Effect of Spinal Cord Stimulation on Heart Rate Variability and Myocardial Ischemia in Patients with Chronic Intractable Angina Pectoris—A Prospective Ambulatory Electrocardiographic Study

RAYMOND W. M. HAUTVAST, M.D., JAN BROUWER, M.D., PH.D., MIKE J.L. DEJONGSTE, M.D., PH.D., K.I. LIE, M.D., PH.D.

Thorax Center, Department of Cardiology, University Hospital, Groningen, The Netherlands

Summary

Background and hypothesis: Spinal cord stimulation is an effective treatment for chronic refractory angina pectoris. Its efficacy is related to an anti-ischemic action, possibly as a result of modulation of the autonomic nervous system. Therefore, the influence of spinal cord stimulation on the autonomic nervous system and myocardial ischemia was prospectively studied in 19 consecutive patients with intractable angina pectoris.

Methods: Patients were included when demonstrating > 0.1 mV STsegment depression on the exercise electrocardiogram (ECG) during two separate treadmill tests. After enrollment, heart rate variability together with ischemic indices were studied with 48 h ambulatory ECG monitoring. Assessments were made at baseline and after 6 weeks of spinal cord stimulation therapy.

Results: After 6 weeks, no significant changes in heart rate variability were detected. However, ischemic indices on the ambulatory ECG, as well as anginal attacks and consumption of sublingual nitrate tablets, were significantly decreased.

Conclusion: Autonomic modulation assessable with heart rate variability analysis may not be the explanatory mechanism of action for the decrease of anginal attacks and ischemia, exerted by spinal cord stimulation used as an adjuvant therapy in patients with chronic intractable angina pectoris.

Key words: spinal cord stimulation, autonomic nervous system, heart rate variability, chronic intractable angina pectoris, myocardial ischemia

Introduction

Electrical stimulation of the spinal cord is a clinically effective treatment of angina pectoris refractory to conventional therapy. It is known to alleviate anginal pain and to prolong exercise duration.^{1–6} The mechanism of action is still a matter of debate, but appears to employ an anti-ischemic effect. Neurostimulation lowers sympathetic activity^{7–9} and induces changes in myocardial blood flow.^{10, 11} Both mechanisms may be related; possible mechanisms are coronary vasodilation by parasympathetic stimulation,¹² reduction of myocardial oxygen demand by beta-adrenergic inhibition,¹³ or inhibition of alpha-adrenoceptor mediated coronary vasoconstriction.¹⁴

Electrocardiographic ambulatory monitoring can be used to study autonomic nervous regulation of the heart by analysis of heart rate variability.¹⁵ In addition, it is an appropriate method to assess effects of anti-ischemic therapy.¹⁶ In a pilot study,¹⁷ reduction of ischemia on the electrocardiogram (ECG) was found. Heart rate variability analysis, performed in some of these patients, showed no changes. In this study, only patients with ischemic signs on 48-h ECG at baseline were evaluated, so a statistical “regression to the mean” effect¹⁸ could not be excluded. Moreover, the study was not designed for heart rate variability analysis. To study the influence of spinal cord stimulation on the autonomic nervous system, we performed a prospective study on heart rate variability in a new, larger group of patients with exercise-induced myocardial ischemia.

Methods

Patient Selection

Consecutive patients, referred to our outpatient clinic for treatment of chronic intractable angina pectoris, were included after giving informed consent. The study had the approval of the hospital's medical ethical board.

Inclusion criteria included angina pectoris class III or IV according to the New York Heart Association, despite maximal tolerated dosage of beta-blocking agents, calcium antagonists, and long-acting nitrates. Significant coronary artery disease (CAD) had to be documented by a recent coronary

Address for reprints:

Raymond W. M. Hautvast, M.D.
Thoraxcenter, Dept. of Cardiology
University Hospital Groningen
P.O. Box 30.001
9700 RB Groningen, The Netherlands

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angiogram, leaving no options for percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. Finally, myocardial ischemia had to be established by at least 0.1 mV ST-segment depression on the ECG during two standardized symptom-limited treadmill exercise tests. The second test was performed after an interval of 1 to 2 weeks. All patients had to have a resting ECG that allowed proper evaluation of ischemic signs during exercise, that is, no intraventricular conduction disturbances or ST-wave abnormalities.

The technique of implantation of the stimulator system has previously been described.¹⁹ The stimulator, a Medtronic Itrell® II (Medtronic, Inc., Minneapolis, Minn.) implantable pulse generator, was connected with an electrode that was positioned in the epidural space at T1 level. Patients were instructed to use the stimulator three times a day for 1 h and additionally whenever anginal complaints occurred. This stimulation regimen had proven not to cause a rebound of ischemia in between periods of stimulation.¹⁷ Medication was kept unchanged during the entire study period.

Electrocardiographic Monitoring (48 h)

At baseline, a 48-h ambulatory ECG recording was made before implantation of the stimulator and after 6 weeks of intermittent stimulation. The method followed has been previously described in detail.¹⁷ A three-channel amplitude-modulated Marquette® (series 8500) (Marquette Electronics, Inc., Milwaukee, Wisc.) recorder was used. The modified leads aVF, V₁, and V₅ were analyzed on a Marquette XP analyzer (software version 5.8) and reviewed by an experienced analyst who was supervised by an independent cardiologist. ST changes caused by posture were eliminated. Ischemic episodes were defined as horizontal or downsloping ST-segment shifts 60 ms after the J point of at least 0.1 mV, lasting for at least 1 min and separated from the previous episode for at least 1 min.²⁰

Primary end point was heart rate variability in relation to the number of ischemic indices on the ambulatory ECG (ischemic episodes, duration of ischemia, and total ischemic burden; the latter is the mathematically calculated "area un-

der the curve," expressed as millimeters $\times$ minutes²¹). Secondary end points were the number of anginal symptoms and consumption of sublingual nitrogen tablets (recorded in a 2-week patient diary, preceding monitoring), arrhythmias, and heart rate.

Heart rate variability was determined using fast Fourier analysis. Conventional time domain and frequency domain parameters were used to assess changes in heart rate variability (Table I). In addition, ventricular and supraventricular extra beats and tachycardias, occurring during 48-h ECG recording, were assessed.

Statistics

Heart rate variability parameters are represented as averages with their standard deviation. All other data are represented as medians with ranges, unless mentioned otherwise. Comparisons between baseline and treatment assessments were made using Student's paired *t*-test and Wilcoxon's rank sum test. All *p* values presented are two-tailed, and *p* values <0.05 were considered significant.

Results

In all, 19 patients, (10 men, 9 women, age 61 ± 7 years) were included. A description of patient characteristics is given in Table II. All patients received a beta-blocking agent in addition to other antianginal medication, except for Patient No. 5 (Table III), who had severe chronic obstructive pulmonary disease. No complications occurred during the study.

After 6 weeks of intermittent spinal cord stimulation treatment, no significant changes in heart rate variability compared with baseline could be detected, both in time domain parameters (Table IIIA) and frequency domain parameters (Table IIIB).

On the 48-h ECGs, ischemic episodes were demonstrated at baseline in 14 of the 19 patients, whereas only 7 showed ischemia after 6 weeks of treatment. Of the five 48-h ECGs without ischemic signs at baseline, three were still without

TABLE I List of used heart rate variability parameters

Time domain parameters	
mean NN	The mean of all normal RR intervals
SDNN	The standard deviation of all normal to normal RR intervals
rMSSD	Root mean square of successive difference: the square root of the mean of the squared differences between successive normal RR intervals
pNN50	The percentage of differences between successive normal RR intervals greater than 50 ms
CV	Coefficient of variance, calculated as $(SDNN/\text{mean NN}) \times 100\%$
Frequency domain parameters ^a	
TP	Total power: energy in the power spectrum between 0.04–0.40 Hz
LF	Low frequency power: energy in power spectrum between 0.04–0.15 Hz
HF	High frequency power: energy in power spectrum between 0.15–0.40 Hz

^aFrequency domain parameters are expressed in absolute units and in normalized units [i.e., as % – age of (total power – power less than 0.04 Hz)].

TABLE II Baseline characteristics—total 19 patients

Sex (M/F)	10/9
Age (years)	61 ± 7
History of coronary artery disease (years)	9 ± 3
Left ventricular ejection fraction (%)	55 ± 14
Number of stenosed coronary arteries	2.3 ± 0.7
Total myocardial infarction (in 8 patients)	14
Total coronary bypass surgery (in 13 patients)	16
Total coronary angioplasty (in 6 patients)	11
Medication	
Beta blocker	18 patients
Calcium reentry blocker	18 patients
Long-acting nitrate	18 patients

ischemia after 6 weeks. During spinal cord stimulation, ischemic episodes were reduced from a median of 2 (range 0–19) to 0 (range 0–12, $p = 0.02$) per 48 h, duration of ischemia was reduced from 2.6 (0–128.9) to 0 (0–55.9, $p = 0.03$) minutes per 48 h, and total ischemic burden was reduced from 4.3 (0–236.5) to 0 (0–123.8, $p = 0.02$) mm/min. In addition, the number of anginal symptoms, as reported in the patient diaries, decreased from a median of 6.4 (range 2–14.6) to 2.8 (range 0–7.6, $p = 0.001$) attacks per 48 h, with a concomitant decrease in use of sublingual nitrate tablets from 5.8 (0–15.2) to 0.2 (0–5.8, $p = 0.001$). No significant change was noticed in

minimal, maximal, and mean heart rate, or in the number of ventricular and supraventricular arrhythmias. Results are presented in Table IV.

Discussion

In the present study, we found that spinal cord stimulation, applied as an adjuvant therapy in patients with chronic intractable angina pectoris, did not influence heart rate variability. Nevertheless, a significant reduction of overall ischemia in daily life activities, with a concomitant reduction of anginal attacks and sublingual nitrogen tablet consumption, was demonstrated. These results confirm previous findings in a smaller group of patients.¹⁷ In contrast with this earlier study, the present study was designed to study heart rate variability parameters in relation to myocardial ischemia. Since ischemic signs on ambulatory ECGs are known to show a large intraindividual variation,¹⁸ repeated ischemia during exercise was required as a ground for inclusion. Thus, ambulatory ECGs with and without signs of ischemia at baseline have been evaluated. Hence, the demonstrated reduction of ischemia and the concomitant reduction of angina in the present study must be considered as a result of therapy and is unlikely to be attributed to a statistical effect.

Effects on heart rate, induced by spinal cord stimulation, have been described in an experimental⁷ and clinical setting,² without simultaneous beta blockade. The aim of the present

TABLE IIIA Heart rate variability values; time domain parameters

Patient No.	mNN baseline	mNN SCS	SDNN baseline	SDNN SCS	rMSSD baseline	rMSSD SCS	pNN50 baseline	pNN50 SCS	CV baseline	CV SCS
1	891	830	84	77	16	19	1.1	1.9	9.4	9.3
2	1120	1176	126	147	77	84	23.4	27.0	11.3	12.5
3	796	760	97	108	14	16	0.6	0.9	12.2	14.2
4	943	890	150	142	31	26	9.2	5.1	15.9	16.0
5	1005	1159	81	128	42	67	23.7	46.6	8.1	11.0
6	759	697	134	89	12	10	3.3	0.1	17.7	12.8
7	854	933	143	148	5	32	4.3	7.7	16.7	15.9
8	964	886	208	153	58	38	29.1	14.4	21.6	17.3
9	875	917	90	104	27	24	3.7	3.7	10.3	11.3
10	1035	1025	77	103	16	17	0.7	0.8	7.4	10.0
11	1245	1286	144	122	24	29	4.0	8.1	11.6	9.5
12	896	852	93	95	18	15	1.3	0.5	10.4	11.2
13	845	916	143	124	28	29	6.2	7.1	16.9	13.5
14	888	862	165	150	30	66	7.0	5.1	18.6	17.4
15	962	689	81	67	61	17	17.6	1.7	8.4	9.7
16	964	1085	155	157	24	32	4.5	10.6	16.1	14.5
17	1150	1162	108	82	32	30	9.4	8.0	9.4	7.1
18	1025	1046	104	155	33	30	9.1	4.2	10.1	14.8
19	825	780	86	54	18	17	1.2	1.3	10.4	6.9
Mean	950	945	119	116	30	31	8.0	8.0	12.8	12.4
SD	126	171	36	33	18	20	9.0	11.0	4.1	3.2

Abbreviations: SCS = spinal cord stimulation, SD = standard deviation.

Other abbreviations as in Table I.

TABLE IIIB Heart rate variability values; frequency domain parameters

Patient No.	Absolute units (in m ²)						Normalized units (in %)			
	TP baseline	TP SCS	LF baseline	LF SCS	HF baseline	HF SCS	LF baseline	LF SCS	HF baseline	HF SCS
1	289	289	81	81	34	64	69.2	55.9	30.8	44.1
2	2304	2601	900	900	676	841	57.1	51.7	42.9	48.3
3	676	576	289	225	25	25	92.0	90.0	8.0	10.0
4	1936	1521	1024	841	121	81	89.4	91.2	10.6	8.8
5	576	1521	100	361	196	529	33.8	40.6	66.2	59.4
6	625	100	225	25	64	9	77.9	73.6	22.1	26.5
7	841	1024	289	361	81	121	78.1	74.9	21.9	25.1
8	2809	1681	1156	729	529	225	68.6	76.4	31.4	23.6
9	676	729	225	289	100	81	69.2	78.1	30.8	21.9
10	484	484	169	169	25	36	87.1	82.4	12.9	17.6
11	361	441	100	121	64	100	61.0	54.8	39.0	45.2
12	400	324	144	100	49	36	74.6	73.5	25.4	26.5
13	1369	1225	576	484	100	121	85.2	80.0	14.8	20.0
14	784	1849	289	841	121	400	70.5	67.8	29.5	32.2
15	1681	484	784	225	441	36	64.0	86.2	36.0	13.8
16	1089	1444	324	484	81	144	80.0	77.1	20.0	22.9
17	625	576	121	100	144	121	45.7	45.2	54.3	54.8
18	529	625	121	169	121	81	50.0	67.6	50.0	32.4
19	225	121	64	25	36	36	64.0	41.0	36.0	59.0
Mean	962	927	367	344	158	162	69.3	68.8	30.7	31.2
SD	708	665	336	283	178	205	15.0	15.6	15.0	15.6

Abbreviations as in Tables I and IIIA.

study was to investigate the influence of spinal cord stimulation as an adjuvant therapy on heart rate variability in relation to ischemia and not to study the mere influence of spinal cord stimulation on heart rate variability alone. Therefore, it was

essential that all antianginal medication, including beta blockers, remained unchanged. Residual ischemia in patients with CAD using beta blockers is associated with a decreased heart rate variability during periods of ischemia.²² Assuming

TABLE IV Ischemic and arrhythmic indices on 48-h ambulatory electrocardiogram and patient diary assessments at baseline and after 6 weeks of treatment

	Baseline	After 6 weeks of treatment	
Ischemic episodes (n/48 h)	2 (0-19)	0 (0-12)	p = 0.02
Total duration of ischemia (min)	2.6 (0-128.9)	0 (0-55.9)	p = 0.03
Total ischemic burden (mm × min)	4.3 (0-236.5)	0 (0-123.8)	p = 0.02
Minimal heart rate (beats/min)	44 ± 8	45 ± 9	
Maximal heart rate (beats/min)	101 ± 21	105 ± 16	
Mean heart rate (beats/min)	65 ± 11	65 ± 11	
Ventricular extra beats (n/48 h)	44 (1-5983)	336 (0-15473)	
Ventricular couplets (n/48 h)	1 (0-45)	0 (0-53)	
Ventricular tachycardias (n/48 h)	0 (0-1)	0 (0-403)	
Supraventricular extra beats (n/48 h)	45 (0-239)	62 (1-246)	
Supraventricular couplets (n/48 h)	2 (0-23)	1 (0-18)	
Supraventricular tachycardias (n/48 h)	1 (0-18)	0 (0-14)	
Patient diary			
Anginal attacks (n/48 h)	6.4 (2-14.6)	2.8 (0-7.6)	p = 0.001
Used sublingual nitrates (n/48 h)	5.8 (0-15.2)	0.2 (0-5.9)	p = 0.001

All values are represented as median with ranges, except heart rate values, which are represented as mean ± standard deviation.

that spinal cord stimulation has an additional beta-blocking effect, this implies that a reduction of ischemia should be accompanied by a change in heart rate variability parameters. Beta-blocking agents have been described to improve overall heart rate variability in patients with CAD, as expressed in an increase of the standard deviation of all normal to normal RR intervals (SDNN).^{23,24} In our study, the values of SDNN are found to be under the normal rate according to the guidelines of the American Heart Association, therefore a change in heart rate variability may very well be detectable. On the other hand, it cannot be excluded that these drugs may potentially mask a further additional heart rate variability improvement as a result of spinal cord stimulation. To our knowledge, little is known about heart rate variability changes after intervention, superimposed on beta-blocker therapy. However, ischemia is markedly reduced due to spinal cord stimulation in the present study, whereas heart rate variability remains unaltered. Therefore, it is less likely that there still may be a relation between ischemia and heart rate variability. An alpha-adrenergic mediated process as a result of spinal cord stimulation, causing a myocardial change of blood flow, may also have been detected if present.²⁵

We have demonstrated that spinal cord stimulation, applied as an adjuvant therapy in medically treated patients with otherwise chronic intractable angina pectoris, does not influence heart rate variability. However, a marked reduction of anginal attacks and ischemia, assessed during 48-h ECG monitoring, was observed. Therefore, modulation of the autonomic nervous system assessed by heart rate variability analysis is less likely to be the explaining mechanism of action for the effect on angina pectoris and myocardial ischemia, exerted by spinal cord stimulation used as an adjuvant therapy together with antianginal medication.

Limitations of the Study

In the present study, the patients' level of activity before and during treatment was not a study objective. In the longer term, patients treated with spinal cord stimulation for angina appear to extend their activities in daily life.⁵ If, despite what is stated above, spinal cord stimulation still has an effect on heart rate variability, changes in heart rate variability and mean and maximal heart rate due to increase in daily activity are compensated by a lowering of sympathetic tone by spinal cord stimulation and therefore may not be detected. However, this possibility is less likely, since in all patients maximal, minimal, and mean heart rate remained unaltered during spinal cord stimulation treatment.

This study was set up in an uncontrolled design, which may imply a risk for observer bias, especially with regard to ischemic indices on the ambulatory ECG. However, ischemic indices on the ambulatory ECG at baseline were not an inclusion criterion, so this risk for bias is likely to be reduced. Apart from that, it is impossible to conduct placebo-controlled trials with spinal cord stimulation,²⁶ for there is no alternative for the paresthesias induced by the neurostimulator.

In many clinical studies on spinal cord stimulation in angina, safety aspects remain a matter of debate, although efficacy seems to be established. The present study likewise gives no answer to safety questions. Sanderson *et al.* reported three deaths in a 5-year follow-up of 23 patients,⁶ concluding that it is a safe therapy. Nonetheless, only a prospective mortality study can confirm this.

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