Clinical research

Effect of spinal cord stimulation on spontaneous and stress-induced angina and ‘ischemia-like’ ST-segment depression in patients with cardiac syndrome X

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Aims A significant number of patients with cardiac syndrome X (CSX) present frequent episodes of severe chest pain, refractory to maximal multi-drug therapy. A few, small, uncontrolled data suggested that spinal cord stimulation (SCS) may have favourable clinical benefits in these patients.

Methods and results We studied 10 CSX patients who were being treated by SCS for refractory angina pectoris for 17 ± 16 months (median 8). Patients were randomized to either continue or withdraw SCS for a period of 3 weeks and were then crossed over to the other condition for a further 3-week period. During each 3-week period patients kept a detailed diary of angina episodes occurring in the last 2 weeks of each phase. Furthermore, at the end of each 3-week period, angina status was also assessed by Seattle Angina Questionnaire (SAQ), a 0–100 visual analogue scale (VAS), and patients underwent 24-h Holter monitoring (HM) and echocardiographic dobutamine stress test (DST). Compared with the withdrawal phase, SCS reduced the number (P = 0.01), duration (P = 0.022), and severity (P = 0.011) of angina episodes, and nitrate consumption (P = 0.042). SAQ scores (P ≤ 0.013 for all) and VAS (P < 0.001) were also improved, the number of episodes of ST-segment depression on HM was decreased (P = 0.014), and time to angina (P = 0.045) and to 1 mm ST-segment depression (P = 0.04) during DST were both prolonged by SCS.

Conclusions Our data point out that SCS may be an effective form of treatment in patients with CSX suffering from frequent angina episodes significantly impairing quality of life (QOL) and refractory to maximally tolerated drug therapy.

KEYWORDS
Cardiac syndrome X;
Refractory angina;
Spinal cord stimulation;
Holter monitoring;
Dobutamine stress test

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Introduction

Several patients with cardiac syndrome X (CSX) present frequent episodes of severe chest pain, refractory to maximal multi-drug therapy, which may severely limit daily activities and impair quality of life (QOL). 1–3

Spinal cord stimulation (SCS) has initially been proposed as a form of treatment for refractory angina pectoris in patients with obstructive coronary artery disease not suitable for coronary revascularization, 4–6 and it has actually been included as a Class IIb form of treatment for refractory angina in the ACC/AHA guidelines concerning chronic stable angina. 7 Recently, SCS has also been suggested to improve anginal symptoms, QOL, and exercise test results in patients with CSX. 8–10 These results, however, were obtained in uncontrolled studies. Moreover, no previous study investigated the effects of neurostimulation on anginal symptoms and electrocardiographic alterations induced by dobutamine administration in CSX patients.

In this study we used a randomized, controlled, crossover design to acquire further evidence on the clinical effects of SCS in CSX patients.

Methods

In this study we enrolled 10 patients with angina and normal coronary arteries (three men, seven women, age 58.6 ± 5.7 years) who were being treated by SCS for angina pectoris refractory to maximally tolerated drug therapy for a variable period of time, but most for ≥6 months (Table 1). Nine patients had a history of typical CSX (predominant effort angina, positive exercise test). The last patient (Patient 3) had a history of recurrent angina with exercise-induced left bundle branch block and repeated evidence of reversible myocardial perfusion defects on radionuclide stress tests.

The internal pulse generator (IPG) device for SCS had been implanted 17 ± 16 months prior to enrolment in the study (median 8, range 1–43), because of invalidating angina episodes resistant to drug treatment.

Study protocol

A schematic view of the study protocol is illustrated in Figure 1. One week after enrolment, patients were randomized to either maintain or withdraw SCS for a period of 3 weeks. They were then crossed over to the other condition (withdrawal or active neurostimulation) for a second 3-week period. During the active phase of SCS, patients used their usual protocol of neurostimulation, which was continuous for all patients. Beta-blocking agents were withdrawn at the onset of the run-in phase of the study, whereas other drug therapy was kept unchanged throughout the whole study period.

Clinical assessment

At the onset of each study phase, patients were given a structured clinical diary in which they reported detailed information about every angina episode occurring in the last 2 weeks of the 3-week trial period, including intensity (1 to 5 scale) and duration of pain, and need for sublingual short-acting nitrates to relieve angina.

Clinical data were acquired in the last 2 weeks of each phase in order to limit possible transient psychological acute effects of withdrawal and of resumption of SCS therapy.

Angina status was also assessed by the Seattle Angina Questionnaire (SAQ) 11 at the end of each period of randomization;
the questionnaire consists of 19 multiple-choice items resulting in five scales that quantify physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. For each scale a 0 to 100 score is obtained, with higher values indicating better angina status.

Finally, patients were also asked to score their QOL using the EuroQOL visual analogue scale (VAS), graduated from 0 (worst imaginable condition) to 100 (best imaginable condition).12

**Holter monitoring**

Twenty-four-hour ambulatory electrocardiographic Holter monitoring (ECG HM) was performed using three-channel recorders (Oxford Medilog FD5, Oxford, Abingdon, UK). Bipolar chest leads CM5, CM3, and modified aVF were always monitored. All HM recordings were analysed by two expert cardiologists who were blinded to the clinical data and form of treatment, using the Oxford Medilog Excel 3.0 device. ST-segment depression was considered significant if it showed a horizontal or downsloping depression ≥1 mm after 0.08 s from the J point, lasting ≥1 min and separated from a previous episode by at least 1 min of isoelectric ST-segment.

Since we used bipolar neurostimulation in all patients, we did not come up against any problems in assessing ST-segment changes on ECG HM, as well as in 12-lead standard ECG.

**Dobutamine stress test (DST)**

All patients underwent echocardiographic DST using the imaging system Toshiba PowerVision 8000 with a 2.5 MHz probe (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands). Standard images (in para-sternal long- and short-axis views, and in apical four- and two-chamber views) were displayed in real time and recorded on a high definition 0.5 in SVHS cassette recorder. A complete cross-sectional examination was done at baseline. During continuous echocardiographic monitoring, an intravenous infusion of dobutamine (5 μg/kg/min) was started. Dobutamine infusion was stopped in cases of intolerable angina, hypertensive response (blood pressure ≥240/140 mmHg), complex ventricular arrhythmias, or any other potentially dangerous clinical condition. ST-segment changes did not constitute a criterion to stop dobutamine infusion. Echocardiographic DST images were interpreted by two experienced echocardiographers who were blinded to the clinical data and form of treatment. Discrepancies were resolved by consensus. Left ventricular end-diastolic and end-systolic volumes were measured using the modified biplane Simpson’s algorithm from apical four- and two-chamber views, and left ventricular ejection fraction was calculated.

Wall motion analysis was performed using a 16-segment model of the left ventricle.13 Particular attention was paid to systolic thickening in the central portion of each segment. For each segment, wall motion was scored as 1 (normal), 2 (hypokinetic), 3 (akinetico), or 4 (dyskinetic). The left ventricular wall motion score index (wall motion score/16) was calculated at baseline and during DST.

**Table 2 Results of clinical assessment**

<table>
<thead>
<tr>
<th></th>
<th>SCS-OFF</th>
<th>SCS-ON</th>
<th>Difference (95% CI)</th>
<th>P*</th>
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</thead>
<tbody>
<tr>
<td>Structured diary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina episodes/week</td>
<td>38 ± 27</td>
<td>10 ± 7</td>
<td>−23</td>
<td>0.010</td>
</tr>
<tr>
<td>(33, 2–78)</td>
<td>(11, 0–20)</td>
<td></td>
<td>(−5.8, −40.4)</td>
<td></td>
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<tr>
<td>Angina episodes duration (min)</td>
<td>22 ± 18</td>
<td>12 ± 15</td>
<td>−10.6</td>
<td>0.022</td>
</tr>
<tr>
<td>(16, 3–56)</td>
<td>(7, 0–48)</td>
<td></td>
<td>(−2.7, −18.4)</td>
<td></td>
</tr>
<tr>
<td>Angina episodes intensity</td>
<td>4.0 ± 1</td>
<td>2.0 ± 1</td>
<td>−1.4</td>
<td>0.011</td>
</tr>
<tr>
<td>(3.7, 2.0–4.5)</td>
<td>(2.2, 0–3.5)</td>
<td></td>
<td>(−0.6, −2.1)</td>
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</tr>
<tr>
<td>Sublingual nitrates/week</td>
<td>6.8 ± 7.7</td>
<td>0.4 ± 1</td>
<td>−6.6</td>
<td>0.042</td>
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<tr>
<td>(3.5, 1.0–23.0)</td>
<td>(0, 0–3.0)</td>
<td></td>
<td>(−1.5, −11.7)</td>
<td></td>
</tr>
<tr>
<td>Angina stayle questionnaire</td>
<td>34.5 ± 13.9</td>
<td>57.2 ± 12.1</td>
<td>22.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical limitation (35.7, 14.3–56.7)</td>
<td>(57.1, 42.9–80.0)</td>
<td></td>
<td>(13.4, 31.9)</td>
<td></td>
</tr>
<tr>
<td>Angina stability (17.0 ± 12.5)</td>
<td>72 ± 13.9</td>
<td>55.0</td>
<td>&lt;0.001</td>
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<tr>
<td>(10.0, 10.0–40.0)</td>
<td>(80.0, 40.0–80.0)</td>
<td></td>
<td>(41.4, 68.6)</td>
<td></td>
</tr>
<tr>
<td>Angina frequency (31.5 ± 10.8)</td>
<td>67.6 ± 10.6</td>
<td>36.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>(33.3, 16.7–50.0)</td>
<td>(66.7, 70.0–83.3)</td>
<td></td>
<td>(25.5, 46.7)</td>
<td></td>
</tr>
<tr>
<td>Treatment satisfaction (53.3 ± 9.7)</td>
<td>65.7 ± 8.0</td>
<td>12.4</td>
<td>0.013</td>
<td></td>
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<tr>
<td>(54.7, 38.1–66.7)</td>
<td>(64.3, 52.4–76.2)</td>
<td></td>
<td>(3.3, 21.5)</td>
<td></td>
</tr>
<tr>
<td>Disease perception (41.3 ± 10.3)</td>
<td>70.0 ± 10.5</td>
<td>28.7</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>(40.0, 26.7–60.0)</td>
<td>(70.0, 50.0–80.0)</td>
<td></td>
<td>(18.5, 38.8)</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>35 ± 8</td>
<td>75 ± 9</td>
<td>34.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual analogue scale (30, 20–50)</td>
<td>(80, 60–85)</td>
<td></td>
<td>(20.3, 48.6)</td>
<td></td>
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</tbody>
</table>

Values as mean ± SD (median, range).

*P* values corrected for sequence (SCS-OFF/SCS-ON vs. SCS-ON/SCS-OFF) and week (first vs. second week) of treatment for diary data and for sequence of treatment for the other data.
SCS indication and implantation

Details about the implant technique of an SCS device have been described elsewhere. Briefly, patients first undergo a trial of temporary SCS. Under sterile conditions and local anaesthesia, the epidural space is punctured at the level of T6 and a quadripolar electrode catheter is introduced and advanced under X-ray control in the epidural space. The adequate position of the electrode catheter corresponds to that where SCS causes paraesthesia in the chest area where spontaneous anginal pain is referred. The ideal stimulation parameters are then identified for the patient and the electrode catheter is connected to an external portable pulse generator. In cases of clinical benefits during a trial period of 2–3 weeks, according to patients’ and physicians’ judgment, an IPG (Irel-2 or Irel-3, Medtronic Italia, Milan, Italy) is placed in a subcutaneous pocket in the abdomen, connecting the electrode by subcutaneous tunnelling.

All patients included in this study used a continuous SCS protocol during the active phase (SCS-ON) of the study, which was also their usual protocol of stimulation.

Statistics

The Kolmogorov–Smirnov test showed that differences of values of each continuous variable between the two phases of the study (SCS-ON vs. SCS-OFF) did not differ significantly from a normal distribution (P > 0.15 for all). Thus, the effect of treatment (SCS-ON vs. SCS-OFF) on the number, intensity, and duration of angina episodes and on nitroglycerin consumption was assessed by analysis of variance (ANOVA) with a repeated measure design, with results adjusted in a multivariable model for both the sequence of treatment (SCS-ON/SCS-OFF vs. SCS-OFF/SCS-ON) and the week of assessment (first vs. second week), which were also included as random factors in the model to take into account possible intra-group correlations.

The same statistical approach was applied to evaluate the effect of treatment on all other endpoint variables which were assessed at the end of each of the two phases of the study, adjusting the results for the sequence of treatment (SCS-ON/SCS-OFF vs. SCS-OFF/SCS-ON) in a multivariable model.

For purposes of analysis, the duration and pain severity rates of angina episodes occurring during the 2-week study periods were averaged for each patient. Peak values during DST were used for values to ST-depression and/or angina in case when these clinical endpoints were not induced. The McNemar test was applied to compare proportions between the two protocol phases.

Data are reported as mean ± SD, unless differently indicated. A two-tailed P-value < 0.05 was always required for statistical significance. All P-values reported in the text and in tables are adjusted for the sequence of treatment and, when applicable, for the week of assessment.

Results

Clinical assessment

The results of clinical findings are summarized in Table 2. The number of chest pain episodes during the 2-week periods, as derived from the structured patient diaries, was 38 ± 27 (median 33) during the SCS-OFF period compared with 10 ± 7 (median 11) during SCS-ON period (Figure 2), for a mean reduction of 23.1 episodes (95% confidence interval (CI), 5.8–40.4, P = 0.01). Furthermore, both duration (P = 0.022) and intensity (P = 0.011) of angina episodes, as well as short-acting nitrate consumption (P = 0.042), were all significantly reduced during the SCS-ON period.

SAQ evaluation showed significant improvement of scores in all five scales during the SCS-ON phase. Finally, QOL, measured by the VAS scale, was 35 ± 8 (median 30) with SCS-OFF compared with 75 ± 9 (median 80) with SCS-ON (P < 0.001, Figure 3).

Holter monitoring

The patient with left bundle branch block (LBBB) was excluded from HM analyses. The episodes of ST-segment depression were 2.5 ± 2.2 (median 3.5) during the SCS-OFF period compared with 0.6 ± 1.3 (median 0) during the SCS-ON period, with a mean reduction of 1.9 episodes/patients (95% CI, 0.5–3.3, P = 0.014). Furthermore, the total time of ischaemia in the 24 h was 28 ± 39 min (median 6) with SCS-OFF compared with 8 ± 21 min (median 0) with SCS-ON, with a mean...
reduction of 20.1 min/24 h (95% CI, −43.4 to +3.2, \( P = 0.08 \)).

**Dobutamine stress test**

DST results are summarized in Table 3. Patient 3 developed LBBB during the test and was excluded from ST-segment analyses. Furthermore, Patient 6 refused to undergo DST without SCS, and therefore he was excluded from DST analyses.

DST duration and heart rate and blood pressure at rest and at peak DST did not differ between the two phases. Angina was induced by DST in eight and in five patients with SCS-OFF and SCS-ON, respectively (\( P = 0.20 \)). Time to angina was significantly increased by SCS from 8.2 ± 5.0 to 12.9 ± 2.7 min (+4.7 min; 95% CI, 0.12–9.2; \( P = 0.045 \)). Furthermore, angina duration tended to be longer (\( P = 0.06 \)) and heart rate at angina higher (\( P = 0.11 \)) during SCS-ON.

ST-segment depression occurred in all eight patients with SCS-OFF, but in only two patients with SCS-ON (\( P = 0.02 \)). Time to ST-depression was significantly prolonged by SCS from 11 ± 3 to 15 ± 2 min (+3 min; 95% CI, 0.1–5.9; \( P = 0.04 \)), and there was also a tendency to a higher heart rate at 1 mm ST (\( P = 0.07 \)) with SCS-ON. No patient developed LV wall motion abnormalities during DST on either study phase.

**Discussion**

Our prospective controlled data show that SCS had significant effects on daily-life anginal symptoms in patients with CSX who had received the treatment because of refractory angina pectoris. Furthermore, SCS was also found to improve anginal pain and ischaemia-like ST-segment depression induced by DST, as well as the number of episodes of ST-segment depression during 24-h HM.

**Clinical effects of SCS**

Patients with angina and normal coronary arteries have an excellent prognosis, but a number of patients have a very poor QOL because of frequent, recurrent anginal pain episodes, which may heavily limit daily activities and result in refractory to maximally tolerated multidrug therapy.\(^1\)\(^-\)\(^3\)

After several studies suggested that SCS may be an effective and safe treatment for refractory angina pectoris in patients with obstructive coronary stenoses, a few recent uncontrolled studies suggested that SCS may represent an effective treatment for refractory angina also in patients with cardiac syndrome X.\(^8\)\(^-\)\(^10\)

In this study, we give evidence of favourable clinical effects of SCS in CSX patients using a controlled,

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In this study, we give evidence of favourable clinical effects of SCS in CSX patients using a controlled,
randomized, cross-over design including a phase of active treatment and a phase of therapy withdrawal. In our patients, SCS considerably reduced daily-life anginal symptoms, according to structured diary reports, in which detailed information on duration and severity of anginal symptoms, and use of short-acting nitrates to relieve chest pain were also reported. Furthermore, SCS was associated with higher scores of a well validated structured questionnaire and of a VAS assessing their anginal status and QOL. Notably, SCS was also able to reduce angina severity induced by intravenous dobutamine administration.

Mechanisms of SCS in CSX

Abnormalities in coronary microvascular function and increased cardiac pain perception appear to be the two major mechanisms contributing to angina chest pain in CSX patients and they could both be related, at least in part, to alterations in cardiac adrenergic function.

The beneficial effects of SCS on anginal pain might be due to the modulation of pain transmission, possibly determined by stimulation of inhibitory neurons in the posterior horns of the spinal cord. Alternatively, in syndrome X, SCS might reduce pain perception through modulation of an abnormal central pain processing of cardiac stimuli. Indeed, Rosen et al. showed evidence of activation of the right anterior insula cortex during angina induced by the dobutamine stress test, in the absence of left ventricular contractile abnormalities, suggesting that syndrome X patients can present an enhanced cortical activity facilitating the transmission to the cortex of pain stimuli through a 'top-down' process.

However, an anti-ischaemic effect, possibly mediated by an improvement of cardiac autonomic function, might play an additional beneficial role. In uncontrolled studies, SCS was indeed found to reduce stress-induced ST-segment depression and reversible myocardial perfusion defects in CSX patients, and transcutaneous electrical neurostimulation, a technique comparable to SCS, was found to improve coronary flow reserve.

In this controlled study we observed a significant reduction of 'ischaemia-like' ST-segment changes during DST, despite a similar maximal dose of the drug and maximal rate pressure product during the test, and the number of episodes of transient ST-segment depression detected during HM, thus supporting the notion that prevention of angina might be, at least in part, mediated by prevention of microvascular dysfunction.

In agreement with previous reports, no LV dysfunction was induced by dobutamine infusion in our patients, despite angina and ST depression. This finding has often been taken as a clue against the presence of myocardial ischaemia in CSX patients. Yet, it has been proposed that patchily distributed myocardial ischaemia does not necessarily translate into abnormal regional left ventricular function even in the presence of objective evidence of scattered myocardial ischaemic areas.

In conclusion, our data indicate that SCS may be an effective form of treatment in patients with CSX suffering from frequent angina episodes significantly impairing QOL and refractory to maximally tolerated drug therapy.

Limitations of the study

A limitation of this study, as of other studies assessing the role of SCS on angina, is the impossibility of obtaining a placebo control, due to the need to induce chest parasthesia to verify the presence of active neurostimulation. Thus a placebo effect of treatment cannot be completely excluded. However, it seems unlikely that a mere placebo effect totally accounted for the clinical benefits from SCS in this study, when considering that all clinical and diagnostic variables assessed in this study were consistently improved by SCS, including ECG abnormalities during DST and Holter monitoring, which were assessed by blinded investigators and were less likely to be influenced by a placebo effect in patients. Furthermore, the fact that withdrawal of SCS after a long-term period of therapy in most of our patients was associated with a significant recurrence of symptoms also suggests that a placebo effect was unlikely to account for all symptomatic benefits, as this latter usually decreases significantly over time.

We should also be aware that we usually only implant the SCS device in patients who show significant clinical benefits during a 2- to 3-week trial period with a temporary external neurostimulator; thus only patients already judged as 'responders' at short-term follow-up were included in this study and, therefore, our results must mainly be intended as a clue to continuing efficacy over time of SCS in patients who were previously found to have benefits from the therapy.

References

Spinal cord stimulation in patients with cardiac syndrome X