthy controls, 16 men and 7 women (aged 51·2 (16·8) years), underwent 24 hour ambulatory pH and pressure monitoring using a system developed by our group.[6 8] Thirteen patients had grade I oesophagitis, seven had grade II, two grade III, and one grade IV. Grade I was defined as one or more superficial linear erosions, grade II as confluent non-circumferential erosions, grade III as circumferential erosions or exudative lesions, and grade IV as ulceration with stenosis. Nineteen of the 23 patients had a sliding hiatal hernia with a distance between the gastro-oesophageal junction and the impession of the diaphragm of more than 2 cm. Patients with secondary or primary peristaltic motor abnormalities such as scleroderma and achalasia were excluded. Five days before the test any medication that might have influenced oesophageal motility or gastric acid secretion was stopped.

Conventional oesophageal manometry was performed in both patients and healthy controls before ambulatory monitoring. A water perfused, three lumen catheter with the openings 5 cm apart and orientated in three different directions was used. The position of the lower oesophageal sphincter was identified by means of the stationary pull through method.

The 24 hour ambulatory pressure and pH recording system developed by our group has been described in detail elsewhere.[6 8] Briefly, the system consists of a microprocessor based portable digital recorder and a personal computer with a dedicated software package written in Turbo Pascal. The system allows continuous recording of two pressure signals (sampled at a rate of 5 Hz) and one pH signal (sampled at a rate of 0·125 Hz) as well as two marker signals. For pH recording a combined glass electrode was used (Ingold A G Urdorf, Switzerland, model LOT 440). Intraoesophageal pressure was recorded using a 5 F custom designed polyurethane transducer catheter (PPG Hellige, Best, The Netherlands). For ambulatory recording, the pH electrode was positioned 5 cm above the upper border of the lower oesophageal sphincter, the pressure transducer was positioned with the distal transducer 5 cm above the lower oesophageal sphincter, and the upper transducer

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15 cm above the lower oesophageal sphincter. Both catheters were fixed to the nose with adhesive tape.

During the study, periods of eating and drinking (maximum allowed, eight periods of 20 minutes each) and periods spent in the supine position were registered by the patient in a diary. Episodes of retrosternal pain or heartburn were registered by pushing the event marker and writing down the time, nature, and characteristics of the symptoms. In the portable recorder, only pressure increases greater than 2 kPa and lasting longer than 0·8 seconds were considered contractile events and stored in the digital memory. Dedicated computer algorithms were developed to study all contractions occurring in the 2 minute period after the onset of each reflux episode. A reflux episode was defined as a fall in pH to a value <4 that lasted longer than 24 seconds.

The 2 minute period was chosen on the basis of studies which have shown that in normal subjects, all but 1 ml of a 15 ml bolus of 0·1 N HCl is cleared by the first peristaltic contraction without changing the pH.[9] In the following 3 minutes, stepwise increases in the distal oesophageal pH occur with subsequent swallows. Two minute periods that overlapped with preceding episodes were excluded from the analysis. For each 2 minute period the duration of the reflux episode (defined as the time with pH<4) and the lowest pH reached were measured automatically.

All contractions occurring within the 2 minute window were examined using dedicated algorithms that measured: the number of contractions at proximal and distal sensor, number of simultaneous and peristaltic contractions, number of repetitive contractions; mean amplitude of peristaltic contractions, and mean contraction duration. The reflux episodes occurring in the upright and supine periods were analysed separately. In addition, the percentages of time during which the pH was below 4 for the entire 24 hour period and for the supine and upright periods separately, and the total number of reflux episodes (pH drops below 4) were calculated.

All mean ambulatory motility values and reflux variables of the patients were compared statistically with those of the normal control subjects applying the Wilcoxon test for unpaired observations.

Gastro-oesophageal reflux over the 24 hour period and in upright and supine periods in 23 patients and 23 controls. (Mean values (SEM))

	Patients	*Controls*	*p*
Percentage recording time pH<4:			
Total	13·3 (1·7)	5·3 (0·9)	p<0·01
Upright	13·3 (1·4)	4·6 (0·8)	p<0·01
Supine	13·4 (3·6)	6·4 (1·7)	NS
No of reflux episodes (pH<4):			
Total	65·3 (5·2)	24·9 (3·6)	p<0·01
Upright	56·8 (5·2)	14·7 (2·4)	p<0·01
Supine	8·5 (2·5)	10·2 (2·2)	NS
Duration of reflux episodes (min):			
Total	3·0 (0·3)	3·7 (0·8)	NS
Upright	2·4 (0·2)	3·4 (0·6)	NS
Supine	11·2 (2·8)	5·1 (1·8)	p<0·01

Results

During the 24 hour recording period, 1513 reflux episodes occurred in the 23 patients and 572 in the 23 controls, 1174 (74·8%) and 428 (77·6%) of which were analysed respectively. The other episodes were discarded because of overlap with preceding or subsequent episodes. As expected, 24 hour oesophageal acid exposure was greater in patients than in controls. In the supine period, however, the difference in oesophageal acid exposure failed to reach statistical significance (Table). Likewise, the number of reflux episodes was significantly higher in the patients than in the controls, but not so in the supine period (Table). The mean duration of the supine reflux episodes was significantly longer in patients than in controls. No significant difference in the duration of the upright reflux episodes was found between patients and controls (Table).

An example of a reflux episode and the oesophageal motor response to it, as recorded in an ambulatory subject, is shown in Figure 1.

In the first 2 minutes after a ph drop below 4 the average total number of oesophageal contractions observed in the oesophagitis patients was significantly higher than the number occurring in healthy controls (mean (SEM) 5·00 (0·41) *v* 3·79 (2·53), p<0·01). The relative frequency of contraction types (peristaltic, simultaneous, and non-transmitted) was not different between the two groups (Fig 2). The total number of contractions occurring in the 2 minute period after reflux that occurred during daytime (upright

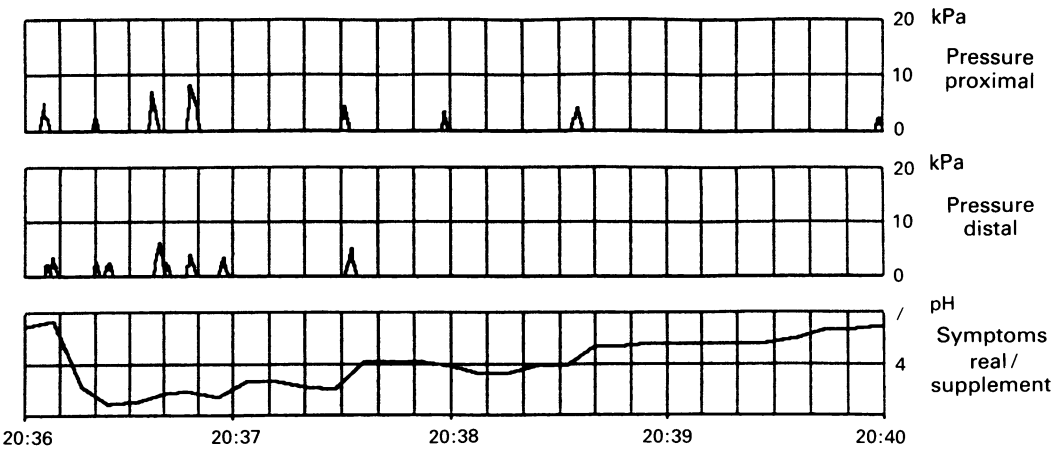

Figure 1: A 4 minute portion of the 24 hour plot of two pressure signals and one pH signal, showing a single reflux episode with the oesophageal motor response to it. Note the stepwise pH increase with each peristaltic wave.

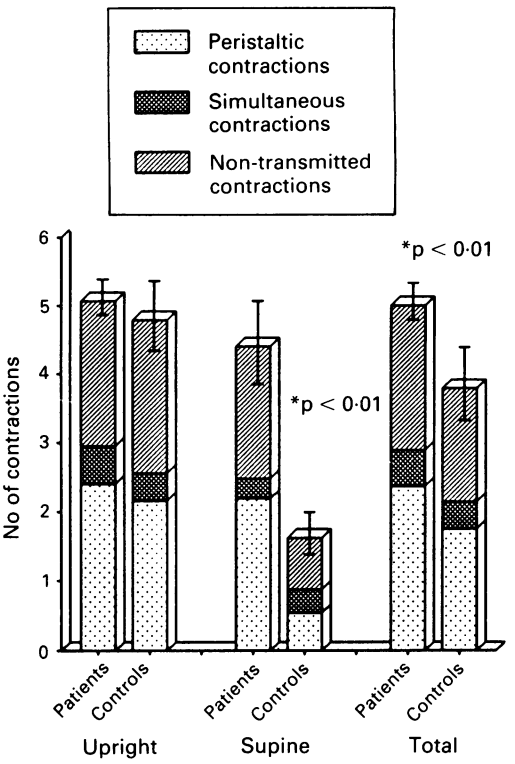

Figure 2: Number and distribution of contraction types (mean (SEM)) occurring in the 2 minute period after gastro-oesophageal reflux for the upright, supine, and total 24 hour periods in healthy controls and patients. The total number of contractions occurring during the supine and total 24 hour periods were significantly higher in patients.

reflux) did not differ between the two groups, nor did the distribution of the contractions (Fig 2). In the supine period, there were significantly more contractions during the 2 minute period after a pH drop below 4 in the patients (4·40 (0·61)) than in the normal subjects (1·62 (0·31)), but the percentage of peristaltic and simultaneous contractions did not show a statistically significant difference (Fig 2).

During the supine period, the contraction amplitude was significantly ($p<0·01$) higher in patients (4·55 (0·42) kPa) than in normal controls (2·99 (0·71 kPa) (Fig 3). Such a difference was not found for the upright and total 24 hour periods. The duration of the reflux induced contractions that occurred during the supine period was significantly ($p<0·05$) higher in the patients (1·86 (0·19) seconds) than in the controls (1·32 (0·29) seconds) (Fig 4). Again, no differences were found between patients and controls in the duration of contractions for the upright and total 24 hour periods.

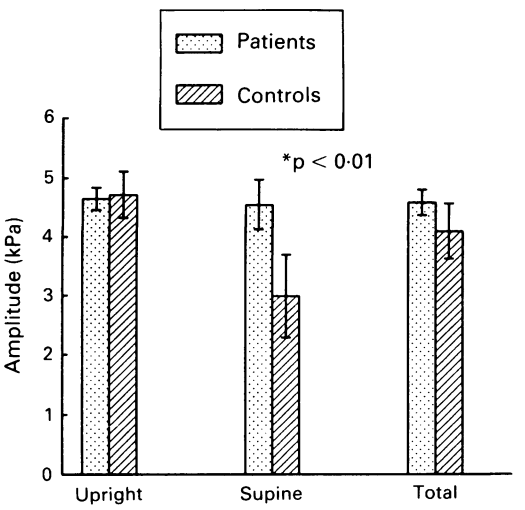

Figure 3: Contraction amplitudes (mean (SEM)) during the 2 minute period after reflux in patients compared with normal controls.

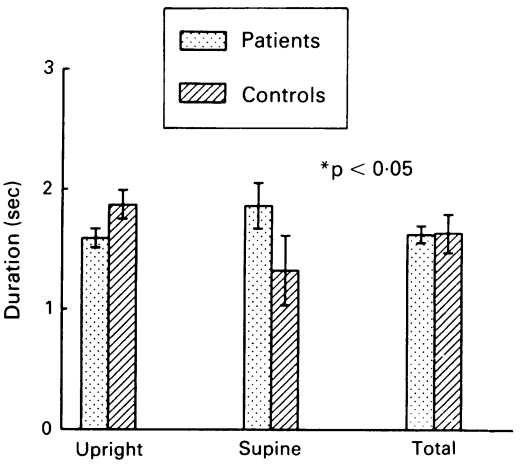

Figure 4: Duration of the contractions (mean (SEM)) occurring in the 2 minute period after reflux in patients compared with normal controls. During the supine period the contraction duration was significantly longer in patients.

Discussion

Changes in the pressure of the lower oesophageal sphincter and a prolonged oesophageal acid clearance time are usually considered to be the two crucial factors in the pathophysiological process leading to abnormal gastro-oesophageal reflux and oesophagitis. Without a transient lower oesophageal sphincter relaxation or a permanently low sphincter pressure, gastro-oesophageal reflux will not occur. After a reflux event, the distal oesophagus has to be cleared of the refluxate.

Two steps can be distinguished in oesophageal clearance, – the first is clearance of the refluxate volume by peristaltic contractions and the second is neutralisation of the remaining acid by saliva.[9-11] Previous studies have shown, either by means of the standardised acid clearance test or by spontaneous reflux occurring during 24 hour oesophageal monitoring, that acid clearance times are generally two to three times longer in reflux patients than in controls.[12-14] It is important, however, to note that the population of reflux patients is heterogeneous, in the sense that some have normal clearance values and others have considerably prolonged values. The two major potential causes of prolonged oesophageal acid clearance are impaired volume clearance and impaired salivary function.[15] As oesophageal motility has been reported to be increasingly impaired with the increasing severity of oesophagitis,[4] it is likely that this defect will contribute to the impaired volume clearance.

This is the first study that has used 24 hour ambulatory pressure and pH monitoring to investigate the reflux induced oesophageal motility in patients with oesophagitis and normal control subjects. Dedicated computer algorithms were developed to study all contractions occurring in the 2 minute period after the onset of each reflux episode, defined as a drop in pH below 4.

The patients had significantly more reflux episodes and a higher percentage of recording time with $pH<4$ during the total 24 hour and upright period, but not during the supine period. The mean duration of the supine reflux episodes was significantly longer in the patients, however, compared with control subjects. This agrees

with the findings of DeMeester *et al*[13] who reported that the mean acid clearance time of 'supine refluxers' was considerably prolonged compared with the values in 15 control subjects.

Paradoxically, during the supine period the reflux induced oesophageal activity was composed of significantly more contractions with a higher amplitude and longer duration in patients with oesophagitis than in the controls. This was not observed during the upright period. In spite of this more vigorous oesophageal motor response, the supine reflux episodes lasted longer in the oesophagitis patients. One of the explanations for this finding could be that this is caused by a different distribution of the contraction types, for example by less peristaltic and more simultaneous and non-transmitted contractions. This was not the case, however, as the percentage of peristaltic and simultaneous contractions occurring in the 2 minute periods did not differ between patients and control subjects. The increased post-reflux contraction rate in the oesophagitis patients might also be caused by a higher swallowing rate, but swallowing was not monitored in this study. As the swallow rate is mainly controlled by the salivary rate, our observations would be consistent with an increased triggering of the oesophago-salivary reflex in the oesophagitis group. As the amplitude of the contractions after supine reflux was higher in the gastro-oesophageal reflux patients, the prolonged reflux episodes cannot be explained by a poor acid clearance caused by peristaltic contractions of low amplitude ($p<30$ mm Hg).[16] However, one should take into account the fact that most patients in this study had a low grade oesophagitis.

As previous analysis of motor impairment in gastro-oesophageal reflux disease suggests that the degree of motor impairment becomes progressively more severe with advanced grades of oesophagitis,[4] it is possible that a diminished incidence or amplitude of peristaltic contractions plays a part in prolonged reflux episodes in patients with severe oesophagitis.

On the basis of the observations made in this study we conclude that the prolonged acid clearance time during the supine period found in patients with oesophagitis is not caused by an impaired oesophageal motor response. Reduced neutralisation of acid by saliva during the sleeping hours is also an unlikely explanation for the delayed supine acid clearance observed in this study. It is known that saliva production is decreased at night,[17] but to our knowledge a difference in saliva composition or saliva production between reflux patients and controls has never been shown.[18] It is far more likely that the stronger oesophageal response is a (inadequate) reaction to continuing acidification of the distal oesophagus, in particular by re-reflux[19] from the hernial sac. Nineteen of our 23 patients had a sliding hiatal hernia. This suggests that gravity plays an important role, as we found no differences during day time. Helm *et al*[9] reported that clearance times were not significantly different, whether measured in the upright or supine postures, suggesting that gravity plays a minor role, but they studied normal individuals, presumably without hiatal hernia. Abnormal clearance has been found to be improved by an upright posture or by bed elevation, suggesting that gravity does help when clearance is abnormal.[20] If re-reflux plays an important role, then the stronger oesophageal motor response found in our study could well be a reaction to insufficient volume clearance associated with hiatal hernia.

1 Marshall JB, Gerhardt DC. Improvement in esophageal motor dysfunction with treatment of reflux eosphagitis: a report of two cases. *Am J Gastroenterol* 1982; **77**: 351–4.
2 Katz PO, Knuff TE, Benjamin SB, Castell DO. Abnormal esophageal pressures in reflux esophagitis: cause or effect. *Am J Gastroenterol* 1986; **81**: 744–6.
3 Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1988; **91**: 897–904.
4 Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1988; **94**: 73–80.
5 Richter JE, Castell DO. 24-hour ambulatory oesophageal motility monitoring: how should motility data be analysed? *Gut* 1989; **30**: 1040–7.
6 Smout AJPM, Breedijk M, van der Zouw C, Akkermans LMA. Physiological gastroesophageal reflux and esophageal motor activity studied with a new system for 24-hour recording and automated analysis. *Dig Dis Sci* 1989; **34**: 372–8.
7 Emde C, Armstrong D, Bumm R, Kaufhold JH, Riecken EO, Blum AL. Twenty-four-hour continuous ambulatory measurement of esophageal pH and pressure; a digital recording system and computer-aided manometry analysis. *J Ambul Monit* 1990; **3**: 47–62.
8 Breumelhof R, Breedijk M, Akkermans LMA, Smout AJPM. An ambulatory system for 24-hour recording of esophageal motility and pH. *J Ambul Monit* 1988; **1**: 311–20.
9 Helm JF, Dodds WJ, Reidel DR, Teeter BC, Hogan WJ, Arndorfer RC. Determinants of eosphageal acid clearance in normal subjects. *Gastroenterology* 1983; **85**: 607–12.
10 Helm JF, Dodds WJ, Pelc LR, Palmer DW, Hogan WJ, Teeter BC. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. *N Engl J Med* 1984; **310**: 284–8.
11 Shaker R, Kahrilas PJ, Dodds WJ, Hogan WJ. Oesophageal clearance of small amounts of equal or less than one millilitre of acid. *Gut* 1992; **33**: 7–10.
12 Booth DJ, Kemmerer WT, Skinner DB. Acid clearing from the distal esophagus. *Arch Surg* 1968; **96**: 731–4.
13 DeMeester TR, Johnson LF, Joseph GJ. Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 1976; **184**: 459–70.
14 Johnson LF. 24-hour pH monitoring in the study of gastroesophageal reflux. *J Clin Gastroenterol* 1980; **2**: 387.
15 Kahrilas PJ. Esophageal motor activity and acid clearance. *Gastroenterol Clin* 1990; **3**: 537–50.
16 Kahrilas PJ, Gupta RR. The effect of cigarette smoking on salivation and esophageal acid clearance. *J Lab Clin Med* 1989; **114**: 41–8.
17 Schneyer LH, Pigman W, Hanahan L, Gilmore RW. Rate of flow of human parotid, sublingual, and submaxillary secretions during sleep. *J Dental Res* 1956; **35**: 109–14.
18 Sonnenberg A, Steinkamp U, Weise A, Berges W, Wienbeck M, Rohner HG. Salivary secretion in reflux esophagitis. *Gastroenterology* 1982 **83**: 889–95.
19 Mittal RK, Lange RC, McCallum RW. Identification and mechanism of delayed esophageal acid clearance in subjects with hiatus hernia. *Gastroenterology* 1987; **92**: 130–5.
20 Stanciu C, Bennett JR. Oesophageal acid clearing: one factor in production of reflux oesophagitis. *Gut* 1974; **15**: 852–7.