Scientific Review Article

Spinal cord stimulation in chronic pain syndromes

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Spinal cord stimulation (SCS) has been used for more than 30 years now, and although it has shown to be effective under certain well-described conditions of chronic pain, conclusive evidence on its effectiveness is still sparse.

There is a need for more prospective and methodological good studies, in order to prove SCS efficacy for new or still questionable indications and to reveal prognostic factors for successful application. Especially at this moment, when governments are trying to control and reduce their health care expenses, studies on the cost-effectiveness of SCS are important.

In contrast to the early years when SCS was applied by independent physicians exploring the field of neurostimulation, the importance of information exchange and coordination of studies has now been recognized. Recent technical improvements of SCS devices may positively influence clinical outcome.

Keywords: spinal cord stimulation; chronic pain; neurostimulation

Introduction

For more than 30 years now, neurostimulation devices have been used in the treatment of various chronic pain syndromes shown to be intractable to other treatment modalities. Neurostimulation includes electrostimulation of neural structures in- and outside the central nervous system (CNS), and encompasses various techniques such as Transcutaneous Electrical Nerve Stimulation (TENS), Peripheral Nerve Stimulation (PNS), Spinal Cord Stimulation (SCS), Deep Brain Stimulation (DBS) and cortical stimulation. In this article we will focus on the most commonly used and most established application of neurostimulation: SCS. The first report on the efficacy of SCS for pain relief,¹ resulted in a widespread rather uncritical use of SCS in the early '70s. This initial enthusiasm, however, was later replaced by a general pessimism on the efficacy of the treatment.^{2–5} Several reasons have contributed to this reappraisal of SCS therapy. For example the lack of distinct criteria for selecting patients, the high incidence of technical problems in the early SCS systems and a poor understanding of the underlying mechanism of SCS treatment. For some time, the application of SCS was confined to only a few dedicated centres and probably this concentration of activity resulted in an improved patient selection and

better understanding of the advantages and restrictions of SCS therapy.³ Better designed clinical studies in combination with refinements made in both electrodes and pulse generator devices, resulted in a regained popularity of SCS therapy in the past decade. The increase in the clinical application of SCS was accompanied by an increased interest of pre-clinicians in the mode of action involved in the pain releasing effect of SCS. Although the understanding of the basic mechanism behind the effects of SCS is still sparse, both experimental and clinical studies have indicated that SCS is mainly beneficial in pain of neuropathic and ischemic origin.

In this article we tempt to give an overview on the current state of SCS therapy, including recent experience on its efficacy in different pain syndromes and the present state of knowledge regarding underlying physiological and neurochemical mechanisms. Also attention will be paid to prerequisites for applying SCS, cost- and reimbursement issues and to the international neuromodulation network.

Equipment and implantation technique

A spinal cord stimulator consists of an electrode lead, surgically implanted epidurally at a vertebral level which is dependent upon the location of the pain, and connected by an extension lead to a receiver or pulse

generator. Electrical pulses transmitted to the electrodes excite fibres in the spinal cord, thereby generating paresthesia in the pain region and decreasing of the pain sensation.

Electrodes

Recent developments in SCS technology have resulted in a wide choice of electrodes in order to achieve adequate paresthesia coverage for various clinical pain syndromes. Available electrodes can be subdivided into percutaneous and plate-type. Early systems required laminotomy for electrode placement. Nowadays, most leads can be placed percutaneously and only introduction of the plate type electrodes still requires a laminotomy. The first percutaneous electrode leads were unipolar, with the cathodal contact placed epidurally and the pulse generator functioning as the anode. However, electrode migration, mostly resulting in a decrease of therapeutic response, became a significant problem in these single contact leads. In patients with repeated episodes of electrode migration after surgical repositioning, a laminotomy was necessary to suture the electrode to the dura. (personal communication M Staal). The development of percutaneous electrode arrays with multiple contacts has significantly improved clinical results.⁵⁻⁷ These leads with four or even eight electrode contacts have the possibility of switching the anode-cathode combination, and can therefore compensate for minor changes in the position of the electrodes.

Pulse-generators

The pulse generator is the power supply for the SCS system. It can be either a fully implanted pulse generator (IPG) containing a battery and electronic circuitry, or an external transmitter containing a battery that sends radiofrequency signals to an implanted receiver (RF system). In the early stimulator devices, programming of stimulation characteristics was limited. In recent models various parameters like pulse width, pulse frequency, pulse rise time etc. can be modified. Recently, dual channel pulse generators have become available, allowing independent parameter control of each channel. Patients provided with an IPG can switch their stimulators on and off by using a magnet, or by using a patient programmer that allows them to adjust the parameters within limits set by the physician. The power requirements of an SCS system depend on the number of activated electrodes, the parameters selected and the amount of time the patient uses the SCS device. The mean predictable lifetime of an IPG varies from 2 to 7 years, depending on patient usage,⁸ and successful SCS therapy may therefore require several surgical IPG replacements. Careful parameter selection and minimum effective output can greatly extend battery life. The development of rechargeable systems may contribute to an improvement in the cost-effectiveness of

SCS therapy. In contrast to IPG's, RF systems are externally powered and surgical replacements of batteries are not required. For an RF system an antenna has to be placed over the skin in the region of the implanted receiver. It is therefore not possible to use the system while swimming or showering. The advantage of an RF system is that higher voltages can be administered, and should therefore be used when stimulation energy requirements are high.

Although the potential for optimal electrode lead positioning has increased by the development of leads with multiple contacts, the large number of available contact combinations can make test procedures time-consuming. A longitudinal lead with four contacts enables 65 anode-cathode combinations, and in an octopolar lead more than 6000 combinations can be selected. Systematic documentation of stimulation parameters by several physicians and advanced computer analysis has provided a more knowledge based approach for selecting the potentially best electrode configuration.⁹⁻¹⁴

Surgical procedure

Implantation of a spinal cord stimulation system is usually performed with the patient in the prone position, although in some cases when patient's spinal anatomy requires a more anterior flexion of the spine, a lateral or even sitting position of the patient may provide better introduction of the epidural electrode lead.

Electrode lead implantation by percutaneous puncture is carried out under fluoroscopic control. The lead is introduced through a Touhy needle into the epidural space on a vertebral level depending on the location of the pain. The tip of the electrode can be manipulated into the intended position. Once this is achieved, the Touhy needle will be removed. The electrode lead will be anchored to the interspinous ligament or to the lumbothoracic fascia in order to increase the intraspinal stability of the lead and thereby decrease the risk of electrode migration. For implantation of plate electrodes, a small laminectomy may have to be performed. After repeated external test stimulation, to ensure the electrode has not moved, the lead will be connected to a receiver or pulse-generator by a subcutaneously tunnelled extension lead. This receiver or pulse generator is implanted in a subcutaneous pocket at a site chosen with physician and patient preferences, mostly in the lateral abdominal wall or subclavicularly.

Electrical stimulation of the spinal nerves generates paresthesia in related body areas, felt by the patient as a pleasant tingling sensation. Superposition of stimulation paresthesia upon patients topography of pain was found to be a statistically significant predictor of successful pain relief.⁵ Therefore, exact positioning of the electrode in relation to the spinal cord anatomy is essential. Since communication with the patient is necessary to obtain information about

the distribution of the produced paresthesia, the operation has to be performed under local anesthesia.

Electrical properties of the spinal cord

The effects of SCS are based on the 'gate control theory' of Melzack & Wall.¹⁵ The theory directed attention to the active role of large cutaneous A β afferents in the suppression of pain sensations. These large fibres enter the spinal cord via the dorsal roots (DR) and proceed towards the dorsal column (DC), where they branch into an ascending and a descending part. By stimulating the spinal cord, both DR and DC fibre activation can evoke paresthesia in corresponding body areas. Since DR fibres mainly correspond to a single dermatome, stimulation of these fibres will result in a segmental distribution of paresthesia. DC fibres on the other hand, contain information from a large number of dermatomes, and activation will therefore result in a broader paresthesia coverage.

Holsheimer *et al*⁹⁻¹² have studied the activation of both DR and DC fibres in a computerized model of the spinal cord. By this model they predicted that at a small electrode-to-spinal cord distance (<2 mm), for example in the cervical spinal cord where the cerebro-spinal fluid (CSF) layer is small, the threshold for excitation of DR and DC fibres is almost identical. However, when CSF width increases, the stimulus threshold for both DC and DR fibres increases, but the DC fibre threshold rises more than the DR fibre threshold. Under these conditions, DR fibres in the neighbourhood of the cathode will usually be activated first because of their lower threshold, and this will result in a segmental paresthesia coverage. When increasing the stimulus strength in order to activate also the DC fibres, unpleasant sensations and motor effects may occur, since SCS not only activates large cutaneous fibres, but DR related proprioceptors as well. Therefore at CSF widths >2 mm, which is the case at spinal levels other than the cervical area, DC stimulation may be limited by motor responses due to activation of DR fibres.¹¹

Since paresthesia has to cover the painful area for successful pain relief, it is important especially in complex and widespread pain patterns, as for example in reflex sympathetic dystrophy, to enhance DC stimulation in order to achieve broad and bilateral paresthesia coverage. Increasing DC activation can be achieved by decreasing the electrode-to-spinal cord distance, or by modifying electrode geometry in such a way that the changed electrical field favours DC activation. Reducing the space between the epidural electrode and the spinal cord can be obtained by the introduction of large electrode leads, or by the placement of two or three percutaneous leads in parallel, thereby pushing the dura mater towards the spinal cord.^{12,13} When using the generally accepted quadripolar percutaneous leads with a rostro-caudal contact array, a lower DC fibre threshold can be favoured by tripolar stimulation with a guarded electrode arrangement (anode-cathode-anode).⁵

The computer model of Holsheimer has enabled the analysis of various electrode configurations, which resulted in suggestions on the design of electrodes that may promote DC stimulation while limiting DR stimulation. As also observed by Law,¹³ they found that a narrow bi-or tripole with small contact separations (2–2.5 mm instead of the standard 6–7 mm), increases DC fibre stimulation.^{11,12} A drawback, however, is that this electrode design strongly increases the stimulation current and voltage needed.¹²

Another electrode design that may limit the spread of stimulation to the DR, is the transverse tripolar lead (TLL). For introducing this plate type lead, a laminotomy is required. The TLL consists of a central cathode flanked by an anode on either side. The cathode inducing nerve fibre depolarization is closest to the DC, whereas the lateral anodes inducing hyperpolarization and inhibition are closest to the DR. This will result in a suppression of DR fibre activation and enhance the stimulation of DC fibres. When powered by a dual channel pulse generator, the voltage applied to each electrode pair can be varied independently, making it possible to move the recruited area to either side of the DC. TLL thereby enables steering of paresthesia to either side of the body, and since DC fibres are stimulated selectively, a broad paresthesia coverage can be obtained. The predicted results of the TLL have recently been affirmed in a clinical study,¹² and the impact of this newly designed electrode seems promising.

Although the computerized model of Holsheimer and co-workers has significantly contributed to an improvement of the technical performance of SCS systems, it does not take into account the variability of spinal cord anatomy among subjects. Clinical distinction between DC and DR fibres is not always possible, since in reality often more than one structure is simultaneously stimulated. This is for example the case at a lower thoracic or lumbar level where cauda equina DR fibres come in close contact with DC fibres.⁶ Furthermore, Meyerson¹¹ found that by increasing the stimulus, motor effects as a result of DR fibre activation may sometimes be replaced by paresthesia. Therefore, many technical challenges remain, and future experimental and clinical studies are still needed.

Mode of action

In contrast to the recent technological advances in neurostimulation systems, the knowledge of SCS related neurochemical pathways for pain relief is still fragmentary and recent experimental data are sparse. According to clinical experience, however, SCS has shown to be more effective in neuropathic pain conditions than in nociceptive pain,¹⁶ but it is particularly effective in ischemic pain despite the fact that this latter pain syndrome is thought to be of principally nociceptive origin.¹⁷

In the following paragraph the most important indications for SCS treatment will be discussed

together with some data on what is known about basic mechanisms that underlie the pain relieving effect of SCS. Because of the basic differences between neuropathic and ischemic pain states, these two pain conditions will be discussed separately.

In general, the inhibitory effects of SCS on the transmission of pain, may be the result of a segmental mechanism in the spinal cord, the result of supraspinal regulatory systems, or both. Clinical and experimental data do not support the idea of a simple conduction blocking mechanism in the spinal cord as suggested in the gate control theory of Melzack and Wall, although the major part of the pain inhibitory effect may be located on a segmental spinal level.^{17,18} Studies have shown that the involvement of an endogenous opiate mechanism for explaining the effects of SCS is not very likely. There are many observations that the pain relief following a period of SCS was not reversed by the opioid antagonist naloxone. However precautions have to be taken when interpreting the results of the antagonistic effect of naloxone, since naloxone exerts its antagonistic effect mainly at μ -receptors. Activation of more short acting opioids such as α - or κ receptor agonists (met-enkephalin or dynorphin) can therefore not be excluded because naloxone has low affinity for these receptors.¹⁹ SCS has shown to be mainly effective in neuropathic pain conditions, and this pain state is considered to be relatively insensitive to opioids.^{20,21}

Several other neurotransmitters in the central neurosystem have been proposed to be involved in the pain alleviating effect of SCS. Experimental studies have shown that substances as for example gamma-amino butyric acid (GABA), serotonin and substance P, noradrenaline as well as glycine seem to increase in the spinal dorsal horn after the use of SCS. Especially in neuropathic pain the release of GABA may be of importance. Although Simpson²² found no increased GABA levels after 90 minutes of SCS, others have reported a significant release.^{23,24} Stiller²⁴ indicated that the development of allodynia, a common symptom in neuropathic pain states, may be linked to a decreased spinal release of GABA. They suggested that an SCS induced release of GABA can be the explanation for the suppression of allodynia observed in rats after SCS. Similar mechanisms could also be involved in the SCS induced alleviation of pain in patients with peripheral neuropathy. The release of GABA was found to be most marked in the fraction following the stimulation period. This delay in GABA release may explain the prolonged pain relief observed after a 20–40 min period of SCS, and might indicate that the release of a preceding transmitter or potentiating substance is needed. Such a substance may be serotonin. In studies on decerebrated cats, Linderöth²³ found a significant release of serotonin as a result of SCS. In these experiments no release of substance P was found, but in the intact cat, however, a significant release was induced. This may indicate that substance P is also involved in the beneficial

effects of SCS on pain, but that this effect requires a supraspinal loop. Almost all of the studies on the neurochemical mechanism behind SCS have been performed in animals. Generalization of these findings to the clinical use of SCS in humans remains to be demonstrated.

The mechanisms involved in suppression of pain from ischemic origin is probably different than that for neuropathic pain. In SCS from ischemic diseases, both pain relief and an increased blood flow have been observed. There is some evidence that the pain reduction in ischemic pain may be secondary to the increased micro-circulation,²⁵ but the exact relationship between pain and ischemia is not clear. The increase in micro-circulation may be the result of antidromic stimulation of dorsal root afferents causing vasodilatation, but it may also be caused by modulation of the autonomic function, i.e. the decrease in sympathetic activity, resulting in vasodilatation and subsequent pain relief.²⁵ Other investigators also speculated on the importance of a local or systemic release of vaso-active substances including vaso-active intestinal polypeptide (VIP), substance P, prostaglandins and more recently calcitonin gene-related peptide (CGRP). It is possible that several mechanisms are active simultaneously, with both inhibition of autonomically mediated vasoconstriction and activation of vaso-active substances.²⁶

The hypothesis that SCS has a direct effect on the suppression of the pain receives little support. This theory suggests that pain reduction will decrease the sympathetic activity resulting in peripheral vasodilatation, which further decreases the ischemic pain.^{27,28} However, ischemic pain seems to be substantially of nociceptive origin, which is a type of pain known to be resistant to SCS, making a direct effect of SCS on pain not very likely.²⁹

The most promising results for SCS in peripheral vascular disease (PVD) have been obtained in cases where a vasospastic component is dominating. Linderöth *et al*³⁰ applied SCS in a rat model, and they found that SCS had a positive effect when it was applied before the appearance of ischemia. The authors noted that this finding has been confirmed by clinical studies in patients treated with SCS for Raynaud's disease, where a much better effect from stimulation was obtained when SCS was used before the provocation of ischemia.

General indications and clinical results

Indications

The number of chronic pain syndromes for which SCS has been applied is enormous. Indications most frequently described in literature are the neurogenic and mixed pain conditions like failed back surgery syndrome, reflex sympathetic dystrophy, post-herpetic pain, peripheral nerve injury, post-amputation pain and spinal cord lesions. There is also an enormous

amount of literature on SCS for ischemic pain conditions such as peripheral vascular disease and angina pectoris. In general SCS is indicated in cases of chronic pain where other, more conventional therapies, have failed and no other options are left to treat the underlying disease. It is important that invasive therapies for pain management like SCS are used within the context of the pain treatment continuum set by the World Health Organization (WHO), using less invasive treatments before more invasive ones.¹⁶

In this paragraph, the clinical results for the different pain syndromes will be discussed as well as the selection criteria for patients who might benefit most from treatment with SCS therapy.

Clinical results

Neuropathic pain conditions

Reflex sympathetic dystrophy An indication in which SCS has shown promising results is reflex sympathetic dystrophy (RSD). RSD, nowadays referred to as complex regional pain syndrome (CRPS), is a pain state characterized by several symptoms which can grossly be divided in sensory disturbances like hyperaesthesia, hyperanalgesia and allodynia, in loss of motor function and trophic changes. The role of SCS in the treatment of RSD is confined to the reduction of pain. As it is the natural course of the disease, the pain expands to multiple body parts. Since effective SCS has to cover the painful area, it is important that in RSD paresthesia regions also include areas likely to become painful. To anticipate the changing focus of the pain, multiple electrodes should be used, carefully positioned for obtaining broad and bilateral paresthesia.^{11,31} The use of dual channel devices allowing independent control of the electrical parameters can yield a major advantage, since voltage requirements for the different body parts may vary. In patients with RSD there is a significant risk of minor trauma in the spinal canal caused by the implantation of the SCS system. The pain that may be experienced as a result of the implantation procedure can evoke reflex vasospasm and consequent ischemia in the spinal cord, causing paralysis, ataxia or allodynia. In order to reduce neurological morbidity, adequate pre- and intra operative anaesthesia while implanting an SCS device is important.³¹ Also should RSD patients be clearly informed about these risks before applying SCS.⁶ Despite the risks, and above all a significantly higher infection rate compared to other SCS indications, the results of SCS in RSD are successful. Robaina³² found that in the long run results from SCS treatment are better than those obtained with more conventional treatment modalities like sympathetic blocks and sympathectomy.

Kumar²⁶ was also of the opinion that SCS is superior to ablative sympathectomy in the management of RSD. At a mean follow up of 41 months, he found in all 12 patients studied good to excellent pain relief as a result of SCS treatment.

Spinal cord lesions Results of SCS in spinal cord lesions are disappointing. Kumar,³³ Richardson³⁴ and Cole *et al*³⁷ could not demonstrate good effects, although results of Richardson's study are possibly distorted by the fact that only one patient out of 10 had paresthesia in the pain region, which is, as formerly mentioned, essential for good results. Barolat³⁵ found pain due to spinal cord injury by far the worst responder of the chronic pain syndromes he had studied.

In a study of Cioni³⁶ it was demonstrated that patients with complete spinal cord lesions did not react on treatment with SCS and that patients with an incomplete lesion had a mean success rate of 23.5% on the long term. The only positive notes are from Buchhass³⁸, who found SCS to be successful, but only when vegetative components predominated.

The reason for the poor results of SCS in this pain syndrome can simply be explained by the fact that fibres that have to be activated by SCS often no longer exist. In total interruption of the primary afferents, the fibres are often degenerated from the lesion up to their synapses with secondary neurons higher in the central nervous system. Before indicating SCS in these patients, it seems important to check the integrity of the fibres by careful clinical examination, if necessary evoked potential recording, and by measurements of the nociceptive flexion reflexes.¹¹

Post herpetic neuralgia Meglio³⁹ reported satisfactory pain relief in patients with post herpetic neuralgia at 3 months after implantation. Although data were few, in other studies the results of SCS for post-herpetic pain seem not to be very encouraging.^{22,23} Failures might be due to the fact that stimulation for this indication is often perceived as a stinging, unpleasant sensation and to the fact that the patients are often old and debilitated.⁶

Post amputation pain There are almost no recent studies on the effect of SCS in stump or phantom limb pain. Studies performed in patients with post amputation pain showed that SCS had almost no effect on the phantom limb sensation but that SCS might have some beneficial effects on stump pain. Nielson,⁴⁰ for example, published a study in which he reported excellent pain relief in five of six patients with stump pain; the phantom sensation however persisted in all patients. He indicated however, that results of his study have to be maintained on the long term and reinforced by other successful cases in order to demonstrate a clear cut advantage of SCS treatment. In 1980, Krainick studied the effects of SCS in a group of 64 amputees.⁴¹ In 29 patients (45%) he found an initial pain relief of more than 50%. After 5 years follow up this percentage had decreased to only 20%. This indicated that the results of SCS were not favourable compared to other operative methods for relieving post amputation pain.

Failed back surgery syndrome The indication for which SCS is most often applied is the failed back surgery syndrome (FBSS). This syndrome which may occur after lumbar surgery is thought to be primarily due to intra and/or extradural postoperative fibrosis.⁴² FBSS is an example of a mixed pain condition, mostly of neurogenic origin but in which nociceptive components might be present as well. Most studies on SCS for FBSS include patients who have undergone previous lumbar surgeries but who are still suffering from chronic low back and/or leg pain.

Although FBSS is a broad diagnostic category, and SCS selection criteria differ widely among studies, the overall results are that approximately 50–60% of the patients with FBSS report a >50% pain relief with SCS at long term follow up visits.⁴³ Most studies have included patients with uni- or bilateral radiating pain, predominating over axial low back pain. Achieving stimulation overlap of the low back is recognized as technically difficult. Although new electrode designs may offer the opportunity for good results in this region as well, axial pain is commonly thought to be of nociceptive origin and may be less responsive to spinal cord stimulation than is pain associated with deafferentation or neural injury.⁴⁴

Despite the extensive literature on SCS for FBSS, only one randomized study has yet been performed.⁴⁵ In this study SCS was compared to re-operation in patients with persistent radicular pain (with and without low back pain) following lumbosacral spine surgery. The primary outcome measure was the frequency of cross over to the alternative procedure, if results of the first intervention were unsatisfactory after 6 months. Initial results for the first 27 patients showed a statistically significant advantage for SCS over re-operation.

In a recently performed prospective study in patients with chronic back and extremity pain by Burchiel,⁴⁶ a variety of pain and functional / quality of life measures were compared before and after SCS treatment. Complete 1 year follow up data were available for 70 patients, and in 55% of the patients at least 50% pain relief was achieved.

Ischemic pain

At present there are two indications for spinal cord stimulation in ischemic pain syndromes: peripheral vascular disease and angina pectoris. The etiologies of ischemia in both groups are atherosclerosis, vasospastic disease or degenerative changes in the vessel wall due to other disease like for example diabetes or systemic sclerosis.⁴⁷

Peripheral vascular disease (PVD) Patients suffering from PVD can be subdivided in four groups according to the Fontaine classification. The main subjects to be selected for SCS are patients in group III of this classification, i.e. patients with rest and night pain without tissue involvement.²⁶ Patients with only

intermittent claudication or severely disabled patients who have also tissue loss like gangrene and ulcers respond less successfully to SCS treatment.⁴⁸ Patients with stage IV disease may respond to SCS, since ischemic ulcers <3 cm in diameter have been shown to heal well in response to stimulation.^{49,50} In patients with established gangrene, no effect from SCS will be obtained.^{27,49} Studies on the effects of SCS on peripheral vascular disease (PVD) have reported that about 80% of the patients experienced good or excellent pain relief at 1 year follow up.^{27,49–52} Patients with pain due to vasospastic disorders (Raynaud's disease) may benefit most from SCS.³²

However, one must be sceptical when generalizing data obtained from separate uncontrolled studies without standardized criteria for patient selection and data collection.

In a prospective Dutch multicentre trial for example, the excellent findings of earlier studies could not be confirmed. In the Dutch trial patients with critical limb ischemia were randomized to either SCS treatment or to conservative medical treatment. At a 2 year follow up, no statistically significant differences could be observed with regard to limb salvage, pain reduction or improvement of quality of life. They concluded that with selection methods based on clinical and macro-circulatory data, no superiority of SCS could be proven over good organized conservative treatment. Micro-circulatory measurements, however, seemed to be a better predictor of limb salvage.⁵³

Jivegard *et al*⁵⁴ also performed a prospective randomized control study to test the effect of SCS on limb salvage in patients with inoperable PVD of atherosclerotic or diabetic origin. Macro-circulatory differences were not different in the SCS group compared to the control group treated with analgesics. Only in the SCS group long term pain relief was observed, but limb salvage at 18 months follow up was not significantly improved by SCS. In patients without arterial hypertension, however, amputation levels may be reduced by SCS.

Jacobs^{55,56} has studied capillary density and diameter and red blood cell velocity in nutritional skin capillaries. It was shown that after SCS, the number of skin capillaries perfused had increased as well as the skin capillary red blood cell velocity. Improved skin nutritive flow resulted in healing of ulcers of moderate size.

Transcutaneous oxygen tension (TcPO₂) for the measurement of oxygen delivery, has also shown to be a useful tool in predicting the effect of SCS in PVD. In a randomized controlled study, Claeys and Horsch⁵⁷ tested 86 Fontaine stage IV patients to investigate whether initial TcPO₂ measurements help to predict clinical outcome in patients treated with SCS. They found that patients with a baseline TcPO₂ > 10 mmHg responded significantly better at 12 months follow up with respect to pain relief, ulcer healing and quality of life. In an earlier study they also reported that TcPO₂ changes correlated with the presence of adequate

paresthesia in the painful area.⁵⁸ The predictive value of TcPO₂ measurements was confirmed by Fiume *et al*⁵⁰ and by Kumar *et al*.²⁶ The latter investigators found that excellent pain relief during trial stimulation combined with an increase in TcPO₂ of 10 mmHg or greater, as well as an increase in peak flow velocity of 10 mm or more were significant predictors for long term pain relief.

Angina pectoris Angina pectoris is the predominant clinical symptom accompanying ischemic heart disease. The anginal pain is often related to an imbalance between myocardial oxygen supply and demand, which in most cases is caused by an atherosclerotic obstruction of the coronary arteries. It can however also be related to a vasospastic disorder, as is probably the case in patients with syndrome X. SCS has shown to be an effective additional tool in patients who are chronically disabled by their anginal complaints. These patients with so-called intractable angina, have significant coronary artery disease with at least one stenosis >70%, and have anginal complaints according to class III–IV of the New York Heart Association (NYHA). SCS has shown to reduce the frequency and severity of the anginal attacks, thereby reducing the necessity for the intake of short acting nitrates and improving the exercise capacity.^{59–61} Although this symptomatic improvement will certainly have a beneficial effect on the quality of life, it will not necessarily improve the prognosis of patients with intractable angina pectoris. If the effect of SCS in angina pectoris is confined to the relief of pain, the treatment may be potentially dangerous, since the suppression of pain might mask the protective anginal warning signal. Sanderson,⁶² however, reported that SCS is a safe therapy, since in his study there were three deaths out of a group of 23 patients over a period of 45 months and this does not appear to be an excess of sudden deaths in this group of patients. In another study by Andersen,⁶³ three patients who had a myocardial infarction reported the pain as different and that it could not be relieved by SCS. Moreover, several studies found evidence for a reduction in myocardial ischemia by SCS therapy. Ambulatory electrocardiographic (ECG) monitoring during 24 h and 48 h showed a decrease in the number and duration of ischemic episodes.⁵⁹ During treadmill exercise testing it was found that SCS significantly reduced the depression of the ST segment, which might be the result of an increased oxygen supply to the heart.

In a positron emission tomography (PET) study by Hautvast,⁶⁴ it was found that after a 6 week period of stimulation, the total cardiac flow remained unchanged, but a redistribution of this flow was found in favour of the ischemic regions. Just recently the results of a study of Mannheimer were published.⁶⁵ In this study 104 patients with severe angina pectoris were randomized to either SCS treatment or coronary bypass surgery (CABG). Six months after the

operation, no difference was found between the SCS and CABG group with respect to symptom relief. Although the CABG patients had a better exercise capacity and less signs of ischemia during exercise, there was a lower mortality rate in the SCS group ($P=0.02$). The authors therefore concluded that SCS may be an alternative therapy for patients who have an increased risk of complications from CABG.

In contrast with other reports on the effect of SCS for pain relief, the majority of the studies on SCS for angina pectoris were prospective and often controlled or randomized. In most trials no percutaneous trial stimulation was performed and yet an overall success rate of 80–90% was found. Therefore, angina pectoris is a condition that turned out to be a cardinal indication for SCS.²⁵

Patient selection

Identification of patients in whom a reasonably long-term pain relief can be expected is difficult.^{66,67} This is especially the case in chronic pain syndromes, which is a multidimensional phenomenon, frequently complicated by psychological issues. Selection criteria for SCS treatment therefore often include psychological or psychiatric screening in order to exclude patients in whom the nature of the pain complaints are primary of psychological origin.^{68,69} Depression, anxiety and sleep disorders may be normal reactions when experiencing chronic pain, and it is therefore not simply a question of identifying psychological factors but one of assessing their importance.⁷⁰ It is generally assumed that patients with the least evidence for psychological involvement, have the most favourable response on SCS treatment.

The precise psychological and psychosocial features that correlate with successful pain relief during SCS have not been clearly defined. Although most studies reported they had used psychological screening prior to SCS implant, the exact tests used for this screening are rarely mentioned. Moreover, the poor methodological set up that attend the earlier SCS studies, questions the actual value of the used tests. Factors found to be prognostic within one study have not proven to be generally predictive of SCS outcome.

More recently, prospective studies have attempted to elucidate the problem of which test to use for determining whether an SCS device has to be implanted or not.^{66,71–73} Dumoulin *et al*⁷¹ developed a 24 item scale to predict SCS outcome and found a high correlation (0.8, with P value = 0.000) between the predicted and the actual outcome of SCS therapy in FBSS patients 6 months after implantation.

Burchiel⁶⁶ found that patient age, the Minnesota Multiphasic Personality Inventory depression subscale and the evaluative subscale of the McGill Pain Questionnaire (MPQe) are important predictors of 3 months postimplant pain status. Younger patients who are less depressed are more likely to receive good pain relief from SCS, and patients who consider their overall pain to be more intense are more likely to

report larger improvements in VAS levels after 3 months of stimulation.

Like Olson,⁶⁷ North⁷² reported some significant associations between psychological test results and the outcome of a therapeutic trial of stimulation, but he found that psychological testing could not explain the variance in long term outcome. He concluded that there was little evidence for selecting patients for SCS on the basis of psychological testing. Psychological preparation of the patient for the SCS implantation procedure might however have some influence on SCS outcome.³⁵ It is important that patients are informed on the possible risks and complications of SCS implantation, that they can deal with the SCS system and understand pain measurement scales that are used to evaluate the effects of SCS therapy.

Trial stimulation is probably still be the best indicator of prognosis.^{4,48} This opinion was confirmed by a study of Barolat³⁵ who found that only patients with at least 50% pain relief at the time of implant were able to maintain the results over time. Different from most series on pain relief, however, Barolat did not use trial stimulation prior to the permanent implant. He reported that in his study the percentage of patients who never felt any pain relief and therefore would have not been implanted by other researchers was 20%. From the patients who initially show only marginal effects (<50% pain relief) very few experienced any pain relief on the long term. These data support the use of a trial period, but the question is how long the trial should be. Literature review showed variations in trial duration ranging from 1 day to more than 2 weeks.⁴³ The rationale for a longer trial, up to several weeks, is that there is a tremendous placebo response to any pain management technique. However, placebo responses are usually short lived and a longer trial would be expected to reduce the number of false positives. The possible advantage of extended trial periods should however been weighted against the higher infection rate associated with percutaneous trials.²²

When patients are considered to be candidates for SCS therapy, there must be an objective basis for the pain complaints,^{33,69} and, as mentioned before, the integrity of the fibres to be stimulated must be guaranteed.

In general, the presence of other implanted stimulating devices like cardiac pacemakers or defibrillators, are regarded as a contra-indication for SCS therapy. In a study of Mazala⁷⁴ however, no adverse reactions were found when using SCS in a patient wearing a cardiac pacemaker. The epidural lead was placed in the thoracic area, and SCS settings were increased up to the maximum tolerated by the patient. The patient's cardiac rhythm and function were monitored for three days and no complications were found.

In patients already provided with an SCS system, MRI scanning seems to be contra-indicated. Reasons for this include the induction of electrical current and excessive heating of the implanted material resulting in

a thermal tissue burn/injury. In patients with chronic pain syndromes, however, MRI scanning may sometimes be indicated, and data on the effect of MRI on implanted neurostimulators are therefore desirable.

Liem⁷⁵ described three patients with an SCS device who underwent MRI scanning. Before the scan was performed, the device was programmed to 0 V and turned off in patients with a fully implantable stimulator. In one patient with an RF system, the external transmitter and antenna were removed prior to the MRI. In none of the patients were adverse effects of scanning noted. Some stimulation parameters did change during scanning, but all were reprogrammable and did not affect patient well-being. It was concluded that MRI can be safely used in certain carefully selected circumstances. If the SCS device is in the scanned area, caution is recommended.

Good results from SCS therapy do however not only depend upon proper patient selection, but also upon thorough follow up in order to recognize and restore equipment failures or side effects, thereby creating optimal conditions for long term success.

Complications and side-effects

In their literature analysis on SCS for FBSS, Turner⁴³ found that complications occurred rather frequently but were of minor severity. The average complications rate found in the literature was 42% (20–75%). Reported complications were infections (0–12%, average 5%) and other biological complications which may include seroma at the IPG site, leakage of cerebrospinal fluid or hemorrhage (0–42%, average 9%). These events almost never resulted in life-threatening situations or new neurological loss. The majority of reported complications associated with SCS application are however device related. Electrode migration was found to be a major problem (0–75%, average 24%), and especially for the initially used monopolar leads this may require re-operation. In the electrode leads with multiple contacts, reprogramming of the electrode configuration by an external programmer will often suffice. This was confirmed by a study of Andersen,⁷ who found a statistically significant reduction in electrode displacements requiring operation in patients provided with quadripolar leads compared to patients having monopolar leads implanted. The use of plate type electrodes can also contribute to a reduction in the incidence of electrode migration.⁷⁶ Average rates of lead breakage and pulse generator complications were found to be respectively 7% and 2%. Burchiel⁴⁶ found that in 17% of the patients, the reported complications required surgical intervention. Comparison of the complication rate of older versus newer SCS systems appeared to be difficult.⁴³

General remarks on clinical studies

The first reports on the efficacy of SCS were, as for many new therapeutic modalities, descriptions of case

studies. Due to the initial optimistic results the therapy gained popularity and separate physicians started to study their own results, often combining data from patients with diverse etiologies of chronic pain. These published retrospective series vary greatly in reliability and methodology.³⁵ The results were often based on a relatively small amount of data, criteria for selecting patients were unclear and assessment of outcome or methods for data collection varied widely.

Moreover, most of the studies did not report the amount of time patients used their stimulator, and no study reported the association between amount of stimulator use and patients symptoms.⁴³ Based on these studies, it is difficult to draw reliable conclusions about the efficacy of SCS relative to other pain treatments or no treatment.⁴³ The need for more structured trials has however been recognized and although the number of well designed trials is gradually increasing, analysing the effect of SCS in a straightforward clinical study remains complicated.

Since the patients' perception of paresthesia in the painful area is critical for success, and placement of the SCS system is an invasive surgical procedure, a suitable control group cannot be defined. An additional complicating factor is the subjectivity of pain relief as a primary outcome measure. Objective criteria for the measurement of this multidimensional phenomenon are scarce and there is lack of consensus on how to measure pain best.^{66,67,69} It is suggested that for a better understanding of the effects of SCS and to improve patient outcome, future studies should focus on a specific pain etiology⁸ in prospective controlled or comparison trials. Multiple outcome dimensions have to be assessed by an independent observer, both pre-operatively and at uniform follow-up times, in order to identify prognostic factors and analyse SCS efficacy on the long term.^{4,43,66}

Critical considerations for SCS application

Prerequisites for applying SCS

The success of an intervention is not only dependent on its therapeutic potential, but also on how well the new technology will work in the field.⁷⁷ This means that beside the efficacy of the treatment under ideal conditions, it is also important to take into account the aforementioned patient compliance, and to what extent the treating physician or institution complies with the requirements for application of appropriate diagnostic and management tools. Accurate patient screening and diagnosis, especially for a complicated phenomenon as chronic pain, requires sufficient resources and facilities.

Many authors have stressed the importance of a multidisciplinary approach of chronic pain.^{16,43,69} Therefore specialized pain centres with experience in invasive neuromodulation techniques, are most suitable for applying SCS.

In a Belgian study on the therapeutic efficacy of SCS, it was found that patients treated in teaching

hospitals had a significantly better outcome of SCS therapy than patients treated in a general hospital. In the opinion of the authors this discrepancy might have been caused by the difference in expertise of the implanters, since in the general hospitals less patients were operated when compared to the teaching hospitals.⁶⁸

Regular follow up evaluations are also important for a successful outcome of SCS therapy. This implies a good documentation of patient data. Before implanting an SCS device, one should therefore consider if proper follow up can actually be guaranteed in their institution in terms of time, equipment and the availability of the physician or a capable back up.

Reimbursement

Although SCS has proven to be effective for several types of chronic pain, the availability and accessibility of SCS devices for patients who might benefit from the therapy is still a major problem. In most countries the costs for an SCS device are not covered by the government or by insurance companies. At present Switzerland and Belgium are the only two countries with an official reimbursement system for SCS devices.⁷⁸

Because of the increased use of SCS devices and therefore growing annual expenses, the Belgian health authorities decided to perform a nation-wide study on the incidence, indications and efficacy of SCS therapy. The current conditions for reimbursement of SCS costs in Belgium are: (1) pain of central neurogenic origin that is refractory to behavioural, surgical or drug treatment; (2) a positive response to a 1 week period of trial stimulation; (3) a sufficient long life expectancy and (4) exclusion of psychiatric contra-indications as assessed by an independent psychiatrist.⁶⁸

Medical treatments are increasingly subjected to economic evaluations. To get SCS devices reimbursed, it is therefore not only important to perform studies on the efficacy of SCS treatment, but also on the costs of the procedure.

Cost-effectiveness

Despite the increase in economic considerations of the government when implementing new technologies, there are hardly any studies on costs of SCS therapy in relation to the benefits or effectiveness of the therapy. The relatively high initial expenses proceed from the costs of the SCS device and from the implantation procedure in combination with a period of hospitalization. However, successful SCS therapy may, in the long term, result in a decreased morbidity with less frequent hospitalizations, a reduction in medication use, improved quality of life and possibly return to work.

In a retrospective study of Bell,⁷⁹ on the medical costs of SCS therapy compared to alternative regimens

of interventions in patients with FBSS, it was found that on average SCS pays for itself within 5.5 years. For clinically successful SCS therapy, however, this period was only 2.1 years. In this study, the amount of pain relief or the improvement in quality of life, was not taken into account.

In a study of Midha⁸⁰ on the efficacy and costs of SCS for patients with spinal cord injury, no favourable results could be found. In these patients SCS did not produce long term relief of spasticity or pain, and this low efficacy in combination with the high initial costs of SCS implantation, suggested that the procedure would not be cost effective.

This again stresses the importance of proper indication and patient selection. Sufficient expertise of the treating physician, may result in better SCS outcomes and thereby increase the cost-effectiveness of the procedure.

International network

In order to improve the application of SCS, a group of scientists and clinicians recognized the importance of coordination and exchange of experiences.

This resulted in a first international congress on this item in 1989 in Groningen, The Netherlands, followed by the foundation of the International Neuromodulation Society (INS) in 1990 and the American Neuromodulation Society (ANS) in 1994.

The objectives of these societies are to exchange mutual experience in research and clinical practice of neuromodulation techniques like SCS, to promote scientific research and education and come to a better definition of indications and development of practical guidelines. The collaborative efforts have resulted in the appearance of the first issue of the official journal of the INS, called 'Neuromodulation', in January this year. It is a multidisciplinary, peer review journal which has the purpose to advance the basic and clinical sciences covering the field of neuromodulation.

Conclusions

SCS has been used for more than 30 years now, and although it has shown to be effective under certain well-described conditions of chronic pain, conclusive evidence on its effectiveness is still sparse.

There is a need for more prospective and methodological good studies, in order to prove SCS efficacy for new or still questionable indications and to reveal prognostic factors for successful application. Especially at this moment, when governments are trying to control and reduce their health care expenses, studies on the cost-effectiveness of SCS are important. In contrast to the early years when SCS was applied by independent physicians exploring the field of neurostimulation, the importance of information exchange and coordination of studies has now been recognized. Recent technical improvements of SCS devices may positively influence clinical outcome.

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