Ambulatory 24 hour intraoesophageal pH and pressure recordings v provocation tests in the diagnosis of chest pain of oesophageal origin

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Abstract
Fifty patients with non-cardiac chest pain underwent 24 hour intraoesophageal pH and pressure recording and provocation tests to determine the relative value of both techniques in establishing the oesophageal origin of the chest pain. Twenty six patients (52%) had at least one positive provocation test: the acid perfusion test was positive related in 18 patients (36%), the edrophonium test in 16 patients (32%), the vasopressin test in five patients (10%), and the balloon distension test (performed in only 20 patients) in one (5%). The 24 hour pH and pressure recording correlated spontaneous chest pain attacks with abnormal motility or gastro-oesophageal reflux in 19 patients (38%). Fourteen of these patients also had at least one positive provocation test. Therefore, 24 hour pH and pressure recordings are only slightly better than a set of provocation tests in identifying the oesophagus as the cause of chest pain (10% diagnostic gain). In the case of oesophageal chest pain, however, 24 hour recording appeared to be the only way to identify the nature of the underlying oesophageal abnormality that caused the spontaneous pain attacks — for example, gastro-oesophageal reflux, motility disorders, or irritability of the oesophagus.

The oesophagus is frequently suspected of being the cause of pain in patients with angina like chest pain of non-cardiac origin, but objective evidence that the oesophagus is indeed the source of the pain is difficult to obtain by conventional examinations.3-9 Gastro-oesophageal reflux or severe motility disorders are usually accepted as the underlying pain mechanism.10,11 The oesophagus may also be hypersensitive to a variety of stimuli, as in the case of the irritable oesophagus syndrome.12 The oesophageal origin of chest pain, however, can only be considered likely when gastro-oesophageal reflux or severe motor abnormalities are shown to correlate in time with the episodes of chest pain. Because of the intermittent and unpredictable character of the pain this proof is only rarely obtained during conventional testing. To increase the chances of recording intraoesophageal pH and pressure during a pain attack, the recording time can be extended or provocation tests can be used. No full paper has been published which has examined systematically the relative value of 24 hour intraoesophageal pH and pressure recording v provocation tests in the diagnosis of oesophageal chest pain. This was the aim of the present study.

Materials and methods
Fifty consecutive patients who gave informed consent were included in the study. There were 30 men and 20 women with a mean age of 54 years (range 37–74 years). The inclusion criterion was the presence of severe angina like chest pain of non-cardiac origin. The Table gives the frequency of the chest pain. Chest pain was exercise related in 37 patients; 19 patients had some (though minor) degree of dysphagia, and 21 patients also experienced heartburn, which, however, was not related to the episodes of pain. Cardiac origin of pain was excluded by the appropriate cardiological investigations including exercise electrocardiogram, thallium scan, and cardiac arteriography in all patients and ergonovine provocation when indicated (20 patients).

Endoscopic examination of the upper gastrointestinal tract was carried out in all patients to exclude severe gastritis, ulcer, or carcinoma as a possible cause of pain. Ultrasonography of the upper abdomen was used to exclude biliary or pancreatic disease. All patients underwent 24 hour intraoesophageal pH and pressure measurements as well as provocation tests.

The study was approved by the ethical committee of the University Hospital.

24 HOUR INTRAESOPHAGEAL pH AND PRESSURE MEASUREMENTS
24 Hour intraoesophageal pH and pressure measurements were performed with a portable recording system (Imcomed, Brussels, Belgium) described in detail elsewhere.13 The intraoesophageal probe was introduced via the nose and was positioned under manometric control in such a way that intraoesophageal pH was measured at 5 cm and pressures at 3, 10, and 17 cm above the lower oesophageal sphincter. The analogue data of the full 24 hour period were recorded on a portable cassette recorder. The patient was asked to note in a diary meal times
and periods of rest and to push a button on the recorder to signal when a chest pain occurred. The entire 24 hour tape recording was replayed on a polygraph for visual analysis of the data. Oesophageal origin of the chest pain was considered likely if analysis of the 24 hour recording showed that the pain episode signalled by the patient by means of the event marker occurred during an episode of acid reflux or severe motor abnormalities or a combination of both. Chest pain was defined as pH associated if it was signalled during or within two minutes of an intraoesophageal drop in pH below 4, provided statistical evaluation showed that the probability that this association in time occurred only by chance was less than 5%. This probability is obtained by the summation of a number of partial probabilities, each of which is found by evaluating the binomial formula:

\[
\frac{n!}{r! (n-r)!} p^r (1-p)^{n-r}
\]

n is the total number of pain episodes signalled by the patient; r ranges from the actual number of pain episodes that fall during or within two minutes of a drop in pH below 4 to n; p is the probability that one pain episode falls during or within two minutes of a drop in pH below 4 only by chance and is calculated from the formula:

\[
\text{total time (min) pH below 4} = \frac{\text{total time (min) of recording}}{(2 \times \text{number of pH drops below 4})}
\]

For the definition of 'severe motor abnormalities' all tracings were analysed in two different ways. The first method of analysis used the same criteria as described by Peters et al.\textsuperscript{11} Contractile complexes recorded during the pain episode (from 2 min before to 5 min after the indication of the onset of the pain) were compared with the contractile complexes of the baseline control. Motor abnormalities were considered to be the cause of the pain (i) when the mean amplitude or duration was greater than the mean (±2SD) of the same parameters during the baseline; (ii) when the maximum amplitudes was greater than the amplitude of the single contraction wave with the highest amplitude observed during the baseline; (iii) when the maximum duration was longer than the duration of the single contraction wave with the longest duration observed during the baseline period; (iv) when the per cent abnormal peristalsis (either non-peristaltic or multiphasic contractions) exceeded the highest frequency during any individual baseline period. The baseline period consisted of a series of five minute samples taken one every hour throughout the recording time and of five minute samples of unusual motor activity observed by visual scanning of the pressure data. The second method of analysis compared the mean (using standard errors) and maximum amplitude and duration and frequency of abnormal peristalsis of contractile complexes recorded during the pain period (from 2 min before to 5 min after the indication of the onset of pain) with the same parameters of complexes of its prepain baseline period starting 20 minutes before the pain attack. In both methods only contractile events in the smooth muscle part of the oesophagus at 3 cm and 10 cm above the lower oesophageal sphincter were taken into account and calculated separately. An episode of chest pain was taken to be associated with abnormal motility if at least one of the above criteria was abnormal.

**PROVOCATION TESTS**

The acid perfusion test,\textsuperscript{14} the edrophonium stimulation test,\textsuperscript{15} and the vasopressin test were performed in all 50 subjects under manometric control using a perfused catheter system (low compliance capillary tube infusion pump, Arndorfer Medical Specialists, Greendale, Wisc; polyvinyl chloride catheters, 0.8 mm ID, 1.5 mm OD). Intraluminal pressures were measured at 3 cm and 10 cm above the lower oesophageal sphincter. The balloon distension test\textsuperscript{16} was performed in 20 patients.

The sequence of the four provocation tests was as follows. The balloon distension test was performed first. After an interval of 15 minutes, the edrophonium test was performed, and after another interval of 15 minutes the vasopressin test was performed. Lastly, after an interval of 30 minutes the acid perfusion test was carried out. Provocation testing lasted for about three hours.

1. **Acid perfusion test**

The acid perfusion test was performed according to the method of Bernstein and Baker.\textsuperscript{16} Through a catheter with an opening 25 cm from the incisors 0.1 N HCl was perfused into the oesophageal lumen at a rate of 7-8 ml/min for a full 30 minutes or until severe discomfort was produced. The test was called positive related if acid perfusion but not saline reproduced the familiar angina like chest pain. When the acid perfusion provoked only substernal burning without the familiar chest pain, the test was called positive unrelated.\textsuperscript{17} Although the acid perfusion test was performed under continuous manometric control, the presence of severe motor abnormalities was not required for the test to be called positive related in case it induced the familiar chest pain.

2. **Edrophonium test**

After a basal period of 10 minutes with at least 10 wet swallows (5 ml H2O), placebo and subsequently 80 µg/kg edrophonium were slowly injected intravenously, and each time 10 swallows were recorded. The test was called positive if edrophonium induced the familiar chest pain in the presence of abnormal motility.\textsuperscript{18}

3. **Vasopressin test**

Forty units of vasopressin were buffered in 50 ml of Sorensen solution (pH 6.5) to be infused into the middle third of the oesophagus via an intraoesophageal catheter at a rate of 2.5 ml/min. The test was performed as follows: after a basal period of 10 minutes with 10 wet swallows (5 ml H2O), 25 ml of saline was perfused and another 10 wet swallows were recorded; after a 10 minute rest 25 ml of the buffered vasopressin solution
was perfused and another 10 swallows recorded; after another 10 minutes' rest, 25 ml vasopressin was perfused once more. The test was called positive if vasopressin induced the familiar angina like chest pain with or without additional motor abnormalities. This new test was performed to induce oesophageal wall ischaemia and chest pain in an attempt to implicate oesophageal ischaemia as a possible cause of angina like chest pain.

4. Balloon distension test
The balloon distension test was performed according to the method recently described by Richter et al. A polyvinyl balloon (length: 30 mm; maximal diameter after 10 ml distension: 27 mm) was positioned 10 cm above the lower oesophageal sphincter and inflated with 1 ml increments of air to a total volume of 10 ml. The test was called positive if distension with a volume of 8 ml or less of air reproduced the familiar angina like chest pain.

Results
The Table summarises the results of the investigations performed in the 50 patients. It also gives data on oesophageal symptoms, frequency of pain episodes, and results of conventional manometry and endoscopic examinations.

24 HOUR INTRAESOPHAGEAL pH AND PRESSURE RECORDING
Twenty one of the 50 patients experienced typical familiar chest pain during the 24 hour recording. A total of 80 pain episodes were signalled by means of the event marker of the recording system. Sixty of these pain attacks were accompanied by a drop in pH below 4 or severe motor abnormalities, or both. In 19 patients (38%) the oesophageal origin of the chest pain could be established because one or more pain episodes coincided in time with a drop in pH or motor abnormalities, or both. In these 19 patients 76 pain episodes occurred, 60 of which correlated with a drop in pH or severe motor abnormalities. Two other patients signalled the remaining four pain episodes which were not accompanied by abnormal oesophageal pH or pressure.

In four of the 19 patients in whom the oesophageal origin of the pain was established pain attacks were accompanied by motor abnormalities alone (without gastro-oesophageal reflux), in 12 patients the pain attacks were always accompanied by gastro-oesophageal reflux alone (without motor abnormalities), and in three patients they were accompanied by a combination of motor abnormalities and reflux. In two of these three patients some pain attacks were accompanied by pure reflux (without motor abnormalities), while other pain episodes in the same patients were accompanied by pure motor abnormalities (without reflux); in the third patient reflux and motor abnormalities always occurred simultaneously during the pain episode.

When an attack of chest pain was found to be accompanied by motility abnormalities defined according to the method of Peters et al, the record was always also abnormal with the other method of analysis (using the individual prepain period as a control instead of time segments spread over the entire recording period) and vice versa.

In all instances the motor abnormalities had already started in the two minute period before the onset of the pain as signalled by the patient.

PROVOCATION TESTS

1. Acid perfusion test
The acid perfusion test was positive related in 18 patients (36%). In 10 the acid induced pain was accompanied by statistically significant motor disturbances. The pain sensation of 11 of the 18 patients with a positive related acid perfusion test started with heartburn, which was subsequently followed by the familiar chest pain.

The acid perfusion test was positive unrelated (inducing only heartburn but not the familiar chest pain) in 18 other patients. In three of these statistically significant motor disturbances were induced during acid perfusion. In the remaining 14 patients the acid perfusion test was negative and pronounced motor disturbances were never induced by acid perfusion.

2. Edrophonium test
Edrophonium, 80 μg/kg intravenous, significantly increased amplitude or duration of the oesophageal contractions, or both, in all 50 patients. The edrophonium test was positive in 16 patients (32%), in whom it induced both the familiar chest pain and motor abnormalities. The mean (SD) amplitude of the contractile complexes in patients with a positive test increased by 107·8 (68·7)% compared to 31·7 (33)% in
patients with a negative test (p<0.01). For the duration of the contraction waves these figures were 74.8 (42.9)% and 51.7 (41.7)% respectively (not significantly different).

4. Vasopressin test
The vasopressin test was positive in five patients (10%). In two of these statistically significant motor disturbances were induced during the test.

5. Balloon distension test
The balloon distension test was performed in 20 of the 50 patients. Only one patient experienced familiar chest pain during intraoesophageal balloon distension at volumes equal to or less than 8 ml. In eight other patients balloon distension produced some discomfort which was clearly different from the familiar chest pain.

OVERALL RESULTS
The Figure and the Table summarise the results of both the 24 hour pH and pressure recordings and the various provocation tests. Twenty six of the 50 patients (52%) had at least one positive provocation test.

Of the 18 patients with a positive related acid perfusion test, 10 also had a positive edrophonium or balloon test, three also had a positive vasopressin test, and two had motor abnormalities alone (without reflux) at the time of spontaneous pain during the 24 hour recording. Likewise, of the 17 patients with a positive edrophonium or balloon test, 10 also had a positive related acid perfusion test, four also had a positive vasopressin test, and four had reflux alone (without motor abnormalities) at the time of their spontaneous pain. Of the 19 patients with a positive 24 hour pH and pressure recording, 14 also had at least one positive provocation test. Together, provocation tests and 24 hour recordings established the oesophageal origin of the chest pain in 31 of the 50 patients (62%).

Discussion
Two main diagnostic techniques have been used to establish the oesophageal origin of non-cardiac angina like chest pain: oesophageal provocation tests and prolonged intraoesophageal pH and pressure recordings in which the patient can signal the occurrence of the chest pain episodes on the recording. The acid perfusion test and the edrophonium stimulation test are generally accepted as the most valuable provocation tests for identifying acid reflux or oesophageal motor abnormalities as the underlying cause of the chest pain. Recently a balloon distension test was introduced by Richter et al in an attempt to study abnormal sensory perception to oesophageal distension as a possible cause of chest pain. Other factors that might contribute to chest pain, such as oesophageal ischaemia, have not yet been studied in detail.

Ambulatory 24 hour intraoesophageal pH and pressure recording is a new technique which was recently introduced in the investigation of patients with angina like chest pain of non-cardiac origin. By prolonging the recording time this technique aims at increasing the chances of recording intraoesophageal pH and pressure changes during an episode of spontaneous chest pain in order to correlate the time of the episode of pain with the occurrence of abnormal oesophageal events – that is, gastro-oesophageal reflux or abnormal motility, or both.

The present study attempts to establish the relative value of 24 hour pH and pressure recordings v provocation tests for the diagnosis of angina like chest pain of oesophageal origin. It also describes a new provocation test that may evaluate the role of oesophageal mucosal ischaemia in producing chest pain. The results show that (i) the 24 hour pH and pressure recordings, the acid perfusion test, and the edrophonium test are almost equally sensitive in establishing the oesophageal origin of chest pain, the tests being positive in 38%, 36%, and 32% of the patients respectively. The vasopressin test and the balloon distension test were positive in only 10% and 5% of the patients respectively. (ii) The combined use of several provocation tests allowed the oesophageal origin of the chest pain to be recognised in 52% of the patients compared to 38% for 24 hour pH and pressure recording. The gain in establishing the oesophageal origin of chest pain by performing 24 hour recordings in patients who had already undergone provocation tests is 10%. Indeed, 14 of 19 patients with a positive 24 hour pH and pressure recording had also at least one positive provocation test. (iii) A major advantage of 24 hour pH and pressure recording over provocation tests is that prolonged monitoring is the only way to identify the nature of the oesophageal abnormality that causes the pain. Of the 12 patients in whom the 24 hour recording showed all spontaneous pain attacks to be exclusively related to acid reflux (without motor disturbances), only six had a positive related acid perfusion test, whereas four patients also had a positive edrophonium test and one also had a positive vasopressin test. Likewise, of the four patients in whom the 24 hour recording showed all spontaneous pain attacks to be exclusively related to motor abnormalities (without gastro-oesophageal reflux), the edrophonium test was positive in only three, and two patients also had a positive related acid perfusion test (one with and one without accompanying motor abnormalities). In several patients, therefore, the oesophagus appeared to be sensitive to more than one stimulus, a condition which has been called 'irritable oesophagus'.

It is obviously important to recognise the specific oesophageal abnormality that causes the pain because this will determine the treatment. Patients with an acid sensitive oesophagus will be treated primarily by measures which reduce or eliminate acid exposure of the oesophageal mucosa. Patients with a sensitive oesophagus will be treated by muscle relaxants such as calcium channel blockers, which if given to patients with an acid sensitive oesophagus may aggravate the condition. Patients with an irritable oesophagus constitute a difficult therapeutic problem. These patients may need drugs that
reduce pain perception rather than drugs which combat gastro-oesophageal reflux or motor abnormalities. Placebo controlled studies are needed to optimise treatment modalities.

This study confirms previous observations indicating that an irritable oesophagus is a frequent cause of non-cardiac chest pain. Fourteen of the 31 patients in whom the oesophageal origin of the chest pain had been established presented with an irritable oesophagus according to the following diagnostic criteria. (a) 24 hour pH and pressure measurements show that the spontaneous pain episodes are sometimes accompanied by acid reflux alone, at other times by oesophageal motility disorders alone. (b) 24 hour recordings show that spontaneous pain is accompanied by acid reflux alone; in addition, the erophenin test or the balloon distension test is positive. (c) 24 hour recordings show that spontaneous pain is accompanied by oesophageal motility disorders alone; in addition, the acid perfusion test is positive. (d) Both the acid perfusion test and the erophenin or balloon distension tests are positive.

In a previous study in 60 patients with non-cardiac chest pain we were able to establish by means of 24 hour pH and pressure measurements the oesophageal origin of the chest pain in 21 (35%) of the 60 patients. Peters et al confirmed this and found a positive correlation between pain and abnormal oesophageal events in 13 of their 22 patients (59%). In the latter study, however, 64% of the 92 pain episodes did not correlate with either a reflux episode or abnormal motility. In the present study only 20 of the 80 (25%) pain episodes signalled by the patients did not correlate with either abnormal motility or reflux. The reason for this discrepancy is unclear but may be related to differences in the patient groups studied. In Peters's study as many as 92 pain episodes were reported by the 22 patients, while our 50 patients reported only 80 pain episodes during the study period.

The definition of chest pain-related abnormal
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osophageal events during a 24 hour pH and pressure recording is still not well established. A fall in pH below 4, occurring immediately before a chest pain episode, is accepted by most investigators as a likely cause of the pain, although it is well known that in the same patient other similar drops in pH may not be accompanied by chest pain. We have accepted the simultaneous occurrence of chest pain and a drop in pH as evidence that reflux was indeed the likely cause of the pain in that particular patient only if statistical analysis showed that the probability that this coincidence occurred by chance was less than 5%. The definition of abnormal motility as a cause of the chest pain is even more difficult. Peters et al defined abnormal (pain producing) motility patterns as contraction complexes that significantly exceeded in amplitude, duration, or peristaltic disorders the contraction waves that were observed during the control period, consisting of a number of five minute periods selected throughout the 24 hour recording time. This method probably represents the most specific definition of abnormal motility during episodes of chest pain. In a recent study in 30 patients Richter and Castell also used a shortened method of analysis defining motor abnormalities as calculated against a control period immediately preceding the pain episode. When they compared both methods of analysis they found 24% of chest pain events identified to be motility related.7 With the shortening of method v 10% using the more extensive method of analysis. In our present study, however, all pain episodes that could be attributed to motility disorders with the analysing method that used segments spread over the entire recording as a control were found to be also abnormal with the short method that used individual pre-pain periods as a control and vice versa. (The short method of defining motor abnormalities could not be used in only three of the 80 pain episodes because the number of contractile events during the prepain control period was too small.) The reason for the discrepancy between Richter’s results and ours is not clear. If a short analysis using only the pre-pain period as a control could be used almost as well (as apparently was the case in our study) it not only would greatly simplify the analysis but would also diminish to a large extent the memory capacity requirements of the recording system.

The sensitivity of the acid perfusion test for the diagnosis of chest pain of oesophageal origin ranges from 7% to 20%.7-9 In the present study as many as 18 of the 50 patients (36%) had a positive related acid perfusion test. Most investigators agree that manometric abnormalities are not regularly observed occurring a positive related acid perfusion test.7-9 This agrees with our finding that only 10 of the 18 patients with a positive related acid perfusion test developed abnormal oesophageal contractility during the acid induced pain, while three of the 18 patients with a positive unrelated acid perfusion test developed abnormal motility. It is interesting that the substernal discomfort in 11 of the 18 patients with a positive related acid perfusion test started as heartburn and that familiar chest pain was reproduced only subsequently by continuing the acid perfusion. This finding may partially explain the higher number of positive related acid perfusion tests in this study.

Several attempts have been made to provoke pharmacologically oesophageal motility abnormalities and chest pain. Bethanecol and penta-gastrin were reported to induce chest pain in 6% and 3% of the patients respectively.8,9 Ergonovine will induce chest pain and associated oesophageal motor abnormalities in 22–60% of patients, but the cardiac risks of the drug limit its use as a test in the motility laboratory.10,11 Edrophonium may yield equivalent results and is safe to use.12 Of patients with chest pain of non-cardiac origin, 28–34% will have their pain reproduced by the intravenous injection of 80–160 μg/kg edrophonium.13,14

In the present study 80 μg/kg edrophonium induced both familiar chest pain and motility changes in 32% of the patients. There is still some controversy whether or not the induction of motility disorders, together with the pain, is a prerequisite for calling the edrophonium test positive. In our study 80 μg/kg IV edrophonium induced appreciable motility changes in all patients, but the change was more pronounced in patients in whom familiar chest pain was reproduced by the administration of the drug.

Recently Richter et al used balloon distension in the lower osophagus as a provoked test.15 Chest pain was induced in 60% of the patients in only 29% of the controls. Analagous to what has been observed in the sigmoid colon of patients with the irritable bowel syndrome, the chest pain patients experienced pain at distension volumes lower than the controls (<8 ml). In the present study in only one of the 20 patients in whom it was performed was typical familiar chest pain reproduced; eight other patients felt a sensation that was different from their familiar angina like chest pain.

Until now acid gastro-oesophageal reflux and oesophageal motor disturbances have been implicated as a possible cause of chest pain of oesophageal origin. Other pain mechanisms, however, may be as well. Rodrigo et al described a receptor like structure in the submucosa of the mid-oesophagus of cats and monkeys composed of non-varicose nerve fibres which formed a series of laminar structures on the surface of blood vessels. The function of these putative arterial receptors is unknown but it cannot be excluded that they transmit an ischaemia-like type of pain. The possibility of oesophageal wall ischaemia in patients with oesophageal motility disorders is also suggested by a recent study of MacKenzie.16 In this perspective we infused locally into the oesophageal lumen a vasospastic drug, vasopressin, in an attempt to induce local ischaemia and pain. When given intraluminally it is most unlikely that vasopressin will be absorbed into the general circulation; and indeed in no instances have we noted any change in blood pressure or heart rate. Although there is not experimental proof that local ischaemia was induced in the oesophagus, in five of the 50 patients familiar chest pain was reproduced by the intra-oesophageal infusion of vasopressin. In two of the five patients vasopressin also induced oesophageal motility...
changes together with the pain, but in the three others the manometric record remained unchanged. In three of the five positive vaso-
pressin patients the acid perfusion test and the edrophonium test were also positive, in one the edrophonium test (but not the acid perfusion test) was also positive, and the last patient had no other positive provocation tests.

It may be argued that the criteria that we have used to identify the oesophagus as the likely cause of chest pain have not really been proved to do so and that the number of false positive results in a control population has not been studied appropriately for most provocation tests. The criteria that we have accepted are, however, the best that are available as there is no gold standard for the diagnosis of oesophageal chest pain.

From this study it may be concluded that the combined use of several provocation tests is perhaps the easiest way to establish the oesophageal origin of non-cardiac chest pain, although it is labour intensive. Intraoesophageal 24 hour pH and pressure recording is at present the only method that can identify the nature of the oesophageal abnormality causing spontaneous chest pain. Besides gastro-oesophageal reflux and oesophageal motor disorders, local ischaemia may have a role. The most frequent abnormality, however, is hypersensitivity of the oesophagus to various stimuli, a condition that has been called 'irritable oesophagus.'

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