Influence of naloxone on the effects of high frequency transcutaneous electrical nerve stimulation in angina pectoris induced by atrial pacing

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SUMMARY The influence of naloxone on the effects of high frequency transcutaneous electrical nerve stimulation in angina pectoris induced by atrial pacing was studied in 11 patients with severe coronary artery disease. The patients were catheterised and treated with transcutaneous electrical nerve stimulation on two occasions, double blind and in random order, with a single intravenous dose of saline or with a single intravenous dose of 50 mg naloxone. Treatment with transcutaneous electrical nerve stimulation increased tolerance to pacing and significantly improved lactate metabolism with placebo and with naloxone. The positive effects of transcutaneous electrical nerve stimulation were thus reproducible and not reversed by single intravenous doses of naloxone.

The results indicate that the effects of transcutaneous electrical nerve stimulation on the heart are not mediated by β endorphin but they do not exclude activation of more short-acting opioids such as δ or κ receptor agonists (met-enkephalin or dynorphin or both) because naloxone has a low affinity for these receptors. Non-opioid mechanisms may also be important.

High frequency transcutaneous electrical nerve stimulation was reported to be beneficial in patients with angina. In one study, transcutaneous electrical nerve stimulation increased work capacity during a bicycle ergometer test, decreased ST segment depression at a comparable workload, and reduced the recovery time. In an invasive study, transcutaneous electrical nerve stimulation increased tolerance to pacing, improved lactate metabolism, and reduced ST segment depression. A decrease in left ventricular afterload caused by a drop in systolic blood pressure was thought to be one explanation for the effects.

Several studies have indicated that the effect of transcutaneous electrical nerve stimulation treatment may be due to activation of endogeneous opioid peptides. If this is true, naloxone, a pure opiate antagonist with no agonistic properties, might abolish the effects induced by transcutaneous electrical nerve stimulation.

Patients and methods

Patients Eleven patients (two women and nine men aged 50–71 years (mean 61 years)) were chosen from among those visiting the outpatient clinic at the medical department, Östra Hospital. All patients had severe angina (functional class III–IV New York Heart Association) despite their taking optimal antianginal medication. No patients had obstructive or restrictive pulmonary disease, intermittent claudication, valvar heart disease, or untreated hypertension. Eight patients had had a myocardial infarction more than six months before the study. All patients had chest pain and ST segment depression (0.1–0.7 mV) during a maximal symptom limited bicycle ergometer test. On scintigraphic examination, ischaemia of the anterior wall of the myocardium was seen in 10 patients when thallium was injected during exercise testing. All patients had been considered for bypass operation: four patients had been operated on but still had disabling angina pectoris, and one was waiting for operation. Four of these patients had three vessel disease, one had two vessel disease, and one had single vessel disease.

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Figure  Schedule, procedures, and statistical comparisons. Roman numerals I to III refer to tests of paired data (see statistical analysis). O, start of pacing; C, maximum pacing without transcutaneous electrical nerve stimulation (TENS) (control); P1, pacing to identical heart rate as C; P2, maximum pacing with transcutaneous electrical nerve stimulation.

Six patients were considered unsuitable for bypass operation. No patient had signs of pulmonary congestion on radiological examination of the heart.

No antianginal medication was given 12 hours before the pacing procedures and no transcutaneous electrical nerve stimulation treatment 48 hours before the trials. The patients were studied in the morning in a non-sedated, fasting state.

The study was approved by the ethics committee of the University of Gothenburg. Oral and written information about the study was given to every patient.

CATHETERISATION

A thermodilution pacing catheter (Wilton-Webster Laboratory) was placed in or near the great cardiac vein within the coronary sinus. If blood could not be sampled from this site, the catheter was pulled back until the backflow was adequate. The position of the catheter was confirmed by injection of radio-opaque dye and was adjusted during flow measurement until a satisfactory stable baseline flow curve was obtained. To exclude reflux from the right atrium a bolus dose of saline was injected into the right atrium while temperature was measured in the coronary sinus.

A catheter was placed percutaneously in a peripheral artery.

MEASUREMENTS

Coronary sinus blood flow was measured by the continuous infusion thermodilution method and isotonic saline solution was therefore infused into the coronary sinus at a rate of 40 ml/minute. Pressures were measured by means of Statham P23 DA transducers and stored on tape for subsequent automatic data processing. Cardiac output was measured by the thermodilution technique (Cardiac Output Computer, WT1). Blood oxygen saturation was measured by an OSM 2 Hemoxymeter (Radiometer, Copenhagen). Lactic acid concentration was assayed enzymatically (Lactate Analyzer 640, Roche Bio-Electronics). Plasma concentrations of adrenaline and noradrenaline were assayed radioenzymatically by the method of Peuler and Johnson, slightly modified by Eriksson.

TRANSCEPTABLE ELECTRICAL NERVE STIMULATOR AND STIMULATION TECHNIQUE

A commercially available transcutaneous nerve stimulator (Neurostal) was used. The stimulator delivers constant current in 0.2 ms pulses and the frequency was set to 70 Hz. Standard electrodes (3M; Tenz Care 6225, 15 × 50 mm) were used. Electrode paste was applied to the contact surface to reduce the skin-electrode impedance. The electrodes were placed 10 to 30 cm apart on the chest of the patient at the site of the most intensive pain. The intensity of the stimulation was adjusted to a level immediately below that producing pain (35 to 50 mA).

PROCEDURE

The patients were studied twice (double blind and in random order): once after a single intravenous dose of 120 ml saline and once after a single intravenous dose of 50 mg naloxone dissolved in 120 ml physiological saline (figure). The interval between the investigations was two to seven days.

Blood samples were drawn from a peripheral artery and the coronary sinus at rest during steady state. Blood pressure and coronary sinus blood flow were measured simultaneously. Coronary sinus pac-
ing was then started at a rate of 80 beats/minute. One patient was started at 90 beats/minute and two patients at 100 beats/minute because of a high resting heart rate. The pacing rate was increased by 10 beats/minute every minute, continuing until the patient could not tolerate a further increase in pain. New measurements and blood samples were taken. Pacing was then stopped. After 25 minutes rest without pacing, transcutaneous electrical nerve stimulation treatment was started. Fifteen minutes later, new baseline measurements and blood samples were taken. After another five minutes the same pacing routine was repeated and repeat measurements were made at the same pacing rate as that at which angina had been produced during the previous control recording. Exactly five minutes before the repeat measurements a single dose of 50 mg naloxone or the equivalent amount of saline as placebo was given by infusion, double blind in random order. The pacing was not interrupted during infusion of naloxone or physiological saline. The pacing rate was then increased until the patient considered the chest pain to be as intense as it was during control registration before treatment with transcutaneous electrical nerve stimulation. New pressure recordings and blood samples were then taken (figure). If the patient did not experience chest pain, pacing was stopped at 170 beats/minute.

CALCULATIONS

Coronary vascular resistance (mm Hg/ml/min) was estimated as mean arterial blood pressure divided by coronary sinus blood flow. The myocardial oxygen consumption (ml/min) was calculated as the myocardial arteriovenous oxygen difference multiplied by coronary blood flow. The myocardial lactate extraction ratio (%) was expressed as 100 × (arterial lactate concentration – coronary sinus lactate concentration) divided by the arterial lactate concentration.

The myocardial arteriovenous difference for adrenaline reflects its extraction from the coronary circulation, because only the brain and the adrenal medulla can synthesise and release adrenaline. Thus adrenaline (A) uptake (nmol/min) equals the arteriovenous difference in adrenaline × coronary sinus blood flow. In addition to being extracted from the coronary circulation, noradrenaline is also released from sympathetic nerve endings and the myocardial arteriovenous difference in noradrenaline is thus the result of a combined uptake and release of the catecholamine and will be referred to as “noradrenaline overflow” (nmol/min), which equals the arteriovenous difference × coronary sinus blood flow. Adrenaline and noradrenaline share the same uptake mechanisms and the extraction ratio seems to be similar as well, so noradrenaline uptake (nmol/min)

Mannheimer, Emanuelsson, Waagstein, Wilhelmsson can be estimated as: percentage adrenaline uptake × coronary sinus blood flow × noradrenaline arterial concentration. Net myocardial noradrenaline release can be calculated by assuming that the inflow of noradrenaline (coronary sinus blood flow × arterial noradrenaline concentration) + release = efflux of noradrenaline (coronary sinus blood flow × coronary sinus concentration)—that is noradrenaline release (nmol/min) equals coronary sinus blood flow × (coronary sinus – arterial noradrenaline concentration) + noradrenaline uptake.

Time to angina (seconds) was calculated as the time from the start of atrial pacing until pain and recovery time (seconds) as the time after the pacing was stopped until pain disappeared.

STATISTICAL METHODS

We used the difference between the corresponding values at rest and during pacing to compare saline and naloxone and control and transcutaneous electrical nerve stimulation. Fisher’s test for pair comparisons was applied to the differences. All tests were two tailed. Whether or not the differences should be used depends on the correlation coefficient between the baseline value and the current value. If the coefficient exceeds 0.50, it is better to use the difference. Excess of this limit was justified in this study. The results were analysed as follows (figure)—(a) resting values were compared with transcutaneous electrical nerve stimulation and without, (b) maximal control pacing rates were compared with those at identical heart rates during transcutaneous electrical nerve stimulation, and (c) the maximal control values were compared with maximal values during transcutaneous electrical nerve stimulation. Because a large number of tests were performed the risk of finding statistical significance by chance was great. A traditional analysis of variance would have restricted the number of falsely significant results per type of variable to one; such a parametric analysis gives inaccurate p values. Because the number of types of variables was also large, it was more appropriate to test the hypothesis with accurate p values for each variable and use the pattern of statistically significant results to examine the possibility of falsely significant results.

Results

HAEMODYNAMIC AND MYOCARDIAL METABOLIC EFFECTS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION AND PLACEBO (Table 1) Transcutaneous electrical nerve stimulation induced no major changes at rest.

During transcutaneous electrical nerve stimulation at comparable heart rates the mean (1 SD)
Table 1 Effects of transcutaneous electrical nerve stimulation (TENS) and placebo at rest and during pacing (mean (SD))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control rest</th>
<th>TENS rest</th>
<th>Control pacing to angina</th>
<th>TENS pacing₁</th>
<th>TENS pacing₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 (14)</td>
<td>77 (19)</td>
<td>134 (18)</td>
<td>134 (18)</td>
<td>146 (22) **</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>154 (30)</td>
<td>160 (20)</td>
<td>155 (24)</td>
<td>159 (20)</td>
<td>155 (25)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>70 (10)</td>
<td>75 (13)</td>
<td>89 (14)</td>
<td>90 (12)</td>
<td>91 (13)</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>103 (20)</td>
<td>104 (16)</td>
<td>110 (18)</td>
<td>114 (18)</td>
<td>111 (19)</td>
</tr>
<tr>
<td>Rate-pressure product (beats/mm Hg/min)</td>
<td>11605 (3666)</td>
<td>12537 (4758)</td>
<td>20720 (5419)</td>
<td>21357 (5218)</td>
<td>23085 (5188)</td>
</tr>
<tr>
<td>Coronary sinus blood flow (ml/min)</td>
<td>104 (43)</td>
<td>118 (46)</td>
<td>194 (49)</td>
<td>208 (76)</td>
<td>255 (135)</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml O₂/min)</td>
<td>14-6 (7-1)</td>
<td>17-5 (7-9)</td>
<td>26-0 (7-3)</td>
<td>27-5 (8-4)</td>
<td>34-0 (14-8)</td>
</tr>
<tr>
<td>Myocardial lactate extraction ratio (%)</td>
<td>13 (12)</td>
<td>15 (7)</td>
<td>-20 (33)</td>
<td>-8 (21)*</td>
<td>-28 (40)</td>
</tr>
<tr>
<td>Arterial concentrations of adrenaline (nmol/l)</td>
<td>0-44 (0-27)</td>
<td>0-30 (0-10)</td>
<td>0-48 (0-19)</td>
<td>0-41 (0-14)</td>
<td>0-47 (0-18)</td>
</tr>
<tr>
<td>Arterial concentrations of noradrenaline (nmol/l)</td>
<td>2-0 (0-9)</td>
<td>2-2 (0-6)</td>
<td>2-6 (1-1)</td>
<td>2-7 (0-9)</td>
<td>3-3 (1-3)</td>
</tr>
<tr>
<td>Calculated net myocardial noradrenaline release (nmol/min)</td>
<td>151 (114)</td>
<td>198 (100)</td>
<td>241 (120)</td>
<td>230 (83)</td>
<td>469 (598)</td>
</tr>
<tr>
<td>Time to angina (s)</td>
<td>118 (48)</td>
<td>123 (83)</td>
<td>239 (83)</td>
<td>239 (83)</td>
<td>425 (196)**</td>
</tr>
<tr>
<td>Recovery time (s)</td>
<td>164 (230)</td>
<td>167 (151)</td>
<td>263 (171)</td>
<td>263 (171)</td>
<td>492 (333)</td>
</tr>
</tbody>
</table>

TENS pacing₁, same pacing rate as control pacing to angina; TENS pacing₂, pacing to angina during TENS; *p < 0.05 compared with control pacing to angina value; **p < 0.01 compared with control pacing to angina value.

Table 2 Effects of transcutaneous electrical nerve stimulation (TENS) and naloxone at rest and during pacing (mean (SD))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control rest</th>
<th>TENS rest</th>
<th>Control pacing to angina</th>
<th>TENS pacing₁</th>
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<td>Heart rate (beats/min)</td>
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<td>135 (14)</td>
<td>135 (14)</td>
<td>148 (20) **</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>162 (30)</td>
<td>164 (29)</td>
<td>155 (28)</td>
<td>152 (21)</td>
<td>140 (8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75 (13)</td>
<td>78 (11)</td>
<td>95 (15)</td>
<td>91 (1)</td>
<td>91 (5)</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>108 (19)</td>
<td>109 (18)</td>
<td>119 (20)</td>
<td>113 (16)</td>
<td>115 (7)</td>
</tr>
<tr>
<td>Rate-pressure product (beats/mm Hg/min)</td>
<td>12172 (4035)</td>
<td>12533 (4157)</td>
<td>21234 (5751)</td>
<td>20696 (4540)</td>
<td>21528 (2362)</td>
</tr>
<tr>
<td>Coronary sinus blood flow (ml/min)</td>
<td>116 (58)</td>
<td>115 (49)</td>
<td>207 (86)</td>
<td>187 (74)</td>
<td>197 (65)</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml O₂/min)</td>
<td>16-3 (9-3)</td>
<td>16-1 (6-6)</td>
<td>27-6 (10-2)</td>
<td>25-7 (9-5)</td>
<td>28-0 (8-7)</td>
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<tr>
<td>Myocardial lactate extraction ratio (%)</td>
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<td>16 (10)</td>
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<td>-19 (37)**</td>
<td>-31 (31)</td>
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<tr>
<td>Arterial concentrations of adrenaline (nmol/l)</td>
<td>0-40 (0-20)</td>
<td>0-36 (0-13)</td>
<td>0-48 (0-24)</td>
<td>0-53 (0-26)</td>
<td>0-57 (0-12)</td>
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TENS pacing₁, same pacing rate as control pacing to angina; TENS pacing₂, pacing to angina during TENS; **p < 0.01 compared with control pacing to angina value.
nerve stimulation at rest, during pacing to the same heart rate, or at maximal pacing (table 1).

HAEMODYNAMIC AND MYOCARDIAL METABOLIC EFFECTS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION AND NALOXONE (TABLE 2)

Transcutaneous electrical nerve stimulation induced no changes at rest. During transcutaneous electrical nerve stimulation at a comparable heart rate the mean lactate production decreased (−28) (35) v −19 (37)%; p < 0·01. All patients experienced chest pain in both pacing procedures, but tolerance to pacing increased after transcutaneous electrical nerve stimulation (135 (14) v 148 (20) beats/minute; p < 0·05) and the recovery time decreased (103 (108) v 52 (73) s; p < 0·01). During pacing to maximal heart rate transcutaneous electrical nerve stimulation did not induce any effects.

Transcutaneous electrical nerve stimulation did not result in any significant changes in concentrations of adrenaline and noradrenaline at rest, during pacing to the same heart rate, or during maximal pacing (table 2).

A COMPARISON OF DIFFERENCES BETWEEN TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION PLUS PLACEBO AND TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION PLUS NALOXONE

There were no significant differences, either at rest or during pacing, in any of the variables, including catecholamines when transcutaneous electrical nerve stimulation plus placebo was compared with transcutaneous electrical nerve stimulation plus naloxone.

Discussion

The results of this study indicate that the positive effects of high frequency transcutaneous electrical nerve stimulation in angina induced by pacing—that is increased tolerance to pacing, improved lactate metabolism, and less anginal pain—are reproducible. None of these effects was reversed by naloxone.

Atrial pacing is considered to be a sufficiently reproducible method if the heart rate is quickly increased to the anginal value and a recovery period of at least 20 minutes is allowed between control and treatment sessions. The recovery period in the present study was 40 minutes. Transcutaneous electrical nerve stimulation was always given as the second part of the test because transcutaneous electrical nerve stimulation has long term effects that could interfere with control pacing.2

Time to angina increased significantly during transcutaneous electrical nerve stimulation and placebo treatment compared with control values.

During transcutaneous electrical nerve stimulation and naloxone there was no significant increase of time to angina compared with control. However, when the differences between time to angina during transcutaneous electrical nerve stimulation plus placebo and control were compared with the difference between transcutaneous electrical nerve stimulation plus naloxone and control there was no significant difference. But the presence of a significant difference between transcutaneous electrical nerve stimulation and no stimulation for placebo treatment and the absence of such a difference for naloxone treatment or the converse must not be interpreted as a statistically significant difference between placebo and naloxone.

Opioids have been suggested as mediators of numerous physiological and pathophysiological processes and opiate receptors have been identified in many peripheral organs, including the adrenal medulla, sympathetic ganglia, and the heart.11,12 The effects of transcutaneous electrical nerve stimulation have been suggested to be at least partly mediated by endogenous opioids.13 Different frequencies of stimulation are assumed to activate different opioid systems. For example, in one investigation Woolf et al found that high frequency transcutaneous electrical nerve stimulation had an opioid-dependent antinoceptive effect in rats that was abolished by naloxone (1 mg/kg).14 However, other studies showed that low frequency electrostimulation releases β endorphins, which can be blocked by naloxone, while high frequency stimulation, which was used in this study, may release met-enkephalin, which was not blocked by conventional doses of naloxone.15,16 This may explain why naloxone did not block the effects of transcutaneous electrical nerve stimulation in this study, in which high frequency transcutaneous electrical nerve stimulation was used.

The single intravenous dose of naloxone needed to block the effects of exogenously administered opioids is 0·4–0·8 mg. Cohen et al showed that systolic blood pressure and respiratory responses increased with the dose of naloxone in normal adults (0·3 mg/kg–4 mg/kg).17 They concluded that the lower doses of naloxone previously used in human studies were not sufficient to block completely endogenous opioid systems. Thus despite the high dose of naloxone used in this study (0·7 mg/kg given as a single dose of 50 mg), it might still have been insufficient to block every type of opioid receptor. Naloxone is known to have high affinity for μ receptors.18 However, the drug only attenuated the response to a δ agonist and was ineffective against the κ agonist, ketazocine.19 Dynorphin is a potent and selective ligand for κ receptors.20 In a previous study an increase of dynorphin was found in two patients studied during
transcutaneous electrical nerve stimulation at the corresponding pacing rate. Thus if the effects of transcutaneous electrical nerve stimulation are mediated by met-encephalin or dynorphin, the doses of naloxone used in this study might have been insufficient to block the $\delta$ and $\kappa$ receptors. $\beta$ Endorphin has high affinity for $\mu$ receptors. It therefore seems less likely that the antianginal effects of high frequency transcutaneous electrical nerve stimulation in pacing induced angina are mediated by $\beta$ endorphin in view of the apparent lack of effect of naloxone in this study. However, it is possible that a more specific $\delta$ or $\kappa$ antagonist blocked the effects of transcutaneous electrical nerve stimulation in the present study.

Evidence suggests that transcutaneous electrical nerve stimulation may influence autonomic systems mainly by suppressing sympathetic overactivity. Evidence from several studies suggests that opioid peptides may act upon cardiovascular receptors. Enkephalin, dynorphin, and the $\delta$ and $\kappa$ opioid receptors have all been shown in guinea pig hearts. It has been suggested that opioid peptides may affect the local modulation of sympathetic cardiac neurotransmission. In general, the opioid systems seem to become active only during pathophysiological conditions such as stress, pain, and hypoxia and they seem to have an inhibitory or modulating influence. They are co-stored with catecholamines in sympathetic ganglia and the adrenal medulla and are believed to modify their release and inhibit sympathetic activity. Transcutaneous electrical nerve stimulation was recently found to increase pacing tolerance, improve lactate metabolism, and reduce ST segment depression. These effects were thought to be caused by a decrease in left ventricular afterload, as reflected by a fall in systolic blood pressure secondary to reduced sympathetic activity; this mechanism accords with the fall in arterial concentrations of adrenaline and noradrenaline during transcutaneous electrical nerve stimulation in those who responded to transcutaneous electrical nerve stimulation. However, in this study, there were no changes in arterial catecholamine concentrations or systemic blood pressure during transcutaneous electrical nerve stimulation. Patient population, timing of blood sampling, and the method of analysing catecholamines were exactly the same in the two studies. There were no other methodological problems that could explain the different results obtained.

It is also possible that non-opioid mechanisms are important in mediating the effects of transcutaneous electrical nerve stimulation. For example parachlorophenylalanine, an inhibitor of serotonin synthesis, reduced the analgesic effect of high frequency electroacupuncture in mice whereas naloxone did not. Conversely, naloxone completely reversed the effects of low frequency stimulation but parachlorophenylalanine did not have any effect. There are serotonergic neurones from the medulla to the spinal dorsal horns. This descending pathway activates inhibitory enkephalinergic interneurones which in turn block the pain signal at the segmental level. High frequency electrostimulation, which is strictly segmental, might activate this inhibitory serotonergic pathway.

The positive effects of high frequency transcutaneous electrical nerve stimulation in angina induced by pacing—increased tolerance to pacing, improved lactate metabolism, and less angina—were reproducible and not reversed by single intravenous doses of 50 mg naloxone. The effects of transcutaneous electrical nerve stimulation therefore seem not to be mediated by $\beta$ endorphin, but the treatment might activate more short-acting $\delta$ or $\kappa$ agonists such as met-encephalin or dynorphin because naloxone has low affinity with these receptors. It is also possible that non-opioid mechanisms are important.

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