Pain Relief in Complex Regional Pain Syndrome due to Spinal Cord Stimulation Does Not Depend on Vasodilation

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Background: Spinal cord stimulation (SCS) is known to relieve pain in patients with complex regional pain syndrome (CRPS) and, in general, to cause vasodilation. The vasodilatory effect of SCS is hypothesized to be secondary to inhibition of sympathetically mediated vasoconstriction, or through antidromic impulses resulting in release of vasoactive substances. The aim of the present study was to assess whether pain relief in CRPS after SCS is, in fact, dependent on vasodilation. In addition, we tried to determine which of the potential mechanisms may cause the vasodilatory effect that is generally found after SCS.

Methods: Twenty-four of 36 patients with unilateral CRPS responded to the test of SCS. Twenty-two of these 24 responders (hand, n = 14; foot, n = 8) who had undergone previous sympathectomy were enrolled for the study. In addition, 20 control subjects (10 controls for each extremity) were studied. By means of laser Doppler flowmetry, the skin microcirculation of the patients was measured bilaterally while the SCS system was switched off and while it was activated. Control subjects (n = 20) were tested once only. The ratio of the rest flow at heart level and the dependent position was defined as the vasoconstriction index.

Results: Both in affected hands and feet, patients were found to have lower vasoconstriction indices (P < 0.01) as compared with controls, indicating a decreased sympathetic tone. Applying SCS did not result in any microcirculatory change as compared with baseline or the contralateral clinically unaffected side.

Conclusions: The current study failed to show that SCS influences skin microcirculation in patients with CRPS and a low sympathetic tone. Therefore, we may conclude that pain relief in CRPS due to SCS is possible without vasodilation. Because sympathetic activity was greatly decreased in our patients, these results support the hypothesis that the vasodilation that is normally found with SCS is due to an inhibitory effect on sympathetically maintained vasoconstriction. (Key words: Electric stimulation therapy; laser Doppler flowmetry.)

SPINAL cord stimulation (SCS) has been used in the treatment of peripheral vascular disease with satisfactory clinical results in terms of increased local blood flow, thus promoting the healing of ischemic ulcers.[1-3] In studies on healthy rats, SCS has also been shown to cause vasodilation.[4,5] The mechanisms behind the vasodilatory effect of SCS have not yet been completely elucidated.

Presently, two hypotheses are available to explain the vasodilatory effect of SCS. The first suggests that vasodilation is mediated by an inhibitory effect on sympathetically maintained peripheral vasoconstriction.[6] The second regards antidromic vasodilation, probably mediated *via* A-δ fibers in the higher part of the velocity spectrum for this fiber group, as the potential mechanism.[5] There is evidence that the effect of antidromic vasodilation is mediated by calcitonin gene-related peptide and that the mechanism is nitric oxide-dependent.[7,8]

Chronic complex regional pain syndrome (CRPS) is a neuropathic pain syndrome. For many years, the syndrome has been considered to result from a hyperactivity of the sympathetic nervous system.[9,10] However, recent studies have shown that in chronic CRPS, sympathetic activity seems to be decreased: the vasoconstrictive response to dependency (defined as skin blood flow at heart level divided by skin blood flow in the dependent position) is attenuated in CRPS patients, whereas the vasoconstrictor responses to stimulation of intramural adrenergic nerves is reduced in isolated subcutaneous arteries taken from these patients.[11] In CRPS, SCS seems to be successful in relieving pain in more than 50% of patients who proved unresponsive to other types of treatment.[12,13] Little is known about the mechanism behind this beneficial effect. Experimental

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studies demonstrate that in the dorsal horn, the concentration of the inhibiting neurotransmitter γ-amino butyric acid (GABA), the levels of which are markedly reduced in animals submitted to peripheral nerve lesions,[14] increases after SCS.[15,16] Increased GABA levels may result in pain relief.

However, in addition to neuropathic pain components, pain in CRPS may be aggravated by disturbed blood flow through the skin.[17] In most patients, the symptomatic skin is abnormally cold as a consequence of vasospasm, because of sympathetic denervation supersensitivity caused by dropout of sympathetic efferents.[18] In addition, both capillary blood cell velocity values—a measure of the nutritive skin capillaries—and laser Doppler flowmetry values—providing an index of thermoregulatory shunt vessels—are significantly lower in the skin of CRPS patients as compared with healthy controls.[19] Dysregulation of peripheral-blood flow has been suggested to cause activation of peripheral nociceptors, resulting in pain and swelling.[20]

In the present study, the specific effect of SCS on the skin microcirculation was measured with laser Doppler flowmetry in CRPS patients with a low sympathetic tone. We tried to assess whether SCS improves or otherwise influences the microvascular blood flow. The aim of the study was to answer the following questions: (1) Is pain relief in CRPS after SCS dependent on vasodilation? and (2) What explains the vasodilatory effect of SCS? (Is the effect dependent on a normal sympathetic tone?)

Materials and Methods

Subjects

Enrollment in the study was considered when patients met the following criteria: age between 18 and 65 yr; CRPS type I according to diagnostic criteria of the International Association for the Study of Pain[21]; CRPS clinically restricted to one extremity, but at least affecting the whole hand or the whole foot; duration of CRPS of at least 6 months; a mean pain intensity of at least 5, as measured on a visual analog scale (VAS) ranging from 0 (no pain) to 10 (very severe pain), according to Jensen and McFarland[22]; and no lasting success of standard therapy, including medication, 6 months of physical therapy, transcutaneous electrical nerve stimulation, and sympathetic blocks (radiofrequency, chemical neurolysis, or surgery). Hence, because of prior sympathectomies, all included patients had a low sympathetic tone.

Exclusion criteria were a previous diagnosis of Raynaud's disease; (a history of) neurologic abnormalities not related to CRPS; conditions affecting function of the diseased or the contralateral extremity, other than CRPS itself; blood clotting disturbances or anticoagulant drug therapy; and an implanted cardiac pacemaker. Test stimulation was performed to assess whether patients respond to SCS positively. The decision to implant the permanent SCS system was made when, during the last 4 days of the testing period, a 50% decrease in original VAS score was measured, or if the patient reported "much improvement" on a seven-point global perceived effect scale, indicating worst ever, much worse, worse, not improved/not worse, improved, much improved, and best ever; these implantation criteria have been described previously.[12] Of 36 patients who met the criteria, 24 responded to test stimulation positively; two of these patients refused to take part in the study.

We thus studied 22 patients—8 men and 14 women—suffering from chronic CRPS of one entire hand or foot. The mean age (± SD) was 42 ± 11 yr, and the mean duration of CRPS (± SD) was 38 ± 29 months. In 14 cases an arm was affected and in 8 cases a leg. Seventeen patients suffered from mechanical allodynia. Implantation of the SCS system (Itrel 3, model 7425; Medtronic, Minneapolis, MN) had been performed 1 month before the study started. Patients could control stimulation intensity by adjusting the amplitude from 0 to 10 V with a patient programmer, whereas the rate was fixed at 85 Hz and pulse width at 210 μs. SCS paresthesiae covered the complete affected area.

Twenty-four hours before the assessment of skin blood flow started, the SCS system was switched off, and subjects were required to stop smoking. As stated previously, none of the patients responded to pain medication and, consequently, none of the patients used them. The patients also did not use any other medication. To achieve acclimatization, subjects were seated in the investigation room 30 min before the start of the assessment. All measurements were performed in the morning, starting at 9:30 AM, and were concluded within 2 h. Room temperature was maintained between 21 and 23°C. A group of 20 age-matched volunteers (mean age, 38 ± 8 yr; 6 men and 14 women) served as controls (10 controls for each extremity). The study complied with the Declaration of Helsinki regarding investigations in humans and was approved by the Medical Ethics Committee of Maastricht University Hospital; all patients gave written informed consent.

Procedure

Laser Doppler flowmetry was used to obtain information about total (mainly thermoregulatory) skin blood flow. The laser light illuminates a skin area with a radius of approximately 1 mm and penetrates the tissue to a depth of several millimeters.[23] The obtained laser Doppler signal is derived from the Doppler shift of back scattered light and is directly proportional to the microcirculatory blood flow, *i.e.*, the product of the number and mean velocity of the moving blood cells. We applied the output from a 780-nm diode laser that produced a divergent continuous wave light with a maximum accessible emission of 1 mW (PeriFlux 4001 Master; Perimed, Järfälla, Sweden) and a standard angled probe. The laser Doppler value was expressed in arbitrary perfusion units; this measure was calibrated using a latex suspension (Perimed) that produces a standard deflection of 2.5 V or 250 perfusion units. Off-line analysis was performed using a software program that had been developed in our institution. Biological zero flow, which is the laser Doppler signal in a "no flow" situation during arterial occlusion, was subtracted from all laser Doppler values measured.

Using double-sided adhesive tape, the plastic probe holder was attached, without pressure, to either the pulp of the great toe or to the pulp of the third finger. Next, the probe itself was secured to the holder. The cable was suspended to avoid pressure or traction on the skin area under investigation. Laser Doppler flowmetry was performed first with the extremity at heart level. Foot patients were tested in the supine position, whereas hand patients sat with their hands lying on the top of a desk. After measurement of rest flow and peak flow (defined as the maximum flow during reactive hyperemia after the release of a 3-min arterial occlusion), the procedure was repeated with the extremity in dependent position. For this purpose, foot patients were tested while sitting with their feet hanging from a bench, whereas hand patients sat with their hands 35 cm below heart level. The laser Doppler probe was kept in place while the patients changed position. The change of posture itself did not influence the patients' pain. This complete procedure was first performed on the unaffected side and then on the affected side. The SCS system was then switched on and, as soon as the patient reported to perceive the usual pain relief, measurements were repeated, first on the affected side and then on the unaffected side. Once SCS was started, stimulation intensity remained constant at a level resulting in pain relief. A 3-min adaptation period was inserted between the vari-

ous processes of assessment during which the parameters were able to return to a steady state once more.

In contrast to patients, control subjects were tested once only in similar conditions and starting at the same time. Because thermoregulatory blood flow is not influenced by diurnal variation but may change as a consequence of acclimatization to the experimental conditions,[24,25] time controls are not required, but all measurements should preferably be performed after a standard period of acclimatization. In both patients and controls, our protocol included an acclimatization period of 30 min.

The following parameters were assessed by laser Doppler flowmetry: (1) rest flow over a 3-min period; (2) peak flow; and (3) the vasoconstriction index, defined as the individual rest flow obtained at heart level divided by the rest flow obtained in dependent position. The vasoconstriction index is to be regarded as an indicator of the effectiveness of the postural vasoconstrictive mechanism, which is primarily sympathetically controlled at the thermoregulatory level of the skin microcirculation. Henriksen[26,27] clearly showed that the vasoconstriction index is capable of evaluating the sympathetic tone: the lower the vasoconstriction index, the more the vasoconstrictive mechanism—and hence the sympathetic tone—is impaired. The vasoconstriction index has been applied to evaluate sympathetic tone in several recent studies.[28–30]

On two occasions during the experiment, patients rated the pain intensity in the affected extremity on VAS: (1) before the first assessment of the rest flow, while the SCS system was switched off; and (2) after activation of the SCS system, as soon as the patient reported perceiving the usual pain relief.

Statistical Analysis

Because of the asymmetrical distribution, skin perfusion data are presented as medians with their interquartile ranges, *i.e.*, the spread from 25th to 75th percentile. The nonparametric Wilcoxon signed rank test was performed to compare data from the affected and the unaffected side or to assess changes resulting from SCS. Comparison between control and patient values was performed using the Mann–Whitney test. Change in pain intensity was assessed by means of a paired t test. Two-sided P values < 0.05, after Bonferroni correction for multiple significance tests, were considered statistically significant.

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Table 1. Baseline Laser Doppler Flowmetry Values of Hands of CRPS Patients and Controls

	Controls (n = 10)	Patients (n = 14)	
		Affected Side	Clinically Unaffected Side
Rest flow (PU)	121 (17–188)	161 (62–228)	125 (39–206)
Peak flow (PU)	222 (179–283)	256 (170–408)	290 (195–351)
Vasoconstriction index	1.64 (1.22–4.06)	1.07* (0.73–1.29)	1.17 (0.99–1.33)

Baseline laser Doppler flowmetry values of affected CRPS hands, contralateral clinically unaffected hands, and healthy (control) hands presented as median values and interquartile ranges. Rest flow and peak flow are measured with hands at heart level. The vasoconstriction index expresses the heart level to dependency ratio of the rest flow.

* $P < 0.05$ *versus* controls.

CRPS = complex regional pain syndrome; PU = perfusion units.

Results

Baseline Values

The mean (SD) pain intensity of the 22 patients at baseline, while the SCS system was switched off, was 6.9 (1.7) on VAS.

Microcirculatory baseline values of affected CRPS hands, contralateral clinically unaffected hands, and healthy control hands are presented in table 1. Both baseline rest flow and peak flow values were found not to be different in affected hands, as compared with clinically unaffected hands and control hands. The vasoconstriction index of the affected side was significantly reduced as compared with controls ($P = 0.02$). A similar tendency was noted on the clinically unaffected side ($P = 0.07$).

Microcirculatory baseline values of affected CRPS feet, contralateral clinically unaffected feet, and healthy control feet are presented in table 2. Similar to the results for CRPS hands, baseline rest flow and peak flow values were not found to be different in affected feet as compared with the clinically unaffected side or control feet. As compared with control values, the vasoconstriction index of the affected side was significantly reduced ($P =$

0.04). On the clinically unaffected side, there was a nonsignificant reduction of the vasoconstriction index ($P = 0.08$).

Effect of SCS on Microcirculatory Parameters

After activation of the SCS system, as soon as the patient reported perceiving the usual pain relief, the mean (SD) pain intensity of the 22 patients decreased significantly to 2.2 (1.3) on VAS ($P < 0.001$). The change in thermoregulatory skin perfusion caused by SCS, if any, was not related to presence or absence of mechanical allodynia.

Figure 1 shows the vascular response to SCS in the affected hands of 14 CRPS patients. Control responses were obtained from the contralateral clinically unaffected hand, which was, in principal, not electrically stimulated by SCS and, indeed, showed no statistically significant changes to SCS. However, applying SCS to the affected side did not result in significant microcirculatory changes either. No significant differences were found between the affected and the unaffected side, as far as blood flow changes from baseline under the influence of SCS were concerned.

As demonstrated in figure 2, SCS also had no effect on

Table 2. Baseline Laser Doppler Flowmetry Values of Feet of CRPS Patients and Controls

	Controls (n = 10)	Patients (n = 8)	
		Affected Side	Clinically Unaffected Side
Rest flow (PU)	11 (8–29)	6 (4–41)	15 (8–49)
Peak flow (PU)	121 (52–180)	94 (25–258)	121 (66–142)
Vasoconstriction index	5.77 (3.85–9.14)	2.78* (1.85–5.27)	3.57 (2.18–5.35)

Baseline laser Doppler flowmetry values of affected CRPS feet, contralateral clinically unaffected feet, and healthy (control) feet presented as median values and interquartile ranges. Rest flow and peak flow are measured with feet at heart level. The vasoconstriction index expresses the heart level to dependency ratio of the rest flow.

* $P < 0.05$ *versus* controls.

CRPS = complex regional pain syndrome; PU = perfusion units.
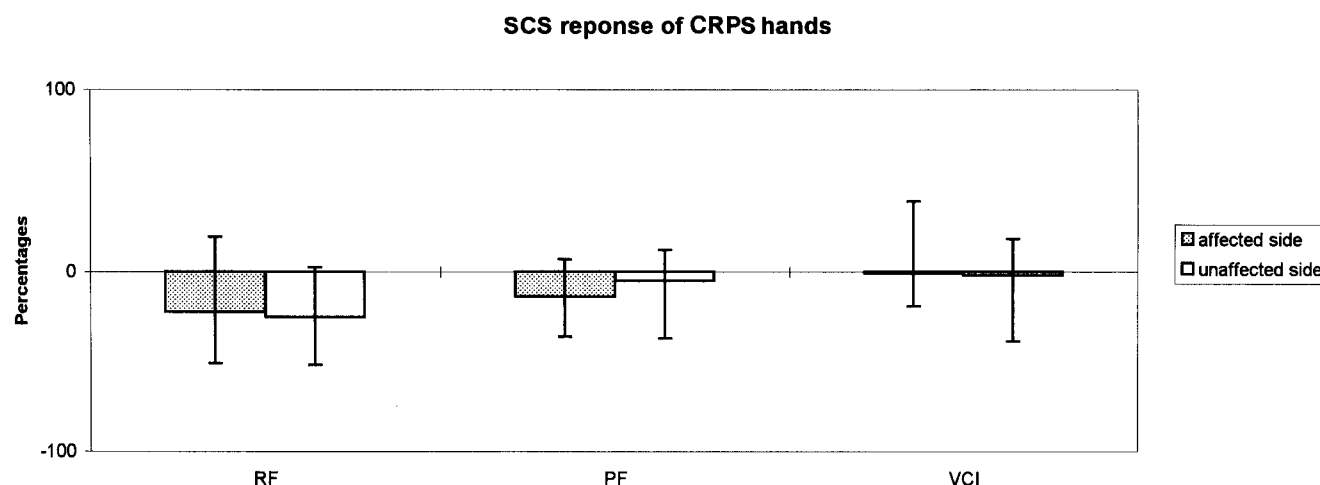
SCS reponse of CRPS hands

Fig. 1. Effect of spinal cord stimulation on microcirculatory parameters in affected complex regional pain syndrome (CRPS) hands and contralateral clinically unaffected hands, presented as median percentage change from baseline and interquartile ranges. Rest flow (RF) and peak flow (PF) are measured with hands at heart level. The vasoconstriction index (VCI) expresses the heart level to dependency ratio of the rest flow. There are no significant differences from baseline or within groups.

cutaneous blood flow in the affected feet of eight CRPS patients. Both on the affected and unaffected side, no significant changes were noted from baseline, and the recorded changes on the affected and the unaffected side were not significantly different from each other.

Discussion

The present study failed to show that SCS induces an increase in thermoregulatory skin blood flow in patients with a low sympathetic tone due to CRPS and a previous sympathectomy, suggesting the absence of a vasodilatory effect. Therefore, the pain relief in these patients caused by SCS is apparently not mediated by influences of the treatment on skin microcirculation. This result supports the hypothesis that the vasodilatory effect of SCS, which has been measured in patients and animals with a normal sympathetic tone,[2–5] is due to an inhibitory effect on sympathetically maintained peripheral vasoconstriction.

This is the first study that has applied laser Doppler flowmetry to measure cutaneous blood flow changes
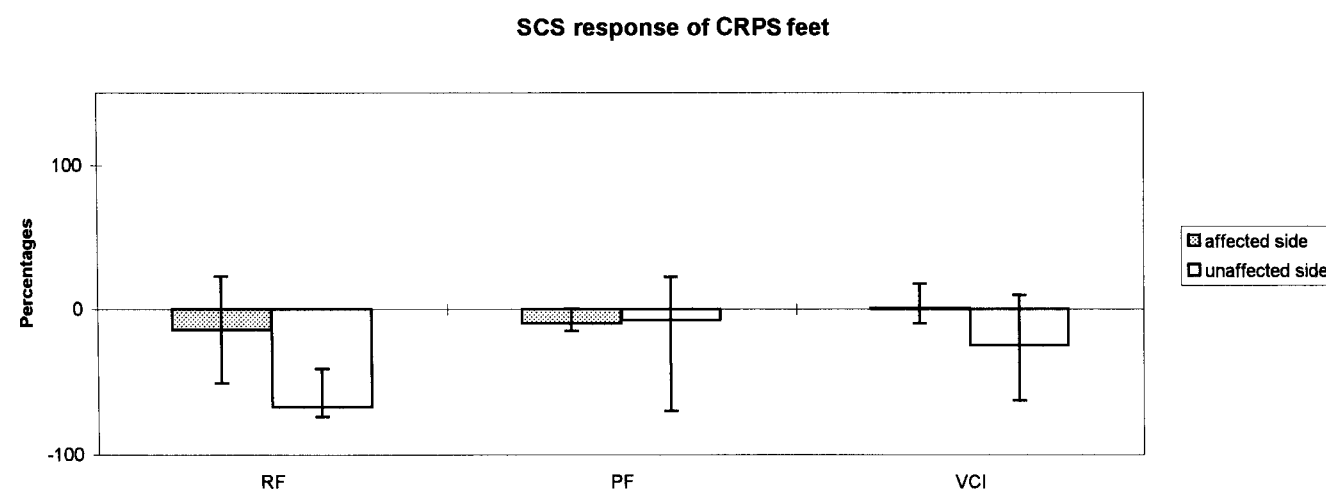
SCS response of CRPS feet

Fig. 2. Effect of spinal cord stimulation on microcirculatory parameters in affected complex regional pain syndrome (CRPS) feet and contralateral clinically unaffected feet, presented as median percentage change from baseline and interquartile ranges. Rest flow (RF) and peak flow (PF) are measured with feet at heart level. The vasoconstriction index (VCI) expresses the heart level to dependency ratio of the rest flow. There are no significant differences from baseline or within groups.

secondary to SCS in CRPS patients. The laser Doppler signal is primarily generated by movement of blood cells in the thermoregulatory vascular bed, *i.e.*, the subpapillary arterial and venous plexa.[31] In the area of the finger and toe pulps, more than 90% of the blood flows through this thermoregulatory vascular bed, whereas less than 10% goes through the nutritional capillaries.[31] For ethical reasons, the effect of SCS on cutaneous microcirculation in healthy subjects is not attainable; however, because SCS has been shown to improve nutritional[2] and thermoregulatory[3] blood flow in humans with severe limb ischemia, as well as thermoregulatory blood flow in rats,[4,5] it seems appropriate to suggest that in healthy subjects, SCS has a vasodilatory effect in the skin.

The high variability in skin perfusion data and the finding that rest flow is lower in feet than in hands are in line with other laser Doppler studies on hands or feet.[28-30] In addition, since laser Doppler evaluates thermoregulatory blood flow, it was to be expected that the figures would be higher in (warm) hands and lower in (cold) feet. In both hands and feet, baseline rest flow and peak flow were similar on the affected and clinically unaffected side and not different from controls. This seems to be contradictory to previous findings[19,32] but may be explained by a lacking relationship between disease duration and the stage of CRPS. In a large prospective patient series, Veldman *et al.*[33] demonstrated that there is no basis for the classical subdivision of CRPS into three consecutive stages: a warm stage, an instable vasomotor stage, and a cold stage. Their study showed that CRPS may start with a cold extremity or may result in a warm extremity after years of disease duration. Reduced rest flow is especially related to stage III (cold stage) disease, whereas a number of the patients included in the present study may still have been in stage I or II disease. Like Kurvers *et al.*,[29] we did find reduced vasoconstriction indices as compared with controls, indicating that sympathetic tone was decreased in our patient population. Impaired vasoconstrictor responses to dependency of thermoregulatory skin microvessels, which are mainly sympathetically controlled,[26-28] suggest sympathetic denervation of these vessels.[29] The vasoconstriction index also tended to be reduced as compared with controls in the clinically unaffected side, although the difference was not statistically significant (*P* between 0.05 and 0.1 in both hands and feet). It has previously been reported that the clinically unaffected side in CRPS also exhibits microvascular abnormalities as compared with controls.[34] This has been suggested to indicate that there is a spinal component to microcircu-

latory abnormalities in CRPS that is initiated by traumatic excitation of a peripheral nerve on the clinically affected side.[30]

Applying SCS to the side of the spinal cord that innervated the CRPS extremity did relieve pain but did not result in any microvascular effect: rest flow, peak flow, and vasoconstriction indices all remained constant. Neither were any effects found on the clinically unaffected side, but because the SCS electrode was positioned in such a way that only the affected side was stimulated, this finding was not unexpected. The fact that in our patients SCS failed to increase thermoregulatory skin blood flow cannot rule out that changes induced by SCS may result from alterations in blood flow in deeper tissues, such as muscles. The animal and human studies that did show alterations in skin perfusion due to SCS also did not measure blood flow in deeper tissues.[2-5] In addition, a change in flow due to SCS that is restricted to deeper tissues seems unlikely because thermoregulatory blood flow is regulated centrally by the sympathetic nervous system. In controls, skin perfusion measurements were performed once only, implicating that no time controls were used. However, applying time controls would not have influenced the results, because thermoregulatory blood flow is not influenced by diurnal variation,[24,25] and all measurements were performed within a few hours in identical conditions.

Our data indicate that pain relief in a previously sympathectomized group of CRPS patients due to SCS is not secondary to vasodilation. Hence, SCS in CRPS can produce pain relief that is not associated with vasodilation. In consequence, the exact mechanism underlying pain alleviation with SCS in CRPS patients still remains to be explained. Several neurophysiologic mechanisms have been proposed, for example: simple blocking of pain transmission by a direct effect on the spinothalamic tracts; activation of descending inhibitory pathways; effects on central sympathetic systems; segmental inhibition *via* coarse fiber activation and brain stem loops; inhibition by increasing GABA levels in the dorsal horn; and thalamo-cortical mechanisms masking the nociceptive input.[15,16,35-38] Further studies are needed to solve this problem, but the net effect will probably be discovered to originate from several sources.

Although we did not find a vasodilatory effect of SCS in CRPS patients, our findings may contribute to the discussion on the possible mechanism of this effect in humans. Currently, there are two potential explanations for the cutaneous vasodilatory effect of SCS: (1) an inhibitory effect on efferent sympathetic activity; and (2)

an antidromic stimulation of afferent fibers, resulting in a local release of vasoactive substances. Several studies support the idea that the vasodilatory effect of SCS is, to a large extent, mediated by an inhibitory effect on the peripheral vasoconstriction that is maintained *via* the sympathetic nervous system.[4,39] In rats, vasodilatory responses were eradicated after any of the following procedures: complete surgical sympathectomy[40]; blocking nicotinic transmission in the ganglia; and blocking postganglionic α_1-adrenoceptors.[6] Blocking muscarinic transmission in the ganglia or postganglionic α_2-adrenoceptors did not alter the effect of SCS, whereas β-adrenoceptors seemed to be differentially involved in the effects on skin and muscle circulation.[6]

On the other hand, there is evidence that vasodilation during SCS is caused by antidromic activation of sensory afferents in the dorsal roots causing release of calcitonin gene-related peptide in the periphery. After an extensive rhizotomy of the T12–L5 dorsal roots in the rat, SCS no longer increased blood flow in the ipsilateral hind paw, whereas the same effect was noted after administration of a competitive antagonist of calcitonin gene-related peptide.[7] The neuronal release of nitric oxide, or the neuronal release of a substance that is nitric oxide-dependent, may also mediate SCS-induced vasodilation, because competitive inhibitors of nitric oxide synthase markedly attenuated cutaneous blood flow increases caused by SCS.[8] These nitric oxide–dependent nerve fibers do not seem to be reliant on efferent autonomic pathways, because the nicotinic ganglionic antagonist hexamethonium did not affect the cutaneous vasodilation caused by SCS.[8] However, there must be an additional non–nitric oxide pathway that causes vasodilation, because after giving hexamethonium, nitric oxide synthase inhibitors no longer attenuated the SCS response.

The affected extremities of the CRPS patients in the present study all had a low sympathetic tone. First, all patients had undergone previous sympathectomy that had not resulted in pain relief and, hence, their pain type can be classified as sympathetically independent pain[9,41,42]—in fact, patients responding to sympathetic blocks (sympathetically maintained pain) had been excluded from the study. Second, as stated previously, the vasoconstriction index in their affected extremity seemed to be impaired, also indicating a reduced sympathetic activity. Our finding that SCS had no influence on the cutaneous blood flow of these patients supports the autonomic inhibition theory as an explanation for the vasodilation normally found after SCS; in patients with a low sympathetic tone, sympathetic inhibition by SCS cannot have a significant effect. Using

microneurography to directly measure sympathetic activity in a patient with CRPS type II (causalgia),[21] it has also been demonstrated that during transcutaneous electrical nerve stimulation no apparent changes occurred in the sympathetic outflow.[43] On the other hand, the results of the present study do not support the antidromic stimulation theory. Antidromic stimulation does not require intact autonomic pathways, so if this theory were the single explanation, SCS should have resulted in cutaneous vasodilation in CRPS patients.

In conclusion, the present study has demonstrated that pain relief in CRPS due to SCS does not depend on vasodilation. Therefore, it seems unlikely that pain decrease is mediated *via* sympathetic pathways. In addition, these data support the hypothesis that the vasodilatory effect of SCS, which is present in other situations, is dependent on the sympathetic nervous system.

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