

Case Series

Spinal Cord Stimulation Inhibits Cortical Somatosensory Evoked Potentials Significantly Stronger than Transcutaneous Electrical Nerve Stimulation

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Background: Despite the good clinical results elicited by spinal cord stimulation (SCS), the physiological basis of action of SCS is widely unknown. Inhibition of somatosensory evoked potential (SEP) amplitudes by SCS has been described, but it is unclear whether this displays dose dependency. Moreover, it is unknown whether the pain-relieving effect elicited by SCS correlates with the inhibition of SEPs. Finally, this study aimed to answer the question whether there is a difference in the effect on SEPs between SCS and transcutaneous electrical nerve stimulation (TENS), thus between central nervous system stimulation and peripheral nervous system stimulation.

Methods: Ten patients (4 men and 6 women, age range 40-77 years) with neuropathic lower limb pain were included in the study. All patients had implanted SCS systems with percutaneous type electrodes. Cortical SEPs under SCS and TENS were measured without stimulation, under stimulation at perception threshold (PT), and at maximal threshold (MT) in a crossover design.

Results: Cortical SEP amplitudes were significantly inhibited by SCS. Stimulation at PT and at MT both led to a statistically significant inhibition of the SEP amplitude. The difference between amplitude reduction at PT and MT showed a tendency towards significance. The degree of SEP amplitude inhibition did not correlate with pain relief. Inhibition of SEP amplitudes by TENS was weaker than that elicited by SCS. The average percentage of amplitude reduction at MT was twice as high under SCS as it was under TENS. No effects on SEP latencies were seen.

Conclusions: SCS exerts a significantly stronger inhibition of SEP amplitudes than TENS. The data hint at a dose dependency of SCS-induced SEP amplitude inhibition. No correlation between SEP amplitude inhibition and pain relief was found.

Key words: spinal cord stimulation, SCS, transcutaneous electrical nerve stimulation, TENS, neuropathic pain, somatosensory evoked potentials, SEP

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Spinal cord stimulation (SCS) has been successfully employed in the treatment of neuropathic pain for more than 3 decades (1) and beneficial effects have been described in various neuropathic pain conditions such as failed back surgery syndrome (2-6), Complex Regional Pain Syndrome (CRPS) (7-9), and post-herpetic neuralgia (2,10). Despite the good clinical results elicited by SCS, the physiological basis of the pain-relieving effect of SCS is widely unknown (11).

The inhibitory effect of SCS on somatosensory evoked potentials (SEPs) has been described in a number of studies (12-14). However it is unknown whether this effect is dose dependent. Moreover it is not clear whether or not this effect correlates with the clinical efficacy of SCS (14). The dose dependency of the clinical pain-relieving effect has recently been demonstrated (15).

In recent years, new stimulation therapies focusing on the peripheral nerve system have arisen. Subcutane-

ous or peripheral nerve field stimulation (16) has been proposed for the treatment of various pathologies such as post-laminectomy syndrome (17), post-thoracotomy pain (18), groin pain (19), and post-herpetic neuralgia (20). Thus in some clinical situations, such as groin pain or post-herpetic neuralgia, both SCS and subcutaneous stimulation are possible. In these situations the use of the more invasive SCS should be weighed according to advantages, such as possibly higher clinical efficacy. Up to now, although not explicitly, SCS therapy has always followed the notion that it is more effective to stimulate the spinal cord (thus the central nervous system) than to stimulate the peripheral nervous system, as for instance with transcutaneous electrical stimulation (TENS).

The present study addressed the following questions:

- Is the inhibition of SEPs elicited by neurostimulation dose dependent?
- Does the pain-relieving effect elicited by SCS correlate with the inhibition of SEPs?
- Is there a difference of the effect on SEPs between SCS (central nervous system stimulation) and TENS (peripheral nervous system stimulation)?

METHODS

Patients

Criteria for eligibility were SCS for neuropathic pain with significant pain relief, capacity to understand the study design, and willingness to fill in pain questionnaires. Exclusion criteria were myocardial infarction in the preceding 3 months (due to the risk of reinfarction), cerebral ischemia in the preceding 3 months, and degenerative central nervous system disease (due to the possible impact on SEPs).

Questionnaires

All patients completed a pain questionnaire including items regarding the mean, minimal, maximal, and tolerable level of pain on an numerical rating scale (NRS) in the 2 weeks prior to baseline.

Study Design and Interventions

Patients were physically examined at baseline. The stimulation pattern and the settings of the SCS device were recorded. Perception thresholds in supine, sitting, and standing positions were registered. The patients had switched off the stimulator for at least one hour prior to the SEP recording. The experimental setting is described in Fig. 1.

SCS and TENS Application

SCS was performed at the intensity and impulse duration which the patients routinely used. Stimulation parameters and threshold are displayed in Table 1.

TENS was applied on the painful leg. TENS electrodes were fixed at the medial side of the foot and at the medial side of the lower leg approximately 15 cm above the ankle. TENS was applied with continuous impulses at the same frequency as SCS. The intensity of stimulation with the TENS device (Arthrostim Select, ORMED GmbH, Freiburg, Germany) was regulated on a 0-60 scale in 0.5 steps. The impulse duration was determined on this scale. The maximum value (60) corresponded to an impulse duration of 250 μ s. Maximal effective current under these conditions and at a maximal voltage of 40V (depending on the individual electrical tissue resistance) was 23 mA. TENS thresholds are displayed in Table 1.

SEP Recordings

The SEP recordings were performed with the patient lying in a supine position. SEP recordings were conducted with an ISIS IOM Neuromonitoring System (Inomed Medizintechnik GmbH, Emmendingen, Germany). Transcutaneous tibial nerve stimulation was done with biphasic square-wave pulses of 0.2 ms at a frequency of 5.3 Hz with the cathode placed proximally at the medial ankle of the painful leg. The stimulation intensity was chosen slightly above motor threshold. Cortical SEP recordings were done using scalp electrodes placed at Fz and Cz'. Two series of 1,000 stimuli were averaged for each measurement. First, one measurement without stimulation was done, then (within 30-60 sec) one measurement under SCS at perception threshold (PT) (defined as the lowest intensity the patient could perceive) followed by one measurement at maximal threshold (MT) (defined as the highest intensity the patient would rate as not painful). After a short pause (2-3 min), identical measurements were performed under TENS. Five patients had measurements of SCS followed by measurements of TENS and 5 patients vice-versa. The allocation to these 2 groups was random (Fig.1).

Statistical Analysis

Computer software packages (GraphPad Prism, Version 5.01, GraphPad Software, Inc. La Jolla, USA, and R, Version 2.11.1, R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. First descriptive statistics were computed for all items. Due to the small number of observations, non-parametric

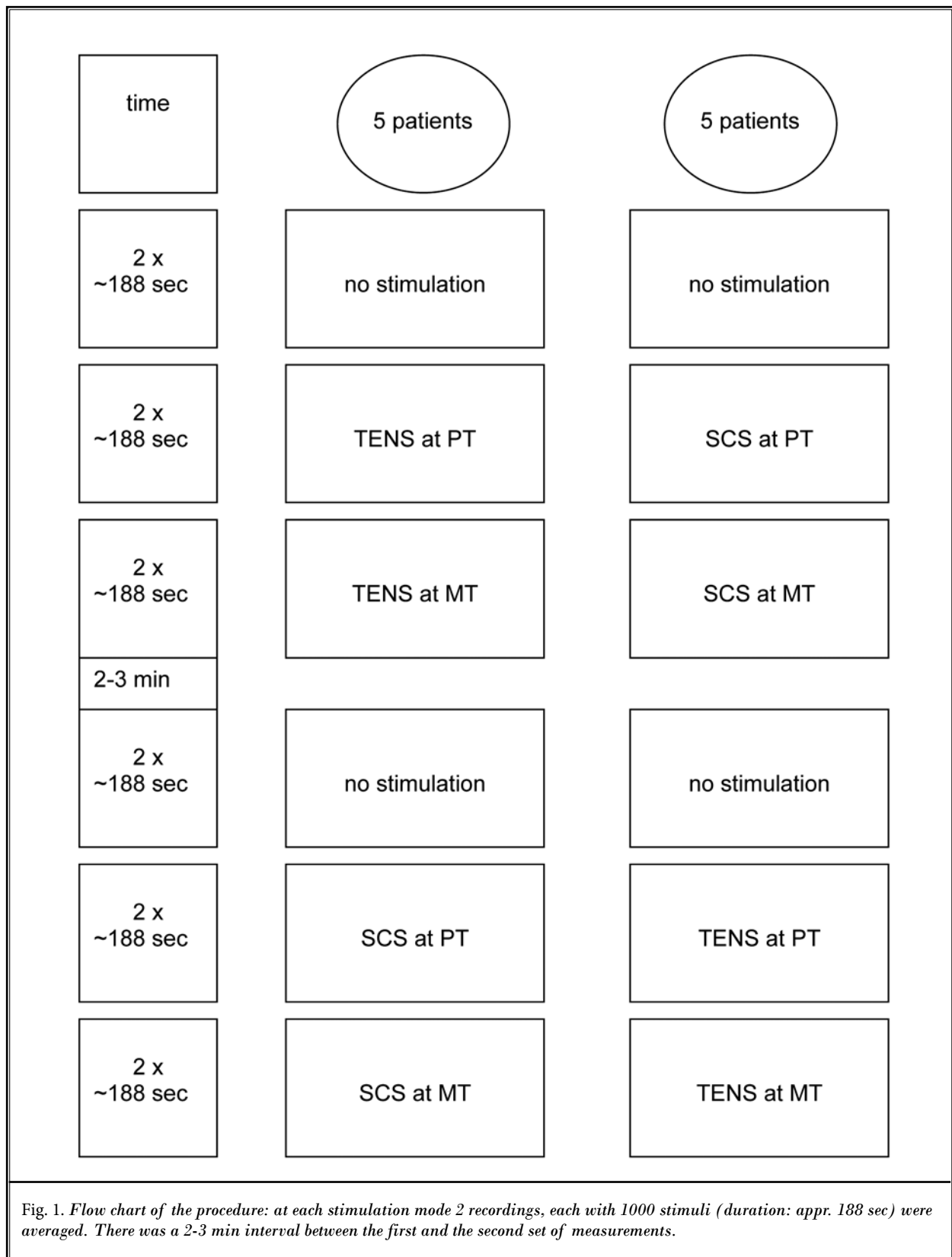


Table 1. Thresholds and stimulation parameters in SCS and TENS

Pat	Leads*	SCS						TENS				
		Perception threshold (PT) / V			Maximal threshold / V			Frequency / Hz	Impulse duration / μ s	Perception threshold (PT) **	Maximal threshold (MT) **	Frequency / Hz
		Sitting	Standing	Lying	Sitting	Standing	Lying					
1	4p	1.3	1.8	1.7	1.8	2.5	2.3	80	300	21.0	56.0	80
2	4p	0.6	1.4	1.4	1.3	1.3	1.3	100	270	4.5	10.5	100
3	8p	1.3	1.7	1.7	1.6	2.3	2.3	100	450	5.0	9.0	100
4	8p	0.4	1.6	1.6	0.7	2.6	0.9	80	450	4.0	5.5	80
5	8p	1.5	3.0	2.9	2.5	4.2	4.3	100	360	20.0	60.0	100
6	4p	1.4	3.2	3.0	2.5	5.0	4.7	130	150	12.0	55.0	120
7	8p	1.8	1.6	1.6	2.8	3.1	2.8	100	450	11.0	38.5	100
8	8p	2.9	3.1	3.9	4.5	4.4	4.4	100	240	6.0	18.5	100
9	4p	2.2	2.5	2.6	4.9	5.0	5.0	80	210	42.0	56.0	80
10	8p	1.8	2.6	2.7	3.7	4.5	4.5	100	240	17.0	45.0	100
mean	4x 4p, 6x 8p	1.5	2.3	2.3	2.6	3.5	3.3	97.0	312.0	14.3	35.4	96.0
SD		0.7	0.7	0.8	1.4	1.3	1.5	14.9	109.7	11.7	22.2	12.6

*all patients had percutaneous type leads: 4p=4 pole, 8p=8pole, ** TENS thresholds are displayed in arbitrary units of 0.5 points on a 0- 60 points scale, a value of 60 corresponds to an impulse duration of 200 μ s

statistics were used. Differences between average amplitudes and latencies were tested with the 2-sided Wilcoxon matched pairs test. Spearman correlations were calculated between the pain scores and the percentage of SEP amplitude reduction.

Sample Size Estimation

With $\alpha = 0.05$ and a power of 0.8, and given a standard deviation (SD) of 0.5 μ V in the amplitudes of the evoked potentials a detectable alternative of 0.5 μ V the sample size for the 2-sided Wilcoxon matched pairs test was estimated to be 10.

Ethics Committee Approval

This randomized controlled study was approved by the ethics committee of our institution.

RESULTS

Patients

Ten patients (4 men, 6 women) were included in the study. Mean age was 54.0 years (range 40.7 – 77.2 years, SD 10.2 years). Mean duration of chronic pain at time of SCS implantation was 5.6 years (range 0.8 – 14.0 years, SD 5.8 years). SCS therapy had been applied for mean 3.9 years (range 0.2 – 12.3 years, SD 3.8 years) prior to the trial. Diagnoses are listed in Table 2 and baseline

stimulator settings are shown in Table 1. All patients were implanted with percutaneous type electrodes. All but 2 patients had non-rechargeable implantable pulse generators (IPG).

Pain Ratings

Without stimulation, average pain scores were mean 7.05 (range 4.0 – 9.5, SD 1.66). Maximal pain scores (NRS) were mean 7.85 (range 6.0 – 9.5 SD 1.20), minimal pain scores were 5.75 (range 3.0 – 8.0, SD 1.65).

Under stimulation, average mean pain scores were 3.45 (range 0.5 – 6.0, SD 1.62), maximal scores were 4.10 (range 1.0 – 7.0, SD 1.77), and minimal pain scores were 2.10 (range 0.0 – 6.0, SD 1.82). Average reduction of pain elicited by SCS was 3.60 (50.3%) (range 2.0 – 8.0, SD 1.82) (Table 2). A strong negative correlation was found between the impulse duration and the percentage of pain reduction ($r(9) = -0.7438, P = 0.0174$). There was no correlation between the SEP amplitude reduction and pain reduction elicited by SCS.

SEPs

The P40N50 amplitude was significantly inhibited by SCS at PT and at MT as well as by TENS at PT and MT. Under SCS at MT amplitudes decreased by mean 48.1% while under TENS at MT the mean amplitude reduction was 22.9%. There was a statistically significant differ-

Table 2. Patient characteristics, pain scores and pain reduction elicited by SCS

Patient	Age/ gender	Diagnosis	Duration of pain at time of implantation / years	Duration of SCS at time of study / years	Pain (NRS) without SCS	Pain (NRS) with SCS	Pain reduction /%
1	59/m	FBSS, radiculopathy L5	2.9	7.1	6	4	33
2	77/f	FBSS, radiculopathy S1	13.6	12.3	7	3.5	50
3	47/f	FBSS, radiculopathy L5	14.3	0.2	8	5	38
4	59/f	FBSS, radiculopathy L5	14.0	0.1	5	3	40
5	54/m	FBSS, radiculopathy L4 and L5, neurinoma	2.1	2.9	9.5	6	37
6	48/f	FBSS, radiculopathy S1, cauda syndrome	3.6	5.5	8.5	0.5	94
7	51/f	FBSS, radiculopathy S1, pseudomeningocele	1.5	2.2	7.5	4.5	40
8	57/m	FBSS, radiculopathy L5, epidural fibrosis	1.1	3.6	4	2	50
9	46/m	neuropathic knee pain after 2x bursectomy	0.8	4.6	8	4	50
10	40/f	FBSS, radiculopathy L5	2.0	0.2	7	2	71
mean	54.0 (6f/4m)		5.6	3.9	7.05	3.45	50.3

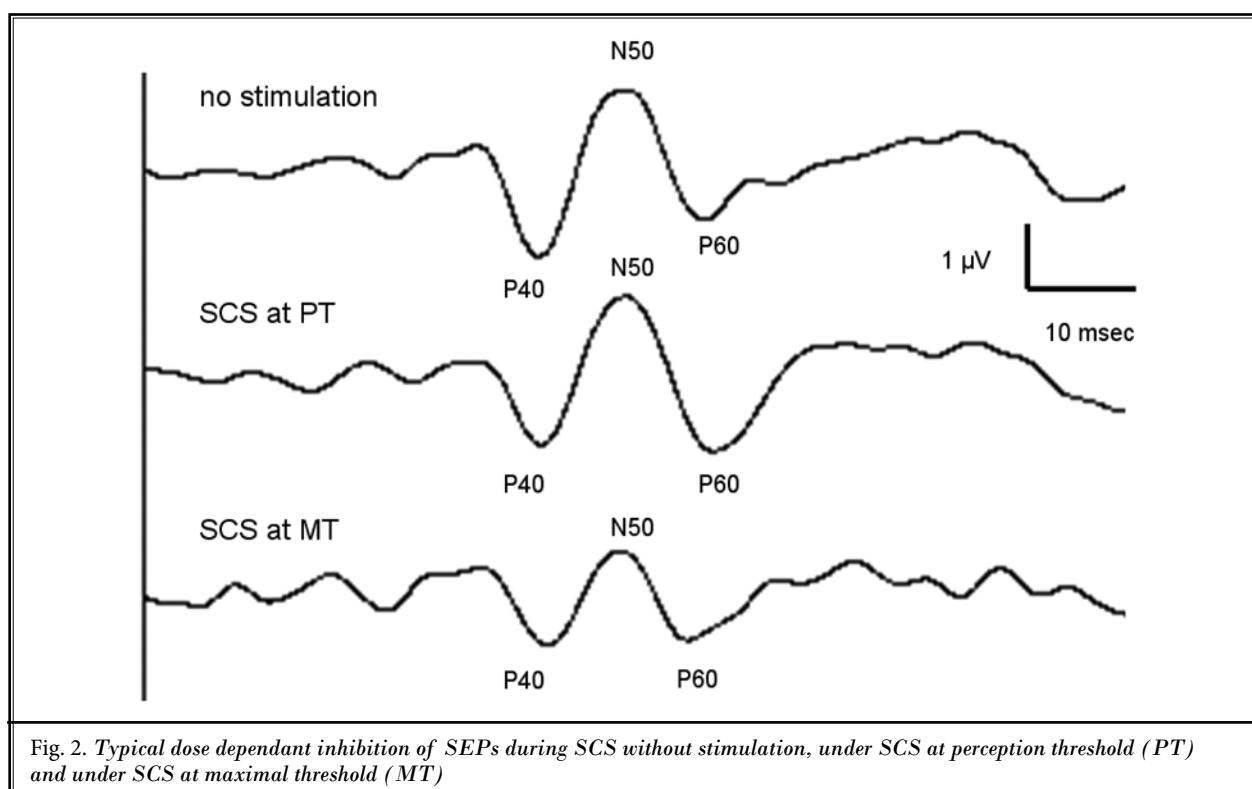


Fig. 2. Typical dose dependent inhibition of SEPs during SCS without stimulation, under SCS at perception threshold (PT) and under SCS at maximal threshold (MT)

ence between amplitudes under SCS and TENS. Also the N50P60 amplitudes showed a decrease under SCS and under TENS. While under TENS the amplitude reduction was only modest and not statistically significant, the amplitude was reduced by 35.2% under SCS at MT.

A typical example of the SEP inhibition under SCS is shown in Fig. 2. An overview of the effect of SCS and TENS on SEP amplitudes is given in Table 3.

SEP latencies were not found to be significantly changed under TENS or SCS. Overall, the latencies were

Table 3. Overview of average amplitudes and their inhibition by SCS /TENS

		no stimulation (0)	SCS perception threshold (PT)*	SCS maximal threshold (MT)**	no stimulation (0)	TENS perception threshold (PT)*	TENS maximal threshold (MT)**
Amplitude P40N50	mean	1.003	0.742	0.544	0.890	0.719	0.700
	range	0.38-2.83	0.0-2.21	0.0-1.73	0.25-2.3	0.11-2.08	0.15-2.08
	median	0.707	0.553	0.389	0.696	0.555	0.520
	SD	0.757	0.700	0.500	0.670	0.606	0.578
	SE	0.239	0.221	0.158	0.212	0.192	0.183
P							
0 vs PT		0.0039			0.0039		
PT vs MT		0.0742			0.7695		
0 vs MT		0.0020			0.0039		
0 vs 0		0.1289					
PT (SCS vs TENS)				0.7695			
MT (SCS vs TENS)						0.0059	
Amplitude N50P60	mean	0.799	0.701	0.575	0.753	0.751	0.677
	range	0.28-2.07	0.0-2.15	0.0-1.67	0.22-2.11	0.16-2.01	0.11-2.01
	median	0.574	0.528	0.423	0.506	0.569	0.447
	SD	0.555	0.644	0.493	0.594	0.607	0.609
	SE	0.176	0.204	0.156	0.188	0.192	0.192
P							
0 vs PT		0.1055			0.9219		
PT vs MT		0.1289			0.1055		
0 vs MT		0.0020			0.1055		
0 vs 0		0.3223					
PT (SCS vs TENS)				0.2754			
MT (SCS vs TENS)						0,1602	

* measurement at the lowest SCS or TENS voltage the patient was able to perceive, ** measurement at the highest SCS or TENS voltage that was not regarded as painful, bold = <0.05

in the range reported in the literature (21). There were no statistically significant differences between the P40, N50, and P60 latencies under TENS, under SCS, and without stimulation (Table 4).

DISCUSSION

The present study shows that cortical SEP amplitudes are significantly inhibited by SCS. Stimulation at PT as well as stimulation at MT led to a statistically significant inhibition of the SEP amplitude. There was also a tendency towards statistical significance regarding the difference between SEP amplitudes under SCS at PT and SCS at MT, which suggests a dose dependency of SEP amplitude inhibition by SCS. The degree of SEP amplitude inhibition did not correlate with the degree

of pain relief reported by the patients. Inhibition of SEP amplitudes under TENS, however, was weaker than that elicited by SCS. The difference between the SEP amplitudes under SCS at MT and under TENS at MT was statistically significant. Thus, it can be concluded that, at the same level of intensity relative to maximal threshold, SCS exerts a stronger inhibition of SEP amplitudes than TENS. The average percentage of amplitude reduction under SCS was twice as high as it was under TENS.

The SEP amplitude reduction exerted by SCS has been described in a number of studies (12-14,22,23).

A neurophysiological mechanism, termed collision of impulses (14,24), was proposed as a putative mechanism to account for amplitude inhibition elicited by SCS. According to this theory, 2 action potentials travelling

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Table 4. Overview over average latencies P40 /N50 an N60.

		no stimulation (0)	SCS perception threshold (PT)*	SCS maximal threshold (MT)**	no stimulation (0)	TENS perception threshold (PT)*	TENS maximal threshold (MT)**
Latency P40	mean	41.22	41.51	41.98	41.93	42.37	41.91
	range	35.83-50.28	36.41-49.05	36.75-50.03	37.07-50.65	37.45-51.45	36.03-50.13
	median	40.18	40.69	40.40	40.18	41.87	40.99
	SD	5.125	4.946	4.779	4.920	4.914	4.863
	SE	1.621	1.564	1.511	1.556	1.554	1.538
Latency N50	mean	50.80	49.59	49.83	49.63	49.72	49.47
	range	40.62-62.90	40.33-57.62	40.76-56.46	40.47-57.77	40.91-58.50	41.35-57.63
	median	52.72	49.49	51.10	51.54	51.62	50.37
	SD	7.086	5.782	5.423	5.560	5.934	5.257
	SE	2.241	1.828	1.715	1.758	1.877	1.662
Latency P60	mean	58.20	58.44	58.24	59.31	57.76	57.46
	range	45.75-68.62	45.75-69.79	48.10-71.11	46.63-69.50	46.78-67.89	46.63-66.86
	median	58.11	58.27	59.06	58.37	57.87	57.32
	SD	6.869	6.791	6.596	6.065	6.047	5.827
	SE	2.172	2.148	2.086	1.918	1.912	1.843

* measurement at the lowest SCS or TENS voltage the patient was able to perceive, ** measurement at the highest SCS or TENS voltage that was not considered painful, no statistically significant differences between mean latencies under the different stimulation modes were detected

in opposite directions would neutralize each other at the moment of their collision. This might partly explain the smaller amplitude inhibition under TENS.

However, a subcortical contribution to the amplitude decreases was considered improbable by Polacek et al (12). They argued that decreased somatosensory input does not explain the increased functional activation in various cortical structures during SCS (25-27). Determining which mechanism might account for SEP inhibition under SCS was beyond the scope of this study; probably both of the above described mechanisms act in concert.

The data of the present study suggest a dose dependency of the SCS inhibition elicited by SCS. Although recent clinical studies have found a dose dependent clinical pain-relieving effect of SCS, and a measurable effect was even observed when stimulation was performed below threshold (15,28) for the inhibitory effects on SEPs elicited by SCS, dose dependency has not yet been confirmed. Moreover, it remains unclear whether SEP inhibition by neurostimulation is correlated to clinical pain relief. The present study failed to demonstrate such a correlation.

Previous studies have shown that TENS can also reduce SEP amplitudes (29-30). The present study compared inhibitory effects on SEPs and found those elicited

by SCS greater than those affected by TENS. It could be objected that, in contrast to SCS, TENS often does not cover the whole painful area and might thus have a smaller pain-relieving effect. This, however, should not influence the extent of SEP amplitude reduction, as the area of SEP recording was completely covered in both TENS and SCS. Moreover in both instances, the same stimulation intensities were chosen relative to PT and MT. A more conclusive explanation for the stronger SEP inhibition under SCS might be given by the above-mentioned collision of impulses mechanism. This, however, implies that stimulation is applied proximal to the pain source (or the SEP stimulation electrode). In the case of TENS, however, stimulation was applied distally to the SEP stimulation electrode. Moreover, animal models have shown that SCS acts via a couple of mechanisms at the segmental level, thus at the location where SCS is applied. Under SCS, attenuation of the pain-induced hyperexcitability of wide dynamic range (WDR) neurons has been found (31). It is believed that increased γ -aminobutyric acid (GABA) release (32-33) from inhibitory interneurons account for that effect, particularly by activation of the GABA-B receptor (34). There also seems to be some contribution of the cholinergic system to SCS effects, as a release of acetylcholine in the dorsal horn was observed and later attributed to activa-

tion of the muscarinic M4 receptor (35). Unlike dorsal column stimulation, dorsal root stimulation failed in a recent study to inhibit windup in WDR neurons in neuropathic conditions in a rodent model (36). This may point towards a neurobiological difference between the mechanisms of SCS and peripheral nerve stimulation as in TENS. An additional mechanism which gives a possible explanation for the stronger SEP inhibition by SCS, is its effect on descending serotonergic fibers (37).

Similar to the results described by Buonocore et al (14), the inhibitory effects of SCS and TENS were more pronounced in the present study at the amplitude P40N50 than at the amplitude N50P60. The P40 is generated in the area 3b, the primary sensible field on the medial side of the gyrus postcentralis. The P60 is thought to be generated symmetrically within the convexity of the parietal cortex. The generators of the P60 thus have a much bigger spatial extension than those of the P40 wave (38). This might lead to a more unspecific response, limiting its clinical significance. The amplitude P40N50 is the only cortical response regarded as suitable for clinical purposes (39).

In the present study, as in others (14,29), the SEP latencies were not influenced by stimulation. Latencies are impacted when the saltatory conduction of a nerve is compromised, a phenomenon which can be initiated by various pathological processes, particularly demyelinating diseases. As nerve fibers and pericarions are not influenced by neurostimulation, an effect on latencies cannot be expected.

Some limitations of the present study have to be addressed. First, the mechanism of regulation in the SCS and TENS devices are different. While the impulse duration was fixed and intensity of stimulation was regulated through the voltage in use in the SCS devices

in our study, the intensity of stimulation was regulated with the impulse duration in the TENS devices. Thus the exact shape of the single stimulus in SCS and TENS may have been unequal. However, in both instances, stimulation modes which are used in routine clinical settings were applied, the frequencies of stimulation were the same and both TENS and SCS were applied at the same intensities relative to PT and MT.

The difference between PT and MT in SCS was not statistically significant but showed a tendency towards significance. This means that the dose dependency of SEP amplitude inhibition only seems probable but is not proven. Apparently, the study is slightly underpowered to provide that evidence. The number of patients is relatively small, but it was based on a sample size calculation. With this sample size, 2 of the 3 principle questions could be answered.

In order to prove a correlation between SEP inhibition and the pain-relieving effect of SCS, pain scores collected directly under stimulation might have been more meaningful. Most patients, however, had difficulties in distinguishing the unpleasantness caused by SEP stimulation and their usual pain, so that these (direct) pain scores were not reliable. We therefore chose to ask the patients for a more global estimation of their pain with and without SCS.

CONCLUSION

In conclusion, SCS exerts a significantly stronger inhibition of SEP amplitudes than TENS. The present data hint at a dose dependency of SCS-induced SEP amplitude inhibition. No clear correlation was found between SEP amplitude inhibition and pain relief by SCS. Further studies should also focus on electrophysiological effects of subcutaneous stimulation.

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