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Epidural spinal electrical stimulation in severe angina pectoris

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SUMMARY The short term effects of epidural spinal electrical stimulation were studied in 10 patients with angina pectoris of New York Heart Association functional class III or IV. The antianginal pharmacological treatment given at entry to the study was regarded as optimal and was not changed during the study. The effects of epidural spinal electrical stimulation were measured by repeated bicycle ergometer tests. Treatment with epidural spinal electrical stimulation increased the patients' working capacity, decreased ST segment depression, increased time to angina, and reduced the recovery time. The observed effects did not seem to be correlated with any changes in myocardial oxygen demand during epidural spinal electrical stimulation and were additional to the benefits of the pharmacological treatment.

Patients with severe angina pectoris treated with transcutaneous electrical nerve stimulation had a reduction of chest pain, an increase in working capacity, and a reduction in ST segment depression.[1] Some patients had skin irritation of different kinds and in some the stimulation equipment restricted physical activity. These patients were offered the opportunity to test epidural spinal electrical stimulation by a fully implanted system. Epidural spinal electrical stimulation has been used successfully to treat chronic intractable pain and peripheral vascular disease.[2]

We have assessed the clinical usefulness of epidural spinal electrical stimulation in the treatment of patients with severe angina pectoris.

Patients and methods

PATIENTS

Ten patients (two women and eight men, aged 51–74 years) were selected from the medical outpatient clinic at Östra Hospital, Gothenburg. Table 1 summarises the patient characteristics. All patients had severe angina pectoris (New York Heart Association functional class III or IV). No patients had obstructive or restrictive pulmonary disease, intermittent claudication, valve disease, or had had a myocardial infarction within the last six months. All patients had been considered for bypass surgery: four patients had had the operation, two were current candidates for surgery, and four patients were not considered suitable for operation. All patients except two had had a myocardial infarction. The antianginal medication that they were taking at entry to the study was regarded as optimal and treatment was not changed during the study. The patients were told not to smoke or take short acting nitrates for at least two hours before the exercise tests. All patients had been treated with transcutaneous electrical nerve stimulation which had to be stopped because of skin irritation (in seven patients) and/or because the treatment markedly restricted the patient's normally high physical activity (six patients).

The patients were fully informed about the study before entering it. All patients gave their verbal consent to inclusion in the trial. The trial was approved by the University of Gothenburg ethical review committee.

SURGICAL TECHNIQUE AND STIMULATION EQUIPMENT

The stimulation equipment was implanted in the operating theatre by a sterile technique. The patient was placed on an *x* ray translucent table. The oper-

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Table 1 *Patient characteristics*

Case No	*Age (yr)*	*Sex*	*Duration of angina (yr)*	*Previous infarction*	*Relative heart volume (ml/m² body surface)*	*Lactate production during atrial pacing*	*Antianginal treatment*	*Other treatment*	*Bypass surgery*
1	72	M	10	+	850	+	SAN, LAN, BB	Digitalis, diuretics	Not suitable
2	61	M	9	+	400	+	SAN, LAN, BB, CA	Digitalis, diuretics	Yes
3	51	F	2	−	370	+	SAN, LAN, BB	—	Current candidate
4	60	M	14	+	420	+	SAN, LAN, BB	Digitalis, diuretics	Yes
5	72	M	8	+	430	+	SAN, LAN, BB, CA	—	Not suitable
6	72	M	10	+	720	Not performed	SAN, LAN, BB	Digitalis, diuretics	Not suitable
7	66	M	11	+	420	+	SAN, LAN, BB	—	Yes
8	64	M	9	+	410	Not performed	SAN, LAN	—	Yes
9	61	F	7	−	390	Not performed	SAN, LAN, BB	—	Current candidate
10	63	M	14	+	480	Not perfomed	SAN, LAN, BB, CA	—	Not suitable

SAN, short acting nitrates; LAN, long acting nitrates; BB, β blockers; CA, calcium antagonists.

ation was performed under local anaesthesia to allow the patient to answer questions from the surgeon during the preoperative test stimulation. The electrode was positioned so that the patient felt a prickling sensation in the region of anginal pain. The ideal position is when the stimulation produces a prickling sensation starting in the precordial area and spreading into the arms as the strength of the current is increased.

The skin incision was made in the midline in the midthoracic region. The epidural space was punctured at the level of T6. A Touhy-type needle was advanced in the midline through the interspaces into the epidural space, which was identified by the loss of resistance method. The stylet of the electrode was bent 20° 10 mm from the distal end to make it easier to manipulate the electrode in the epidural space. The electrode tip was placed in the midline or a few millimetres to the left at the level of T1–T2. The distal end of the intraspinal electrode is sigma shaped to prevent migration. The electrode was firmly sutured to the fascia for the same reason. Unipolar stimulation was used. The pulse generator was placed in a subcutaneous pouch below the left costal arch. An extension lead was tunnelled subcutaneously to the midline incision and connected to the electrode. The pulse generator was telemetrically programmed. We used a commercially available electrical device (Mectronic., Minneapolis, MN, USA). The pulse width was 210 μs, frequency 85 Hz, and an appropriate amplitude was used to produce for comfortable paraesthesia (usually 3–6 V). The pulse generator is turned on or off by a quick touch with an external magnet on the skin over the pulse generator.

DESIGN OF THE STUDY AND EFFECT EVALUATION

The study consisted of three parts:

A run in period (one to two weeks) to standardise the exercise test for each patient and to confirm that the patients were suitable candidates. Three or four tests were performed.

A treatment period (two weeks) when the individually standardised exercise tests were performed. Each patient performed four tests with stimulation and four without, in alternate order.

A post-treatment period (two days) to measure the patient's working capacity after the study.

After the run in period, the stimulator was implanted (see below) and the patients then had a one week postoperative convalescence before the treatment period started.

The following variables were used to assess the effect of epidural spinal electrical stimulation: (*a*) Pulse rate, blood pressure, and the product pulse rate × blood pressure before, during, and after exercise; (*b*) maximal total work during exercise; (*c*) estimated anginal pain and dyspnoea score during and after exercise; (*d*) ST changes during and after exercise; (*e*) the time until the occurrence of angina during exercise tests (time to angina) and recovery time after maximal total work until the pain disappeared; (*f*) the reason for stopping the exercise test. The electrocardiographic characteristics of the patients were analysed with a Marquette CASE 1 electrocardiogram apparatus (Marquette Electronics, Milwaukee, WI, USA), which was used for continuous monitoring throughout the exercise session. This device eliminates noise and baseline variations in the electrocardiogram and can measure ST segment

displacement with an accuracy of 0·1 mm (0·01 mV), which is five times better than can be done by ocular assessment. The systolic blood pressure was measured by a sphygmomanometer.

Exercise tests were always performed both in the morning and in the afternoon. During the treatment period, the order of the daily runs with and without stimulation was alternated randomly. An electrically braked bicycle ergometer (Siemens-Elema) was used and the test was always performed in the same room, at the same temperature, and at the same time of the day. The workload was increased every minute. An increase of 5 or 10 W was used for each patient. The starting load was chosen so that the patient reached his maximum total work after 5–9 minutes. The total work was calculated as the sum of the load-time products for each minute. During the exercise tests with stimulation, the stimulator was switched off for the last 15 seconds of each minute to avoid the stimulator interfering with the electrocardiogram.

Chest pain and dyspnoea were rated according to a common scale ranging from 0 to 5: where 0 represents no discomfort, 3 discomfort equivalent to that which normally stopped the patient's activities, 4 severe, and 5 maximum discomfort. To reach maximum discomfort, the patients were urged to continue their exercise to levels producing either pain or dyspnoea of grade 4 or 5. When the maximal workload was reached, the degree of anginal pain and dyspnoea was recorded each minute until angina score was 0 (recovery time).

To evaluate the statistical significance of the effects of epidural spinal electrical stimulation, the data were grouped in three ways: (*a*) Run in values were compared with those recorded without epidural spinal electrical stimulation in the treatment period, (*b*) values recorded without epidural spinal electrical stimulation were compared with those during epidural spinal electrical stimulation; and (*c*) run in values were compared with post-treatment values.

Data were compared by Fisher's test for paired comparisons.[3] The test is non-parametric. Two-sided tests were used.

Results

No complications or adverse effects were seen during the exercise tests and all 10 patients completed the study. In one patient, the tip of the electrode was initially placed too high and in another patient the electrode migrated. These two patients were easily reoperated on and electrical stimulation was later successful.

Table 2 shows the heart rate, mean systolic blood pressure, and product of heart rate and blood pressure at maximal work, and table 3 shows the same variables at maximal comparable work. Maximal comparable work is defined as the lowest individual maximal work that a patient reached in the series of tests and thus represents the highest workload that can be used for a comparison study. There were no differences between the group treated with epidural spinal electrical stimulation and the untreated groups for data in table 4.

Time to angina was shorter during the post-treatment period than during the run in ($p < 0·05$, table 4). No further statistically significant effects were seen when run in data were compared either with data recorded without epidural spinal electrical stimulation or with post-treatment data.

The following differences between values on and off epidural spinal electrical stimulation were statistically significant: an increase in maximal work capacity ($p < 0·01$, table 5), a decrease in the magnitude of ST segment depression at the highest comparable workload ($p < 0·01$, table 6), an increase in

Table 2 *Mean systolic blood pressure (SBP), mean heart rate (HR), and mean product of systolic blood pressure and heart rate at maximal work*

	Run in			*Treatment period*						*Post-treatment*		
				Without ESES			*With ESES*					
Case No	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*
1	106	130	13750	113	123	13600	105	117	12243	103	121	12643
2	67	127	8537	77	120	9230	79	137	10817	73	135	9750
3	128	150	19197	125	158	19793	150	176	25925	132	165	21695
4	97	155	15078	94	169	15885	102	155	15739	90	178	15968
5	85	165	14082	95	177	16683	89	167	14781	86	165	14190
6	126	220	27720	115	224	25575	118	224	25908	118	120	25960
7	97	148	14385	98	146	14244	109	143	15565	96	145	13950
8	134	207	27707	132	201	26631	141	194	27225	139	195	27105
9	124	217	26643	114	223	25380	124	203	25196	109	210	22785
10	105	170	17793	106	184	19501	109	175	18820	103	190	19750
Mean	107	169	18469	107	173	18652	113	169	19221	105	172	18361
SD	21	34	6699	16	37	5813	22	33	6273	21	32	5923

ESES, epidural spinal electrical stimulation.

Table 3 *Mean systolic blood pressure (SBP), mean heart rate (HR), and mean product of systolic blood pressure and heart rate at maximal comparable work*

	Run in			Treatment period: Without ESES			With ESES			Post-treatment		
Case No	HR	SBP	HR × SBP	HR	SBP	HR × SBP	HR	SBP	HR × SBP	HR	SBP	HR × SBP
1	106	130	13750	110	123	13600	103	127	13087	105	129	13229
2	66	127	8407	74	116	8562	69	127	8865	67	130	8850
3	122	145	17755	117	155	18313	128	169	21649	114	158	17878
4	93	163	15070	91	171	15495	97	161	15609	89	178	15620
5	84	152	12815	95	177	16683	92	165	15207	84	165	13860
6	129	217	27993	111	219	24229	111	215	23814	112	220	24530
7	90	145	13532	92	146	13436	103	143	14793	94	145	13625
8	128	203	25983	130	201	26031	130	193	25019	133	195	25935
9	116	215	24912	109	216	23796	110	196	21723	104	200	20700
10	103	170	17425	206	284	19501	109	170	17970	103	190	19570
Mean	104	167	17764	104	171	17965	105	167	17774	100	171	17350
SD	21	34	6470	16	36	5543	18	29	5176	18	31	5428

See table 2 for abbreviations.

Table 4 *Mean time to angina (min), mean recovery time (min), and reason for interrupting the test*

	Run in			Treatment period: Without ESES			With ESES			Post-treatment		
Case No	Time to angina	Recovery time	Reason to stop	Time to angina	Recovery time	Reason to stop	Time to angina	Recovery time	Reason to stop	Time to angina	Recovery time	Reason to stop
1	2	15·5	Angina	1	12	Angina	2·6	9	Dyspnoea	2·5	13	Angina
2	0·7	7·7	Angina, dyspnoea	0·5	7·3	Angina, dyspnoea	7	1·5	Dyspnoea	1·0	7	Angina, dyspnoea
3	1	1·3	Angina, dyspnoea	3·8	1	Angina, dyspnoea	6·6	0·3	Dyspnoea	4·5	0·5	Angina, dyspnoea
4	1	9·8	Angina, dyspnoea	2·5	5	Angina, dyspnoea	7	1	Dyspnoea	4	5·5	Dyspnoea, angina
5	3·3	1	Dyspnoea	5	1	Dyspnoea	7·3	0	Dyspnoea	6	1	Dyspnoea
6	2	4·7	Angina	3·2	5	Angina	8·8	0	Dyspnoea	3	5	Angina
7	3·3	3·3	Angina	3·0	3·0	Angina, dyspnoea	5·5	2·8	Dyspnoea	3·0	3·5	Angina
8	1·7	3·7	Angina	1·8	3·0	Angina, dyspnoea	8	0	Dyspnoea	2·0	2·5	Angina, dyspnoea
9	2	2·3	Angina	2·3	3	Angina	3·8	1·5	Dyspnoea	2	3·5	Angina
10	1·0	3·0	Angina	1·3	3·3	Angina	3	1·3	Dyspnoea	2·0	3·5	Angina
Mean	1·8	5·2		2·4	4·4		6·0*	1·7*		3·0†	4·5	
SD	0·9	4·5		1·4	3·3		2·2	2·7		1·5	3·6	

*$p < 0.01$ for comparison of values with epidural spinal electrical stimulation and without epidural spinal electrical stimulation;
†$p < 0.05$ for comparison of run-in and post-treatment values.

Table 5 *Mean exercise tolerance (expressed in W. min)*

		Treatment period		
Case No	Run-in	Without ESES	With ESES	Post-treatment
1	200	218	255	255
2	295	319	650	393
3	523	593	713	680
4	423	386	460	385
5	362	362	412	385
6	362	385	520	385
7	523	516	590	505
8	967	830	1083	910
9	523	598	780	620
10	303	330	356	330
Mean	448	453	581*	483
SD	213	180	240	199

*$p < 0.01$ for comparison of values with epidural spinal electrical stimulation (ESES) and without epidural spinal electrical stimulation

time to angina and a decrease in recovery time ($p < 0.01$ for both, table 4).

The reasons for stopping the exercise were different during epidural spinal electrical stimulation when nine patients stopped because of dyspnoea and one patient stopped because of a combination of angina and dyspnoea.

Discussion

The results of the study accord with the short term effects of transcutaneous electrical nerve stimulation on angina pectoris.[1] Thus epidural spinal electrical stimulation reduced chest pain, increased working capacity, reduced ST segment depression, increased time to angina, and reduced the recovery time. The

Table 6 *Mean ST segment depression (mm) at highest comparable workload and at maximal workload*

	Run in		*Treatment period*				*Post-treatment*	
			Without ESES		*With ESES*			
Case No	*Comparable workload*	*Maximal workload*	*Comparable workload*	*Maximal workload*	*Comparable workload*	*Maximal workload*	*Comparable workload*	*Maximal workload*
1	−0·6	−0·6	−0·7	−0·7	−0·7	−0·7	−0·7	−0·7
2	−0·1	−0·1	−0·1	−0·1	−0·1	−0·1	−0·2	−0·2
3	−2·0	−1·9	−1·8	−1·9	−1·0	−1·8	−1·9	−2·3
4	−2·4	−2·7	−3·0	−3·3	−2·2	−2·7	−2·6	−2·6
5	−0·7	−0·9	−0·2	−0·2	+0·3	+0·2	−0·1	−0·1
6	−3·8	−3·8	−3·4	−3·5	−2·5	−3·0	−4·0	−4·3
7	−2·0	−2·1	−1·8	−2·1	−1·4	−1·8	−2·0	−2·3
8	−2·3	−3·1	−2·4	−2·6	−1·8	−3·1	−2·8	−3·1
9	−2·7	−3·1	−3·1	−3·6	−1·8	−3·2	−2·6	−3·6
10	−2·6	−2·6	−2·6	−2·6	−1·8	−1·8	−2·7	−2·7
Mean	−1·9	−2·1	−1·9	−2·1	−1·3*	−1·8	−2·0	−2·2
SD	1·1	1·2	1·2	1·3	0·9	1·3	1·3	1·4

*$p < 0·01$ for comparison of values with epidural spinal electrical stimulation (ESES) and without epidural spinal electrical stimulation at comparable workload.

patients remained on optimal antianginal treatment during the study. These effects are additional to those produced by conventional medical treatment of angina. In a previous study, the pain relieving effects of transcutaneous electrical nerve stimulation were investigated in patients with severe angina pectoris in pacing induced angina.[4] The treatment had beneficial effects; it increased tolerance to pacing, improved lactate metabolism, and produced less ST segment depression.

The symptoms of angina pectoris are subject to various placebo influences and there is reason to believe that surgical procedures are especially likely to produce such effects,[5 6] It is not possible to design a blind study of epidural spinal electrical stimulation since there is no acceptable placebo equivalent to the sensation of stimulation. Placebo effects must therefore be expected in this study.

"Soft" indices, such as time to angina, recovery time, and working capacity, are especially subject to the influence of placebo effects while "hard" data like the rate-pressure product and ST segment depression are probably less influenced by such effects. Because these variables were altered by electrical stimulation it seems reasonable to assume that physiological mechanisms other than the placebo effect are of importance in this study.

Previous studies have demonstrated that changes in the rate-pressure product are good predictors of myocardial oxygen consumption in patients with angina pectoris.[7] At maximal comparable workload, the rate-pressure product did not differ between the patients treated with electrical stimulation and controls. Thus the effects of epidural spinal electrical stimulation on exercise induced angina pectoris seem not to be correlated to any changes in myocardial oxygen demand.

We believe that transcutaneous electrical nerve stimulation and epidural spinal electrical stimulation reduce some aspects of sympathetic activity. This explanation of their beneficial effects on angina pectoris is supported by the fact that treatment with transcutaneous electrical nerve stimulation reduced arterial concentrations of noradrenaline and adrenaline during atrial pacing.[8] In two patients there was also an increase of dynorphin during transcutaneous electrical nerve stimulation suggesting that the endogenous opoid systems were affected.

In conclusion, the results of the study indicate that the antianginal effect of epidural spinal electrical stimulation is associated with decreased myocardial ischaemia, as shown by the reduction of ST segment depression. The effect seems to be additional to that of pharmacological treatment. The treatment was especially suitable for patients who had to withdraw from treatment with transcutaneous electrical nerve stimulation because of skin irritation and/or because the stimulation restricted their normally high physical activity.

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