The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris

CLAS MANNHEIMER M.D., CARL-AXEL CARLSSON, M.D., HÅKAN EMANUELSSON, M.D., ANDERS VEDIN, M.D., FINN WAAGSTEIN, M.D., AND CLAES WILHELMSSON, M.D.

ABSTRACT The pain-relieving effects of transcutaneous electrical nerve stimulation (TENS) were investigated in patients with severe angina pectoris first with respect to systemic and coronary hemodynamics and myocardial metabolism during pacing-induced angina and second in a controlled long-term study. Two series of patients with severe angina pectoris (NYHA class III to IV) were studied (13 patients in the pacing study and 23 in the long-term study). In the pacing-induced angina study there was increased tolerance to pacing (142 ± 23 compared with 124 ± 20 beats/min tolerated, $p < .001$), improved lactate metabolism (2 ± 36% compared with −18 ± 43%, $p < .01$), and less pronounced ST segment depression (2.3 ± 1.1 compared with 2.9 ± 2.6 mm, $p < .05$) with TENS. In the long-term study the effects of TENS were measured by means of repeated bicycle ergometer tests, frequency of anginal attacks, and consumption of short-acting nitroglycerin. TENS was used regularly for 1 hr three times per day. The TENS treatment group had increased work capacity (637 ± 308 vs 555 ± 277 W·min, $p > .001$), decreased ST segment depression (2.3 ± 1.1 vs 3.6 ± 1.6 mm, $p < .001$), reduced frequency of anginal attacks ($p < .05$), and reduced consumption of short-acting nitroglycerin per week ($p < .05$) compared with the control group. The observed effects were mainly due to decreased afterload resulting from systemic vascular dilatation.
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THE PAIN-RELIEVING effects of transcutaneous electrical nerve stimulation (TENS) have been tested in patients with severe angina pectoris in a short-term study.[1] The TENS treatment has been shown to have beneficial effects, as evidenced by increased working capacity and decreased ST segment depression. The mechanisms of these effects are unclear but there is evidence that TENS, along with relieving pain, e.g., after surgery[2] and in patients with arthritis,[3] may influence autonomic systems by suppressing sympathetic overactivity.[4, 5]

The aim of the study was to investigate the effects of TENS in patients with severe angina pectoris, first during pacing-induced episodes of angina to determine systemic and coronary hemodynamics and myocardial metabolism, and second in a controlled long-term study.

Patients and methods

Patients (pacing-induced angina). Thirteen consecutive patients with severe angina pectoris resistant to medical treatment (two women and 11 men) and between the ages of 45 and 64 years (mean 55) with a mean weight 84 kg were chosen for the study. All had been previously seen at the outpatient clinic of the Medical Department, East Hospital, Göteborg, Sweden. All had severe angina pectoris (duration 1 to 11 years) and were considered not to have obtained sufficient relief of symptoms from the medications they were given. No patient had obstructive or restrictive pulmonary disease, valvular heart disease, or myocardial infarction within the preceding 6 months. Twelve patients had previous myocardial infarction. All patients had chest pain and ST segment depression (2.0 to 7.0 mm) during maximal symptom-limited bicycle ergometer tests. On thallium scintigraphic examination ischemia involving the anterior wall of the myocardium was noted in 12 patients during exercise testing. Nine patients had three-vessel disease, three had two-vessel disease, and one had single-vessel disease.

The long-term antianginal drug treatment given to each patient had been carefully selected with respect to compounds and doses and was therefore regarded as optimal and was not changed during the last 2 months before the study. In our patients antianginal treatment was generally started with a β-blocker, most commonly metoprolol. The dose was gradually titrated, until control of angina was achieved, to a maximum of 400 mg daily. If anginal symptoms were insufficiently controlled long-acting nitrates, most commonly isosorbide dinitrate, and nifedipine were then consecutively added and doses were adjusted in a manner similar to that for β-blockers. All patients were on short-acting sublingual nitroglycerin to relieve attacks. Three patients received digitalis and five diuretic treatment. No antianginal drug treatment was given 12 hr before the pacing procedure and no TENS treatment was permitted 48 hr before the trial. The patients were studied in the morning while in a fasting state.

From the Department of Medicine, Östra Hospital, and the Department of Neurosurgery and Division of Cardiology, Department of Medicine I, Sahlgren's Hospital, Göteborg, Sweden.

Address for correspondence: Clas Mannheimer, M.D., Department of Medicine, Östra Hospital, S-416 85 Göteborg, Sweden.

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All patients had been considered for bypass surgery: one patient had previously undergone aortocoronary bypass surgery, 10 were waiting for surgery, and the remaining two were considered unsuitable candidates for bypass surgery.

Patients (long-term study). Twenty-three consecutive patients (four women and 19 men) between the ages 41 and 71 years (mean 58) with a mean weight 78 kg were recruited from the outpatient clinic at the Medical Department, Östra Hospital, Göteborg. All patients had severe angina pectoris (duration 1 to 20 years, functional class III or IV, New York Heart Association). No patient had obstructive or restrictive pulmonary disease, intermittent claudication, valvular heart disease, or had had a myocardial infarction within the last 6 months. All but four patients had had a previous myocardial infarction. All patients had been considered for aortocoronary bypass surgery: one patient had undergone such an operation, five were waiting for surgery, and the remaining were being considered for surgical treatment.

The antianginal drug treatment being given the patients at entry into the study was regarded as optimal and had been carefully chosen in the same way as mentioned above. No changes in treatment were made during the study. Nine patients received digitalis and 12 diuretics.

Before entering the study all the patients in the two series were completely informed regarding their respective studies and all verbally consented to participate. The trials were approved by the University Ethical Review Committee.

Methods (pacing-induced angina)

Catheterization. A Swan-Ganz thermodilution catheter was positioned in the pulmonary artery and a femoral artery catheter was placed percutaneously in each patient.

A coronary sinus thermodilution pacing catheter (Wilton-Webster Laboratory) was inserted in or near the great cardiac vein. If blood sampling could not be performed in this way, the catheter was withdrawn until adequate back-flow was accomplished. The position of the catheter was confirmed by injection of radiopaque dye and was adjusted during flow measurement until a satisfactory, stable baseline flow curve was obtained. A bolus dose of saline was injected into the right atrium during simultaneous temperature registration in the coronary sinus of each patient to exclude reflex from the right atrium.

Measurements. Coronary sinus blood flow was determined with the continuous-infusion thermodilution method[6] and therefore an isotonic saline solution was infused into the coronary sinus at a rate of 40 ml/min. Pressures were measured by Statham P 23 Da transducers and stored on tape for subsequent automatic data processing. Cardiac output was determined by the thermodilution technique (Cardiac Output Computer, WTI).

Blood oxygen saturation was determined with an OSM 2 Hemoximeter (Radiometer, Copenhagen). Lactic acid concentration was assayed by an enzymatic method (Lactate Analyzer 640, Roche Bio-Electronics). The electrocardiogram was continuously recorded with a bipolar chest lead with one electrode in the V_5 position and the other in the right subclavian region.

Electrical nerve stimulator and stimulation technique. A commercially available transcutaneous nerve stimulator (Neurostal, Dan-Sjo Electronics, Bromma, Sweden) was used. The stimulator delivers constant current 0.2 msec pulses and the frequency was set to 70 Hz. Standard electrodes (3M; Tenzcare 6225, 50 × 50 mm) were used. Electrode paste was applied to the contact surface to lower the skin-electrode impedance. The electrodes were placed 10 to 20 cm apart on the chest of the patient at the site of the most intense pain. The intensity of the stimulation was adjusted to a level immediately below that producing pain (35 to 50 mA).

Procedure. At rest during steady state blood samples were withdrawn from the coronary sinus and the femoral artery and blood pressure, cardiac output, and coronary sinus blood flow were measured simultaneously (figure 1). Atrial pacing was then started at a frequency of 80 beats/min. One patient was started at 100 beats/min because of a high resting heart rate. Heart rate was increased by 10 beats/min every minute and continued until the patient could tolerate no further increase in pain, at which point new measurements and blood samples were taken and pacing was stopped. After 15 min rest without pacing, TENS treatment was started. Fifteen minutes later new baseline measurements and blood samples were taken, the same pacing routine was repeated and, at the pacing rate at which angina had been produced during the previous control recording, repeat measurements were made. The pacing rate was increased until the patient considered the chest pain to be of the same degree as during control registration before TENS treatment. Pain was graded according to a scale ranging from 0 to 5 (see below). New pressure recordings and blood samples were then made (figure 1).

Calculations. Coronary vascular resistance (mm Hg/ml/min) was estimated as mean arterial blood pressure divided by coronary sinus blood flow. Myocardial oxygen consumption (ml/min) was derived as myocardial atrial-ventricular oxygen difference multiplied by coronary blood flow. Myocardial lactate extraction ratio (%) was expressed as 100 × (arterial-coronary sinus lactate concentration)/arterial lactate concentration. Systemic vascular resistance (dynes × sec × cm^{-5}) was expressed as 80 × (mean arterial pressure − right atrial pressure)/cardiac output. Pulmonary vascular resistance (dynes × sec × cm^{-5}) was expressed as 80 × (mean pulmonary artery pressure − mean pulmonary capillary wedge pressure)/cardiac output.

Methods (long-term study). The long-term study consisted

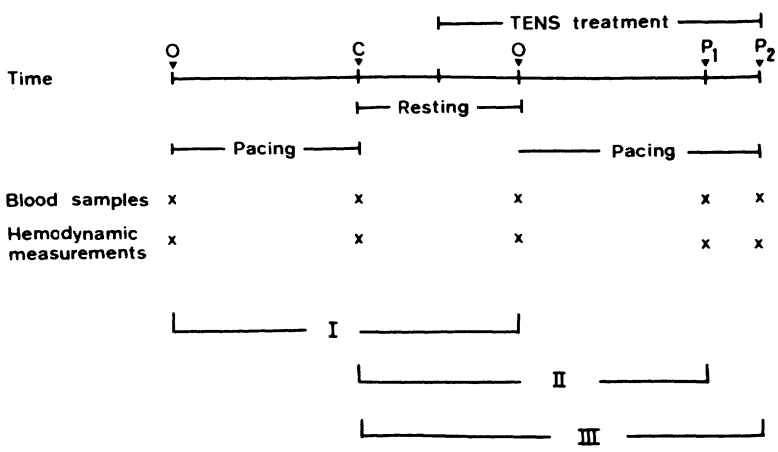

FIGURE 1. Time schedule, procedures, and statistical comparisons. Roman numerals I to III refer to tests of paired data (see Statistical methods). 0 = start of pacing; C = maximum pacing without TENS (control); P_1 = pacing to identical heart rate as in C; P_2 = maximum pacing with TENS.

of three parts: a run-in period, the treatment period, and a posttreatment period.

During the first week of the 3 week run-in period patients became familiarized with the testing procedure. In the remaining 2 weeks the average work capacity of the patients was established. Through repeated exercise testing an individual exercise procedure was established (see below).

At the start of the treatment period the patients were randomly allocated to TENS treatment (12 patients) or to a control group (11 patients). The patients in the treatment group were carefully instructed about the use of TENS and they treated themselves at home according to a certain schedule (see below). The treatment period lasted 10 weeks with one exercise test every second week. Except for the TENS treatment this period was identical for the control group.

The posttreatment period was also identical for both groups. They performed one ergometer test per week over a 2 week period. During this period the treatment group did not receive TENS.

Each patient performed exercise tests at the same time of the day throughout the entire study. An electrically braked bicycle ergometer (Siemens-Elema) was used. The initial workload was 30% to 50% of maximum and was increased stepwise in 5 or 10 W increments each minute so that the patient reached his or her maximal workload within 4 to 9 min. The starting levels and the per minute increments, once established, were unchanged for each patient throughout the study. The patients were urged to continue their exercise to levels producing grade 4 or 5 pain or dyspnea (grades are described below).

The study patients were outpatients and so were instructed to abstain from tobacco and short-acting nitrates for at least 2 hr before exercise tests. Those belonging to the TENS treatment group also abstained from TENS 2 hr before and during the exercise tests.

During the treatment period the control patients received no TENS treatment but continued their antianginal medication. The treatment group maintained their drug regimens but were instructed to use TENS first in the event of an anginal attack and to use short-acting nitroglycerin only if TENS failed to give relief. In general management of the patients did not differ between the two groups.

A commercially available transcutaneous nerve stimulator (Neurostal) was used. The stimulator delivers constant current 0.2 msec pulses and the pulse frequency was set to 70 Hz (the standard frequency). The intensity of the stimulation was individually adjusted to a level immediately below that producing pain (15 to 50 mA). Silicon rubber electrodes (3M; Tenzcare 6225, 50 × 50 mm) and electrode paste were used. The electrodes were placed on each patient's chest at the site of the most intense pain. The patients carried the electrodes in this way during daytime. They were instructed to take three TENS treatment sessions of at least 1 hr each per day (morning, noon, and evening). These treatment sessions could be taken regardless of activity. In addition to this the patients were instructed to use TENS for 1 to 10 min in the event of anginal attacks. The safety of TENS used in this way has been carefully studied.[7]

The following variables were studied: (1) Maximal total work during exercise was determined as a product of workload in watts and time in minutes (W·min). (2) Pulse rate, blood pressure, and the product of pulse rate and blood pressure before, during, and after the exercise tests were determined. (3) Pain and dyspnea reported by the patient were recorded during and after exercise testing. The chest pain and dyspnea reported by the patient were graded according to a visual scale placed in front of the patient. The scale ranged from 0 to 5, with 0 signifying no discomfort, 3 discomfort equivalent with that which ordinarily stopped the patient's activities, 4 severe, and 5 maximal discomfort. To reach maximal discomfort, the patients were urged to continue their exercise to levels producing grade 5 in either pain or dyspnea. After each patient reached his or her maximal workload the time to reach grade 0 for both symptoms (recovery time) was recorded. (4) Electrocardiograms were recorded by a 12-channel recorder. ST segment depression was measured by one observer. The measurement was then independently checked by another observer. The discrepancy between the two values was considered to represent a rough estimate of the size of the measurement error. Differences of as much as 0.5 mm were encountered in only a few instances. (5) Recovery time (min), as defined above, was determined. (6) The frequency of anginal attacks and the consumption of short-acting nitroglycerin per week were registered. In both studies the ST segment changes were measured blindly by two independent observers, the results were cross-tabulated, and the few inconsistencies were resolved by consensus.

Statistical methods

Pacing-induced angina. Comparisons between treatments were performed by Fisher's test for paired comparisons.[8] All tests were two-sided. The results were analyzed in the following fashion (figure 1): (I) Resting levels were compared without and with TENS, (II) the maximal control pacing levels were compared with those at identical heart rates during TENS, and (III) the maximal control levels were compared with maximal levels during TENS.

Long-term study. The treatment group and the control group were compared with respect to run-in values, differences between run-in values and treatment values, and with respect to differences between run-in and posttreatment values by means of Fisher's permutation test.[8, 9] All p values were determined by two-sided tests.

Results

Pacing-induced angina

Systemic hemodynamic effects. There were no hemodynamic changes induced by TENS treatment in patients at rest (table 1). During pacing to the same heart rate the systolic blood pressure was lower with TENS treatment than at control (140 ± 20 vs 153 ± 22 mm Hg, $p < .05$) and consequently the product of heart rate and blood pressure was also lower with treatment (17,137 ± 3372 compared with 19,017 ± 4081 beats mm Hg/min, $p < .05$). Systemic vascular resistance was reduced (1710 ± 714 vs 2151 ± 746 dynes × sec × cm^{-5}, $p < .05$) and cardiac index was increased (3.0 ± 0.8 compared with 2.5 ± 0.8 liter/min/m^2, $p < .05$) with TENS (table 1).

At the maximal pacing rate during TENS treatment, the product of heart rate and blood pressure increased compared with that at control (21,022 ± 4509 vs 19,017 ± 4081 beats mm Hg/min, $p < .05$). There were no changes in systemic arterial pressure, pulmonary arterial pressure, or cardiac index during maximal pacing with TENS compared with at control (table 1).

Coronary hemodynamic effects. In patients at rest there were no major changes induced by TENS treatment, only a small rise in oxygen saturation of coronary sinus blood ($p < .05$; table 2). During pacing to the same

TABLE 1
Pacing-induced angina study: systemic hemodynamic and metabolic findings in patients at rest and during pacing before and with TENS

	At rest		During pacing		
	Control	TENS	C	P_1	P_2
Heart rate (bpm)	70 ± 13	70 ± 14	124 ± 20	124 ± 20	142 ± 23[C]
Systemic arterial pressure (mm Hg)					
Systolic	152 ± 17	152 ± 26	153 ± 22	140 ± 20[A]	148 ± 21
Diastolic	78 ± 11	80 ± 12	96 ± 12	92 ± 13	100 ± 115[B]
Mean	107 ± 11	108 ± 15	120 ± 14	112 ± 15	119 ± 16
Pulmonary arterial pressure (mm Hg)					
Systolic	28 ± 8	26 ± 8	38 ± 18	38 ± 9	36 ± 14
Diastolic	9 ± 5	9 ± 2	19 ± 10	17 ± 5	21 ± 11
Mean	17 ± 5	17 ± 5	27 ± 15	24 ± 7	28 ± 13
Mean pulmonary capillary wedge pressure (mm Hg)	10 ± 5	8 ± 4	17 ± 11	14 ± 9	21 ± 15
Mean right atrial pressure (mm Hg)	1 ± 2	0 ± 2	1 ± 4	0 ± 13	1 ± 3
Rate-pressure product (beats mm Hg/min)	10,693 ± 2646	10,641 ± 3190	19,017 ± 4081	17,137 ± 3372[A]	21,022 ± 4509[A]
Cardiac index ($l/min/m^2$)	2.5 ± 0.5	2.6 ± 0.5	2.5 ± 0.8	3.0 ± 0.8[A]	2.6 ± 0.6
Stroke volume index (ml/m^2)	39 ± 9.3	40 ± 6.2	21 ± 9	25 ± 9[A]	19 ± 7
Systemic vascular resistance (dynes × sec × cm^{-5})	1809 ± 573	1739 ± 448	2151 ± 746	1710 ± 714[A]	2060 ± 879
Pulmonary vascular resistance (dynes × sec × cm^{-5})	141 ± 36	123 ± 51	163 ± 152	114 ± 63	141 ± 108
Arterial lactate concentration (mmol/l)	0.51 ± 0.17	0.64 ± 0.28[A]	0.57 ± 0.18	0.61 ± 0.26	0.63 ± 0.28
Oxygen saturation of arterial blood (%)	96.7 ± 1.2	96.5 ± 2.6	98.1 ± 1.3	96.9 ± 2.7	97.4 ± 2.2

C = maximum pacing without TENS (control); P_1 = pacing to identical heart rate as in C; P_2 = maximum pacing with TENS.
Statistical comparisons at rest: C vs TENS; during pacing: C vs P_1 and C vs P_2: [A]$p < .05$; [B]$p < .01$; [C]$p < .001$.

heart rate there were no changes during TENS in coronary sinus blood flow, coronary vascular resistance, myocardial arteriovenous oxygen difference, or myocardial oxygen uptake (table 3).

TABLE 2
Pacing-induced angina study: coronary hemodynamic and metabolic findings in patients at rest before and with TENS

	Control	TENS
Coronary sinus blood flow (ml/min)	112 ± 41	112 ± 35
Coronary vascular resistance (mm Hg/ml/min)	0.75 ± 0.19	0.77 ± 0.24
Oxygen saturation of coronary sinus blood (%)	25.1 ± 4.3	28.0 ± 5.7[A]
Myocardial arteriovenous oxygen difference (ml/l)	145.9 ± 22.0	141.5 ± 31.0
Myocardial oxygen uptake (ml/min)	16.6 ± 7.5	16.2 ± 6.8
Myocardial lactate extraction ratio (%)	23 ± 18	25 ± 18

[A]$p < .05$.

There were no differences in coronary hemodynamics or metabolic effects during pacing to maximal heart rate during TENS when compared with control (table 3). At the maximal pacing rate during TENS coronary sinus blood flow and myocardial oxygen consumption tended to be higher compared with control levels.

Arterial lactate concentration and oxygen saturation. In patients at rest during TENS the arterial lactate concentration was higher (0.64 ± 0.28 vs 0.51 ± 0.17 mmol/liter, $p < .05$) (table 1) and the oxygen saturation of arterial blood decreased at comparable heart rates (96.9 ± 2.7 vs 98.1 ± 1.3%, $p < .01$) (table 1).

Effect on myocardial ischemia

ANGINA PECTORIS. At the same heart rate that produced angina pectoris in the control situation 10 patients did not report pain during TENS treatment and could therefore be paced to a higher frequency (124 ± 20 compared with 142 ± 23 beats/min, $p < .001$) (table 3). Four patients had no anginal pain at maximal pacing during TENS treatment. The pacing procedure was interrupted because of equal or more pronounced ST

TABLE 3

Pacing-induced angina study: coronary hemodynamic and metabolic findings during pacing before TENS (C) and with TENS during pacing to identical heart rate (P_1) and to maximal heart rate (P_2)

Patient No.	HR (beats/min)			MLEX (%)			ST (mm)		
	C	P_1	P_2	C	P_1	P_2	C	P_1	P_2
1	90	90	90	8	6	6	3.5	2.5	2.5
2	100	100	120	5	14	13	1.0	—	1.0
3	120	120	150	0	13	3	1.5	1.5	2.0
4	130	130	170	28	53	22	3.0	2.0	3.0
5	130	130	150	−95	−33	−34	11	5.0	9.0
6	120	120	140	24	17	17	2.0	2.0	2.0
7	140	140	140	18	23	11	2.5	2.0	3.5
8	140	140	160	−68	−7	−45	2.0	1.5	2.0
9	120	120	140	−58	−43	−61	4.0	3.5	4.0
10	110	110	110	−8	25	25	3.0	2.5	2.5
11	120	120	140	3	23	13	1.0	1.0	1.0
12	130	130	150	−4	14	−3	1.5	1.5	2.0
13	170	170	170	−87	−84	−84	2.0	2.5	2.5
Mean	124	124	142	−18	+1.6	−9	2.9	2.3	2.8
SD	20	20	23	43	35	35	2.6	1.1	2.0
p value[A]	NS			<.01			<.05		
		<.001			NS			NS	

HR = heart rate; MLEX = myocardial lactate extraction ratio; ST = segment depression; CBF = coronary sinus blood flow; CR = coronary vascular resistance; AV diff = myocardial arteriovenous oxygen difference; MVO_2 = myocardial oxygen uptake.

[A]The upper p value refers to the C-P_1 difference and the lower to the C-P_2 difference.

segment depression in three (Nos. 4, 7, and 8) and because of extreme exhaustion in one (No.2).

ST SEGMENT DEPRESSION. At comparable heart rates ST segment depression decreased during TENS treatment compared with control pacing (2.9 ± 2.6 compared with 2.3 ± 1.1 mm, $p < .05$) (table 3). During maximal pacing during TENS ST segment depression did not change (table 3).

MYOCARDIAL LACTATE METABOLISM. For all patients the mean lactate production during control pacing was 18 ± 43% and it changed to extraction of 2 ± 36% during TENS at comparable heart rates ($p < .01$; table 3). Seven patients exhibited myocardial lactate production; in three of them production changed to extraction during TENS treatment, in three there was a considerable decrease in lactate production, and in one there was definitely improved lactate metabolism after treatment (table 3). There were no differences in lactate production at maximal heart rate during TENS compared with control (table 3).

Long-term study. Twenty-one of 23 patients completed the study. One patient in the treatment group was excluded because of skin irritation from the electrodes and one patient in the control group was excluded because of severe angina pectoris during the treatment period that necessitated immediate bypass surgery. No other complications or adverse effects were observed during the treatment period.

The treatment and the control groups were comparable during the run-in period with one exception: the mean recovery time in the control group was shorter (recovery times 5.2 ± 2.4 and 3.0 ± 0.7 min).

Mean exercise tolerance in the two groups is shown in table 4. The mean exercise tolerance during the treatment period was significantly higher compared

TABLE 4

Long-term study: mean exercise tolerance (W·min)

	Run-in	Treatment period	Post-treatment period
Treatment group (n = 11)			
Mean	555	637	523
SD	277	308	231
Control group (n = 10)			
Mean	588	564	532
SD	186	179	139
	NS[A]	$p < .001$[B]	NS[C]

[A]Difference between run-in values; [B]differences between run-in values and treatment values; [C]differences between run-in values and post-treatment values.

TABLE 3
(Continued)

CBF (ml/min)			CR (mm Hg/ml/min)			AV diff (ml/l)			MVO_2 (ml/min)		
C	P_1	P_2	C	P_1	P_2	C	P_1	P_2	C	P_1	P_2
161	149	149	0.67	0.69	0.69	175.6	172.6	172.5	28.2	25.6	25.6
165	140	146	0.47	0.48	0.48	109.7	102.8	105.0	18.2	14.4	16.4
155	177	207	0.57	0.54	0.51	192.9	196.4	188.0	30.0	34.8	38.9
161	131	229	0.47	0.66	0.38	129.1	139.4	142.9	20.8	18.3	32.7
171	127	135	0.56	0.60	0.66	130.7	108.8	112.6	22.4	13.8	15.2
148	133	157	0.60	0.69	0.62	148.2	149.6	140.2	22.0	19.3	22.0
165	146	212	0.59	—	0.48	114.6	122.0	118.1	18.9	17.5	25.0
171	161	165	0.57	0.60	0.64	151.8	156.2	149.6	26.0	25.2	24.7
162	174	203	0.58	0.52	0.54	135.4	134.5	134.5	21.9	23.4	27.3
104	95	95	1.12	1.04	1.04	140.0	136.6	136.6	14.6	13.0	13.0
100	111	105	1.09	1.05	1.20	167.6	163.2	160.4	16.6	18.1	16.8
108	151	142	0.97	0.62	0.85	151.6	155.3	152.4	16.4	23.5	21.6
—	—	—	—	—	—	131.4	132.0	131.9	—	—	—
148	141	162	0.69	0.68	0.67	144.8	143.8	142.7	21.3	20.6	23.2
27	24	43	0.23	0.19	0.24	23.6	25.8	24.2	4.8	6.2	7.6
NS			NS			NS			NS		
NS			NS			NS			NS		

with during the run-in period in the treatment group compared with the control group ($p < .001$).

During the treatment period the mean ST segment depression at the highest comparable workload and immediately after exercise in the treatment group decreased compared with during run-in ($p < .001$; table 5). These differences between the groups persisted during the posttreatment period ($p < .01$).

Mean systolic blood pressure, heart rate, and the product of heart rate and blood pressure at maximal work are shown in table 6. During the treatment period heart rate and the product of heart rate and systolic blood pressure reached higher levels compared with those in the run-in period ($p < .05$). At the highest comparable workload no differences were found.

Mean recovery time decreased in the treatment group both during the treatment period (5.2 ± 2.4 vs 3.6 ± 2.4 min, $p < .001$) and during the posttreatment period compared with that in the run-in period (5.2 ± 2.4 vs 4.0 ± 2.2 min, $p < .05$).

The frequency of attacks of angina pectoris and the consumption of short-acting nitrates decreased in the treatment group both during the treatment period ($p < .05$) and the posttreatment period compared with the run-in period ($p < .05$; table 7).

All but one of the patients in the treatment group

TABLE 5
Long-term study: mean ST segment depression (mm) at highest comparable workload during and immediately after maximal exercise

	Run-in		Treatment period		Posttreatment period	
	During exercise	After exercise	During exercise	After exercise	During exercise	After exercise
Treatment group (n = 11)						
Mean	3.6	3.7	2.3	2.5	2.8	3.0
SD	1.6	1.6	1.1	1.3	1.3	1.2
Control group (n = 10)						
Mean	2.9	2.9	2.9	3.0	3.0	2.8
SD	1.5	1.7	1.4	1.6	1.4	1.5
	NS[A]	NS[A]	$p < .001$[B]	$p < .001$[B]	$p < .001$[C]	$p < .01$[C]

[A]Difference between run-in values; [B]differences between run-in values and treatment values; [C]differences between run-in values and posttreatment values.

TABLE 6
Long-term study: mean systolic blood pressure (SBP), heart rate (HR), and product of SBP and HR at maximal and at highest comparable work

	Run-in			Treatment period			Posttreatment period		
	HR	SBP	HR × SBP	HR	SBP	HR × SBP	HR	SBP	HR × SBP
Maximal work									
Treatment group (n = 11)									
Mean	119	150	18,036	122	153	18,971	118	155	18,412
SD	19	24	4,953	21	25	5,764	15	23	4,896
Control group (n = 10)									
Mean	109	149	16,219	105	146	15,428	105	150	15,740
SD	15	32	4,338	11	37	4,726	10	33	4,010
	NS[A]	NS[A]	NS[A]	$p < .05$[B]	NS[B]	$p < .05$[B]	NS[C]	NS[C]	NS[C]
Highest comparable work									
Treatment group (n = 11)									
Mean	115	155	18,017	115	152	17,602	114	153	17,778
SD	18	24	5,239	17	21	4,573	14	22	4,343
Control group (n = 10)									
Mean	104	150	15,758	103	144	14,886	103	147	15,108
SD	12	29	4,189	9	34	3,999	10	30	3,487
	NS[A]	NS[A]	NS[A]	NS[B]	NS[B]	NS[B]	NS[C]	NS[C]	NS[C]

[A]Difference between run-in values; [B]differences between run-in values and treatment values; [C]differences between run-in values and posttreatment values.

wanted to continue the TENS treatment after the end of the trial and reported the beneficial effect of a reduction in anginal attacks. In the only patient who did not report subjective relief angina frequency and nitroglycerin consumption were reduced 50%.

Discussion

All of our study patients had clinically severe manifestations of heart disease corresponding to at least functional class II (NYHA) and were on individually titrated maximal oral drug treatment. In the investigation of coronary circulation and myocardial metabolism, atrial pacing, rather than dynamic exercise, was used as a model for several reasons. In a stationary patient pacing is a simple way to influence the myocardial oxygen demand. Furthermore, during dynamic exercise there are problems with securing a stable position of the catheter in the coronary sinus. Physical work also results in a marked rise in the arterial lactate concentration with a large variance that may make it more difficult to detect small differences in cardiac lactate metabolism.[10]

The duration of atrial pacing is important for the reproduction of pacing-induced myocardial ischemia. Ihlen et al.[11] reported that myocardial ischemia elicited by atrial pacing was reproducible after at least 20 min

TABLE 7
Long-term study: mean frequency of angina attacks and the consumption of short-acting nitroglycerin per week

	Run-in		Treatment period		Posttreatment period	
	Frequency of angina per week	Nitroglycerin consumption per week	Frequency of angina per week	Nitroglycerin consumption per week	Frequency of angina per week	Nitroglycerin consumption per week
Treatment group (n = 11)						
Mean	27	39	15	21	19	31
SD	22	53	13	28	23	43
Control group (n = 10)						
Mean	19	13	22	15	23	14
SD	18	11	20	11	19	11
	NS[A]	NS[A]	$p < .01$[B]	$p < .05$[B]	$p < .05$[C]	$p < .05$[C]

[A]Difference between run-in values; [B]differences between run-in values and treatment values; [C]differences between run-in values and posttreatment values.

of recovery when the heart rate was quickly increased to the anginal level. When the pacing frequency was slowly increased a reduced ischemic response was observed during a repeat procedure. In another study Thadani et al.[12] found that the tolerance to pacing-induced anginal pain was the same after 20 min of rest when the heart rate was increased every 1.5 min, but was significantly increased when the pacing was prolonged to 3 min at each level.[12] In the present study the heart rate was increased by 10 beats every minute and the second pacing period was started after at least 30 min of rest. Therefore, the present model may be considered valid and sufficiently reproducible for the study of metabolic and hemodynamic effects. TENS was performed as the second intervention in all patients because of the previous suggestions of protracted effects after TENS.

It is impossible to assess exactly levels of pain in order to interrupt the pacing at identical pain levels during TENS and at control. However, it is unlikely that the patients were paced to more severe myocardial ischemia during TENS, since lactate production was not increased significantly more during maximal pacing in the treatment situation compared with at control. Furthermore, in the patients in whom there was myocardial lactate production, it turned to extraction during pacing with TENS.

Our long-term study was open and therefore exposed to various kinds of bias. Under different pain conditions it is assumed that the placebo effect accounts for up to 35% of the pain reduction during treatment.[13] It is virtually impossible to design a blind study of treatment with TENS since there is no placebo equivalent for the sensation of stimulation. Therefore, a "nonspecific" placebo effect in studies with TENS must be anticipated. Recent data suggest that placebo analgesia is mediated by release of endorphin.[14] This implies that TENS and placebo may employ a common mechanism and that nonspecific placebo effects may influence the "real" effect of stimulation in a unpredictable way. Since it is known that the placebo effects subside with time,[15] it seems reasonable to assume that mechanisms other than nonspecific placebo effects are of major importance with respect to our results. During TENS treatment the patients reached higher workloads before comparable electrocardiographic changes were noted, which supports the supposition that changes in patient motivation were not responsible for the effects.

In the pacing study the systolic blood pressure was reduced, the cardiac index increased, and systemic vascular resistance diminished. This was probably caused by a general arteriolar dilatation and implies an afterload reduction leading to a decrease in myocardial oxygen consumption. A possible explanation for the peripheral vasodilatation might be decreased sympathetic activity. This would also result in reduced myocardial contractility, which further lowers oxygen needs of the heart. This might explain why the anginal threshold was reached at a higher heart rate–blood pressure product after TENS.

Generally our understanding of the effects of TENS in patients with pain is based on the theory of segmental pain inhibition postulated by Melzack and Wall[16] in their gate control theory, which states that the inhibition of the flow of pain impulses occurs at the first synaptic station in the spinal cord by means of a presynaptic neuron system. It was assumed that this system was fed by collateral nerves from both large afferent nerve fibers, which do not transmit pain, and small pain-transmitting afferent fibers. These small pain-transmitting fibers inhibited the system and thus prepared the way for increased synaptic transmission (the gate was opened) while activity in large fibers excited the system, resulting in the suppression of transmission to the next neuron chain (the gate was closed). They also assumed that efferent descending systems of supraspinal origin contributed to the inhibition of pain by activating enkephalinergic neurons in the spinal cord. There is additional evidence that TENS might act by releasing endorphins and inhibiting transmission of noxious stimuli on various levels.[17, 18] TENS obviously has a powerful pain-reducing effect in patients with angina pain. In four patients anginal pain could not be induced by pacing during TENS stimulation but in three of these patients the pacing procedure was stopped because of equal or more pronounced ST segment depression than in the control situation. TENS might exert its pain-reducing effect on anginal pain by activating enkephalinergic systems, either at segmental levels in the spinal cord or possibly locally in the heart.[19, 20] High-frequency electrical stimulation is known to increase levels of met-enkephalin in cerebrospinal fluid in man.[21] The associated or possibly specific effect of TENS on certain autonomic functions has recently been reported,[4] but its neurophysiologic basis has not been completely explored. Thus, it is not known if the pain-reducing and autonomic effects are the result of a common mechanism or if they are two parallel phenomena.

Elicitation of visceral effects by stimulation of the skin or peripheral nerves is well documented in animal experiments.[22–24] A recent study showed that low-frequency (3 Hz) stimulation of the sciatic nerve resulted in a significant decrease in the blood pressure of hyper-

tensive rats.[25] This effect could be reversed by naloxone, indicating that the effect is exerted via neuronal systems using endorphins. In man Kaada[26] induced vasodilatation by TENS in patients with peripheral arterial diseases but the vasodilatation was not blocked by conventional doses of naloxone. Electrical stimulation via epidurally applied electrodes can improve circulation, resulting in healing of ulcers, in patients with vascular disorders of the legs[27] and TENS used to control delivery pain has been shown to increase placental blood flow.[28]

Thus, there are reasons for the assumption that electrical stimulation can influence the function of various organs, probably by changing reflex mechanisms and their control from higher centra. It is quite possible that the pain-reducing effect of TENS also may inhibit sympathetic outflow, since in the dorsal horn of the spinal cord there are connections between pain fibers and sympathetic neurons. On the other hand, it might be that electrical stimulation blocks sympathetic activity peripherally or centrally and that this sympathetic blockade may be responsible for analgesia. Upper thoracic sympathectomy has been used to treat patients with severe anginal pain.[29] Although the operation was devised to cut the afferent pain fibers it seems possible that the pain-reducing effect was the result of the removal of efferent sympathetic innervation of the heart. This possibility is supported by the similar effect of β-blockade.[30]

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