Original articles

Spinal cord stimulation in patients with refractory anginal pain and normal coronary arteries

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Key words:
Normal coronary arteries; Quality of life; Refractory angina; Spinal cord stimulation; Syndrome X.

Background. **Spinal cord stimulation (SCS) has been shown to be effective in patients with refractory angina and coronary artery disease. No previous study assessed the clinical effects of SCS in patients with refractory angina who present angiographically normal coronary arteries.**

Methods. **SCS was performed in 7 patients (4 men, 3 women, mean age 59.3 ± 11 years) with refractory angina and normal coronary arteries. Clinical status was assessed 1 month after SCS device implantation and at a mean follow-up of 11 months (range 2-17 months) by: 1) an estimate of the number of anginal attacks and nitrate consumption in the 2 weeks prior to implantation and to follow-up visits; 2) a score of quality of life by a visual analogic scale; 3) a five-item questionnaire assessing effort angina and satisfaction with treatment; 4) treadmill exercise testing.**

Results. **At the last follow-up the number of anginal episodes ($p < 0.001$) and nitrate consumption ($p < 0.004$) were both reduced by SCS. Visual analogic scale score improved from 2.1 ± 0.98 to 9.0 ± 0.9 ($p < 0.001$) at 1 month and to 6.4 ± 2.3 ($p < 0.01$) at the last follow-up. Questionnaire analysis showed that mild ($p = 0.006$) and moderate ($p = 0.000$) physical activity, as well as patient satisfaction with anginal status ($p = 0.000$) and with current treatment ($p = 0.000$) all improved by SCS. Finally, time to 1 mm ST segment depression, time to angina, and exercise duration were all prolonged by SCS.**

Conclusions. **Our data point out that SCS may considerably improve anginal symptoms and exercise tolerance in a significant number of patients with refractory angina and normal coronary arteries and therefore it should be considered as a valuable treatment option in this group of patients.**

(Ital Heart J 2001; 2 (1): 25-30)

Received October 25, 2000; revision received November 22, 2000; accepted November 27, 2000.

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About 20% of patients with typical chest pain indicative of the need for coronary angiography show normal coronary arteries[1]. The causes of chest pain in these patients remain controversial and may be heterogeneous[2,3]. A dysfunction of small coronary artery vessels has been suggested, particularly in those patients with transient electrocardiographic changes during chest pain[4-6]. Moreover, an enhanced perception of potentially painful cardiac stimuli has been reported in most such patients[7,8].

Although prognosis of patients with angina and normal coronary arteries is excellent[9], a substantial number continues to suffer from frequent episodes of severe chest pain, refractory to medical therapy, which may severely limit daily activities and impair quality of life[10-12].

Spinal cord stimulation (SCS) has been proposed as an alternative form of treatment for angina refractory to medical therapy in patients with documented coronary artery disease not suitable for coronary interventions[13-16]. Furthermore, SCS has been reported to improve exercise test results in patients with syndrome X[17]. Neurostimulation has also been reported to increase coronary blood flow in these patients[18], although this finding has not been confirmed by other studies[19,20]. On the other hand, no previous study has investigated the effects of neurostimulation on anginal symptoms in patients with cardiac syndrome X.

Methods

From March 1999 to June 2000 an SCS device was implanted in 7 patients (4 men and 3 women, mean age 59.3 ± 11 years)

with refractory anginal chest pain episodes who showed normal coronary arteries at angiography (Table I). The duration of angina ranged from 1 to 8 years (average 5 years) and, because of the persistence or worsening of symptoms, coronary angiography was repeated twice in 5 patients and 3 times in one.

Five patients initially had predominant effort angina with a positive exercise test (typical syndrome X), but during follow-up pain developed also at rest, without apparent causes, and became more and more invalidating. Patient no. 3 was a 45-year-old woman who presented in 1996 with an unheralded acute anterior myocardial infarction which was treated with rt-PA; after discharge, she continued to complain of recurrent episodes of chest pain on effort and at rest, in the absence of diagnostic electrocardiographic changes; two coronary angiograms showed normal coronary arteries, and left ventricular angiogram and two-dimensional echocardiography showed a normal left ventricular function; stress thallium myocardial scintigraphy showed a persistent small septal perfusion defect.

Patient no. 1 was a 60-year-old man who also had an acute anterior myocardial infarction in 1994; subsequently, he developed typical anginal pain on effort and at rest. In June 1996, coronary angiography showed a 70% stenosis of the left anterior descending artery and he underwent percutaneous coronary angioplasty with stent implantation. However, he continued to complain of recurrent anginal episodes despite documentation of the absence of restenosis in three subsequent coronary angiograms. Intracoronary ergonovine test induced his typical pain in the absence of significant constriction of angiographically visible coronary vessels; left ventricular angiogram and two-dimensional echocardiography showed a mild reduction in left ventricular ejection fraction (40%).

At the time of the evaluation for SCS, all patients had frequent, often prolonged, episodes of chest pain under full medical treatment (12 to 24 episodes per week); pain was often induced by minimal effort and also frequently developed at rest; all patients had undergone one to three hospitalizations because of recurrent chest pain in the last 6 months.

Several forms of therapy had been tried in these patients, including a xanthine derivative (bamiphylline 600 mg bid) in 3, imipramine (25 mg once a day) in 2, and left stellate gangliectomy in 1, without detectable benefits. Drug therapy at the time of screening for SCS device implantation is shown in table I. For the purposes of the study this drug therapy was left unchanged throughout the entire study period.

Spinal cord stimulation device implantation. All patients first underwent temporary SCS implantation for 2-3 weeks. Under sterile conditions and local anesthesia, the epidural space was punctured at the level of T6 and a quadripolar electrode catheter was introduced and advanced under X-ray control into the epidural space so as to place the catheter tip at the level of T1-T2. A suitable position for the electrode catheter was then sought for and corresponded to the site where a prickling sensation (paresthesia) was felt covering the area of radiation of anginal pain under neurostimulation. The ideal stimulation parameters were then found for the patient and the electrode catheter was connected to an external portable pulse generator. All patients reported significant symptom relief during temporary SCS and then agreed to proceed with permanent implantation.

A quadripolar Itrel 2 pulse generator (Medtronic Inc., Minneapolis, MN, USA) was placed in a subcutaneous pocket below the left costal arch. An extension lead was connected to the electrode by subcutaneous tunneling. The device was programmed telemetrically with two preset stimulation powers, the weaker being used for continuous prophylactic treatment and the stronger for treatment of acute anginal attacks. The patient can switch from a preset stimulation strength to another by briefly touching the skin over the device with an external magnet. The same magnet can be used to turn the generator "off" and "on". A continuous stimulation protocol was advised but the patient was free to turn the device on and off as desired.

Clinical assessment and follow-up. All patients were evaluated 1 month after SCS device implantation and in

Table I. Main baseline characteristics of the patients.

Patient	Sex	Age (years)	Symptom duration (years)	Hospital admissions*	No. coronary angiograms	ExT	Holter	Drugs	Follow-up (months)
1	M	60	4	3	3	-	-	N, CA, AC	17
2	M	48	8	2	2	+	+	BB, N	15
3	F	45	4	3	2	-	-	-	14
4	M	68	8	3	2	+	+	BB, N	14
5	F	69	6	3	2	+	+	BB, ACE-I	10
6	F	56	1	1	1	+	+	CA, N	5
7	M	70	3	1	2	+	+	CA, ACE-I, ASA	2

AC = anticoagulants; ACE-I = ACE-inhibitors; ASA = acetylsalycilic acid; BB = beta-blockers; CA = calcium antagonists; ExT = exercise test; N = nitrates. * hospital admissions in the last 6 months.

July 2000, at an average of 11 months (range 2 to 17 months) from SCS implantation. The primary end-point of this study was the effect of SCS on symptoms and on quality of life. The number of anginal episodes and sublingual nitrate consumption in the last 2 weeks prior to hospitalization and in the last 2 weeks prior to follow-up visits were recorded. Patients were also asked to score their quality of life using an analogic scale, ranging from 0 (worst imaginable condition) to 10 (best imaginable condition).

A simple five-item questionnaire was also administered at medical visits (Table II). The first three questions concerned limitations of patients as a result of typical chest pain in performing mild, moderate and heavy physical activities, respectively; the other two questions concerned satisfaction of patients with their current anginal status and current treatment, respectively. There were five possible answers for each question, which, for statistical analyses, were scored from 1 (worst condition) to 5 (best condition).

Tolerance of effort was also assessed by the standard treadmill exercise Bruce protocol. An exercise test was terminated in the case of physical exhaustion, unbearable angina or clinically dangerous conditions (e.g., hypotension, ventricular arrhythmias). Occurrence of typical angina was recorded and ST segment depression was considered significant when it was rectilinear or downsloping and ≥ 1 mm at 0.08 s from the J point. Exercise tests at follow-up were always performed with the stimulator at the "on" position.

Statistical analysis. Analysis of variance with a repeated measure design was used to assess changes in clinical and exercise variables at the three time points considered (pre-implant, 1-month follow-up, last follow-up). In the case of global statistical significance, multiple comparisons were done by Newman-Keuls t-test.

Changes in exercise parameters at 1 mm ST segment depression were only assessed in the 5 patients showing ST segment changes at the pre-implant test. In follow-up tests peak values were used for values at ST segment depression in absence of significant ST segment changes. The same approach was used for exercise parameters at angina. Data are reported as mean ± SD, unless differently indicated. A p value of < 0.05 was considered statistically significant.

Results

The main results of the study are summarized in table III. The average number of anginal episodes and sublingual nitrate consumption were considerably reduced by SCS from pre-implant to both the 1-month and last follow-up. On average, the visual analogic scale score improved from 2.1 ± 0.9 (range 1-3) to 9.0 ± 0.8 (range 1-10) ($p < 0.001$) at 1 month and was 6.4 ± 2.3 ($p < 0.01$) at the last follow-up. Moreover, tolerance of mild and moderate physical activities had significantly improved, whereas there was no significant improvement in tolerance of heavy physical activities, which were usually avoided by several patients. Furthermore, patient satisfaction for current anginal status and current treatment had also significantly improved at the two follow-up points.

When considering the effect of SCS in individual patients, at 1-month follow-up considerable benefits were observed on the frequency and severity of anginal episodes in all patients. At the last follow-up, on the oth-

Table II. Questionnaire for clinical assessment.

Question 1.	To what extent are you limited in performing usual mild physical activities (e.g., dressing, washing, walking on the level ground)?		
Question 2.	To what extent are you limited in performing moderate physical activities (e.g., walking at a brisk pace, walking uphill, climbing a flight of stairs, gardening, carrying groceries)?		
Question 3.	To what extent are you limited in performing heavy physical activities (running, jogging, moving or lifting heavy objects)?		
	Answers for questions 1-3:	severely limited	score 1
		moderately limited	score 2
		sometimes limited	score 3
		rarely limited	score 4
		not limited at all	score 5
Question 4.	To what extent are you satisfied with your current chest pain?		
Question 5.	To what extent are you satisfied with the current treatment of your chest pain?		
	Answers for questions 4-5:	not satisfied at all	score 1
		poorly satisfied	score 2
		partially satisfied	score 3
		very satisfied	score 4
		totally satisfied	score 5

Table III. Main clinical results.

	Pre-implant	1-month follow-up	Last follow-up	p
Anginal episodes/week	17.3 ± 4	0.86 ± 1.5*	2.86 ± 2.1*	< 0.001
Sublingual nitrates/week	16.3 ± 12	0.29 ± 0.8**	1.79 ± 1.2**	< 0.004
Visual analogic scale score	2.1 ± 0.9	9.0 ± 0.8*	6.4 ± 2.3*§	< 0.002
Questionnaire				
Mild activity	2.57 ± 1.4	4.43 ± 0.5*	3.71 ± 1.4**	0.006
Moderate activity	1.57 ± 0.8	3.71 ± 0.8*	2.57 ± 1.4**§	0.000
Heavy activity	1.14 ± 0.4	1.57 ± 0.5	1.43 ± 0.5	0.09
Anginal status	1.14 ± 0.4	3.86 ± 0.7*	2.57 ± 1.5*§	0.000
Treatment efficacy	1.43 ± 0.5	4.29 ± 0.5*	3.43 ± 1.3*	0.000

* $p < 0.001$ vs pre-implant; ** $p < 0.01$ vs pre-implant; § $p < 0.01$ vs 1-month follow-up.

er hand, treatment still appeared very effective in 4 out of 7 patients, as indicated by the individual visual analogic scale scores of patients shown in figure 1. Three of these 4 patients (all men) did not have to recur to physicians for angina recurrence after 2, 10 and 11 months from implantation, respectively. The fourth patient had recurrence of angina after 4 months, but reprogramming of the device was followed by a significant improvement in symptoms. Three patients, on the other hand, reported recurrence of symptoms requiring hospitalization after 3, 5 and 6 months from SCS implantation, respectively, and attempts to improve the effect of therapy, by reprogramming of the device or repositioning of the catheter, were followed only by partial improvement.

Exercise results. The results of the exercise test are shown in table IV. Angina was reported by all patients prior to SCS, by 5 patients at 1-month follow-up and by 6 patients at the last follow-up. ST segment depression occurred in 5 patients at baseline, and in 3 patients at both the 1-month and last follow-up.

SCS did not cause any significant changes in average rate-pressure product at angina and ST segment depression. However, both time to angina and time to ST segment depression were significantly improved by SCS, as was exercise duration.

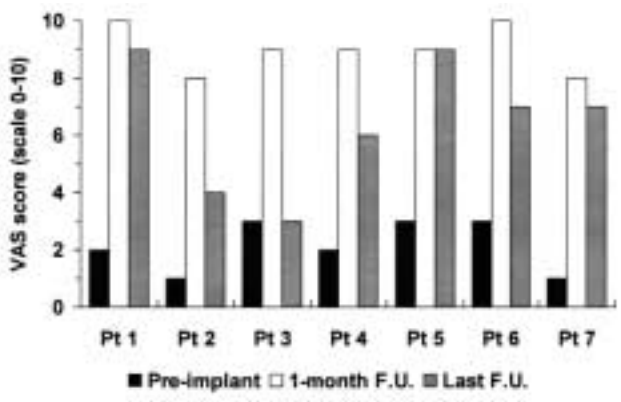

Figure 1. *Visual analogic scale (VAS) score of quality of life of individual patients prior to spinal cord stimulation device implantation, at 1-month and at an average follow-up (FU) of 11 months (see table I for the duration of follow-up of individual patients).*

Complications of spinal cord stimulation device implantation. There were no major complications related to SCS device implantation. Skin infection at the level of puncture for catheter introduction into the epidural space occurred in 1 patient, requiring explantation of the device, and reimplantation of another system after control of the infection.

Discussion

SCS has been proposed for treatment of patients with refractory angina and flow-limiting coronary stenoses, not eligible for coronary revascularization procedures[13-16]. Our data show that SCS may represent an effective treatment for patients with refractory angina pectoris and normal coronary angiography.

All 7 patients included in our study, severely affected by anginal recurrences, reported a dramatic improvement of symptoms in the first 2-4 months after SCS device implantation. Furthermore, 4 patients showed a considerable sustained improvement of symptoms and quality of life during the follow-up (up to 14-15 months in 2).

Patients with angina and normal coronary arteries have an excellent prognosis[9], but in several cases they have a bad quality of life because of frequent recurrence of anginal pain, which may heavily limit daily activities and also induce patients to retire from work[10-12]. Abnormalities in coronary microvascular function[4-6] and increased pain perception[7,8] are the most common findings in these patients and they could be related, at least in part, to alterations in cardiac adrenergic function, shown to be present in most such patients[21,22].

The beneficial effects of SCS on anginal pain could be due to a modulation of pain transmission, possibly determined by stimulation of inhibitory neurons in the

Table IV. Main exercise test results.

	Pre-implant	1-month follow-up	Last follow-up	p
Pre-exercise				
Heart rate (b/min)	77 ± 16	82 ± 19	75 ± 21	0.47
Systolic BP (mmHg)	120 ± 25	124 ± 12	122 ± 24	0.77
RPP (b/min × mmHg)	9338 ± 3721	10 175 ± 2947	9227 ± 3401	0.62
Peak exercise				
Heart rate (b/min)	128 ± 20	142 ± 25	132 ± 23	0.27
Systolic BP (mmHg)	149 ± 32	168 ± 27	153 ± 33	0.18
RPP (b/min × mmHg)	19 405 ± 5841	23 795 ± 5893	19 880 ± 4188	0.13
Exercise duration (s)	296 ± 162	461 ± 101*	406 ± 173*	0.037
ST depression				
No. patients	5	3	3	
Heart rate (b/min)	117 ± 21	120 ± 12	122 ± 26	0.75
Systolic BP (mmHg)	145 ± 29	163 ± 31	158 ± 38	0.26
RPP (b/min × mmHg)	16 929 ± 4193	19 607 ± 4045	19 072 ± 5389	0.30
Time to ST	261 ± 134	400 ± 111*	426 ± 142*	0.04
Angina				
No. patients	7	5	6	
Heart rate (b/min)	118 ± 17	132 ± 25	120 ± 27	0.46
Systolic BP (mmHg)	146 ± 35	161 ± 32	147 ± 35	0.33
RPP (b/min × mmHg)	17 738 ± 6268	21 486 ± 6675	17 525 ± 4991	0.29
Time to angina (s)	223 ± 165	397 ± 185*	403 ± 174*	0.034

BP = blood pressure; RPP = rate-pressure product. * $p < 0.05$ vs pre-implant.

posterior horns of the spinal cord[23,24]. However, an anti-ischemic effect[25-27], possibly mediated by an improvement in cardiac autonomic function[28], has also been suggested.

In fact, in agreement with previous data[17], we also observed an increase in time to angina and time to ST segment depression on exercise testing during SCS in patients with angina and normal coronary arteries, whereas there was no increase in rate-pressure product, an established indirect measure of myocardial oxygen consumption. This finding suggests that the beneficial effect observed during exercise was more likely related to a modulation of the variables responsible for myocardial oxygen consumption, than to an improvement in coronary perfusion.

Of note, differently from clinical variables, the average improvement in temporal exercise variables remained unchanged at the last follow-up. The reason for this difference is not clear. Although a training effect cannot be excluded, it seems unlikely because patients were used to exercise testing, most having undergone several tests for many years, and because the follow-up tests were performed at a significant interval from the basal test. It is also possible, on the other hand, that patients who had clinical recurrences of symptoms were subjected to exercise tests during quite a "good period" of their disease at follow-up.

In 3 of our patients anginal episodes recurred at follow-up and new attempts to obtain symptom control by adjustment of SCS therapy led to no or partial success. We were unable to identify distinctive features for these "non responders" to SCS, but there are several possible explanations for the failure of SCS treatment.

First, the initial beneficial effect of SCS could simply be a placebo effect; however, this seems unlikely, considering that the benefit persisted at 10 and 11 months in 2 patients and significant symptoms recurred only after 6 months in 1 patient. Second, tolerance of SCS may develop over time, but the long-term persistence of the benefit in 2 patients also makes this hypothesis unlikely. Third, local phenomena causing non optimal stimulation by the electrocatheter could develop in some patients, making SCS ineffective; they may include microdislodgments of the catheter, not detectable with usual X-ray control or, possibly, scar fibrous tissue formation at the site of the catheter tip, resulting in changes in the electrical field. This latter possibility is supported by the observation that all patients in whom symptoms recurred reported a sudden change in the somatic distribution of chest paresthesias during SCS, in the absence of detectable changes in the position of the catheter at spinal column X-ray.

In conclusion, our data suggest that SCS significantly improves symptoms in patients with refractory angina and normal coronary arteries, but in some the benefits may be transient. Since all patients showed an improvement in anginal episodes during temporary external device implantation and at a short follow-up, an acute beneficial effect is not necessarily predictive of a long-term therapeutic effect. Whether the recurrence of symptoms in some patients is related to changes in the features of SCS or to differences in the mechanisms of angina among patients remains to be established.

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