

PAPERS

Temporal relationships between episodes of non-cardiac chest pain and abnormal oesophageal function

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Abstract

Analysis of the association between symptoms and abnormal oesophageal function is a central part of 24 hour oesophageal pressure and pH recording in patients with non-cardiac chest pain. Such studies have used different time windows including a period after the onset of pain. Since stress and pain can induce oesophageal motor abnormalities and transient lower oesophageal sphincter relaxations, a proportion of the motor abnormalities and the reflux episodes observed after the onset of pain may be a consequence rather than the cause of that pain. This study aimed to assess this possibility in patients with chest pain that was presumed to be of oesophageal origin by comparing the results of analysis using time windows before and after the onset of pain. Forty eight patients experienced a total of 166 spontaneous chest pain episodes during 24 hour ambulatory monitoring. A time window beginning two minutes before and ending at the onset of pain (-2/0) was compared with a window beginning at the onset of pain and ending two minutes afterwards (0/+2). The percentage of episodes related to reflux, abnormal oesophageal motility, or neither were 22.9%, 24.7%, and 52.4% in the -2/0 time window and 9.0%, 22.3%, and 68.7% in the 0/+2 time window, respectively. However, 11 of the 37 episodes associated with abnormal motility in the 0/+2 time window were preceded by a reflux episode, and 19 of these 37 episodes had abnormal motility in the -2/0 time window. Consequently, in only seven of the 166 chest pain episodes (4.2%) in two patients were the findings consistent with secondary oesophageal motor disorders provoked by pain. Likewise, only six of the 166 chest pain episodes (3.6%) were consistent with reflux provoked by pain. These findings indicate that in patients with non-cardiac chest pain, gastro-oesophageal reflux and oesophageal motor abnormalities are rarely a consequence of the pain.

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The technique of 24 hour oesophageal pressure and pH recording is a relatively new research tool for the investigation of non-cardiac chest pain. It allows monitoring of the oesophagus over a long period and, therefore, has several advantages over conventional oesophageal tests. The greatest advantage is that it offers the possibility of establishing a correlation between the patient's chest pain and abnormal oesophageal motility or acid reflux, or both. Study of outpatients in their daily activities, especially during activities that normally provoke their chest pain, is obviously more physiological than subjecting them to provocation tests. In non-cardiac chest pain patients, investigation of the temporal association between chest pain episodes and oesophageal function abnormalities is the most important part of the data analysis. Several studies dealing with this type of analysis have been published.¹⁻⁶ Until now, all groups have used different time windows in analysing the association between symptoms and oesophageal abnormalities. All groups have included a period of two or more minutes after the onset of the pain in the analysis window.

It is known from laboratory studies that stress and pain can induce oesophageal motor abnormalities.⁷ It has recently been suggested that a proportion of the oesophageal motor abnormalities observed after the onset of pain is a consequence rather than a cause of that pain.⁸ Likewise, episodes of gastro-oesophageal reflux may be induced by pain. In a recent preliminary publication, stress was reported to induce transient relaxations of the lower oesophageal sphincter.⁹

This study aimed to assess the likelihood that chest pain is the cause of oesophageal dysfunction (reflux or motor abnormality) in patients with chest pain of oesophageal origin. This was accomplished by comparing the yield of symptom association analysis using windows before and after the onset of pain.

Methods

Signals recorded in 48 patients (24 men and 24 women) with a mean age of 63.1 years (range 40-76) were analysed. All patients consulted our department because of recurrent chest

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pain of unexplained origin. Only patients who had had at least one chest pain episode during 24 hour oesophageal pressure and pH recording were included in the study. All patients had been seen first by a cardiologist, who considered that coronary artery disease was unlikely on the basis of a negative exercise test, a negative thallium scintigram, and a normal cardiac ultrasound study. Coronary angiography was carried out in 32 patients. Pulmonary disease as a cause of chest pain was excluded by physical examination and a chest radiograph. A musculoskeletal cause for the chest pain was not considered to be present as these patients had no replication of their pain on palpation of the anterior chest wall. All patients had a normal upper gastrointestinal endoscopy.

The ambulatory monitoring device used in this study was developed in our hospital and has been described in detail elsewhere.^{10 11} Oesophageal pressures were measured with a 5F polyurethane catheter with two solid state pressure transducers mounted 10 cm apart (PPG, Hellige, Best, The Netherlands). Oesophageal pH was recorded using a combined glass electrode (Ingold AG, Urdorf, Switzerland, model LOT 440). 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). Only pressure increases higher than 2 kPa (15 mmHg) and with a duration longer than 0.8 seconds were considered contractile events and stored in a digital memory. Before and after each study, the pressure catheter was calibrated in a water filled cylinder. The pH catheter was calibrated using a neutral buffer (pH 7) and an acid buffer of pH 4. All drugs known to alter oesophageal motility or to reduce gastric acidity were stopped for 48 hours before the study and for the duration of the study.

During ambulatory recording, the pH electrode was positioned 5 cm above the lower oesophageal sphincter (LOS). The position of the LOS in respect of the nose was determined manometrically. The distal and proximal pressure transducers were positioned 5 and 15 cm above the LOS, respectively. The probes were secured to the nose and face with tape and the leads connected to the recording unit were worn on a belt around the waist. During the study, the patients recorded the beginning and ending of meals, onset and duration of pain episodes, and the supine period in a diary. At the onset of each pain period, the patient also pushed the event marker button on the recording device.

After the 24 hour period the data were analysed automatically, as previously described.⁵ In this analysis, each patient served as his own control as described by Peters *et al.*² The analysis of both pressure and pH signals was done separately for periprandial and interprandial portions of the recording and also for the supine (night time) and upright (day time) portions. The analysis technique determined the patient's baseline data during asymptomatic periods. The 97.5th centiles of amplitude and duration of all contractile

events in the symptom free episodes were automatically calculated and used as a cut off limit between normal and abnormal. This was done for the proximal and distal pressure signals separately. Since no deglutition signal was monitored during the 24 hour study, swallow induced and spontaneous contractions could not be differentiated.

In the symptom analysis, two different symptom time windows were used. The first was a two-minute time window beginning two minutes before and ending at the onset of pain (-2/0 window). The second window began at the onset of pain and ended two minutes afterwards (0/+2 window).

The χ^2 test was used to determine whether the distribution of contraction types (peristaltic, simultaneous, non-transmitted) in the symptom episode (observed frequencies) were statistically different from the distribution in the entire recording period (expected frequencies). A symptom episode was considered to be associated with abnormal motility when the distribution of contractile events was significantly ($p < 0.025$) different from that during the entire 24 hour period (χ^2 method) and/or amplitude or duration exceeded the 97.5th (centile and/or repetitive contractions were present. A symptom episode was considered to be associated with reflux when a pH drop > 1 unit occurred within eight seconds, or when the pH fell below 4, or when both criteria were met during that episode.

For the two time windows the number of pain episodes that were related to reflux, the number of pain episodes related to motor abnormalities, and the number of pain episodes with no apparent relation to reflux or dysmotility were determined. The last step in the analysis consisted of the calculation of the symptom index (SI) for both reflux and dysmotility. The SI was calculated according to Wiener *et al.*¹² as: number of symptom episodes associated with reflux (or motility) divided by the total number of symptom episodes, multiplied by 100%.

Results

During the 24 hour monitoring period the 48 patients experienced a total of 166 spontaneous episodes of chest pain. The mean (SEM) number of episodes per patient was 3.5 (0.4) and the range was 1 to 13.

Analysis of the two minute time window preceding the onset of pain (-2/0 window) showed that 38 chest pain episodes (22.9%) were related to reflux and 41 (24.7%) were related to abnormal motility (abnormal amplitude/duration in 61.8%, abnormal propagation in 29.3%, and both abnormalities in 8.9%). Eighty seven pain episodes (52.4%) were not related to reflux or oesophageal abnormalities.

Analysis of the two minute time window after the onset of pain (0/+2 window) showed that 15 chest pain episodes (9.0%) were related to reflux and 37 (22.3%) were related to dysmotility (abnormal amplitude/duration in 77.8%, abnormal propagation in 17.5%, and both abnormalities in 4.7%). One

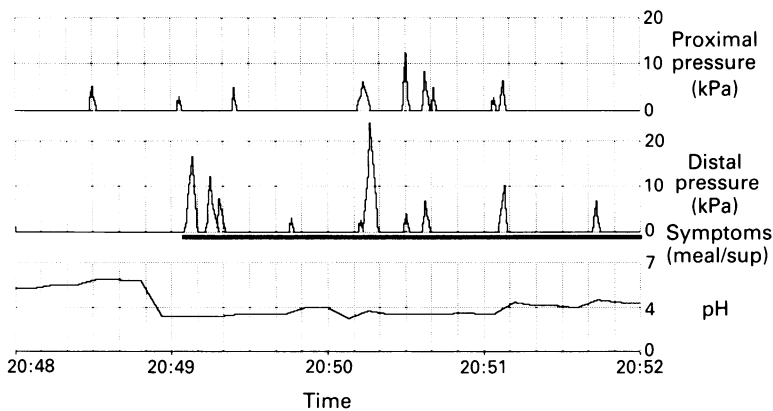


Figure 1: Four minute plot of two pressure signals and one oesophageal pH signal. Note the strong contractions after the pH drop, the amplitude of which exceeded the upper limit of normal (97.5 percentile) for this patient.

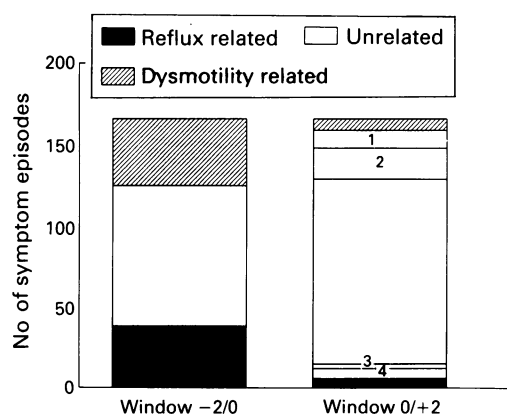


Figure 2: Correlation of the 166 spontaneous chest pain episodes with reflux and dysmotility in the two time windows. (1)=Dysmotility related in the 0/+2 window, but associated with reflux in the -2/0 window. (2)=Dysmotility related in the 0/+2 window, but also dysmotility related in the -2/0 window. (3)=Reflux related in the 0/+2 window, but dysmotility related in the -2/0 window. (4)=Reflux related in the 0/+2 window, but also reflux related in the -2/0 window.

hundred and fourteen pain episodes (68.7%) were not related to any oesophageal functional abnormality. However, 11 of the 37 episodes associated with abnormal motility were immediately (within two minutes) preceded by a reflux episode. In these cases the motor abnormality detected by the analysis consisted of high amplitude peristalsis. An example of this reflux induced 'dysmotility' is shown in Figure 1. These 11 symptom episodes were consequently considered 'unrelated' in the 0/+2 window. In addition, 19 of the 37 episodes associated with abnormal motility in

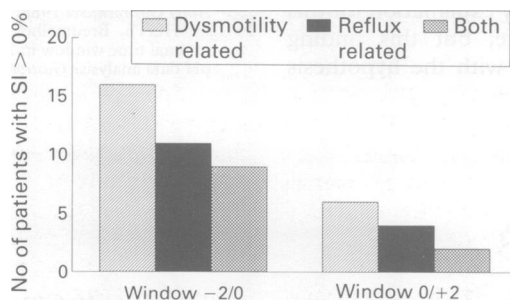


Figure 3: Distribution of related pain events in patients with one or more related events (Symptom index (SI) > 0%).

the 0/+2 time window also had abnormal motility in the -2/0 time window. Consequently, in only seven of the chest pain episodes (4.2%) were the findings consistent with pain provoked secondary oesophageal motor disorders. Three of the 15 reflux related chest pain episodes were preceded by a motor abnormality in the -2/0 time window; six of the 15 episodes also showed a pH < 4 in the -2/0 time window. Therefore, these nine symptom episodes were regarded as 'unrelated' in the 0/+2 window analysis. Only six of the chest pain episodes (3.6%) showed reflux in the 0/+2 time window, with no oesophageal abnormalities in the -2/0 time window. Figure 2 summarises the results of association analysis of the 166 chest pain episodes in the various time windows.

Figure 3 shows that 36 of 48 patients (75%) had one or more correlated chest pain events (SI > 0) in the analysis of the -2/0 window. Eleven of the 48 patients (22.9%) had reflux related chest pain, 16 (33.3%) had one or more chest pain episodes related to oesophageal motor disorders, and nine (18.8%) had both dysmotility and reflux related episodes.

In the analysis of the 0/+2 window, 11 of the 48 patients (22.9%) had one or more correlated chest pain events. Four of the 48 patients (8.3%) had reflux related chest pain, five (10.4%) had dysmotility related chest pain, and two (4.2%) had both dysmotility and reflux related chest pain. Six of the 48 patients (14.6%) had a reflux related episode in the -2/0 window, followed by abnormal motility in the 0/+2 window. Only two of the 48 patients (4.2%) had no reflux or dysmotility related pain episodes in the analysis of the -2/0 window but abnormal motility in the 0/+2 window.

Using the criterion that the SI had to be 75% or higher, 17 of the 48 patients (35.4%) had a positive diagnosis with the -2/0 window and only two (4.2%) with the 0/+2 window.

Discussion

This study aimed to evaluate the cause-effect relationships between oesophageal chest pain on one hand and oesophageal motor abnormalities and acid reflux on the other. The traditional concept, supported by observations made with 24 hour oesophageal pH and pressure monitoring, is that angina-like chest pain can be caused by spastic motor abnormalities and by reflux. It has been reported, however, that pain and stress can induce oesophageal motility abnormalities.⁷ A recent report also suggests that transient lower oesophageal sphincter relaxations, and thereby gastro-oesophageal reflux, might occur in response to stress and pain.⁹ It is possible that the temporal relationships between chest pain and oesophageal abnormalities observed in 24 hour monitoring studies in patients with non-cardiac chest pain are partly due to provocation of abnormalities by stress.

The extent to which the phenomenon affects

the results of 24 hour oesophageal monitoring obviously depends on the time window used in the analysis of the temporal association. Until now all research groups who have published results of 24 hour oesophageal monitoring in non-cardiac chest pain patients have used time windows which extended beyond the onset of pain. Peters *et al* used a time window beginning two minutes before the onset of pain and ending at the end of the pain episode.² Soffer *et al* used a time window starting five minutes before and ending five minutes after the onset of pain.³ Ghillebert *et al* employed a time window beginning two minutes before and ending five minutes after the onset of pain.⁴ Our group has used a time window starting two minutes before and ending two minutes after the onset of chest pain.^{5 6} Probably the most important rationale for including a period after pain onset is that patients, anxious not to miss a pain episode, may push the event button too early – that is, at the ill defined sensations that precede the pain.

It is also obvious that there is a major inconsistency in the analysis of gastro-oesophageal reflux episodes as compared with oesophageal motor disorders. An association between an oesophageal motility event and chest pain is only accepted when the motility event is clearly abnormal (outside the range observed in the same patient during asymptomatic periods). For gastro-oesophageal reflux, any fall in pH below a certain level is used for calculating the association, even if many similar reflux episodes go unnoticed by the patient, since all groups who used the technique of combined 24 hour oesophageal pressure and pH have used this criteria.

In the present study we analysed 166 spontaneous chest pain episodes occurring in 48 patients, once using a window from two minutes before pain onset to pain onset, and secondly using window from pain onset to two minutes afterwards. Whereas 41 of the 166 symptom episodes (24.7%) were found to be correlated with abnormal motility in the pre-pain window, only seven episodes (4.2%), occurring in two patients, were correlated with dysmotility in the post-pain window. Thus, in only 4% chest pain episodes were the findings consistent with provoked secondary oesophageal motility disorders. It remains possible that these abnormalities were partly induced by the pain and could even enhance the pain.

In only six of the 166 chest pain episodes (3.6%) was reflux found to follow the onset of chest pain. The most likely explanation for this is coincidence by chance, but this finding would also be consistent with the hypothesis

that in a small percentage, stress or pain induces reflux. Another possible explanation is that in these six pain episodes the gastric acid refluxing into the oesophagus was perceived by the patient immediately, but reached the pH electrode after some delay.

The observation that only 13 of the 166 chest pain episodes (7.8%) were associated with oesophageal function abnormalities occurring after the onset of pain implies that the error in using a window with a short post-pain extension is not a major one. Other preliminary observations also indicate that the optimal time window for symptom analysis in 24 hour pH and pressure monitoring is the window beginning two minutes before the onset of pain and ending at the onset of pain.¹³

In summary, the findings made in this study indicate that in patients with non-cardiac chest pain, gastro-oesophageal reflux and oesophageal motor abnormalities are very infrequently, if ever, induced by the pain. The results rather lend support to the view that chest pain is commonly the consequence of abnormal oesophageal events.

- 1 Janssens J, Vantrappen G, Ghillebert G. 24-hour recording of esophageal pressure and in patients with noncardiac chest pain. *Gastroenterology* 1986; **90**: 1978–84.
- 2 Peters L, Maas L, Petty D, Dalton C, Penner D, Wu W, *et al*. Spontaneous noncardiac chest pain. Evaluation by 24-hour ambulatory esophageal motility and pH monitoring. *Gastroenterology* 1988; **94**: 878–86.
- 3 Soffer EE, Scalabrini P, Wingate DL. Spontaneous noncardiac chest pain: Value of ambulatory esophageal pH and motility monitoring. *Dig Dis Sci* 1989; **34**: 1651–5.
- 4 Ghillebert G, Janssens J, Vantrappen G, Nevens F, Piessens J. Ambulatory 24 hour intraoesophageal pH and pressure recordings, versus provocation tests in the diagnosis of chest pain of oesophageal origin. *Gut* 1990; **31**: 738–44.
- 5 Breumelhof R, Nadorp JHSM, Akkermans LMA, Smout AJPM. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. *Gastroenterology* 1990; **99**: 1257–64.
- 6 Lam HGTh, Dekker W, Kan G, Smout AJPM. Acute non-cardiac chest pain (NCCP) in a coronary care unit (CCU): a diagnostic challenge. *Gastroenterology* 1992; **102**: 453–60.
- 7 Ayres RCS, Robertson DAF, Naylor K, Smith CL. Stress and oesophageal motility in normal subjects and patients with irritable bowel syndrome. *Gut* 1989; **30**: 1540–3.
- 8 Orr W. Noncardiac chest pain: Conundrum of cause and effect. *Am J Gastroenterol* 1991; **86**: 1548–50.
- 9 Zacchi P, Falchini M, Rossi A, Surrenti C. Lower esophageal sphincter but not esophageal body responds to stress. *Gastroenterology* 1992; **102**: A538.
- 10 Breedijk M, Smout AJPM, van der Zouw C, Verwey H, Akkermans LMA. A microcomputer-based system for 24-hour recording of oesophageal motility and pH profile with automated analysis. *Biol Med Eng Comput* 1989; **27**: 41–6.
- 11 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.
- 12 Wiener GJ, Richter JE, Copper JB, Wu WC, Castell DO. The symptom-index: a clinically more important parameter of ambulatory 24-h esophageal pH monitoring. *Am J Gastroenterol* 1988; **83**: 358–61.
- 13 Lam HGTh, Breumelhof R, Smout AJPM. What is the optimal time window in 24-hour esophageal pressure and pH data analysis? *Gastroenterology* 1991; **100**: A103.