Spinal Cord Stimulation in Diabetic Lower Limb Critical Ischaemia: Transcutaneous Oxygen Measurement as Predictor for Treatment Success

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Objectives: to evaluate whether transcutaneous oxygen tension (TcpO2) measurements could be used as a specific prognostic parameter in selecting diabetic patients for permanent device implantation.

Methods: sixty consecutive diabetic patients (28 with autonomic neuropathy), classified as Fontaine stage III or IV, underwent spinal cord stimulation (SCS) for ischaemic pain, after failed conservative or surgical treatment. Pedal TcpO2 on the dorsum of the foot and ankle-pressure Doppler measurements were performed before, and 2 and 4 weeks after implantation.

Results: limb salvage and good pain relief were achieved in 35 patients, while in 12 partial pain relief and limb salvage for at least 6 months were obtained. In 13 patients the method failed and the ischaemic limbs were amputated. Only 3 of the 28 patients with neuropathy had any long-term benefit. Limb salvage was achieved in those patients with a significant increase in TcpO2 within 2 weeks of stimulation. The stage of the neuropathy was inversely related to the success of SCS therapy. The ankle-brachial pressure index (ABPI) did not change after stimulation.

Conclusions: diabetic patients with significant increase of TcpO2 and pain relief during a 2-week test period may be successfully treated by long-term SCS unless they have advanced autonomic neuropathy.

Key Words: Spinal cord stimulation; Diabetes; Neuropathy; Lower-limb ischaemia; Transcutaneous oxygen tension (TcpO2).

Introduction

Spinal cord stimulation (SCS) seems an established treatment for patients with peripheral arterial occlusive disease (PAOD).1–5 Initially, the method was used to manage patients with chronic intractable pain,7 or to improve motor function in patients with partial spinal cord lesions.7 SCS has also been used successfully to manage diabetic patients with advanced peripheral neuropathic pain.8 Peripheral neuropathy is a common long-term complication of diabetes9 and about 7.5% of the diabetic population have painful neuropathic symptoms, mainly affecting the lower limb.9

SCS has beneficial effects on peripheral blood flow of the lower limbs, with improvement of walking ability, healing of trophic lesions, increase in cutaneous temperature and reduction or disappearance of skin discoloration.10 Non-invasive (Doppler, rheology, plethysmography, thermography) and invasive (201Ti muscle scintigraphy, xenon clearance) techniques have been applied in the effort to quantify the SCS effect on blood flow. Transcutaneous oxygen tension (TcpO2) measured by Clark’s electrode seems to be a reliable non-invasive method of tissue perfusion, useful for assessing PAOD.11–18 TcpO2 measurement has already been used as a predictive parameter to evaluate ulcer-healing in end-stage vascular patients treated with SCS.11

The efficacy of SCS in diabetic patients with severe lower-limb ischaemia and peripheral neuropathy has not, to our knowledge, been investigated before. The purpose of this prospective study was to investigate whether the TcpO2 measurements before and during the SCS treatment in diabetic patients could be used to predict therapy success and to select patients for permanent device implantation.

Patients and Methods

Sixty consecutive insulin-dependent type I diabetic patients, 35 men, 25 women (28 with autonomic neuropathy), mean age 60 years (range 46–75) with non-reconstructible PAOD of the lower limbs and ischaemic...
pains were selected, by an independent vascular surgeon, from the outpatients attending our institution. The median duration of their diabetes was 22 (range 15–40) years. Patients underwent a full history and examination, which included the assessment of neuropathic symptoms and deficit scores. Local exclusion criteria included unmeasurable ankle pressure due to non-compressible calcified arteries, deep ulceration, osteomyelitis, wet gangrenous lesions >3 cm$^2$, peripheral neuropathy due to other causes (e.g. alcohol) and inability to perform selective angiography. Systemic exclusions included a life-expectancy of less than 18 months due to concomitant diseases, significant heart failure, severe pulmonary or renal insufficiency, unstable angina, a non-cooperative patient and spinal disease.

The duration of vascular history ranged from 6 months to more than 6 years. Prior to implantation, all patients had received conservative treatment (pentoxiphylline, antiplatelet agents, defibrotide, bufomedil), including management of risk factors, pain therapy (tricyclic antidepressants, non-steroid anti-inflammatories, or dihydrocodeine plus paracetamol) and surgical foot care.

Intra-arterial subtraction or intraoperative selective arteriograms were obtained from all patients and showed occluded distal vessels, unsuitable for a bypass procedure or angioplasty. If only ankle or foot arteries were available to bypass, but autogenous vein unavailable, the patient was regarded as non-reconstructible. Failed bypass-procedures in the involved leg were noted in 27 patients, while, in 24, exploration of tibial or/and popliteal arteries demonstrated advanced diabetic atherosclerotic disease. Five patients had a contralateral amputation. Twenty diabetic patients Fontaine’s stage III (7 with neuropathy) with ischaemic rest pain of at least two months’ duration, 20 diabetic patients stage IV (9 with neuropathy) with ulcers <3 cm$^2$ and 20 (12 with neuropathy) with trophic lesions >3 cm$^2$ with dry gangrene of one or two toes, were included in the present study and were treated with SCS. All patients gave informed consent to participate in the study.

**Assessment of autonomic neuropathy**

Autonomic neuropathy was evaluated using the cardiovascular autonomic neuropathy tests according to Ewing and Clarke.$^{19}$ These tests give a practical guide that we consider reliable, reproducible, simple and non-invasive. The total time required was about 20 min and the equipment needed includes a sphygmonometer, an electrocardiograph, an aneroid manometer, a handgrip dynamometer, plus couch and chair. The flow plan, in order, for performing tests of cardiovascular autonomic function was the following:

(A) Tests reflecting cardiac parasympathetic damage;

1. Heart-rate response to Valsalva manoeuvre (patient position: sitting);
2. Heart-rate (R-R interval) variation during deep breathing (sitting);
3. Immediate heart-rate response to standing (lying 5–10 min to standing).

(B) Tests reflecting cardiac sympathetic damage;

4. Blood-pressure response to standing (lying 5–10 min to standing) and

Orthostatic hypotension was defined as a drop of at least 20 mmHg in systolic or diastolic blood pressure upon standing. All the subjects were carefully instructed before test start. The neuropathic score, ranging from 0 to 5, was calculated assigning zero for normal values, one point for every abnormal test and half a point for borderline value test. Early neuropathy was defined as an abnormality of one of the three tests of parasympathetic function, and definite neuropathy corresponded to two or more abnormal parasympathetic tests with or without abnormal sympathetic tests. The 28 patients with diabetic neuropathy had one or more complications of diabetes mellitus such as retinopathy, peripheral neuropathy and nephropathy. In 15 patients early autonomic neuropathy (1–1.5 points in five patients and 2 in 10 patients) and in 13 patients definite autonomic neuropathy combined with sympathetic damage (from 2.5 to 3.5) were found.

**Transcutaneous oxygen tension (TcpO$_2$) protocol**

TcpO$_2$ (in mmHg) at the dorsum of the foot was measured using the Microspan Combo TcpO$_2$/pCO$_2$ monitoring system (Biochem International Inc., WI, U.S.A.), to evaluate the reduction in skin circulation. The severity of PAOD was accurately determined using the TcpO$_2$, which is known to correlate with the clinical stage of the disease.$^{12-18}$ The TcpO$_2$ was measured by Clark’s electrode and seems to be a reliable non-invasive index of tissue perfusion, useful for assessing peripheral arterial occlusive disease.$^{12-14}$ The electrode, attached to the dorsum of the foot, was warmed to 44°C, causing maximum vasodilatation of the underlying skin circulation and was allowed to stabilise on the skin for 15 minutes before the measurement was taken.$^{13,15}$ TcpO$_2$ measurements were performed with the transducer.
placed at the same site, marking the skin with permanent ink, at the dorsum of the foot before, 2 and 4 weeks after SCS device implantation, with the patient in a supine position in a controlled room temperature (25 °C), after a rest lasting at least 30 min.

Systolic arterial ankle and toe pressures (in mmHg) were measured using bi-directional Doppler ultrasoundography in the posterior tibial and pedal arteries, respectively and then in the toe artery. The ABPI was determined by dividing systolic ankle pressure by systolic brachial artery pressure.

**Clinical improvement and pain relief evaluation**

Analysis of patient pain relief and clinical improvement were evaluated before implantation, then 2 and 4 weeks after. Thereafter patients were seen every three months for a minimum of 18 months. The presence of comfortable paraesthesia instead of pain, feelings of warmth, reduction in size of the trophic lesions, improvement of the pain-free walking interval under standard conditions (treadmill), an uninterrupted sleep, were evaluated. The pain relief and the method success were based on the intake of analgesic drugs (minor or narcotics) and patients' self-evaluation using a visual analogue scale (VAS). Success was defined as pain relief of >75% and limb salvage for at least 18 months with only minor amputation (toe). Partial success was defined as limb salvage for at least 6 months associated with pain relief evaluated between 50% and 70%. Failure was defined as pain relief evaluated as <50% and limb loss within the first 6 months.

**Implantation technique**

A quadripolar electrode (Pisces-Quad 3487A, Medtronic, Minneapolis, MN, U.S.A.) was placed in the epidural space by percutaneous lumbar puncture between L2 and L3 or L3 and L4. The electrode was positioned in the midline in most cases, under fluoroscopic guidance up to level T10–11. Connecting a portable stimulator to the electrode allowed intraoperative test stimulation producing comfortable paraesthesias in the painful foot or limb. The clinical effects were tested during a 2-week trial period and in the cases where the patient had a significant pain relief, an implantable pulse generator (Itrel II IPG, Medtronic Inc. Minneapolis, U.S.A.) was placed in an abdominal subcutaneous pocket. Various settings of the active quadripolar extremities of the electrode were studied to evaluate the most appropriate combination for pain relief. The presence of paraesthesia and a feeling of warmth in the painful area indicated optimal stimulation. The setting parameters were pulse amplitude between 1.0 and 5.0 V, frequency between 40 and 120 pps and pulse width from 150 to 450 ms. Stimulation was continuous, lasting 24 h a day to obtain the maximum information on the clinical outcome. During follow-up the parameters of stimulation can be reset with the help of a portable computer, according to the patient clinical status.

**Statistical analysis**

The TcpO2 data were calculated as mean values and standard deviations. Paired t-tests with appropriate correction to reduce type-I errors and Fisher's exact test were applied. A p value of <0.05 was considered statistically significant.

**Results**

All patients experienced some pain relief during the test stimulation period. Among the 20 patients with rest pain, limb salvage for more than 18 months and pain relief >75% were obtained in 15. Partial success was achieved in four patients (pain relief >50% and limb salvage for at least 6 months). In one patient SCS failed to salvage the limb and the patient underwent major amputation within 6 months (Table 1). Among the 20 patients with trophic lesions >3 cm² (dry gangrene), limb salvage for more than 18 months and pain relief >75% were obtained in eight patients, while in four patients partial success with pain relief >50% and limb salvage for at least 6 months (mean 9 months range 6–12) was achieved. After this period the ischaemic pain recurred and major amputation was unavoidable. The other eight patients initially achieved minor pain relief <50% but within 2 months additional analgesic medication was necessary. Within 6 months all these patients underwent major amputation (Table 1).

TcpO2 foot values, within the first 2 weeks of the test period, increased from 21.4 s.d. 5.7 mmHg to 31.5 s.d. 5.4 mmHg (p = 0.030) in the patients with rest pain and limb salvage. In the patients with trophic lesions...
Table 1. Pain relief and clinical results after SCS treatment. The diabetic patients with therapy success (A) achieved a pain relief >75% and long-term limb salvage, while those with partial success (B) achieved a pain control >50% without or without intake of minor analgesics and limb salvage for at least 6 months. Patients with SCS failure (C) underwent major amputation after a short time-period from the implantation (<6 months).

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<th>A</th>
<th>B</th>
<th>C</th>
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<tbody>
<tr>
<td>Rest pain, 20 patients</td>
<td>15</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Trophic lesions &lt;3 cm², 20 patients</td>
<td>12</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Trophic lesions &gt;3 cm², 20 patients</td>
<td>8</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Overall series, 60 patients</td>
<td>35</td>
<td>12</td>
<td>13</td>
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<3 cm², and limb salvage, TcpO₂ mean foot values, showed an average improvement from 15.1 s.d. 6.4 to 22.0 s.d. 5.1 mmHg (p = 0.030) (Table 2). In patients with trophic lesions >3 cm² (dry gangrene) and limb salvage, after 2 weeks of test period, TcpO₂ increased from 12.1 s.d. 5.1 to 17.9 s.d. 4.7 mmHg (p = 0.025) (Table 2). Major changes in TcpO₂ values were achieved within the first 2 weeks after temporary implantation, while a further, but minimal, increase of TcpO₂ after 4 weeks was revealed in the diabetic patients with limb salvage, compared to the values obtained before treatment. Changes of TcpO₂ in all diabetic amputees, where SCS failed to control the ischaemic pain and to save the limb, were not significant either after 2 or 4 weeks from the device implantation (Table 3). No significant changes were observed in the ABPI or toe-pressure values before permanent implantation (test period) and during the follow-up.

The patients with long-term SCS success had an impressive clinical course, with comfortable paraesthesia instead of pain, feelings of warmth, improved pain-free walking interval under standard conditions (treadmill), reduction in size of the trophic lesions, and undisturbed sleep without requiring analgesics. These patients were mainly those with rest pain without neuropathy. The 25 patients with only partial success or failure of the method were among the 28 patients with neuropathy (early or definite) as reported in Table 4. In only three patients (two with rest pain and one with trophic lesions <3 cm²) with early neuropathy did SCS therapy have a long-term positive effect. Patients with early neuropathy had a better outcome compared to those with definite neuropathy (p = 0.008) (Table 4). Eleven of 13 patients where the method failed to save the limb within the first 6 months had definite (combined) neuropathy (p<0.001). The overall success and partial success rate for SCS therapy was 78%, while in 22% the method failed.

**Discussion**

Angiopathy and autonomic neuropathy is a common long-term diabetic complication.²⁰,²¹ The pain varies from mild paraesthesia in a few toes to severe unremitting pain in both legs.⁵,²² Night-time exacerbation of the pain plus contact hypersensitivity to bedclothes results in loss of sleep.⁶ The cause of chronic sensory–motor diabetic neuropathy or indeed neuropathic pain is not known although metabolic and microvascular systems may be involved.²³,²⁴ Whilst the search for potential therapeutic agents to halt or reverse the neuropathic process continues,²⁴ current treatment is largely aimed at pain relief. Some authors have demonstrated that, in patients with PAOD, SCS recruits small capillaries not ordinarily perfused, enhancing skin blood flow, improvements that may explain the beneficial clinical effects experienced by these patients.¹²,²⁶ However, their data and the use of SCS in the treatment of POAD were recently criticised,

<table>
<thead>
<tr>
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<th>Before treatment</th>
<th>After 2 weeks</th>
<th>p Value</th>
<th>After 4 weeks</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Rest pain, 19 patients</td>
<td>21.4 (5.7)</td>
<td>31.5 (5.4)</td>
<td>=0.030</td>
<td>32.4 (6.4)</td>
<td>=0.025</td>
</tr>
<tr>
<td>Trophic lesions &lt;3 cm², 16 patients</td>
<td>15.1 (6.4)</td>
<td>22.0 (5.1)</td>
<td>=0.030</td>
<td>24.2 (6.2)</td>
<td>=0.025</td>
</tr>
<tr>
<td>Trophic lesions &gt;3 cm², 12 patients</td>
<td>12.1 (5.1)</td>
<td>17.9 (4.7)</td>
<td>=0.025</td>
<td>20.7 (5.3)</td>
<td>=0.020</td>
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<tr>
<th></th>
<th>Before treatment</th>
<th>After 2 weeks</th>
<th>p Value</th>
<th>After 4 weeks</th>
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<tbody>
<tr>
<td>Rest pain, 1 patient</td>
<td>18.1</td>
<td>19.4</td>
<td>NS*</td>
<td>20.2</td>
<td>NS</td>
</tr>
<tr>
<td>Trophic lesions &lt;3 cm², 4 patients</td>
<td>14.7 (5.1)</td>
<td>15.4 (4.8)</td>
<td>NS</td>
<td>16.1 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Trophic lesions &gt;3 cm², 8 patients</td>
<td>9.1 (5.6)</td>
<td>9.6 (4.9)</td>
<td>NS</td>
<td>10.8 (5.8)</td>
<td>NS</td>
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* Non-significant.
Table 4. Outcome of the SCS treatment in 28* PAOD diabetic patients according to the neuropathic stage of the diabetic disease. Partial success was achieved in 10 patients with early neuropathy vs. 2 with definite (p=0.008)** while in 11 patients with definite neuropathy vs. two with early the method failed (p<0.001)**

<table>
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<tr>
<th>Partial success</th>
<th>Failure</th>
<th>Partial success</th>
<th>Failure</th>
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<tbody>
<tr>
<td>Rest pain (7 patients)*</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Trophic lesions &lt;3 cm² (9 patients)*</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Trophic lesions &gt;3 cm² (12 patients)</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total (25 patients)*</td>
<td>10</td>
<td>2</td>
<td>2</td>
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* In two rest-pain diabetic patients and one with trophic lesions <3 cm² with early autonomic neuropathy, SCS therapy success was achieved.
** Fisher’s exact test.

because the indications for SCS implantation have not been defined. In critical limb ischaemia, the aim of the SCS should be not only the effective analgesia (which nowadays might be obtained by other less expensive techniques), but also to obtain limb salvage.

This study investigated for the first time whether in patients with PAOD and diabetes, the severity of the autonomic neuropathy should be assessed before a decision for permanent implantation is taken. Applying the simple tests allow clinicians to give some diagnostic precision to the autonomic abnormalities presented in 20–40% of the diabetic population.22–28 The relief of ischaemic pain with SCS is probably secondary to the positive effects on microcirculation rather than vice versa. Pain relief may also result in attenuation of sympathetic activity with vasodilatation, leading to further pain relief. The inhibitory effects of SCS on the transmission of nociceptive impulses may be exerted segmentally29 in the spinal cord and/or at a supraspinal level.30 Clinical observations indicate that the mechanisms involved in the stimulation-induced relief of ischaemic pain are different from those related to relief of other types of pain.30 Indeed, nociceptive pain is more resistant to SCS and significant pain relief is almost never obtained before a couple of days, while neuropathic pain of peripheral origin responds well and directly to SCS.31,32 Both components, nociceptive as well as neuropathic, are present in ischaemic pain. Several authors have postulated that the principal factor in the relief of ischaemic pain is the inhibition of the pain signal per se, leading to a decrease in sympathetic activity and improved skin microcirculation.31–35 Another hypothesis is that stimulation depresses autonomic sympathetic activity and affects30,34 vasomotor tone by improving cutaneous circulation in ischaemic limb and could be assessed by the TcpO₂ measurement.12–18

Assessment of TcpO₂ measurement, a non-invasive method, is reliable and suitable for evaluation of skin circulation and has been chosen to evaluate microcirculatory changes induced by SCS in many studies.12–16 The accuracy of the method in selecting patients with severe PAOD is over 80%,13,15 while authors report a positive predictive value of 77% in the detection of ischaemia, when a cut-off value of 30 mmHg was applied as in our series of patients.18 The TcpO₂ changes related to an increase in skin perfusion, are not a result of improved arterial inflow.1,35 SCS has no effect on macrocirculation,31,32 as demonstrated by the absence of ABPI modifications after stimulation. The feeling of warmth and paraesthesia caused by SCS was probably related to the increased TcpO₂ due to amelioration of the microcirculation.

In diabetic patients with definite neuropathy the vasomotor tone is already affected.21,24,27,28 Indeed, in our study these PAOD patients achieved minimal TcpO₂ changes before and after SCS treatment, despite the relief of the neuropathic pain, which was always obtained. The diabetic patients with neuropathy generally had a worse course after SCS treatment that was inversely related to the stage of neuropathy. During the test stimulation all implanted patients noted immediate significant pain relief, while only those with limb salvage achieved significant increase of TcpO₂ value following stimulation. It is our opinion that PAOD diabetic patients with additional autonomic neuropathy, without significant increase of TcpO₂ after 2 weeks of the testing period, should be excluded from permanent device implantation for reasons of lack of long-term success and cost effectiveness.

All diabetic patients who benefited from SCS had a significant increase of TcpO₂ within the first 2 weeks of the temporary implantation, suggesting that this time is appropriate as testing period. The success of the therapy and limb salvage depends on the obtained differences of TcpO₂ values before and after implantation rather than the stage of the disease. Indeed, patients with partial success or failure of the method even with high initial value of TcpO₂ but with minimal change after implantation, whatever the stage of the disease, had amputation within 6 months after SCS therapy. The sympathetic activity in these cases is probably depressed and the vasomotor tone and the
vascular compliance are already damaged. Therefore SCS therapy has little or nothing to contribute. We excluded patients with non-measurable ankle pressure due to non-compressible calcified arteries. Even in absence of advanced neuropathy the vascular compliance and the microcirculation in these patients are affected by the advanced calcified process and are likely to have poor results after SCS therapy.

In conclusion, changes in TcpO2 during the test period seems to correlate with the degree of pain relief from SCS therapy in diabetic patients, perhaps indicating preservation of certain autonomic mechanisms that produce peripheral vasodilatation in response to SCS. The long-term success of SCS in PAOD patients with diabetes is inversely related to the stage of autonomic neuropathy. Diabetics with PAOD and severe autonomic neuropathy and those without an increase of TcpO2 in the test period should be excluded from permanent device implantation, on the basis of poor long-term results and cost.

References