

PAPERS

A prospective study of oesophageal function in patients with normal coronary angiograms and controls with angina

R A Cooke, A Anggiansah, J B Chambers, W J Owen

Abstract

Aims—To compare the incidence of oesophageal abnormalities and their correlation with chest pain in patients with normal coronary angiograms, and in controls with angina.

Patients—Sixty one patients with normal coronary angiograms (NCA group) referred to a single cardiac centre between March 1990 and April 1991; 25 matched controls with confirmed coronary artery disease (CAD group).

Setting—Cardiac referral centre and oesophageal function testing laboratory.

Main outcome measures—Oesophageal manometry, provocation tests, and 24 hour ambulatory pH monitoring.

Results—Simultaneous contractions were more common (6.7% versus 0.8%, $p < 0.01$), and the duration of peristaltic contractions was longer (2.9 versus 2.4 seconds, $p < 0.01$) in the NCA group than in the CAD group. There were no group differences in the amplitude of peristaltic contractions, and none had nutcracker oesophagus. Ten (16%) patients with NCA and no patients with CAD had diffuse spasm ($p = 0.03$). Twenty one (34%) patients with NCA, and five (20%) patients with CAD had abnormal gastro-oesophageal reflux ($p > 0.05$). There was no significant difference between the groups in the number of patients whose pain was temporally related to pH events. Particular chest pain characteristics, or the presence of additional oesophageal symptoms, were not predictive of an oesophageal abnormality.

Conclusion—Oesophageal function tests commonly implicate the oesophagus as a source of pain in patients with normal coronary angiograms. With the exception of simultaneous contractions during manometry however, the incidence of abnormalities and in particular the correlation of pH events with chest pain are as common in patients with normal coronary angiograms as in controls with angina. The oesophagus may often be an unrecognised source of pain in both groups of patients.

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Keywords: oesophageal function; coronary artery disease; chest pain

The oesophagus is commonly implicated in patients with chest pain and normal coronary angiograms. Previous studies using oesophageal function tests however, have recruited patients referred to the oesophageal laboratory, raising the possibility of selection bias.¹⁻³ Furthermore, there is little published data about the prevalence of oesophageal dysfunction in patients with angina. Svensson *et al* reported a similar incidence of oesophageal abnormalities. This study however used old technology and the robustness of the diagnosis of angina was in doubt on account of a high incidence of "atypical" symptoms.⁴ More recent reports have generally involved small, poorly defined groups and incomplete oesophageal investigations.^{5 6}

The objective of the present prospective, observational study was to compare the incidence of oesophageal abnormalities, and their correlation with chest pain in patients with normal coronary angiograms, and in a small but representative group of controls with angina.

Subjects

Between March 1990 and April 1991, 1022 consecutive patients underwent coronary angiography as part of the investigation of chest pain. Of these, 84 (8.2%) had completely normal angiograms and no evidence of spontaneous coronary spasm. Patients with mitral valve prolapse (three patients), left ventricular hypertrophy (four patients), or abnormalities of resting wall motion on echocardiography (five patients) were excluded. In addition, five patients were excluded because of previous myocardial infarction, and six declined entry to the study. There remained a study group of 61 patients (normal coronary artery (NCA) group). Table 1 lists their demographic data and symptom characteristics.

Twenty five sex matched controls with angina were recruited (coronary artery disease (CAD) group). All had "typical" symptoms and evidence of ischaemia during exercise treadmill testing as a requirement for entry. In

Department of
Cardiology
R A Cooke
J B Chambers

Department of
Surgery, Guy's
Hospital, London, UK
A Anggiansah
W J Owen

Correspondence to:
Dr R A Cooke, Suite 303,
Emblem House, London
Bridge Hospital, 27 Tooley
Street, London SE1 2PR,
UK.

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Table 1 Demographic data and symptoms in patients with normal coronary angiograms (NCA), controls (CAD), and 65 matched consecutive admissions with confirmed coronary artery disease (Parent CAD)

	NCA (n = 61)	CAD (n = 25)	Parent CAD (n = 65)
Age (mean (SD))	54 (9)	59 (8)	61 (9)
Sex (M/F)	23/38	10/15	24/41
Smokers	12 (20)	5 (20)	23 (35)
Cholesterol (mmol/l) (mean (SD))	6.0 (1.5)	7.0 (1.1)	6.8 (1.5)
Diabetes	0	0	0
Hypertension	20 (33)	11 (44)	28 (43)
Abnormal rest ECG	14 (23)	2 (8)	8 (12)
Abnormal exercise ECG	14 (23)	25 (100)	37/56 (66)
Chest pain characteristics			
Chest pain on exertion	58 (95)	25 (100)	65 (100)
Chest pain at rest	50 (82)	10 (40)	35 (54)
Usual duration ≤ 5 min	22 (36)	22 (88)	56 (86)**
Predictability <10/10	38 (62)	5 (20)	14 (22)**
Rest pain ≥2/10	40 (66)	4 (16)	19 (29)**
Radiation to arms	40 (66)	12 (48)	36 (55)
Radiation to back	17 (28)	7 (28)	20 (31)
Nocturnal	20 (33)	7 (28)	12 (19)
Frequency of pain			
Daily	32 (52)	18 (72)	53 (81)
Weekly	23 (38)	6 (24)	8 (13)
Occasional	6 (10)	1 (4)	4 (6)
Additional symptoms			
Heartburn	21 (34)	8 (32)	25 (38)
Dysphagia	14 (23)	0	3 (5)**
Waterbrash	20 (33)	6 (24)	19 (29)
Flatulence	26 (43)	6 (24)	20 (31)
Variable stool habit	12 (20)	0	2 (3)**

Results are expressed as n (%) except where shown.

**p < 0.01 v NCA group. There were no significant differences between CAD and Parent CAD groups.

addition, all had significant obstructive coronary disease defined as greater than 70% luminal diameter narrowing in at least one major epicardial artery and no previous myocardial infarction. They were compared with a sex matched parent population of 65 consecutive patients with significant obstructive coronary disease and no previous infarction. There were no significant differences in age, incidence of risk factors for coronary disease, chest pain characteristics, or incidence of oesophageal symptoms between the control CAD group and the parent population (table

1). All controls had chronic stable angina. None had left main stem stenoses, three vessel disease, or critical stenoses of the proximal left anterior descending artery.

None of the patients or controls had previously been investigated by a gastroenterologist or had prominent symptoms of gastro-oesophageal reflux disease. All medication likely to interfere with oesophageal motility or affect the incidence of gastro-oesophageal reflux with the exception of short acting nitrates was discontinued for 48 hours before testing. Written, informed consent was obtained, and the study had the approval of the hospital's ethics committee.

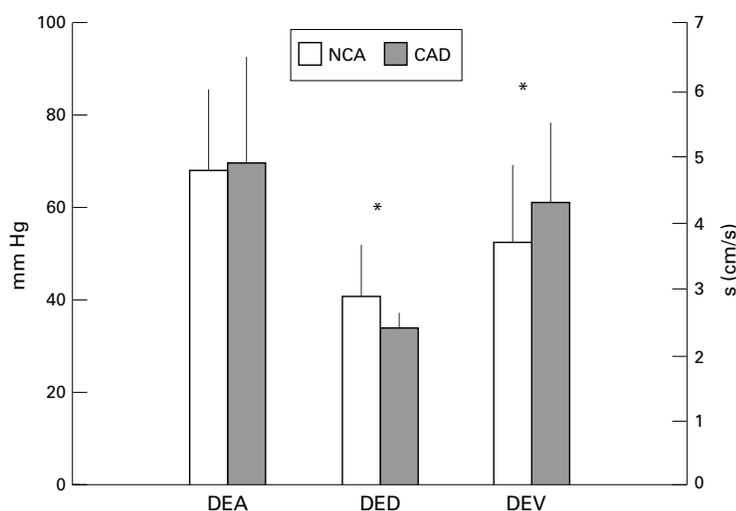
Methods

PATIENT CHARACTERISTICS

Patient demographic and symptom characteristics were recorded using standard questionnaires. For the purposes of the study chest pain was considered "typical" where it occurred on exercise and satisfied at least two of the following criteria: reproducibly provoked by exercise; rest pain accounting for no more than 10% of pain episodes; or duration of pain of five minutes or less. Pain which occurred at rest, or which satisfied none or only one of the above criteria was considered to be "atypical".

MANOMETRY

Baseline manometry was performed after a four hour fast with the patient sitting upright. A pressure catheter (2.5 mm external diameter) (Gaeltec Ltd, Scotland, UK) consisting of six surface mounted microtransducers arranged at 5 cm intervals was passed transnasally into the stomach. After a five minute resting period, the lower oesophageal sphincter was located using the station pull through technique, and a minimum of 10 wet swallows (5 ml bolus) recorded in the oesophageal body. The electrocardio-



Data are expressed as mean (SD).

†95% Confidence interval (CI) 0.2 to 0.7; ‡95% CI 0.04 to 1.2.

Figure 1 Comparison of distal peristaltic amplitude (DEA), duration (DED), and velocity (DEV) in NCA and CAD groups. *p < 0.05.

Table 2 Incidence of oesophageal abnormalities in NCA and CAD groups

	NCA (n = 61)	CAD (n = 25)
Manometric abnormalities		
Diffuse spasm	10 (16%)	0*
Nutcracker	0	0
Achalasia	0	0
Non-specific	2 (4%)	1 (4%)
Provocation testing		
Acid perfusion	20 (33%)	5 (20%)
Edrophonium	0	NA
Ambulatory pH monitoring		
Abnormal reflux	21 (34%)	5 (20%)
SI \geq 25%	14 (23%)	6 (24%)

* $p < 0.03$.

gram was monitored throughout using a two channel recorder (Siemens, Stockholm, Sweden).

The pressure recordings were stored on disk for off line analysis using an IBM compatible computer and commercially available software (Aspen Medical GR 800). Interpretation was by two experienced observers who were unaware of the clinical details or the results of the other tests. Standard definitions of dysmotility were used.⁷

PROVOCATION TESTING

The acid perfusion test was performed by first instilling normal saline into the oesophageal body at a rate of 10 ml per minute (or less if this rate was not tolerated), and then switching to 0.1 M hydrochloric acid. The acid infusion was stopped after a maximum of 100 ml or sooner if chest pain developed. A test was defined as positive if the patient's usual chest pain was reproduced by acid but not saline.

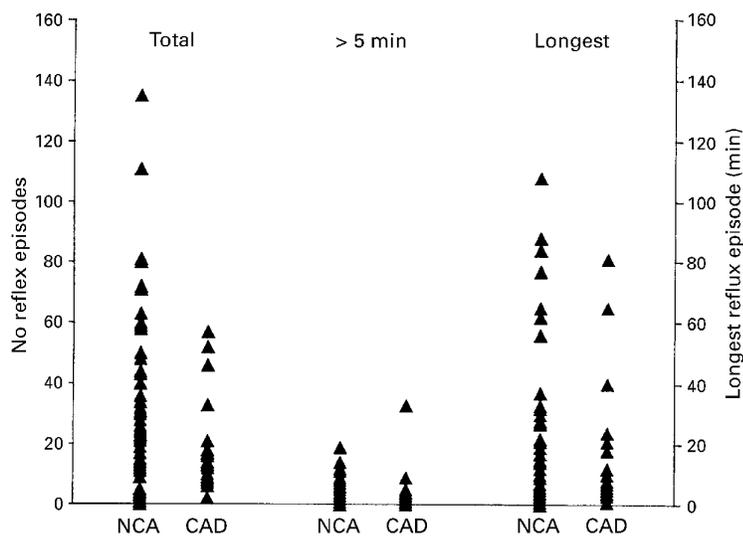
The edrophonium test was performed only in patients in whom there were no contraindi-

cations. It was not performed in controls (CAD group) since this was not considered ethical. Normal saline placebo (10 ml) was injected intravenously followed by 10 mg edrophonium hydrochloride provided that no symptoms were reported. As with the acid perfusion test, a positive edrophonium test was defined by the reproduction of the patient's usual chest pain. In addition, however, the occurrence of a new motility disorder was required for a test to be positive.⁸

TWENTY FOUR HOUR AMBULATORY pH MONITORING

Twenty four hour ambulatory pH monitoring was performed using a probe (external diameter 2.1 mm) with a distal antimony monocrySTALLINE pH sensor and external cutaneous reference electrode. The sensor was positioned 5 cm cephalad to the upper margin of the manometrically defined lower oesophageal sphincter. Changes in distal oesophageal pH were recorded on a "Digitrapper" (Synectics Medical, Sweden) which was strapped to the patient's waist. The system was calibrated at pH 1.0 and 7.0 (Synectics buffer solution) before insertion and after each study. Gastric acidity was confirmed in all patients by passing the probe into the stomach before its final placement above the lower oesophageal sphincter. The probe was secured by tape to the nostril. A diary card and an event marker button were used to record the time of onset of symptoms during the 24 hour ambulatory period. Alcohol, and food or beverages with pH values less than 5 were avoided, but otherwise the subjects were unrestricted.

On completion, data were transferred from the Digitrapper to an IBM compatible personal computer for graphical display and numerical analyses using commercially available software (Esophagram Version 5.5, Gastrosoft Inc.). All recordings were checked visually for technical quality to exclude artefact. A reflux episode was defined as any fall in distal gastro-oesophageal pH below a threshold of 4 pH units for more than 10 seconds. Abnormal reflux was defined by the oesophageal pH falling below 4 pH units for more than 5.5% of the 24 hour period.⁹ A symptom index was expressed for symptoms occurring spontaneously during the 24 hour period. This was calculated by dividing the number of pain episodes which were temporally related to gastro-oesophageal reflux by the total number of pain episodes.¹⁰ A temporal relationship was defined by chest pain beginning within two minutes before and two minutes after a reflux episode. A symptom index of at least 25% was used to define symptomatic reflux.¹¹



Reflux episodes	NCA	CAD	p Value*
Total number	20 (3.2 to 39.0)	12.0 (7.5 to 17.5)	0.3
Number >5 min	1.0 (0.0 to 5.0)	1.0 (0.0 to 3.0)	0.9
Longest duration	9.0 (1.2 to 21.7)	7.0 (5.0 to 15.0)	0.7

Data are expressed as median (interquartile range).

*Mann-Whitney U test.

Figure 2 Comparison of parameters of gastro-oesophageal reflux during ambulatory pH monitoring: percentage reflux episodes.

STATISTICS

The data were described as either the mean (SD) or median (interquartile range), and group comparisons were made by Student's *t* test or the Mann-Whitney U test depending on the distribution of the variables. The χ^2 test with Yates's correction, or the Fisher exact test were used for discrete variables. A *p* value of

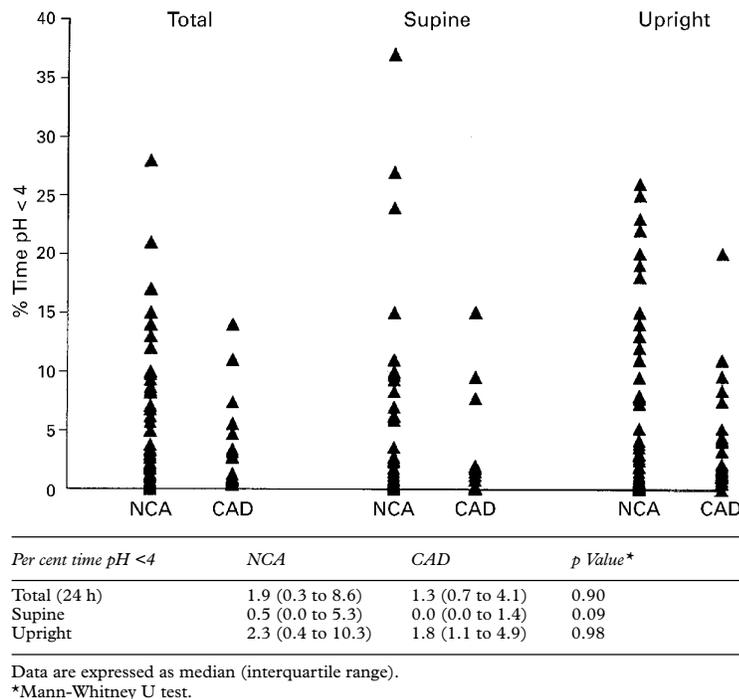


Figure 3 Comparison of parameters of gastro-oesophageal reflux during ambulatory pH monitoring: reflux episodes.

less than 0.05 was considered to be statistically significant.

Results

PATIENT CHARACTERISTICS

Fifty eight (95%) patients with NCA, and all patients with CAD had a history of exertional chest pain. There were however, significant differences between the groups in the reproducibility of pain with exercise, the duration of pain, and the frequency of rest pain (table 1). Thirty three (54%) patients with NCA, and nine (36%) patients with CAD had additional oesophageal symptoms (table 1). The incidence of heartburn and waterbrash were similar, but intermittent dysphagia was more common in NCA (14 (23%) patients), than in patients with CAD (no patients) ($p < 0.01$). Twelve (20%) patients with NCA, and no patients with CAD had variable stool habit ($p = 0.015$).

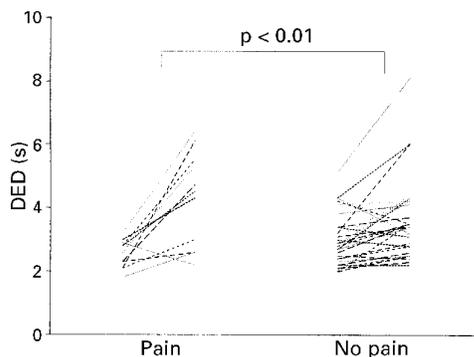


Figure 4 Mean distal peristaltic duration (DED) at baseline and after edrophonium in patients who reported pain, compared with patients who did not report pain.

MANOMETRY

Simultaneous contractions accounted for 6.7% of the total number of contractions in the NCA group, but only 0.8% in the CAD group ($p < 0.01$). There were no significant differences between the groups in the mean distal amplitude of peristaltic contractions, though the mean distal duration of peristaltic contractions was significantly longer, and the mean distal velocities significantly shorter in the NCA group, compared with the CAD group (fig 1).

Ten (16%) patients with NCA, and no patients with CAD had diffuse spasm ($p = 0.03$) (table 2). All had normal or low amplitude and duration contractions and none had chest pain at the time of manometry. Overall, 12 (20%) patients with NCA, and one (4%) patient with CAD had abnormal oesophageal manometry ($p > 0.05$) (table 2).

TWENTY FOUR HOUR AMBULATORY OESOPHAGEAL pH MONITORING

Gastro-oesophageal reflux was more common in the NCA group compared with the CAD group, but there were no significant differences between the groups in the distribution of any of the measured parameters of gastro-oesophageal reflux (figs 2 and 3). Twenty one (34%) patients with NCA and five (20%) patients with CAD had abnormal gastro-oesophageal reflux ($p > 0.05$) (table 2).

Thirty five (57%) patients with NCA had chest pain during ambulatory pH monitoring. Thirteen (37%) of these had abnormal gastro-oesophageal reflux, of whom 10 (77%) had pain which was temporally related to episodes of reflux. A further four patients had pain which was temporally related though their reflux parameters were normal. For those patients whose pain was temporally related to episodes of reflux their mean number of symptoms per patient was 3.4 (SD 2.4); their mean symptom index score was 68% (SD 31%, median 59%, and interquartile range 37% to 100%).

In the CAD group, 13 (52%) patients reported chest pain during ambulatory pH monitoring. In six (46%) of these their pain was temporally related to episodes of gastro-oesophageal reflux. The mean number of chest pain episodes per patient was 2.3 (SD 1.0); their mean symptom index score was 64% (SD 29%, median 50%, and interquartile range 46% to 100%) ($p > 0.05$ versus NCA group).

PROVOCATION TESTS

Overall, the acid perfusion test and/or a temporal correlation of symptoms with episodes of gastro-oesophageal reflux during ambulatory pH monitoring identified the oesophagus as a probable source of chest pain in 27 (44%) patients with NCA, and in nine (36%) patients with CAD ($p > 0.05$).

The acid perfusion test was positive in 20 (33%) patients with NCA, and also in five (20%) patients with CAD ($p > 0.05$). None of the patients in either group had simultaneous electrocardiographic abnormalities. The maximum increase in heart rate was nine beats per

Table 3 Clinical correlates

	Patients (n = 61)	PT (+) (n = 26)	Motility (n = 12)	GOR (n = 21)	SR (n = 14)
Chest pain characteristics					
Duration ≤5 min	36	31	33	57	57
Predictability 10/10	38	35	50	38	50
Rest pain ≤2/10	34	35	33	48	57
Typical pain	28	31	33	43	57
Symptoms of GORD					
Heartburn	34	35	33	33	43
Dysphagia	23	31	8	24	36
Waterbrash	33	38	33	38	43
Any of the above	54	54	50	52	64
Abnormal ECG	23	19	17	24	14

Results are expressed as percentages.

PT (+), provocation test positive; GOR, abnormal gastro-oesophageal reflux during ambulatory pH monitoring; SR, symptomatic reflux during ambulatory pH monitoring.

minute, and in most patients there was no significant change in heart rate.

The edrophonium test was performed in the NCA group only. It reproduced their pain in 13/50 (26%) patients, but in none was this associated with the production of a new motility disorder. In three patients manometry was abnormal at baseline. Figure 4 shows that the duration of peristaltic contractions in the distal oesophageal body increased significantly more in patients who reported pain compared with those who did not report pain. Seven of the 13 (54%) patients with pain during the edrophonium test also had their pain reproduced by acid perfusion testing, and four (31%) had pain which was temporally related to acid reflux during ambulatory pH monitoring.

CLINICAL CORRELATES

In the NCA group the proportion of patients with "typical" pain was higher in patients whose pain was temporally related to pH events during ambulatory monitoring than in the group as a whole. There were no chest pain characteristics, however, which were strongly predictive of an oesophageal abnormality (table 3). Similarly, the incidence of oesophageal abnormalities was as high in patients with additional oesophageal symptoms as in those with no symptoms (table 3).

In the CAD group four of nine (44%) patients with, compared with four of 16 (25%) with no additional oesophageal symptoms had abnormal gastro-oesophageal reflux or pain which was temporally related to pH events during ambulatory pH monitoring. Oesophageal symptoms were present in four of five (80%) patients with positive, compared with five of 20 (25%) patients with negative acid perfusion tests. Only one patient in this group had abnormal manometry (non-specific). They did not report oesophageal symptoms.

Discussion

In this prospective observational study there was a high incidence of oesophageal abnormalities in patients with normal coronary angiograms. With the exception of simultaneous contractions during manometry, however, the incidence of abnormalities was not significantly different to that in controls with confirmed angina.

A diagnosis of diffuse spasm was made in almost a fifth of patients with NCA, and in no

controls. Only one of these had a history of intermittent dysphagia consistent with impaired oesophageal transit. The incidence of simultaneous contractions in the control group was low, and similar to that reported in healthy volunteers by Richter *et al.*⁷ The observation confirms the importance of oesophageal spasm as a potential cause of chest pain in patients with normal coronary angiograms.

Despite previous reports of an association of high amplitude peristalsis with non-cardiac chest pain there were no differences between the groups in peristaltic amplitude, and none had nutcracker oesophagus.¹² Differences in catheter sizes and recording assemblies may explain the relatively low peristaltic amplitudes in our study (mean (2 SD) less than 130 mm Hg) compared with Richter *et al* (mean (2 SD) greater than 180 mm Hg). The Gaeltec catheter (2.5 mm diameter) used in our laboratory is 2 mm smaller than that used by Richter *et al* (4.5 mm).⁷ The distribution of peristaltic amplitudes in our study is in close agreement with that reported by Wilson *et al* for a normal population, using a similar Gaeltec pressure monitoring system.¹³

PREVIOUS STUDIES

The observation that the oesophagus may produce pain which may resemble, or even provoke angina is not recent.^{14 15} In a prospective study Schofield *et al* reported abnormal gastro-oesophageal reflux during ambulatory pH monitoring in 11/51 (21%) patients with normal coronary angiograms, and induced gastro-oesophageal reflux which coincided with the onset of chest pain during treadmill testing in a further 13 (23%).¹⁶ The observation in the present study of a high incidence of gastro-oesophageal reflux and its coincidence with chest pain in the majority of cases is in agreement with this study, but unlike their study we included both patients with "typical" and "atypical" symptoms. In a more recent study Nevens *et al* reported abnormal gastro-oesophageal reflux in 15/37 (47%) patients, and a motility disorder in a further 11 (30%).¹⁷ As in the study of Schofield *et al* they studied only patients with "typical" pain. Only eight patients had symptoms during ambulatory monitoring though in six of these pain was considered to be related to an oesophageal event.

The observation that the incidence of oesophageal abnormalities was as high in patients with "typical", as in patients with "atypical" pain is important. The incidence of abnormalities moreover was high even where there were no additional oesophageal symptoms. Thus all patients with unexplained chest pain following coronary angiography should be considered for oesophageal testing.

The importance of the prospective design of the present study is illustrated by the study of Hewson *et al* in which "nutcracker" oesophagus was reported in 29% of 45 patients referred to the oesophageal laboratory.¹⁸ The study was repeated prospectively in a sample of 100 patients and the incidence was only 6%.¹¹ One might expect high amplitude contractions in anxious patients selected for oesophageal investigations either because of refractory symptoms or a failure of negative cardiac investigations to reassure.^{19,20} Since our patients were unselected this might explain the relatively low incidence of "nutcracker" oesophagus. It is possible however that the incidence of "nutcracker" oesophagus has been overestimated in the past due to the use of normal values based on studies using poorly compliant manometry systems.²¹

A high incidence of oesophageal abnormalities has previously been reported in patients with coronary heart disease, and with suspected non-cardiac chest pain.^{22,23} Few studies have described the incidence of oesophageal abnormalities in patients with confirmed angina. DeCaestecker *et al* reported abnormal motility in three of 10 (30%) patients, though the high incidence of dysmotility in their study may have been due to a failure to withdraw β blockers.⁶ Schofield *et al*, in a study of 20 patients, and in agreement with our study, reported a significantly lower incidence of abnormal motility.⁷

Since each of our controls had "typical" chest pain, significant ST depression during treadmill stress testing, and angiographically confirmed obstructive coronary heart disease, there is little doubt that their chest pain was cardiac. One explanation of the association of pain with pH events in this group might be an inability of patients with angina to differentiate ischaemic cardiac chest pain from oesophageal pain.¹⁴ The association may however be explained by "linkage" or the so called "viscero-cardiac reflex". Thus Alban Davies *et al* reported a reduced exercise threshold and earlier onset of ischaemia compared with placebo after acid infusion of the distal oesophagus.²⁴ Mellow *et al* provoked chest pain which was indistinguishable from their usual angina during acid perfusion testing in 10 of 25 (40%) patients.²⁵ In three of the 10 patients it is likely that angina was provoked by the stress of oesophageal intubation, but in the remaining patients, as in the present study, there were no significant changes in the heart rate/blood pressure products.

None of our patients developed significant motor disturbances with edrophonium though the peristaltic duration increased significantly more in patients who reported pain compared

with those who did not report pain. This is in agreement with previous observations.²⁶ In seven of 13 (54%) patients whose pain was reproduced by edrophonium it was also reproduced by acid perfusion. In addition, four (31%) patients with pain provoked by edrophonium had acid related pain during ambulatory pH monitoring. The poor specificity of edrophonium has been noted.²⁷ The observations support the concept of polymodal pain receptors in the distal oesophagus, but may also be explained by increased somatic awareness.²⁸

LIMITATIONS

There are a number of limitations to the study. The sample of controls with confirmed angina is small, though it represents one of the largest series reported to date. It is our experience, and that of others, that such patients often decline oesophageal testing.⁵ No differences in age, sex, smoking habits, chest pain characteristics, or oesophageal symptoms were noted between our sample and a larger group of patients with confirmed coronary artery disease. We therefore consider it reasonable to conclude that the sample was representative. The withdrawal of medication for 48 hours before testing was considered reasonable but it is accepted that in the case of β blockers a longer period of withdrawal may have been required for complete washout of the drug.

CONCLUSIONS

In conclusion, oesophageal function tests are useful and commonly implicate the oesophagus as a source of chest pain in patients with angiographically normal coronary arteries. With the exception of a lower incidence of simultaneous contractions during manometry, however, the incidence of abnormalities and in particular the correlation of pH events with chest pain are as common in patients with normal coronary angiograms as in controls with confirmed angina. The oesophagus may be a commonly unrecognised source of pain not only in patients with negative cardiac investigations but also in patients with angina.

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