Pain perception and brain evoked potentials in patients with angina despite normal coronary angiograms

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Abstract

Objective—To evaluate the role of nociception in patients with angina despite normal coronary angiograms and to investigate whether any abnormality is confined to visceral or somatosensory perception.

Methods—Perception, pain threshold, and brain evoked potentials to nociceptive electrical stimuli of the oesophageal mucosa and the sternal skin were investigated in 10 patients who had angina but normal coronary angiograms, no other signs of cardiac disease, and normal upper endoscopy. Controls were 10 healthy volunteers. The peaks of the evoked potential signal were designated N for negative deflections and P for positive. Numbers were given to the peaks in order of appearance after the stimulus. The peak to peak amplitudes (P1/N1, N1/P2) were measured in μV .

Results—(1) Angina pectoris was provoked in seven patients following continuous oesophageal stimulation. (2) Distant projection of pain occurred after continuous electrical stimulation of the oesophagus in four patients and in no controls. (3) Patients had higher oesophageal pain thresholds (median 16.3 mA *v* 7.3 mA, $P = 0.02$) to repeated stimuli than controls, whereas the values did not differ with respect to the skin. There were no inter-group differences in thresholds to single stimuli. (4) Patients had substantially reduced brain evoked potential amplitudes after both single oesophageal (P1/N1, median values: 7.2 μV , controls: 29.0 μV ; N1/P2: 16.5 μV , controls: 66.0 μV ; $P < 0.001$ for both) and skin (N1/P2: 13.5 μV ; controls: 76.0 μV ; $P < 0.001$) stimuli despite the similar pain thresholds.

Conclusion—Central nervous system responses to visceral and somatosensory nociceptive input are altered in patients who have angina despite normal coronary angiograms.

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Keywords: angina pectoris; electrical stimulation; nociception; stimulus-response

Several pathophysiological explanations have been suggested for the pain syndrome in patients with angina and normal coronary

angiograms: abnormal cardiac nociception following intracardiac catheter manipulation^{1,2} or intracoronary adenosine infusion³; reduced capacity of minor coronary vessels to dilate⁴; a generally elevated sympathetic activation^{5,6}; gastrooesophageal reflux⁷ and oesophageal motility disturbances⁸; a combination of oesophageal and cardiac aetiology⁹; insulin resistance¹⁰; psychiatric illness¹¹⁻¹³; and musculo-skeletal disorders of the chest.¹⁴⁻¹⁶ A general abnormality of nociception could incorporate many of the results from previous studies¹⁷ and recently this hypothesis has found support in a clinical trial where imipramine, a cyclic antidepressant with general antinociceptive properties, given to patients with angina and normal coronary angiograms resulted in a reduction of pain episodes.¹⁸

In order to evaluate the role of nociception further and to investigate whether any abnormalities are confined to visceral or somatosensory perception, we employed an experimental model of electrical stimulation of the oesophageal mucosa and the presternal skin in patients with angina despite normal coronary angiograms and in healthy controls. The applied stimuli were evaluated by brain evoked potentials, which facilitates a quantitative measure of the central responses.^{19,20}

Methods

SUBJECTS

Five women and five men (median age 55 years, range 40 to 67) with angina of median two years duration were studied. All had a normal resting electrocardiogram. No patients had evidence of left ventricular hypertrophy or valvar heart disease on echocardiography, all had normal coronary angiogram with left ventricular ejection fraction $> 50\%$, and none had electrocardiographic signs of coronary vasospasm, either spontaneously or in response to hyperventilation.²¹ Evaluation of cardiac metabolism during atrial pacing²² did not show lactate production in any patient. Five of the 10 patients had an abnormal response to exercise testing (≥ 1 mm horizontal or downsloping ST segment depression on the electrocardiogram). Further cardiological characteristics are listed in table 1. Oesophago-gastro-duodenoscopy revealed no erosive or exudative oesophagitis, gastritis, duodenitis, peptic ulcers, or malignancy. The cardiological and gastrointestinal investigations were carried out three to 12 months

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Table 1 Characteristics of 10 patients with angina despite normal coronary angiograms

Patient	Age (years)	Sex	Duration (months)	Pain frequency (attacks/month)	Referred pain	Exercise ECG	Ejection fraction (%)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Cholesterol (mmol/l)	HDL (mmol/l)	Triglycerides (mmol/l)	β blockers	Calcium antagonists	Nitrates
1	49	M	7	8	+	Positive	68	110	80	5.4	1.01	ND	+	+	+
2	53	F	61	90	+	Normal	65	100	70	8.1	1.76	1.06	+	–	–
3	56	M	24	120	+	Positive	65	140	80	4.6	1.06	1.07	–	+	+
4	67	F	15	60	+	Normal	83	160	90	6.2	0.90	1.69	+	+	–
5	58	M	20	60	+	Normal	75	130	70	6.2	0.80	2.30	–	+	+
6	56	M	36	90	+	Normal	80	125	80	6.2	1.03	2.10	–	+	–
7	52	M	71	180	+	Positive	62	160	90	6.3	1.21	1.53	+	–	–
8	40	F	16	120	+	Positive	77	105	70	6.0	1.65	1.14	+	–	+
9	53	F	25	12	+	Normal	65	110	70	6.9	1.54	1.87	+	+	+
10	57	F	24	60	+	Positive	82	120	80	ND	ND	ND	–	+	–

Duration, disease duration; HDL, high density lipoprotein cholesterol; ND, not done.

before the present study. All medication was withdrawn 72 h before the study. Five women and five men (median age 49 years, range 33 to 59) served as controls. They were free of cardiopulmonary symptoms, were normal on clinical investigation, had a normal response to exercise electrocardiographic testing and no history of gastrointestinal or cardiologic diseases, and were on no treatment. None of the patients or controls had neurological or endocrinological disorders.

ELECTRICAL STIMULATION

Electrical stimulation of the oesophageal mucosa 38 cm from the nostrils was delivered through a bipolar electrode as described previously.¹⁹ Stimuli were short trains of square wave pulses (each stimulus consisted of five pulses of 1 ms duration separated by 4 ms) delivered by a computer controlled constant current stimulator. Before measurements, test stimuli were applied to make subjects familiar with the study regimen. Three thresholds were determined: (1) the threshold of perception; (2) the pain threshold; (3) the pain threshold of summation by applying five stimuli trains separated by 0.5 s (each stimulus consisted of five pulses of 1 ms duration separated by 4 ms): the threshold where the persons described the repeated nociceptive stimuli as increasingly painful through the series. At the end of the stimulation series a continuous 40 Hz stimulation (each pulse of 1 ms duration) was applied and the stimulus intensity was slowly increased until the subject asked for termination due to discomfort. The persons were asked to describe the sensations after single and continuous stimulation but they were not provided with descriptive words. Thereafter the patients were asked to answer “yes” or “no” depending on whether the sensations were similar to their usual episodes of angina.

Cutaneous stimuli were delivered through a surface electrode (Dantec 13L22, Copenhagen, Denmark) with 23 mm between the two saline soaked felt tips (3 mm diameter) placed at the sternum 12 cm distal to the jugular incisure. Cutaneous stimuli characteristics were identical to the oesophageal stimuli (short trains of square wave pulses, five per stimulus each of 1 ms duration, 4 ms apart).

All thresholds were determined as the mean of two measurements.

EVOKED POTENTIALS

Evoked vertex potentials were assessed by stimulating the oesophageal mucosa and the sternal skin at amperages 1.3 times the previously determined pain thresholds. The evoked potentials were recorded with a platinum needle electrode (Disa 25C04, Copenhagen, Denmark) inserted at C_z with reference to linked earlobes as previously described.^{19 20} The electroencephalogram was filtered by a second order filter (0.5–12 Hz), amplified, and sampled by a computer at 64 Hz. On average 16 stimuli were used since this is sufficient to obtain an acceptable signal to noise ratio.²³ A test stimulus was delivered before each series, and 2 s before each stimulus the subjects received an auditory warning stimulus to minimise variability.²⁴ The subjects were asked to keep their eyes open, and eye movements which could contaminate the evoked potentials were monitored continuously. The peaks of the evoked potential signal were designated N for negative deflections and P for positive. Numbers were given to the peaks in order of appearance after the stimulus. The P1, N1, and P2 peaks were determined independently by two blinded observers. The peak to peak amplitudes (P1/N1, N1/P2) in μ V and latencies of P1, N1 and P2 in ms with respect to trigger onset were measured by computer.

STATISTICS

The Mann-Whitney test for unpaired observations was used to compare median values between groups. Bivariate correlations were evaluated by Pearson’s least square regression. $P < 0.05$ was considered significant.

ETHICS AND SAFETY

The study was approved by the local ethics committee. Written informed consent was obtained from all subjects and the entire study was carried out in a cardiac clinic with continuous monitoring by electrocardiogram, intravenous access established, and resuscitation stand by.

Results

There was no significant difference in age between patients and controls. All subjects completed the study. One patient had atrial capture during continuous oesophageal stimu-

Figure 1 Brain evoked potentials following electrical stimulation of the oesophageal mucosa at 1.3 times the pain threshold. (A) Female patient with a 6 year history of angina despite normal coronary angiogram. (B) Female control.

Figure 2 Individual values of evoked potential amplitudes of 10 patients with angina despite normal coronary angiograms and 10 healthy controls. Top panels show values following electrical stimulation of the oesophageal mucosa; bottom panels show values following electrical stimulation of the sternal skin. The peaks of the evoked potential signal were designated N for negative deflections and P for positive. The peak to peak (P1/N1, N1/P2) amplitudes in μV are shown.

lation which returned to sinus rhythm immediately after stimulus cessation. ST segment depression of the electrocardiogram was not seen in any subjects during the study.

SENSATION

Angina similar to their habitual pain episodes was provoked in two patients following single oesophageal stimuli and in seven following continuous stimulation. Continuous oesophageal stimulation resulted in the following distant projections in four patients: (1) to the shoulders and the proximal part of both arms, (2) to the neck and jaws, (3) to the left hemithorax, and (4) to the right elbow and left radial fingers. The controls described the nociceptive oesophageal stimulation as either “artificial” or “resembling heartburn”. No patients experienced projection following skin stimulation and no controls reported projection from either oesophageal or cutaneous stimulation.

THRESHOLD DETERMINATION

Oesophageal thresholds of perception (median (range), patients: 3.2 mA (2.1 to 7.8 mA); controls: 5.0 mA (3.0 to 7.5 mA)) and of pain (patients: 15.8 mA (7.5 to 37.0 mA); controls: 15.8 mA (6.0 to 25.0 mA)) were not statistically different between groups ($P = 0.22$ and 0.97 , respectively). The oesophageal pain threshold of summation (patients: 16.3 mA (6.0 to 27.5 mA); controls: 7.3 mA (4.5 to 16.0 mA)) was significantly higher in the patient group ($P = 0.02$).

The sternal skin threshold of perception (patients: 0.73 mA (0.28 to 1.00 mA); controls: 0.83 mA (0.48 to 1.38 mA)), of pain (patients: 7.38 mA (2.63 to 13.00 mA); controls: 5.94 mA (3.38 to 8.80 mA)), and the pain threshold of summation (patients: 6.00 mA (1.88 to 14.0 mA); controls: 5.75 mA (4.38 to 15.00 mA)) did not differ between groups ($P = 0.20$, 0.53 , and 0.82 , respectively).

BRAIN EVOKED POTENTIALS

Evoked potentials were recorded in all 20 subjects. The amplitudes of the P1/N1 and N1/P2

Table 2 Latencies and interpeak amplitudes of vertex evoked potentials (measurements taken at Cz) in 10 patients with angina and normal coronary angiograms and in 10 controls following electrical stimulation of the oesophagus 38 cm from the nares and of the sternal skin. The evoked potentials were measured as an average of 16-stimulus series 1.3 times the previous determined pain threshold. Values are median and (quartiles)

	Patients (n = 10)	Controls (n = 10)
Latency (ms)		
Oesophagus		
P1	106 (96–131) NS	102 (70–109)
N1	156 (135–162) NS	141 (125–156)
P2	219 (219–232) NS	227 (226–246)
Sternum		
P1	102 (94–109) NS	86 (78–100)
N1	125 (117–148) NS	133 (133–139)
P2	203 (188–219) *	211 (211–242)
Amplitude (μV)		
Oesophagus		
P1/N1	7.2 (5.4–9.6) **	17.5 (10.8–40.2)
N1/P2	16.5 (4.4–23.0) **	71.8 (45.6–93.4)
Sternum		
P1/N1	8.4 (6.1–14.1) NS	15.7 (8.1–27.1)
N1/P2	12.2 (9.8–21.7) **	53.4 (33.7–98.9)

N, negative; P, positive, * $P < 0.05$; ** $P < 0.001$.

peaks following oesophageal stimulation and of the N1/P2 peaks following sternal stimulation were significantly lower in patients compared with controls (table 2, figs 1 and 2). The oesophageal pain thresholds and the N1/P2 amplitudes of the evoked potentials correlated in the patient group ($r = 0.97$, $y = 10.2 + 1.8x$) but not in controls ($r = 0.26$, $y = 43.3 + 2.3x$). The sternal pain thresholds and the N1/P2 amplitudes showed some correlation (patients: $r = 0.61$, $y = 1.83 + 2.3x$; controls, $r = 0.62$, $y = 17.3 + 12.2x$). The only latency that differed between patients and controls was that of the P2 peak following sternal stimulation (table 2).

Discussion

The results of the present study suggest that patients with angina, despite normal coronary angiograms, have altered processing of nociceptive inputs. Despite similar pain thresholds the evoked potential amplitudes following nociceptive electrical stimulation of both the oesophagus and the skin were substantially lower in patients than in controls. Only a few studies of evoked potential responses have been carried out in patients with visceral pain. Reduced evoked potential amplitudes have been found after nociceptive somatosensory stimulation of chronic cancer pain patients, with the low amplitudes apparently restricted to input from pain affected regions.²⁵ Reduced evoked potentials were also described following non-nociceptive oesophageal balloon distension in patients with angina-like chest pain, in a study where the mean age of the control group was significantly lower than that of the patient group.²⁶ By contrast, a study of patients with chronic burning pain in the mouth showed increased brain evoked potential amplitudes to intraoral pain stimulation compared to a matched control group.²⁷ Using positron emission tomography, Rosen *et al* recently showed that dobutamine-induced angina in patients with coronary artery disease resulted in thalamic and frontal cortical activity during angina but only the thalamic activity persisted through the postangina scan.²⁸ They concluded that the thalamus may act as a gate to afferent pain signals. A strong thalamic gate in patients with angina and normal coronary angiograms could also contribute to explaining the reduced vertex evoked potentials of the present study.

Brain evoked potentials are generally regarded as the summated electrical fields of a large number of neuronal membranes acting in synchrony.²⁹ Age, neuropathy, and the level of arousal are critical factors for the amplitudes and latencies of brain evoked potentials.^{30–32} In the present study there were no differences in age (or sex) between patients and controls, no subjects had endocrinological disorders or neuropathy, and in order to reduce and standardise arousal, test stimuli were applied to make subjects familiar with the study regimen. Amplitude increases of the evoked potential responses could be due to additional recruitment of non-nociceptive

nerve fibres.²⁹ However, there is no reason to believe that such sources of error might influence the results in a specific direction when comparing findings of patients and controls. We have previously shown that there was no systematic difference in evoked potential latency values following oesophageal stimulation on two occasions six months apart.²⁰ However, in that study we found a significantly higher amplitude in the first compared with the second measurement, which could reflect the fact that subjects were more aroused at their first session. In the present study no subjects had any previous experience with this kind of investigation. Previous studies have shown positive correlations between evoked potential amplitudes and the intensity of pain, and little relation between amplitudes and stimulus intensity (cited in ²⁹) as in the present study.

A lowered threshold for visceral pain in patients with angina despite normal coronary angiograms has been suggested.^{3,33} In the present study no thresholds differed between patients and controls except the visceral threshold of summation, which was higher in the patient group. An explanation which combines both the finding of normal pain thresholds and reduced brain evoked potentials could be a raised concentration of endorphins in the patient group since morphine and other opiates are known not to affect acute pain thresholds,³⁴ despite the fact that they reduce the amplitudes of brain evoked potentials.^{35,36} Electrical stimulation of the oesophageal mucosa did simulate angina qualitatively in seven of 10 patients and caused pain projection to remote areas such as the jaws, the upper extremities, and fingers in four. The controls reported the sensation as "artificial" or "resembling heartburn" and no controls reported projection. However, the anatomical specificity of oesophageal provocation is questionable: oesophageal balloon distension in patients with atherosclerotic heart disease may reproduce chest pain^{37–39} and coronary blood flow may be altered in relation to oesophageal balloon distension⁴⁰ and acid perfusion.⁴¹ This is in line with the central convergence hypothesis of cardiac and oesophageal visceral pathways entering the spinal cord from the sympathetic limb of the autonomic nervous system (oesophagus: C8–T10; heart: T1–T4).^{42,43} In addition, reference of visceral pain to somatic structures near the midline contributes to the fact that pain originating in one viscus cannot easily be differentiated from pain originating in another viscus by the quality, localisation, or intensity of the sensation alone.⁴⁴ Therefore positive oesophageal provocative procedures do not necessarily imply that the usual pain of the patient arises from the oesophagus.

Temporal summation, that is, repeated nociceptive stimuli of equal intensity building up so that stimuli in the end of a series are experienced as more painful than the first stimuli,⁴⁵ was found in all subjects. The fact that the oesophageal but not the cutaneous pain threshold of summation was higher in the

patient group might be a result of central nervous system modulation of visceral nociceptive input. It has previously been shown that pain summation is of importance for hyperexcitability related to cutaneous pain,⁴⁶ whereas further studies are needed to evaluate the pathophysiological importance in visceral pain syndromes.

A key question in studying patients with angina and normal coronary angiograms is whether they suffer from unrecognised cardiac disease. One cardiological hypothesis of the underlying mechanism of chest pain in this patient group has been "microvascular angina"—that is, a reduced ability of the minor cardiac vessels to dilate.^{4,47,48} This idea has recently lost credence somewhat since it is hard to imagine that restrictions in cardiac flow conceivably capable of producing pain are almost never associated with detectable myocardial ischaemia.^{49,50} Abnormal cardiac nociception represents one of the most recent hypotheses. Clinical observations during cardiac catheterisation have shown that intracardiac catheter manipulation may provoke angina in chest pain patients with normal coronary angiograms, in contrast to observations in other patient categories.^{1,51} Many clues to an extracardiac disorder have been provided, with the majority of studies being conducted in the search of an oesophageal abnormality.^{52,53} Musculoskeletal disorders of the chest and back may also account for anginal attacks.¹⁴⁻¹⁶ Neuroticism, "vital exhaustion", "type A behaviour",¹¹ panic disorders,¹³ and general psychiatric illness¹² have been associated with chest pain and normal coronary angiograms.

The substantially reduced amplitudes of brain evoked potentials of these patients, as in other conditions of chronic pain, stress the fact that angina—despite a normal coronary angiogram—is a chronic, disabling disease. The findings indicate altered central nervous system responses particularly to visceral but also to somatosensory nociceptive input in these patients. The study does not allow us to draw conclusions about a possible oesophageal role in the origin of pain of this patient group but it supports the concept of a general abnormality of nociception.

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