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Efficacy of Spinal Cord Stimulation as Adjuvant Therapy for Intractable Angina Pectoris: A Prospective, Randomized Clinical Study

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Objectives. **In a prospective, randomized study with an 8-week follow-up period, we evaluated the efficacy of spinal cord stimulation on exercise capacity and quality of life in patients with intractable angina.**

Background. **Despite important achievements in therapy for ischemic heart disease, there remain patients with intractable symptoms of angina. In uncontrolled observations, several investigators have reported beneficial effects of spinal cord stimulation as an additional therapy for patients with angina pectoris.**

Methods. **Seventeen patients were randomly assigned to the treatment (implantation within 2 weeks, eight patients) or control (implantation after 8 weeks, nine patients) group. Assessment of exercise capacity was performed by treadmill exercise testing. Quality of life was evaluated by daily and social activity scores and recording sublingual glyceryl trinitrate intake and angina pectoris attacks in a diary. After the 8-week study period, the control group also received the spinal cord stimulation device, and all patients were followed up for 12 months.**

Results. **The treatment but not the control group demonstrated a significant increase in exercise duration ($p < 0.02$), rate-pressure product ($p < 0.03$) and time to angina ($p < 0.04$), with a decrease in ST segment depression ($p < 0.05$). This was associated with an increase in daily life ($p < 0.008$) and social activity ($p < 0.005$) scores and a reduction in glyceryl trinitrate intake ($p < 0.004$) and episodes of angina pectoris ($p < 0.003$). During the 1-year follow-up, improvement in all quality of life variables was linear for the entire group compared with baseline. The time to angina, exercise duration and ST segment depression showed a second-order trend.**

Conclusions. **Spinal cord stimulation significantly improves exercise capacity and quality of life. On the basis of an increase in exercise capacity and rate-pressure product, the mechanism by which spinal cord stimulation acts may be related to improved oxygen supply to the heart combined with an analgesic effect.**

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The theoretic background for treatment of pain with electricity is largely based on the classic "gate control theory" (1), which provided a model for the modulation of the nociceptive input to the dorsal horn of the spinal cord. Stimulation of large, nonnociceptive A-fiber afferents reduces activity in small, nociceptive C-fiber afferents and thereby reduces the transmission of "pain" impulses. On the basis of this theory, Wall and Sweet (2) applied electrical current for treatment of chronic cutaneous pain to the sensory nerves or roots that supplied the painful area. Since 1987, spinal cord stimulation has been advocated as an adjuvant therapy for conventionally therapeutic refractory angina (3–6), and all four studies reported an improvement in symptoms and an increase in exercise capacity with spinal cord stimulation. In addition, two of the four studies reported a decrease in ischemia during exercise testing. However, these studies have serious limitations, largely related to their nonrandomized study design, the requisite to provoke paresthesias and the occurrence of artifacts on the surface electrocardiogram (ECG) during spinal cord stimulation, making blinded therapy analysis impossible.

Therefore, we performed a randomized study on the efficacy of spinal cord stimulation in patients with otherwise intractable angina with a parallel design and a follow-up period of 8 weeks.

Methods

Study group. Patients considered for spinal cord stimulation were referred to our outpatient clinic by their cardiologists. They were included in the study if they were judged to have intractable angina, thereby fulfilling the following criteria: 1) angiographically documented significant coronary artery disease (maximum 6 months before inclusion) not suitable for revascularization procedures, such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; 2) New York Heart Association functional class III or IV angina pectoris; 3) reversible ischemia documented at least by a symptom-limited treadmill exercise test; and 4) pharmacologically optimal drug treatment for at least

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1 month. Optimal medical therapy included the maximal tolerated use of at least two of the following antianginal medications: long-acting nitrates, beta-adrenergic blocking agents or calcium channel antagonists. The patient's medication was kept constant during the study.

Exclusion criteria were 1) inability to perform treadmill exercise tests; 2) age >76 years; 3) myocardial infarction or unstable angina during the last 3 months; and 4) somatic disorders of the spine, leading to insurmountable technical problems in treatment. In addition, patients were excluded if significant valve abnormalities were demonstrated by a prestudy echocardiographic examination. All patients provided written informed consent certified by the Hospital Ethics Committee. Blinding of therapy was not possible because our Hospital Ethics Committee judged it unethical to implant an inactive device in patients unaware of the nature of the treatment.

Study protocol. *Randomized study period.* Patients were randomized by means of an independent telephone service (7). Primary end points of the study were exercise capacity, as assessed by treadmill testing, and quality of life, as measured by standardized questionnaires. At baseline and after 6 to 8 weeks, two exercise tests were performed at an interval of at least 1 week.

The number of angina pectoris attacks and amount of sublingual glyceryl trinitrate intake were registered in a diary during 2 weeks to evaluate the quality of life, both at baseline and during weeks 6 to 8. In addition, scoring of daily and social activities was assessed by a questionnaire at baseline and at week 8.

The patients were randomized to two groups. In the treatment group, the device was implanted and adjusted to the active stimulation mode within 2 weeks after group assignment. In the control group, the stimulator was implanted only after the 8-week follow-up period.

Either a unipolar (n = 8) or bipolar (n = 9) device was implanted in the patients. The pulse generator was programmed to standard settings, except for the pulse intensity, which was tailored to the individual sensation of paresthesias in the affected anginal pain area. Stimulation was applied three times a day for 1 h at a 210-ms pulse width, 85 cycles/s, using continuous square wave pulses. In addition, the patients were instructed in the elective use of the device during anginal attacks. The stimulation threshold that provoked paresthesias was redetermined (single blinded) at regular intervals by means of a standardized protocol.

Follow-up period. After the randomized 8-week period, the control group received spinal cord stimulation devices under similar protocols, and all patients were followed up for 1 year. During this long-term follow-up period, treadmill exercise tests, diaries and daily and social activity scores were repeated at 14, 26 and 52 weeks of spinal cord stimulation. Results were compared with baseline measurements.

Furthermore, at baseline and after 6 weeks of spinal cord stimulation, left ventricular ejection fraction was assessed by radionuclide angiography. At baseline and after 6 weeks of spinal cord stimulation, 24-h ambulatory ECG recordings were performed for analysis of the average, minimal and maximal heart rate, ischemia and arrhythmias. Standard laser equipment was used for ST segment analysis. Ischemic periods were considered significant when 1-mm ST depression was recorded during at least 1 min, separated by at least a 1-min interval (8).

Treadmill exercise test protocol. In a previous study (9) it was demonstrated that exercise variables were not influenced when intermittent spinal cord stimulation was withheld during exercise testing. Thus, in addition to alternating stimulation, all exercise tests in this study were performed with active spinal cord stimulation during exercise, as previously described (3). Except for short periods to record ECGs, the patients used spinal cord stimulation while active, according to a standardized protocol (8). All treadmill exercise tests were performed between 10:00 and 12:00 AM. The exercise was performed on a Quinton Q55 treadmill ergometer, with gradually increasing work loads, according to the Weber-Janicki (10) (i.e., Naughton modification) cardiopulmonary exercise protocol for treadmill exercise. All exercise tests were conducted by only one physician. At regular intervals, one of two well trained assistants measured the patient's blood pressure with a sphygmomanometer connected through a cuff to the patient's upper right arm. During the treadmill exercise test, handrail support was obligatory for all participants (11). Patients were instructed to use a subjective scale from 0 to 3 to indicate their anginal complaints (0 = no angina; 1 = slight chest discomfort; 2 = moderate pain; 3 = unbearable pain). Onset of pain was scored as a 1; at level 3 the exercise test was stopped. End points were anginal pain, fatigue, shortness of breath, onset of threatening arrhythmia or exertional hypotension. If the patient did not experience anginal pain during the exercise, total exercise duration was considered the time to angina.

Exercise test results were interpreted by two independent physicians. In case of doubt, a third physician was consulted, giving a final judgment. Because spinal cord stimulation induces artifacts on the ECG, a blinded analysis was not possible.

Daily activity score. A standardized questionnaire was used to score both physical exercise (daily activity) and social activities and has been validated for exercise testing and functional classification and corresponds to the specific activity scale (12).

Surgical implantation procedure. The complete standard implantation procedure has been described elsewhere (13). A unipolar Itrell 1 or quadripolar Itrell 2 pulse generator (Medtronic Inc.) was placed in the left subcostal retrofascial pocket and connected to the epidural electrode (either a unipolar Pisces Sigma or a quadripolar Quad electrode [Medtronic Inc.]) through an extension lead after the epidural space was punctured between the T_4 and T_5 levels. Under fluoroscopy an electrode was inserted into the epidural space. The final position (usually T_1, slightly left from the midline) was determined by sensation of paresthesias in

the thoracic area, sometimes also including the left arm, corresponding to the area of anginal pain, as indicated by each patient.

Statistical analysis. The randomized study period data (baseline vs. 6 to 8 weeks) were analyzed for within- and between-group comparisons with the Student *t* test, to compare the mean values of continuous variables, or the Wilcoxon rank-sum or Mann-Whitney *U* test for skewed or ordinal data and the chi-square test with continuity correction, or, where appropriate, with the Fisher exact test for discrete variables. In addition to the follow-up period, a trend analysis was performed using a repeated measures analysis of variance (SAS, PROC GLM, Version 6.08, SAS Institute), based on orthogonal polynomials, to access linear, quadratic and higher order trends in the repeated measures. All tests presented here are two-sided, and $p < 0.05$ was considered significant. The statistical analyses were performed with the statistical package SPSS/PC+, Version 4.0 (SPSS Inc.) and the Confidence Interval Analysis, Version 1.0 (BMJ).

Results related to the treadmill exercise are represented as mean values ± SEM. For treadmill exercise tests, assessment of therapy was performed by comparing the mean value of exercise data for weeks 6 and 8 with that of the two baseline tests. The follow-up exercise data for the entire group were analyzed by comparing mean value of the total group of the two baseline treadmill tests with those obtained at 6 and 8 weeks of spinal cord stimulation and after 14, 26 and 52 weeks. Quality of life variables are presented as the median values with 95% confidence intervals, unless otherwise indicated.

Results

Enrollment. Between January 1, 1990 and March 1, 1992, of 60 patients with intractable angina pectoris referred to our hospital for spinal cord stimulation, 43 were excluded from study. The remaining 17 patients were enrolled in this study.

Clinical characteristics of the patients. The 17 patients (15 men, 2 women, mean age 62.5 years) were randomly assigned to the treatment (8 patients) or the control (9 patients) group. No statistically significant differences in baseline characteristics were observed between the groups (Table 1). The majority of the 17 patients in this study had a long history of angina, multiple-vessel disease, previous myocardial infarction, revascularization procedures and left ventricular impairment.

Treadmill exercise test. Results of the exercise tests are presented in Table 2. Because the patients were used to exercising during pain, the relatively high level of exercise capacity is not surprising. The mean rate-pressure product of the treatment group differed significantly from that of the control group at baseline ($p < 0.02$). However, for within-group comparisons, total exercise duration and rate-pressure product at maximal exercise in the treatment group were significantly increased compared with baseline. The increase in rate-pressure product was mainly due to a significant increase in systolic blood pressure at maximal exercise. Moreover, in the treatment group a significant increase in time to angina ($p < 0.04$) and significant reduction in ST segment depression at maximal exercise ($p < 0.05$) were observed. In the control group no significant changes in exercise variables were observed. The differences in changes in exercise variables between the groups were statistically significant for exercise duration ($p < 0.03$), time to angina ($p < 0.05$) and ST segment depression ($p < 0.02$).

Table 1. Baseline Clinical Characteristics of the 17 Study Patients*

	Treatment Group (n = 8)	Control Group (n = 9)
Age (yr)	62.3 ± 2.6	63.2 ± 3.6
M/F	7/1	8/1
CAD (yr)	9.8 ± 0.8	10.9 ± 1.0
AP (yr)	2.5 ± 0.2	2.8 ± 0.3
MI	8	10
PTCA	5	3
CABG	9	9
No. of native diseased vessels (per pt at last CAG)	2.8	2.5
LV ejection fraction	50.2 ± 11.9	46.5 ± 13.4
Medication		
Ca-antagonist	8	9
Beta-blocker	7	6
Long-acting nitrates	8	9
Aspirin/coumarin	8	9

*No significant differences were observed between groups. Data presented are mean values ± SE or number of patients. AP = angina pectoris; Ca = calcium; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CAG = coronary angiography; F = female; LV = left ventricular; M = male; PTCA = percutaneous transluminal coronary angioplasty; pt = patient.

Quality of life. The results of the quality of life scores are shown in Table 2. A significant improvement in quality of life was demonstrated by repeated comparison of daily ($p < 0.008$) and social ($p < 0.005$) activities scores for the treatment group. In the treatment group, the number of angina attacks per week decreased ($p < 0.003$), with a concomitant significant reduction in sublingual glyceryl trinitrate intake ($p < 0.004$). In the control group, no significant change was observed. In addition, a statistically significant improvement in daily and social activity scores was observed in the treatment compared with the control group.

Long-term follow-up. *Treadmill exercise testing and quality of life.* All 17 patients entered the long-term follow-up phase. Of the 17 patients with ST segment changes during maximal exercise, 14 completed the 1-year follow-up period. In these 14 patients, the time to angina and the exercise duration demonstrated a second-order (quadratic) polynomial trend ($p = 0.02$ and $p = 0.06$, respectively) (Fig. 1). The time trend for ST segment depression at maximal exercise testing could be expressed most accurately by a second-order polynomial, although it was not significant ($p = 0.12$). A linear increase was demonstrated for rate-

Table 2. Outcomes of Primary Study End Points

	Treatment Group (n = 8)		Control Group (n = 9)	
	Baseline	6 to 8 Weeks	Baseline	6 to 8 Weeks
Exercise duration(s)	659 ± 121	827 ± 138*†	705 ± 136	694 ± 67
Rate-pressure product (beats/min^{-1} × mm Hg × 10^3)	12.9 ± 0.75	13.8 ± 1.3*	14.8 ± 9.1	14.2 ± 13.9
Time to angina (s)	520 ± 138	691 ± 174*	380 ± 78	393 ± 91
Heart rate$_{max}$ (beats/min)	90.1 ± 5.1	91.8 ± 4.4	97.7 ± 8.1	97.9 ± 7.2
SBP$_{max}$ (mm Hg)	139.8 ± 3.4	152.9 ± 7.0*	148.7 ± 6.3	144.5 ± 6.2
ST ↓$_{max}$ (mV)	0.09 ± 0.01	0.05 ± 0.02*†	0.13 ± 0.03	0.11 ± 0.02
ADL score	1.37 (1.15–1.67)	2.06*† (1.65–2.26)	1.24 (1.06–1.5)	1.25 (1.1–1.71)
SAS score	1.28 (0.99–1.69)	2.10†‡ (1.61–2.44)	1.3 (0.6–2.0)	1.39 (1.1–1.65)
Angina pectoris (per week)	16.6 (11.4–26.1)	9.0†‡ (4–14.2)	16.5 (9–23.9)	13.6 (7.7–20.8)
GTN (per week)	13.3 (8.8–17.7)	1.6†‡ (0.3–6.9)	8.3 (3.3–32.6)	8.5 (2.8–27.1)

*$p < 0.05$ versus baseline. †$p < 0.05$ change in treatment group versus change in control group. ‡$p < 0.005$ versus baseline. Data related to treadmill exercise are presented as mean values ± SE. Data related to quality of life are presented as median values ± 95% confidence intervals. ADL = daily activity score; GTN = glyceryl trinitrate intake per week; Heart rate$_{max}$ = heart rate at maximal exercise; SAS = social activity score; SBP$_{max}$ = systolic blood pressure at maximal exercise; ST ↓$_{max}$ = ST depression at maximal exercise.

pressure product ($p = 0.02$), systolic blood pressure ($p = 0.03$) and heart rate ($p = 0.04$). Quality of life variables showed the statistically most significant linear improvement trends ($p = 0.0001$) throughout the 1-year follow-up period (Fig. 2).

Left ventricular ejection fraction, 24-h ECG recording and stimulation threshold. Left ventricular ejection fraction, as determined by radionuclide angiography, was not influenced by spinal cord stimulation (48.2 ± 2.9% before spinal cord stimulation and 47.1 ± 3.2% after 6 weeks of spinal cord stimulation).

Spinal cord stimulation also did not influence the mean values of average minimal or maximal heart rate during 24-h ambulatory ECGs. In addition, no influence of spinal cord stimulation on supraventricular and ventricular premature beats or arrhythmias could be demonstrated by analysis of the 24-h ECGs. According to the 24-h ECGs before spinal cord stimulation, 7 of the 17 patients demonstrated signifi-

Figure 1. Exercise data of the patients who completed the 1-year long-term follow-up period. The initial increase in exercise duration (Ex dur) and time to angina pectoris (AP) during the study period was maintained during follow-up. BP max = systolic blood pressure at maximal exercise (mm Hg); HR max = heart rate (beats/min) at maximal exercise; RPP = rate-pressure product. Data presented are mean values and SE (error bars). See text for details.

Figure 2. Long-term follow-up results of quality of life variables in the study patients. The initial improvement in all quality of life variables was maintained during the 1-year follow-up period. ADL = daily activity score; AP = angina pectoris attacks; SAS = social activity score; NTG = glyceryl trinitrate intake per week. Data presented are median values and confidence intervals (error bars).

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cant ST segment changes, but only 3 of the 17 patients showed significant ST segment changes after spinal cord stimulation. Total ischemic burden was reduced from a baseline of 48.0 ± 12.0 to 20.2 ± 10.8 mm × min after spinal cord stimulation. In addition, the duration of the ischemic episodes and the number of episodes were reduced from 39.4 ± 4.6 to 6.7 ± 2.3 min with spinal cord stimulation and from three to one episodes, respectively. The groups were too small for statistical analysis.

The stimulation variables at which paresthesias were provoked did not change significantly during the 52-week follow-up period (median [±SE] 3.95 ± 0.50 V during the 1st 6 weeks and 4.55 ± 0.49 V after 52 weeks). In addition, the total stimulation time per day was decreased slightly, from 3.1 ± 0.9 h/day during the 1st 6 weeks after implantation to 2.8 ± 1.2 h/day after 52 weeks.

Adverse events. No adverse events occurred during either the operative procedure or the randomized study period. During follow-up, two patients had electrode dislodgments requiring intervention. Three patients were not included in the long-term follow-up period because of paroxysmal atrial fibrillation (one patient) and death (two patients). The two deaths were unrelated to spinal cord stimulation. One of the two patients died of gradually deteriorating heart failure and the other during a nonrelated surgical procedure.

Discussion

We found significant improvement in exercise variables associated with a concomitant increase in quality of life scores in this group of patients with intractable angina pectoris when they were treated with spinal cord stimulation. Our clinical observations might be attributed to improvement in left ventricular function, improvement in myocardial perfusion, a modification in pain perception or a combination of these factors.

Left ventricular function. No significant change in left ventricular ejection fraction was found after 14 weeks. This corroborates another study in which patients at rest before and after spinal cord stimulation showed no significant difference in ejection fraction (14). However, these investigators reported an improvement in left ventricular function in adenosine-induced ischemic left ventricular dysfunction after spinal cord stimulation. The latter observation suggested that the improvement in total exercise duration with spinal cord stimulation appeared to be related to better left ventricular function during exercise.

Myocardial ischemia. Spinal cord stimulation increases the anginal pain threshold, enabling the patient to prolong the complaint-free period during exercise. Our findings of a reduction in both symptomatic ischemia (i.e., time to angina) and clinically recognizable signs of ischemia (i.e., ST segment depression) during exercise are in agreement with other uncontrolled observations (3,5).

The improvement in exercise duration with a concomitant increase in rate-pressure product, time to angina and reduction in ischemia at 6 to 8 weeks in the treatment group strongly implicates an improved oxygen supply to counterbalance the increased myocardial oxygen demand.

In contrast to our findings, Mannheimer et al. (15) concluded that the antianginal and anti-ischemic effects seem to be secondary to a decrease in myocardial oxygen consumption. However, in view of the mechanisms of action, published data and those from our study support a combined electroanalgesic and anti-ischemic effect of spinal cord stimulation.

After 1 year of follow-up only the time to angina continued to be increased. The lack of a sustained improvement in the other exercise variables might be related to the relatively small sample size of patients (16). Further, our findings show that 7 of the 17 patients had ST segment depression during the 24-h ECG before spinal cord stimulation, whereas only three patients demonstrated these signs after stimulation. More sophisticated techniques will be required to elucidate the anti-ischemic mechanism of spinal cord stimulation.

Electroanalgesic modulation of pain. If the only result of spinal cord stimulation was its analgesic effect, which might mask the manifestation of myocardial ischemia, restrictions in its application would be necessary. However, spinal cord stimulation does not suppress angina completely; rather, it makes life more bearable for the patients. In addition, several studies, including this randomized 1-year follow-up study, have shown its beneficial effects on cardiac function (3–6).

The neural and neurohumoral mechanisms that may be responsible for the analgesic effect of spinal cord stimulation are not well understood. Linderoth et al. (17) have argued that the occurrence of a supraspinal neural mechanism is not necessary to explain the pain-relieving effects. Some investigators consider that neuroactive compounds are responsible for the analgesic effect of spinal cord stimulation (18,19), but others could not demonstrate a relation between release of stress hormones and pain intensity (20).

Because the effects of spinal cord stimulation lasted for the entire day after only three daily 1-h applications, it is likely that a supraspinal circuit modulated by spinal cord stimulation is involved. This is also in accord with reduced activity of spinothalamic tract cells by spinal cord stimulation (21).

Quality of life. Equally important for patients with intractable angina, spinal cord stimulation produces a higher daily activity score, with fewer anginal attacks and reduced sublingual glyceryl trinitrate intake. It is well documented that glyceryl trinitrate intake may be related to adverse effects, such as headache (10% to 90%), flushing and hypotension (22). It is very possible that these adverse effects might hamper exercise performance and quality of life. In our study, the reduction in anginal attacks and glyceryl trinitrate intake was not associated with an increased use of the spinal cord stimulation device. On the contrary, the patients adapted the use of the stimulator to their activities. The

significant improvement in quality of life that we found in our study seems to be the result of both analgesic and anti-ischemic effects.

Long-term follow-up. During the 1-year follow-up period, time to angina, exercise time and ST segment depression at maximal exercise showed a second-order trend, whereas the other exercise variables demonstrated a linear trend. All exercise variables remained improved compared with those at baseline. All quality of life variables demonstrated linear improvement. The initial improvement in exercise capacity may be related to a frequently performed exercise. The ensuing gradual decrease in variables associated with exercise capacity may be due to disease progression.

A placebo effect is unlikely because the effects lasted for 1 year (5). Although long-term randomized follow-up studies are needed of patients with angina treated by spinal cord stimulation, our data suggest that survival during a 1-year follow-up period is not adversely affected.

Conclusions. This randomized study demonstrates that spinal cord stimulation is an effective treatment for patients with intractable angina refractory to standard therapy. During long-term follow-up of 1 year, both exercise and quality of life variables remained improved compared with those at baseline. Further investigations are underway to unravel the mechanisms of action; however, before this therapy becomes widely available for angina, other studies, particularly those addressing mortality and morbidity, are needed.

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