Long-term effects of spinal cord stimulation on myocardial ischemia and heart rate variability: results of a 48-hour ambulatory electrocardiographic monitoring

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Key words:
Ambulatory electrocardiography (Holter); Angina pectoris; Spinal cord stimulation.

Background. **Spinal cord stimulation (SCS) has analgesic properties and may be used to treat pain in patients with therapeutically refractory angina who are unsuitable for myocardial revascularization. Some studies have also demonstrated an anti-ischemic effect. The aim of this study was to evaluate the long-term persistence of the effects of SCS on myocardial ischemia and on heart rate variability.**

Methods. **Fifteen patients (9 males, 6 females, mean age 76 ± 8 years, range 58-90 years) with severe refractory angina pectoris (Canadian class III-IV), on optimal pharmacological therapy, unsuitable for myocardial revascularization and treated with SCS for a mean follow-up of 39 ± 27 months (range 9-92 months) were studied. Eleven patients had had a previous myocardial infarction and 5 a coronary artery bypass graft. The mean ejection fraction was 54 ± 7% (range 36-65%). All patients underwent 48-hour ambulatory ECG monitoring and were randomly assigned to 24 hours without SCS (off period) and 24 hours with SCS (on period). The primary endpoints were: number of ischemic episodes, total duration of ischemic episodes (min), and total ischemic burden (mV*min).**

Results. **The heart rate was not statistically different during the off and on SCS periods (median 64 and 67 b/min respectively). The number of ischemic episodes decreased from a median of 6 (range 0-29) during the off period to 3 (range 0-24) during the on period ($p < 0.05$). The total duration of ischemic episodes decreased from a median of 29 min (range 0-186 min) during the off period to 16 min (range 0-123 min) during the on period ($p < 0.05$). The total ischemic burden decreased from a median of 2.5 mV*min (range 0-19.5 mV*min) during the off period to 0.8 mV*min (range 0-13 mV*min) during the on period (p = NS). The heart rate variability parameters were similar during the on and off periods.**

Conclusions. **SCS exerts long-term anti-ischemic effects.**

(Ital Heart J 2001; 2 (9): 690-695)

Received May 14, 2001; revision received July 25, 2001; accepted July 26, 2001.

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Spinal cord stimulation (SCS) was introduced in the 1960's to control chronic neuropathic pain[1]. It consists of high frequency selective stimulation of inhibitory large A afferent fibers that, according to the Melzack and Wall's gate theory[2], reduces the input to the supraspinal area from the peripheral pain receptors. This technique is performed with a small catheter introduced into the epidural space and connected to a pulse generator. In 1976 its use was extended to the treatment of chronic ischemic pain due to peripheral vascular disease[3]. In 1987, Murphy and Giles[4] treated for the first time a patient with refractory angina pectoris and unsuitable for surgical revascularization with SCS. Since then, the technique has been used in patients with refractory angina, with an improvement in anginal symptoms in more than 80% of cases[5-15].

Some studies have suggested that SCS, in addition to its analgesic effects, is able to reduce myocardial ischemia[5,6,12,13,16] probably through mechanisms that involve the adrenergic nervous system[17,18]. These studies have shown that such effects are present mainly during the acute phases while data concerning the persistence of the anti-ischemic effects over time are limited and not conclusive[7,19].

This study was designed to evaluate the long-term effects of SCS on myocardial ischemia and heart rate variability in patients chronically treated with SCS by means of ambulatory ECG monitoring.

Methods

Patients. From October 1990 to September 1998, 47 patients, suffering from severe refractory angina (Canadian class III-IV) despite optimal drug therapy and unsuitable for myocardial revascularization, underwent SCS. Fifteen of these patients were selected according to the following criteria:
• consent to be enrolled in the study;
• absence of left bundle branch block, atrial fibrillation and cardiac pacemaker;
• angiographic evidence of significant coronary artery disease (at least one severe stenosis in a principal coronary branch), or a history of myocardial infarction;
• evidence of reversible ischemia before SCS during at least one of the following techniques: ECG during pain, exercise stress test, myocardial stress scintigraphy;
• SCS with bipolar electrode;
• minimum follow-up period of 6 months.

Ambulatory electrocardiographic monitoring. All 15 patients underwent 48-hour ambulatory ECG monitoring on 2 consecutive days: 24 hours with the stimulator on (on period), and 24 hours with the stimulator off (off period). This sequence was randomized.

In 5 patients (no. 4, 9, 11, 12, and 13) SCS artifacts were eliminated by modifying the stimulator programming using bipolar stimulation and changing the pulse frequency, duration and amplitude. The stimulation electrodes and the amplitude of the stimulus were programmed so as to reproduce the same paresthesia experienced previously by the patient. The ECG electrodes were applied to the chest in such a way as to obtain three ECG leads (V_2, V_5 and aVF) which were not significantly affected by any change in posture. All patients were asked to keep a diary and to record any anginal attack. Recording and analysis of the ECG were performed using Synesis recorders, an Elatec reader and Software Elatec 3.03 (Ela Medical, France). Recordings were read by an expert cardiologist who was unaware of which period (stimulator on or off) the traces referred to. Any basal ST segment depression was corrected taking into account the degree of depression of the ST segment outside myocardial ischemic episodes. All episodes of at least 0.1 mV of transitory ST segment depression at 60 ms after the J point, lasting for at least 1 min and separated from another episode by at least 1 min of normal ST segments, were defined as ischemic episodes. Only those recordings, in which the total duration of artifacts was < 10% of the total recording period, were considered valid. The following parameters were analyzed: average, minimum and maximal heart rate, heart rate at the onset of ischemia and at the maximum ST segment depression, number and duration of ischemic episodes, degree of maximum depression of the ST segment, ischemic burden of each ischemic episode, and number of anginal attacks. Analysis was automatic after the positioning of the referral markers and the correction of the ST segment when necessary. Moreover, in 11 patients heart rate variability was determined with the Software Elatec 3.03 (Ela Medical). In 4 patients heart rate variability parameters were not available because of technical reasons and were excluded from the analysis. The following time domain parameters were calculated: the average length of all RR intervals included in the analysis (mean RR); the standard deviation of all intervals included in the analysis (SD); the standard deviation of the 5 min means (SDANN/5); mean of the standard deviation for 5 min segments (ASDNN/5); square root of the sum of the squares of differences between successive intervals (rMSSD); percentage of differences for RR intervals> 50 ms (pNN50). The following frequency domain parameters were calculated: energy in the power spectrum between 0.04-0.40 Hz (TP 24 hours); energy in the power spectrum between 0.04-0.15 Hz (LF 24 hours); energy in the power spectrum between 0.15-0.40 Hz (HF 24 hours); the ratio which reflects the autonomic tone (LF/HF)[20].

The primary endpoints were the number of ischemic episodes, the total duration of the ischemic episodes, and the total ischemic burden detected by ambulatory ECG monitoring. The secondary endpoints were the number of anginal attacks, the heart rate at the onset of ischemic episodes, the heart rate at the maximum ST segment depression, the duration and the degree of maximum ST segment depression, and the ischemic burden of each ischemic episode.

Statistical analysis. Given the rather low sample size, comparison of the primary endpoints of the on periods with those of the off periods was carried out using the Wilcoxon test. Comparison of the secondary endpoints, on the other hand, was carried out using the Student's t test for unpaired data. Values of $p < 0.05$ were considered statistically significant.

Results

The baseline characteristics of the patients included in the study are shown in table I. Of the 15 patients, 9 were male and 6 female. The mean age was 76 years (range 58-90 years). One patient was in Canadian class III and 14 in class IV when the stimulator was implanted. Eleven had had a previous myocardial infarction and 6 had diabetes mellitus. The mean ejection fraction was 54 ± 7% (range 36-65%). Eleven patients presented with three-vessel disease and 2 with two-vessel disease. Two patients did not undergo coronarography but, owing to the fact that both had had a previous myocardial infarction, were all the same included in the study. On clinical grounds, these 2 patients were not considered as candidates for revascularization and did not undergo coronary angiography. Five patients had had coronary artery bypass grafts. Three patients were in Canadian class I, 9 in class II, 1 in class III and 2 in class IV when

Table I. Clinical data.

No.	Age (years)	Sex	Diabetes	CCS	Previous MI	EF (%)	Vessels	CABG	Follow-up (months)	Therapy
1	81	M	No	IV	Yes	55	3	No	84	nt ,ca, asa
2	81	F	Yes	IV	Yes	57	2	No	18	nt, ca, bb, asa
3	62	M	Yes	III	Yes	58	3	No	72	nt, ca, bb, asa
4	58	M	Yes	IV	No	60	3	Yes	61	nt, ca, asa
5	79	F	No	IV	Yes	64	NA	No	10	nt, ca, asa
6	69	M	No	IV	Yes	45	3	Yes	72	nt, ca, ac
7	90	F	No	IV	Yes	36	NA	No	9	nt, ca, asa, bb
8	76	M	Yes	IV	Yes	37	3	No	10	nt, ca, asa
9	82	F	No	IV	No	64	3	No	53	nt, ca, asa, bb
10	76	M	No	IV	Yes	62	3	Yes	14	nt, ca, asa, bb
11	81	M	No	IV	Yes	48	3	Yes	13	nt, bb, ca
12	70	M	No	IV	No	60	3	No	92	nt, ca, asa, bb
13	76	F	Yes	IV	No	60	3	Yes	20	nt, ca, asa, bb
14	72	M	Yes	IV	Yes	55	3	No	34	nt, ca
15	84	F	No	IV	Yes	65	2	No	17	nt, ca, bb, ac

ac = oral anticoagulants; asa = acetylsalicylic acid; bb = beta-blocker; ca = calcium antagonist; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; EF = ejection fraction; MI = myocardial infarction; NA = not available; nt = nitrate; Vessels = number of diseased vessels.

enrolled for the study. The characteristics of the SCS stimulation during ambulatory ECG monitoring are shown in table II. All patients were treated with SCS for a mean period of 39 ± 27 months (range 9-92 months). Eight patients had an Itrel3 (Medtronic Inc., Minneapolis, MN, USA), 4 had a radiofrequency Xtrel (Medtronic Inc.) and 3 had a Dual 916 (Advanced Neuromodulation Systems, Dallas, TX, USA): the tip of the electrode was positioned between C6 and T2. Stimulation was programmed so as to provoke tolerable paresthesia in the area of anginal pain. At the time of the study, stimulation was continuous, 24 hours per day, in 13 patients and cyclic in the other 2 patients (50 s on and 10 s off in one and 50 s on and 60 s off in the other). The mean pulse duration was 268 ± 45 μs (range 180-330 μs), the mean pulse amplitude was 2.2 ± 1.1 V (range 0.6-4.3 V), and the mean stimulation frequency was 80 ± 11 Hz (range 70-100 Hz).

Table II. Stimulation characteristics.

No.	IPG	Electrode	Width (μs)	Frequency (Hz)	Amplitude (V)
1	Xtrel	3487A	210	70	0.9
2	Itrel3	3487A	300	70	1.6
3	Itrel3	3487A	270	70	0.6
4	Itrel3	3487A	270	85	2.3
5	916	2198 ANS	300	100	2.5
6	Xtrel	3487A	300	85	2.7
7	Itrel3	3487A	180	70	1.8
8	916	2198 ANS	300	85	2.1
9	Xtrel	3487A	210	70	2.2
10	Xtrel	3487A	300	85	3.5
11	Itrel3	3487A	300	85	4.0
12	Itrel3	3487A	330	85	1.1
13	Itrel3	3487A	210	70	2.8
14	916	2198 ANS	275	100	4.3
15	Itrel3	3487A	270	75	0.6

IPG = internal pulse generator.

The results of the Holter study are shown in tables III to V. The median heart rate was similar during the off and on periods (off period 64 b/min, on period 67 b/min). The number of ischemic episodes dropped significantly from a median value of 6 (range 0-29) during the off period to 3 (range 0-24) during the on period ($p < 0.05$). The total duration of ischemia decreased significantly from a median value of 29 min (range 0-186 min) during the off period to 16 min (range 0-123 min) during the on period ($p < 0.05$, 45% reduction). The median duration of each ischemic episode decreased from 3 min (range 1-54 min) during the off period to 2 min (range 1-42 min) during the on period (p = NS). The median value of the maximum ST segment depression was similar during the off and on periods (off period 0.16 mV, on period 0.14 mV, p = NS). The total ischemic burden decreased from a median value of 2.5 mV*min (range 0-19.5 mV*min) during the off period to 0.8 mV*min (range 0-13 mV*min, p = NS) during the on period. The median number of anginal attacks was 0.13 (range 0-1) during the off period and 0.13 (range 0-2) during the on period. The proportion of symptomatic episodes to total ischemic episodes was 2.5% during the off period and 1.7% during the on period. The median number of nitroglycerin consumption was 0.13 (range 0-1) during the off period and 0.13 (range 0-2) during the on period.

The heart rate at the onset of ischemia increased from a mean value of 70.1 ± 3.5 b/min during the off period to 73.7 ± 2.1 b/min during the on period ($p = 0.08$). The heart rate at the maximum ST segment depression increased from a mean value of 70.3 ± 12 b/min during the off period to 73.8 ± 11.3 b/min during

Table III. Results of electrocardiographic monitoring (patients).

No.	Mean HR/24 hours (b/min)		Ischemic episodes		Duration (min)		Total ischemic burden (mV∗min)		Max ST depression (μV)	
	Off	On	Off	On	Off	On	Off	On	Off	On
1	60	65	1	2	19	22	2.5	2.9	230	240
2	69	69	0	0	0	0	0	0	0	0
3	79	75	9	6	84	48	11.5	4.1	210	210
4	68	70	1	1	7	16	0.3	2	130	300
5	67	67	11	5	31	7	2.5	0.3	180	130
6	72	72	0	0	0	0	0	0	0	0
7	77	78	4	3	29	8	2.8	0.6	150	140
8	51	50	20	3	129	6	19.5	0.6	400	190
9	64	62	11	8	68	77	9.4	13	230	390
10	61	64	2	6	8	17	0.8	0.8	120	140
11	59	55	29	24	186	58	15.7	2.5	180	210
12	61	61	8	5	31	18	2.2	1.3	140	140
13	64	69	6	2	18	4	1.3	0.3	160	120
14	59	60	14	13	124	123	15.5	11.5	250	270
15	65	69	0	0	0	0	0	0	0	0
Median	64	67	6	3	29	16	2.5	0.8	160	140
Mean	65.1	65.7	7.7	5.2	48.9	26.9	5.6	2.7	158.7	165.3
SD	7.3	7.4	8.4	6.3	57.3	35.2	6.8	4.1	106.4	112.4

Duration = total duration of ischemia; HR = heart rate. Number of ischemic episodes on vs off: $p < 0.05$; duration of ischemic episodes on vs off: $p < 0.05$.

Table IV. Results of electrocardiographic monitoring (ischemic episodes).

	HR onset (b/min)		HR max ST (b/min)		Duration (min)		Ischemic burden (mV∗min)		Max ST depression (μV)	
	Off	On	Off	On	Off	On	Off	On	Off	On
Median	70.0	72.0	69.0	72.0	3.0	2.0	0.2	0.1	140.0	140.0
Mean	70.1	73.7	70.3	73.8	6.5	5.2	0.7	0.5	220.0	195.0
SD	13.4	17.2	13.2	15.9	8.2	8.4	1.2	1.3	50.4	57.9

Duration = duration of single episodes; HR onset = heart rate at the onset of the ischemic episode; HR max ST = heart rate at the maximum ST segment depression; Ischemic burden = ischemic burden of single episodes; Max ST depression = maximum ST segment depression of single episodes. HR onset off vs on: $p = 0.08$; hour max ST off vs on: $p = 0.10$.

the on period ($p = 0.10$). Heart rate variability parameters were analyzed in 11 patients and no significant differences were observed between the on and off periods (Table V).

Discussion

Our data indicate that in patients chronically treated for severe refractory angina SCS produces a significant reduction in transient myocardial ischemia as detected by ECG monitoring during daily life. In particular, we observed a significant reduction (50%) in the number of ischemic episodes and in the total duration of ischemia (45%). The reduction of the total ischemic burden was substantial but it did not reach statistical significance probably because of the small sample size.

No relevant difference in the number of anginal attacks and in the consumption of glyceryl trinitrate between the on and off periods was seen. The number of anginal attacks was rather low (median value 0.13) and the proportion of the number of symptomatic episodes to the number of ischemic episodes was about 2% both during the off and on periods, less than that generally reported in the literature which is about 20%[21]. The low percentage of symptomatic episodes during both periods may be due to the analgesic effect of SCS and to a persistence of this effect after cessation of the stimulus. Actually data gathered from experimental and clinical studies suggest that the analgesic effect of SCS persists for several hours, while the hemodynamic and anti-ischemic effects of SCS decrease soon after interrupting stimulation[17,22,23]. These data support the concept that SCS may have different effects on anginal pain and on myocardial ischemia. Indeed, the effect on anginal pain may be long lasting while the effect on myocardial ischemia may be short lasting. An addi-

Table V. Results of electrocardiographic monitoring (heart rate variability).

	SCS off	SCS on
Time domain parameters		
Mean RR (ms)	927.18 ± 117	926.18 ± 130
SD (ms)	120.09 ± 29	125.52 ± 34
SDANN/5 (ms)	105.77 ± 26	105.36 ± 27
ASDNN/5 (ms)	45.10 ± 18	52.55 ± 24
rMSSD (ms)	41.07 ± 25	60.20 ± 52
pNN50 (%)	8.64 ± 7	11.18 ± 10
Frequency domain parameters		
TP 24/h (ms^2)	1918.20 ± 2144	2402.90 ± 2836
LF 24/h (ms^2)	425.50 ± 768	665.20 ± 996
HF 24/h (ms^2)	169.00 ± 134	435.60 ± 747
LF/HF	2.63 ± 2.7	2.30 ± 2

ASDNN/5 = mean of the SD for 5 min segments; HF 24/h = energy in the power spectrum between 0.15-0.40 Hz; LF 24/h = energy in the power spectrum between 0.04-0.15 Hz; pNN50 = percentage of differences for RR intervals > 50 ms; rMSSD = square root of the sum of the squares of differences between successive intervals; SCS = spinal cord stimulation; SD = standard deviation for 24 hours; SDANN/5 = SD of the 5 min means; TP 24/h = energy in the power spectrum between 0.04-0.40 Hz. There were no statistically significant differences between time domain heart and frequency rate variability parameters during SCS off vs SCS on.

tional explanation could be the short duration of each ischemic episode in our study (median 3 min during the off period and 2 min during the on period) and, as a consequence, the probability that it be symptomatic is low[24]. However, the low occurrence of angina could simply be a consequence of the fact that in such stable patients, symptoms spontaneously decrease during follow-up such that it is difficult to assess the effect of SCS on anginal pain.

The effects on ischemia observed in our study were less than those reported by DeJongste et al.[13] probably because these authors evaluated patients who had just been implanted and who presented a high number of ischemic episodes, while our patients had undergone implantation some time before and were evaluated in a period of relative well-being as demonstrated by the Canadian class in which they were included at the time of the study. Another explanation may be that, due to a possible persistence of some anti-ischemic action during the off period, we underestimated the anti-ischemic effect since no wash-out was planned between the on and off periods. However, in agreement with other data[19], the interruption of SCS does not produce an immediate rebound effect on anginal pain. In a recent study[25] addressing the long-term effects of SCS on myocardial ischemia as detected by Holter monitoring, the authors observed that the number and the duration of ischemic episodes were not significantly different at baseline and after 6 months of stimulation. These observations, in contrast with our results, do not support the hypothesis of the long-term persistence of the anti-ischemic effect of SCS. However the follow-up analysis in this study was performed in patients in whom stimulation was discontinued 24 hours before and during Holter monitoring. This substantial protocol difference may explain the different results.

As regards the mechanisms of action of SCS on ischemia, the absence, in the 24-hour period, of any significant effect on heart rate and on heart rate variability does not allow us to sustain the hypothesis of an anti-adrenergic effect. Other studies, carried out using similar techniques and evaluating the effects of SCS on heart rate variability, report the same negative results[26,27]. This would suggest that the anti-adrenergic effect observed in animals[28,29] is not detectable in humans using the techniques which analyze the systemic effects of the adrenergic nervous system, while we cannot exclude an effect at levels that have not yet been adequately studied. At the onset of ischemic episodes, the heart rate showed a trend towards higher values during active stimulation, suggesting that the mechanism through which stimulation acts can be related to an increase in blood flow. This is in agreement with animal[28] and human studies[17,30].

Study limitations. Some limits must be underscored. This study could not be designed as double blind because paresthesia, produced by SCS, is indicative of the effectiveness of treatment and cannot be abolished. However, ECG analysis was performed by a cardiologist who was blind to treatment. In addition, the sample size was small and does not allow us to draw definite conclusions regarding the anti-ischemic mechanisms.

A more adequate assessment of the long-term effects of SCS on myocardial ischemia would have necessitated knowledge regarding the preimplant ischemic burden. Indeed, the results of this study do no clarify whether the observed long-term anti-ischemic effects of SCS are similar, greater or lower than those observed in the short term.

Conclusions. Our results suggest that SCS exerts anti-ischemic effects which persist over a long period of time. The effects of SCS on ischemia cease immediately, while the effects on anginal pain persist at least 24 hours after having interrupted stimulation. The absence of a relevant effect on the 24-hour heart rate and the trend towards a higher heart rate at the onset of ischemic episodes suggest that the anti-ischemic effects are probably due to an increase in myocardial blood flow. In the clinical setting described in the present study, no effect was detected on the autonomic nervous system.

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