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Spinal cord stimulation for ischemic heart disease and peripheral vascular disease

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Abstract

Ischemic disease (ID) is now an important indication for electrical neuromodulation (NM), particularly in chronic pain conditions. NM is defined as a therapeutic modality that aims to restore functions of the nervous system or modulate neural structures involved in the dysfunction of organ systems. One of the NM methods used is chronic electrical stimulation of the spinal cord (spinal cord stimulation: SCS).

SCS in ID, as applied to ischemic heart disease (IHD) and peripheral vascular disease (PVD), started in Europe in the 1970s and 1980s, respectively. Patients with ID are eligible for SCS when they experience disabling pain, resulting from ischaemia. This pain should be considered therapeutically refractory to standard treatment intended to decrease metabolic demand or following revascularization procedures.

Several studies have demonstrated the beneficial effect of SCS on IHD and PVD by improving the quality of life of this group of severely disabled patients, without adversely influencing mortality and morbidity. SCS used as additional treatment for IHD reduces angina pectoris (AP) in its frequency and intensity, increases exercise capacity, and does not seem to mask the warning signs of a myocardial infarction.

Besides the analgesic effect, different studies have demonstrated an antiischemic effect, as expressed by different cardiac indices such as exercise duration, ambulatory ECG recording, coronary flow measurements, and PET scans. SCS can be considered as an alternative to open heart bypass grafting (CABG) for patients at high risk from surgical procedures. Moreover, SCS appears to be more efficacious than transcutaneous electrical nerve stimulation (TENS).

The SCS implantation technique is relatively simple: implanting an epidural electrode under local anesthesia (supervised by the anesthesist) with the tip at T1, covering the painful area with paraesthesia by external stimulation (pulse width 210, rate 85 Hz), and connecting this electrode to a subcutaneously implanted pulse generator.

In PVD the pain may manifest itself at rest or during walking (claudication), disabling the patiënt severely. Most of the patients suffer from atherosclerotic critical limb ischemia. All patients should be therapeutically refractory (medication and revascularization) to become eligible for SCS. Ulcers on the extremities should be minimal.

In PVD the same implantation technique is used as in IHD except that the tip of the electrode is positioned at T10-11. In PVD the majority of the patients show significant reduction in pain and more than half of the patients show improvement of circulatory indices, as shown by Doppler, thermography, and oximetry studies. Limb salvage studies show variable results depending on the stage of the trophic changes. The underlying mechanisms of action of SCS in PVD require further elucidation.

Keywords: Neuromodulation; spinal cord stimulation; ischaemic heart disease; peripheral vascular disease; pain.

Preface

Neuromodulation (NM) is defined as the recruitment of nerves through electrical stimulation as a therapeutic approach for patients with chronic non-fatal anomalies varying from neuropathic and ischemic pain to movement and psychiatric disorders. One of the therapeutic options is chronic electrical stimulation of neural structures, including peripheral nerves (PNS: peripheral nerve stimulation), the spinal cord (SCS: spinal cord stimulation) and part(s) of the brain (DBS: deep brain stimulation). Although the use of electrical current might be associated with empirical and medically obscure treatments, the value of chronic electrical stimulation of neural structures has been demonstrated on a long term base over the last 40 years. It sometimes shows dramatic, instant and long-lasting effects on pain, improvement of circulatory insufficiency or movement and psychiatric anomalies. It produces convincing improvement in quality of life and social rehabilitation.

Multidisciplinarity is the key word in NM. NM is applied by a variety of medical specialists: e.g. vascular surgeons, cardiologists, anaesthesiologists, rehabilitation specialists, neurologists, and neurosurgeons, supported by dedicated paramedical personnel. The clinical application and the background research require the ability to think and work together in an interdisciplinary way. This makes NM such an attractive, challenging and often a very rewarding concept. Nevertheless it is remarkable how little representatives of the various medical disciplines are engaged in NM despite its high level of efficacy in otherwise therapeutically refractory chronic anomalies. How is it that it is relatively unknown that “untreatable” angina pectoris or chronic back and/or leg pain (“failed back surgery syndromes”) is suitable for NM treatment? And why are so few neurosurgeons interested in NM? We sincerely hope that this monograph will draw the attention of the neurosurgical reader to two severe ischemic diseases: ischemic heart and peripheral vascular diseases (PVD). Both anomalies are very suitable targets for NM treatment with SCS. These patients have very little to loose (except their legs in cases of PVD). NM offers real possibilities for substantial pain relief and improvement of quality of life.

Part I: Spinal cord stimulation for ischemic heart disease

Introduction: Background and definition

Increased knowledge of the pathophysiology of ischemic heart disease has generated improved diagnostic opportunities, which in turn has promoted the development of a large armamentarium of therapies for this illness. However, to date ischemic heart disease is still one of the most substantial plagues, concerning morbidity and mortality, in the Western World [54]. In addition to the reduction in mortality from cardiovascular disease during the last three decades, the quality of life of patients suffering from ischemic heart disease has been improved. This can be attributed to improved primary prevention measures, such as lifestyle changes and treatment of risk factors for heart diseases, advances in pharmacotherapeutical and surgical treatment strategies. Subsequently, more patients survive their heart disease for longer periods of time, albeit ultimately without options for further treatment [72]. So, in general, notwithstanding the therapeutic merits usually supplying appropriate symptom relief in the majority of patients [83], in an increasing number of patients with ischemic cardiovascular disease the major goal of control of pain is not met [60]. These patients, with an unmet medical need, have severe disabling chest pain, occurring during minimal exercise or even at rest. They are suffering from chronic pain that is therapeutically refractory to standard therapies. The term "chronic stable refractory cardiovascular pain" has been designated to patients with severe pain, resulting from (coronary) artery disease that is uncontrollable by both pharmacological (aspirins, β-blocking agents, calcium-channel blockers, long-acting nitrates etc.) and revascularization procedures (percutaneous coronary interventions [PCI] and coronary artery bypass surgery [CABG]) [37]. However, the severity of pain is to the judgement of the patients. Therefore, the European Study Group on the treatment of refractory angina pectoris has recently redefined the cardiac disorder as: "a chronic condition characterized by the presence of angina, caused by coronary insufficiency in the presence of coronary artery disease, which cannot be adequately controlled by a combination of medical therapy, angioplasty, and coronary artery bypass surgery. The presence of myocardial ischemia should be clinically established to be the cause of symptoms" [46].

Patients enduring this condition are usually characterized by a long history of artery disease, have often been treated with revascularization procedure(s) previously, are in their sixties, predominantly male and, have on the average a slightly reduced left ventricular ejection fraction. Furthermore, as a result of an acute worsening of their disease, these patients frequently need hospital admissions [55]. Therefore, the search for and evaluation of adjunct therapies has to be encouraged in order to identify novel strategies which are capable of reducing the burden of ischemic pain and subsequently improve the quality of life, without adversely influencing the prognosis, of these often severely disabled patients.

For these patients suffering from chronic debilitating ischemic pain, refractory to conventional therapies such as pharmacological approaches and revascularization procedures, adjunct therapies have become available. One of the most promising of these additional therapies appears to be electrical neuromodulation, albeit that the accumulating body of clinical and experimental data is still not very dramatic, mainly related to the lack of studies with a large sample size. However, electrical neuromodulation has become accepted as an additional therapy for refractory angina pectoris in the ACC/AHA guidelines, since 2002 [28].

It is our purpose to discuss the literature on electrical neuromodulation for ischemic cardiovascular disease and provide practical strategies.

History of neuromodulation for ischemic heart disease

Since 1967 modulation of the nervous system has been performed to obtain a reduction in pain in ischemic cardiovascular disease [9]. Starting with transthoracic [58], or endoscopic [40, 78] denervation of specific parts of the sympathic nerve such as the stellate ganglion [79], gradually medical attention has become re-focussed on modulation of nerves. This may be performed by means of vagal stimulation [82], by creating a temporary sympathetic block through injections with local anesthetics into the stellate ganglion [14], or through application of electrical current on different sites (nerves, spine, skin, subcutis) of the body (i.e. 'electrical neuromodulation'). The latter is either executed by spinal cord stimulation (SCS) or by transcutaneous electrical nerve stimulation (TENS). Among the available adjunct therapies SCS may be considered as one of the most effective and safe adjuvant treatments for patients with ischemic cardiovascular pain resistant to conventional strategies [23, 52].

The first report on antianginal effect of SCS on the dorsal aspect of the spinal cord in patients with chronic refractory angina pectoris was published by Murphy and Giles, in 1987 [53]. They observed a reduction in both the frequency and severity of angina attacks in conjunction with a reduction in sublingual intake of nitrogen tablets. In contrast with the favorable results, the therapy initially met with great skepticism [45]. Since the nineties many authors have advocated SCS as an effective additional approach for patients chronically disabled by their angina [2, 7, 18, 19, 23, 28, 29, 31, 37, 45, 46, 48, 53, 55, 63, 69, 77, 83]. To date, in selected patients, SCS may even be considered as an alternative to bypass surgery [48]. However, in view of the partially understood mechanism of action, it is substantive to demonstrate the safety of SCS in patients suffering from chronic refractory angina pectoris, resulting from unmanageable coronary artery disease. Therefore, recent research has been performed to determine whether the observed electro-analgesic effect of SCS is accompanied by an antiischemic effect.

Effects of SCS

The analgesic effect

Both observational and randomized studies on SCS have demonstrated beneficial effects, expressed in a reduction in severity of angina complaints and the number of short acting nitrate tablets, and perceived quality of life [77], in conjunction with an improvement in exercise capacity [19, 31, 48]. In approximately 80% of patients the beneficial effects of SCS last for at least one year [2, 19, 31, 37, 48, 55] and in nearly 60% of these patients improvement in exercise capacity and quality of life has been reported for up to 5 years [7]. There has been concern with regard to the safety of spinal cord stimulation as it might deprive the patient of an important angina 'warning' signal. The fear of a potential increase in myocardial events does not seem to be justified [2, 7, 48, 55, 57]. Rather than abolishing anginal pain, SCS enhances the angina threshold. As a consequence patients report an increase in exercise capacity and a reduction in the severity, without a complete elimination, of symptoms of angina on intact pain perception during acute myocardial infarction [2, 7, 38, 57]. This is congruent with the absence of an adverse effect on mortality as demonstrated in prospective and retrospective studies on SCS for refractory angina pectoris [48, 69]. In addition, SCS was not able to suppress the conduction of cardiac pain signals to the cerebrum during cardiac distress [32].

The antiischemic effect

In addition to analgesic achievements, SCS employs antiischemic effects. Both, open and randomized studies have demonstrated that the reduction in anginal pain during SCS enables the patient to prolong the exercise without aggravating myocardial ischemia. Furthermore, the antiischemic effects of SCS have been demonstrated by a reduction in ST-T segment depression on ECG recordings during exercise stress testing [19, 31, 48, 63] and ambulatory ECG monitoring [18, 31]. One study showed an increased tolerance to atrial pacing and delayed onset of anginal complaints during SCS [47]. All patients ultimately experienced angina pectoris. In addition, Chauhan *et al.* [13] demonstrated an increase in coronary flow velocity, using Doppler flow catheters following 5 min of transcutaneous electrical neuromodulation. The rise in the anginal threshold is likely to be related to a redistribution of coronary blood flow from myocardial regions with a normal perfusion in favor of regions with impaired myocardial perfusion [30]. Therefore, the reduction in ischemia appears to be related to homogenization of myocardial blood flow, most likely this phenomenon is resulting from improved collateral flow. Since collateral flow is individually determined, this might very well be the explanation why in some patients ischemia is improved instantaneously and in others it may take up to a year [20]. In spite of the

above, many concerns remain among physicians regarding the potential risk on an increase in myocardial ischemia through SCS, when spinal cord stimulation is indeed depriving the patient of the anginal 'warning' signal. Because SCS elevates the anginal threshold and patients are subsequently reporting a reduction, and not a complete elimination of anginal attacks during SCS, this concern is obviously not rational.

Moreover, evidence is growing that electrical neuromodulation prevents and reduces ventricular arrhythmia's [34, 84].

In conclusion, since SCS appears to employ an antiischemic effect, without increasing mortality [48, 69] and without concealing the anginal warning signal during an acute myocardial infarction [27, 31, 32, 38, 57], or increasing serious arrhythmia's, neuromodulation is considered a safe therapy for patients invalidated by chronic therapeutically refractory angina pectoris.

Mechanisms of action of spinal cord stimulation

At the level of the central nervous system

In 1965, Melzack and Wall published the 'gate-control theory' [51]. The model was based on the theory that stimulation of myelinated relatively fast conducting A-fibers modulate the processing of "pain" signals in the non-myelinated slower conducting C-fibers in the dorsal horn. Following ischemia, which is the consequence of a divergence between myocardial oxygen supply and demand, primary nociceptive nerve endings containing capsaicin (vanilloid receptor 1 or VR_1) receptors are stimulated in the heart or around the peripheral arteries [59].

It has been postulated that electrical neuromodulation can effectively remodel neural pathways [43], and subsequently re-scales the neural hierarchy in cardiac control [4]. At the most peripheral level, the intra-cardiac neurons (ICN) are considered as the final common integrator of the nervous system in the heart [5]. Preliminary data of animal experiments showed that SCS modulates, in a consistent pattern, the firing rate of ICN. Furthermore, during ischemic challenges, it was demonstrated that SCS stabilizes the activity of ICN [25]. In higher brain centers, both angina pectoris and neuromodulation have been found to affect areas involved in cardiovascular control [32, 62].

In addition to these putative actions at different levels in the central nervous system (CNS), a variety of neurotransmitters and vasoactive compounds, like GABA, adenosine, bradykinin, K^+, lactate, endorphins etc, are thought to link shifts in the activity in CNS' centers to control cardiovascular state.

At the cardiac level

In both open and randomized studies it has repeatedly been demonstrated that the reduction in anginal pain during spinal cord stimulation enables the patients

to prolong their exercise. In this respect it was found that SCS was not able to suppress conduction to the cerebrum of a cardiac pain signal, acting as an alarm signal of cardiac distress [32]. Initially, the antiischemic effect of SCS was subscribed to modulation of the autonomic nervous system, more specifically, to the sympathetic branch. However, clinical data does not support this hypothesis, since no change in heart rate variability, or in (nor)-epinephrine metabolism has been found during spinal cord stimulation [19, 31, 33, 56].

The rise in the anginal threshold, causing the delayed onset of angina, may be related to a redistribution in coronary blood flow from normal perfused (non-ischemic) to impaired perfused (ischemic) myocardial regions, causing a homogenization of myocardial perfusion [30]. Subsequently, the moment of critical balance between myocardial oxygen supply and demand is deferred. Whether or not this suggested redistribution in coronary blood flow results from recruitment of collaterals [39] or that other mechanisms are involved such as angiogenesis [71] or preconditioning [49] is a matter of further research.

The increased anginal threshold was emphasized by a study in which patients with refractory angina and a SCS were randomized to control or stressed by right atrial pacing until ischemic threshold [45]. During SCS the anginal threshold was higher, perhaps secondary to the antiischemic effect, albeit that all patients ultimately reported angina. In a letter to the editor it was claimed that the results could be alternatively explained by preconditioning [49]. Preconditioning and collateral recruitment are likely to play an important role in determining the ischemic threshold in patients with refractory angina pectoris. Furthermore, preconditioning can be induced by either pharmacological or ischemic stimuli. Electrically induced preconditioning may interact with both pathways. With regard to pharmacological preconditioning adenosine and opoids are found to influence the G protein-coupled receptors which, on their turn up-regulate protein kinase C, that is thought to phosphorylate the ATP-sensitive K channel, playing a key role in preconditioning. Since adenosine has vasodilatory effects and is involved in pain transmission adenosine may couple the involved neural and cardiac interactions. Moreover, SCS may blunt the effect of dipyridamole, an adenosine re-uptake inhibitor [30].

Finally, the intake of caffeine, which influences the adenosine handling via xanthine metabolism, has been demonstrated to impair the effects of neuromodulation [50].

Patients selection

Patients who are referred to our hospital and fulfil the inclusion criteria (see Table 1) are considered for SCS. A team consisting of an anesthesiologist, a cardiologist, a neurosurgeon, a nurse practitioner and a psychologist make the final decision, whether to implant a SCS. For a beneficial outcome it is essential

Table 1. *Inclusion and exclusion criteria SCS for IHD*

Inclusion criteria
1. Severe chest pain (NYHA classes III–IV or VAS score >7)
2. Optimal tolerated pharmacological therapy
3. Significant coronary artery disease (i.e. >1 stenosis of 75%)
4. Not eligible for Percutaneous Transluminal Intervention or Coronary Artery Bypass Surgery
5. No prognostic benefit from surgical revascularization (according to guidelines)
6. Patient considered intellectually capable to manage the SCS device
7. No acute coronary syndrome during last 3 months
Exclusion criteria
1. Myocardial infarction within the last 3 months
2. Uncontrolled disease such as hypertension or diabetes mellitus
3. Personality disorders or psychological instability
4. Pregnancy
5. Implantable cardioverter defibrillator (ICD) and pacemaker dependency
6. (Local) infections
7. Insurmountable spinal anatomy
8. Contraindication to withheld anti-platelet agents or coumarins
9. Addictive behavior

to perform cardiac, neuro-logical/-surgical and psychological examination, provide essential information (brochure with "frequently posed questions", device information) and train the patients to let them adequately manage the device, making use of a rehabilitation program. In this respect TENS application before implanting a SCS is not used for screening, but merely for getting the patients used to the paresthesias. Clinically we sometimes have to deal with patients who are upset when confronted with a device that has to be implanted. Some patients therefore insist to remain on TENS therapy. Others later proceed to SCS, mainly for reasons of an ortho-ergic reaction, which is rather frequently observed when TENS, or occasionally other external stimulating devices, are applied onto the chest [66].

In and exclusion criteria are mentioned in Table 1.

Implantation technique

The implantation device (Fig. 1) consists of a lead, eventually an extension cable and a pulse generator, all parts to be implanted internally. An external patients programmer is used after the operation to program the pulse generator through the skin. The key to the success of SCS is an accurate placement of the stimulation lead in the dorsal epidural space. The procedure is performed under local anesthesia, with the patient in prone position.

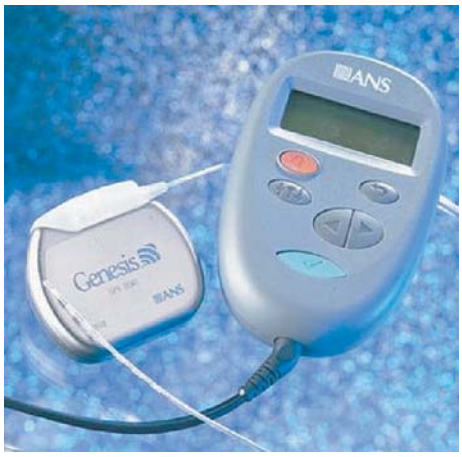

Fig. 1. Complete SCS system: electrode, pulse generator and patient programmer

However in IHD the presence and the vigilance of an anesthesiologist is mandatory: most of these patients have a high cardiac risk even for a "local anaesthesia" operation, specifically when aspirin is withheld. Haemodynamic monitoring is essential. To increase the patients comfort additional i.v. analgesics and/or anesthetics can be used, all to be given in close interdisciplinary communication. The patient is in a prone and comfortable position. Fluoroscopy is used to verify the position of the lead. Peri-operative antibiotics are administered (1 gr cephazoline). After infiltration of the soft tissue with a local anaesthetic at the level of T4–5, an incision is made up to the spinous processus and the epidural is punctured with a Touhy needle. The lead is introduced through this needle into the dorsal epidural space.It is connected to an external stimulator to elicite paraesthesia that have to be felt by the patient within the area of pain.

When the tip of the electrode is correctly positioned, usually at the T1 level (see Figs. 2 and 3) the lead is anchored and (eventually via an extension cable) connected to a pulse generator, generally placed in a subcutaneous pocket

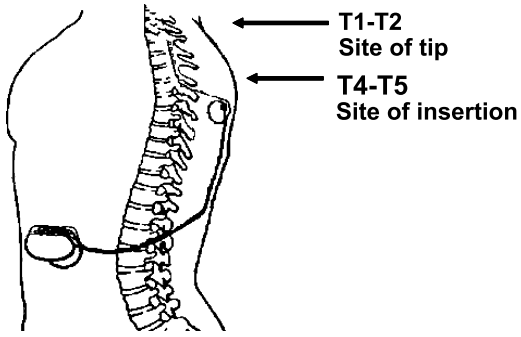

Fig. 2. Diagram of implanted SCS system

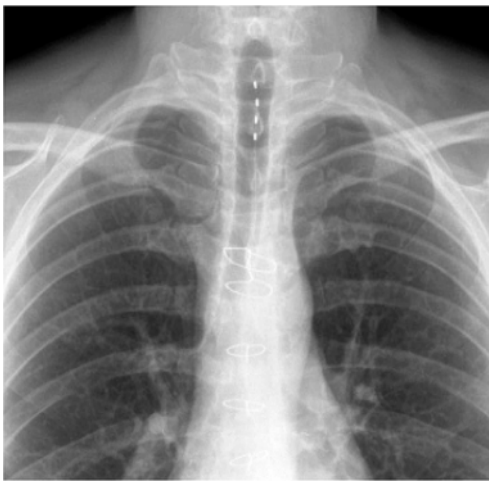

Fig. 3. Epidural quapripolar SCS electrode placed at T1

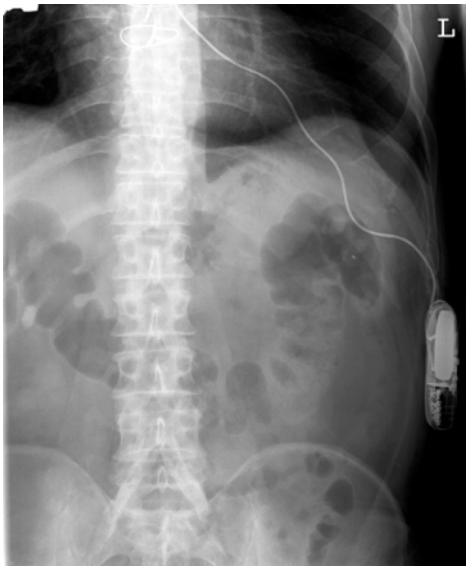

Fig. 4. Pulse generator in the lateral abdominal wall

in the lateral abdominal wall (see Fig. 4). The stimulator can be activated (or deactivated) by the patient, by using a patient programmer.

Cost-effectiveness

Several studies have consistently showed that SCS is cost-effective following a variable period (16 months–3 years) after the initial costs for the system have

been made. After 2-year follow-up of 104 randomized patients participating in the ESBY study (electrical stimulation versus coronary artery bypass surgery in severe angina pectoris) hospital care costs, morbidity and causes of death after spinal cord stimulation (SCS) and coronary artery bypass grafting (CABG) were assessed. SCS was less expensive than CABG ($p < 0.01$) and the patients had fewer hospitalization days related to the primary intervention ($p < 0.0001$) and fewer hospitalization days due to cardiac events ($p < 0.05$). The groups did not differ with regard to causes of death. No serious complications were observed related to the SCS treatment [66]. In a retrospective study Wei and colleagues showed that 16 months after the implantation of the device, SCS was already cost-effective compared to a control group with respect to the prevention of, among others hospitalizations [3]. Taylor *et al.* performed a systematic review and identified and evaluated 14 studies of the cost effectiveness of spinal cord stimulation (SCS) for the treatment of chronic pain [68]. They demonstrated that the initial costs of the SCS are offset by a reduction in post-implant healthcare resource demand and costs. The need for acute admissions for chest pain in patients with refractory angina pectoris was, in retrospect, analyzed in 19 consecutive patients implanted for SCS by Murray *et al.* [55]. Annual admission rate after revascularization was 0.97/patient/year and 0.27 after SCS ($p = 0.02$). The average time the patients were in the hospital after revascularization was 8.3 days per year versus 2.5 days per year after SCS ($p = 0.04$). The authors concluded that SCS was effective in preventing hospital admissions in patients with refractory angina, without masking serious ischemic symptoms or leading to (silent) myocardial infarction.

Conclusions

SCS is an effective and safe additional therapy that improves the quality of life of patients who are severely disabled by their angina complaints. In addition, SCS improves exercise tolerance in conjunction with antiischemic properties and does not mask angina pectoris during a myocardial infarction. The mechanisms of action are multi-factorial and are thought to take place at different levels in the heart and the brain.

Suggestions for further reading

Electrical Stimulation and the Relief of Pain. (2003) In: Simpson BA (ed), Pain research and clinical management, vol 15. Elsevier, Amsterdam

Operative Neuromodulation vol 1: Functional neuroprosthetic surgery. An introduction. (2006) In: Sakas D, Simpson B, Krames E (eds) Acta Neurochin Suppl 47 (7)

Part II: Spinal cord stimulation for peripheral vascular disease

Introduction: Background and history

Peripheral vascular disease (PVD) and spinal cord stimulation (SCS) have a long history in common. Cook was the first to notice that spinal cord stimulation in patients with a neurological disease such as multiple sclerosis and spinal cord lesions, resulted in autonomic changes. He assumed that a regional increase in blood flow might be the underlying mechanism. Three years later he published a small study of nine patients, with varying degrees of limb ischemia resulting from failure of sympathectomy or bypass procedures. He observed a striking pain relief, while infarcted tissue was not restored but healing of wounds was promoted after SCS. He concluded: "It is indeed probable that persistent spinal cord stimulation will avert the need for amputation in some patients. It certainly can be considered as another alternative before progression to amputation after failure of all other known therapeutic modalities" [16]. Dooley observed the same phenomenon of increased blood flow in patients stimulated for central nervous system disorders such as multiple sclerosis, olivopontocerebellar atrophy, amyotrophic lateral sclerosis and Friedreich's ataxia [21]. Trying to elucidate the phenomenon he used transcutaneous electrical stimulation in a patient with a cervical radiculitis. Electrodes were placed over the right side of the cervical spine. A one-channel impedance plethysmograph was connected to the right finger. Electrostimulation during 2½ minutes resulted in a fall in impedance that was interpreted as equivalent to a 154% increase in blood flow to the finger. He concluded: "Electrostimulation over the posterior spinal roots and the spinal cord, although not new, has not been used extensively for the treatment of patients with arterial disease. Electrostimulation of the nervous system is not designed to replace standard therapeutic measures of treatment of patients with vascular disease, but to supplement them."

In the second half of the eighties and the beginning of the nineties, epidural SCS was seen as a possible alternative treatment for patients with peripheral arterial occlusive disease (PAOD) who were no longer eligible for vascular reconstruction. Spinal cord stimulation seemed to be useful whatever the origin of pain. Relieving pain would result in improved mobilization of the patient, which in turn would enhance blood flow and heal ulcers. If this was indeed the case, then the need for amputation would decrease.

Over a period of 10–15 years, case reports and series of patients have been published demonstrating that SCS was a very effective pain treatment. As inclusion criteria were frequently ill-defined, many reports contained a highly inhomogeneous group of patients (atherosclerosis, vasospastic diseases, like Raynaud's and Buerger's disease, and others) sometimes at different stages of

the disease. As pain treatment was the first objective of SCS, many reported an excellent result of pain relief following SCS. Due to the success with pain relief and the fact that patients without pain could walk again, the next step towards possible limb salvage was obvious. The belief that an amputation could be avoided in at least in 40–50% of the patients, motivated an increasing number of physicians to use the technique.

The positive sentiment towards the therapy was further driven by the publication of Augustinsson, who stated that indeed almost all patients (90%) conservatively treated were amputated, while in the case of SCS this was only 34% [6]. Some reports mentioned a near normalization of the blood flow in larger vessels as seen by a normalization of Doppler ankle pressure or even Doppler waves. Although one might expect some criticism on these data, reports of a significant increase in microcirculatory parameters sustained the effect of SCS. Due to a growing evidence, but considering the different way these results were reported, vascular surgeons produced a European Consensus document in order to at least harmonize the patient population under treatment.

If SCS could avoid limb amputation in a substantial proportion of the patients with critical limb ischemia, this would be an important gain for patients in whom the mortality rate was already 45–75% within 5 years [8, 22].

Mechanisms of action

Tallis suggested three possible mechanisms whereby SCS could influence blood flow [67].

1. Conventional pain relief might reverse the sympathetic vasoconstriction that occurs in response to pain. The observation that adequate pain relief correlates with improved capillary flow would be in accordance with this.
2. SCS induces an electrical sympathetic paralysis (with or without concomitant stimulation of cholinergic vasodilators).
3. The antidromic stimulation of dorsal root afferents causing sustained vasodilatation has been demonstrated both in man and animals.

Ghajar found that depending on the level of stimulation, there was an increase in capillary blood flow and skin temperature if the stimulation electrode was placed below the vertebral level T10 or preferably at T12 [27].

In his thesis, Linderoth [44] formulated the following general conclusions on the possible action of SCS:

1. In man dorsal column stimulation (DCS) induces increased CSF levels of substance P (SP), presumably of spinal origin.
2. Spinal microdialysis is suitable for studies of SP-release in the dorsal horn in response to noxious electrical stimulation of a peripheral nerve.

3. In response to peripheral noxious stimuli SP is released both in the ipsi- and contralateral dorsal horn of the spinal cord.
4. In the cat DCS induces release of both serotonin and SP in the dorsal horn of the spinal cord as measured with microdialysis.
5. The activation of SP release by DCS probably requires the involvement of supraspinal mechanisms. SP released in the dorsal horn by noxious stimulation and that released by DCS presumably originate from separate neuronal pools, possibly with different functional properties.
6. The alleviation of ischemic and other types of pain by DCS may involve at least partly different mechanisms.
7. The vasodilatation hypothetically underlying the suppression of the ischemic pain is not dependent on intact connections with the supraspinal centres or on antidromic activation of primary afferent fibres, whether of large or small diameter.
8. The vasodilatory effects of DCS involve spinal and segmental mechanisms and require intact transmission through the ventral roots and sympathetic paravertebral ganglia via postganglionic noradrenergic neurones.
9. DCS exerts its influence in the peripheral vascular bed predominantly via transitory suppression of sympathetic vasoconstrictor control.

Some of the biochemical aspects of pain have been described in greater detail in many review articles. In his thesis, Cui gives an extensive description of the history of SCS and the pathophysiological and biochemical background of neuropathic pain [17]. If spontaneous pain due to a hyperexcitatory state of primary or secondary order neurones, SCS seems to be able to inhibit the excitatory status. Recent publications on the pathophysiological processes involved in the generation of different types of pain indicate that tremendous progress has been made in unravelling the biochemical processes involved. The rapid evolution in genetic manipulation also provides the opportunity in pain research to "turn genes on and off", producing specific alterations in animals and thus facilitating the study of specific characteristics of receptors and the related neurotransmitters.

Patients selection

The second European consensus document on chronic critical leg ischaemia defines critical limb ischaemia (CLI) in non-diabetic patients as the presence of rest pain or tissue necrosis (ulceration or gangrene; Fig. 5) with an ankle systolic pressure of 50 mm Hg or less, or a toe pressure of 30 mm Hg or less [64]. Normal oxidative processes of cells need an oxygen supply. When blood flow to a tissue drops below the level needed for normal metabolic function, anaerobic metabolism temporarily tries to compensate. This phenomenon is known as ischaemia. It becomes critical when blood flow drops to a level

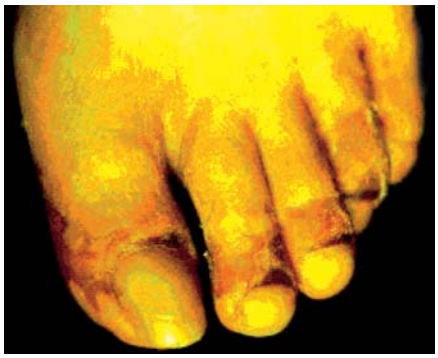

Fig. 5. Ischemic ulcers of the foot

where cell survival is in danger. Cell death results in tissue necrosis. The best known symptom in the early stages of tissue necrosis, is intermittent pain (vascular claudication).

CLI as defined is equivalent to Fontaine stages III and IV plus the blood pressure criteria. None of the criteria of the European consensus have been evaluated for its prognostic value in predicting outcome of the threatened limb. Jacobs and Thompson both found in their series that 50% of the patients classified as severely ischaemic fulfilled the criteria of the consensus document [35, 70]. The other 50% had an ankle systolic pressure greater than 50 mm Hg and an outcome similar to those with an ankle systolic pressure less than 50 mm Hg. It is, however, agreed that patients with ulcers greater than 3 cm^2 have a much lower limb salvage rate [10, 67]. Wolfe and Wyatt [80] presented an overview of the different definitions of CLI. Their suggestion to look for high- and low-risk patients is a step in the right direction. However, they do not mention the microcirculatory measurements. Carter [12] and Bunt and Holloway [11], proposed modified haemodynamic definitions for critical and subcritical ischaemia, which include measurements of pressures and indices of microcirculation.

The debate which might lead to a better classification of patients with CLI belongs to the vascular surgeons. An important part of the discussion will certainly be the value of microcirculatory measurements.

There are different ways to assess blood flow and there is no consensus on the best prognostic indicator. In a leading article [36] Jacobs and Jorning stated: "systolic ankle/arm pressure measurements at rest and after treadmill exercise are generally accepted as the best non-invasive method to document arterial obstruction of lower extremities. It should be emphasised, however, that in patients with Fontaine stages III and IV not only is the macrocirculation inadequate but, especially in patients with ulcerations and gangrene, the microcirculation is also threatened. Tissue oxygen pressure measurement,

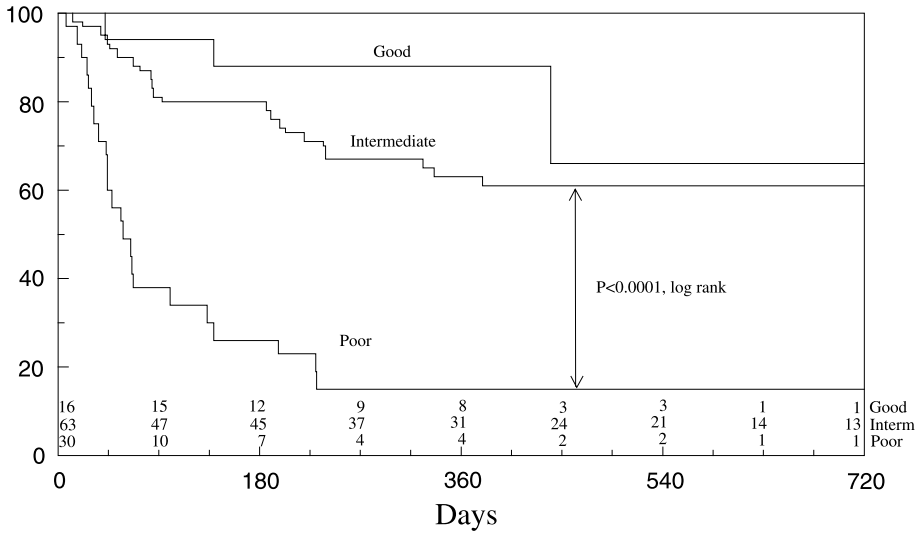

Fig. 6. Cumulative limb survival in the three microcirculatory categories. A dotted line indicates a standard error >10%. The numbers per category indicate the number of patients at risk. Good = $TcpO_2$ >30 mm Hg, Intermediate = $TcpO_2$ between 10 and 30 mm Hg, Poor = $TcpO_2$ <10 mm Hg [76, 77]

laser Doppler flowmetry and isotope clearance techniques can be performed to study cutaneous blood flow. Intravital skin capillary microscopy is a direct and non-invasive method of studying the morphological pattern of skin microcirculation and allows the measurement of red blood cell velocity in the skin capillaries, which specifically reflects nutritional blood flow". This means that further studies are needed to find out which method has the best prognostic value and can discriminate responders (limb salvage) from non-responders. Ubbink suggests that a combination of toe blood pressure and transcutaneous oxygen tension (TcpO2), using cut-off values of 38 mm Hg for toe blood pressure and 35 mm Hg for TcpO2 in the supine position, has a better prognostic value [75, 76] (Fig. 6). Gersbach uses the difference between sitting and supine TcpO2 as a better predictor of outcome [26]. Fiume reported that pain relief was obtained only in patients who showed an improved TcpO2 during trial stimulation [24], an observation also made by Jacobs [36].

Petrakis suggested that a trial period of two weeks should be considered before final implantation, because those who show a significant increase in TcpO2 in that period have a better outcome [61]. The criteria of the second European consensus document concern patients with 'chronic' CLI. This means a constant pain persisting for at least more than 2 weeks as used in the Dutch trial [41]. Kumar included only those patients treated conservatively

for 6 months; this represents a different population [42]. With regard to limb survival of patients with CLI, it is obvious that the first two to three months after the diagnosis of CLI are very important because a large number of patients undergo amputation within this period. Recently, in a consensus document on the definition of CLI, some recommendations have been proposed both for the definition and for the trials on CLI. It is clear from this document that there is no real consensus on inclusion criteria and investigation of patients at risk of an amputation within months of diagnosis of CLI [15].

Patients selected for SCS are surgically non reconstructable and must have a critical limb ischemia, not evolving dramatically in a couple of days or weeks to a situation urging a minor or major amputation. In general they belong to the clinical grading of Fontaine III and IV. This means that patient has pain at rest and/or skin lesions in the region of the foot which may not exceed 3 cm^2.

In addition macrovascular criteria were added as Doppler ankle systolic pressure $\leq$50 mm Hg or a ankle/brachial index $\leq$35%. More recently microvascular criteria completed selection criteria adding transcutaneous pO2 (TpO2). Values between 10 and 30 mm Hg were accepted as compatible with CLI. General accepted selection criteria are found in Table 2.

Table 3 shows characteristics of patients included in the Dutch trial [41] for standard or SCS treatment. It also shows the high rate of other concomitant ischemic diseases.

Table 2. *Inclusion and exclusion criteria SCS for PVD*

Inclusion criteria

1. Persisting pain at rest for at least 2 weeks,
2. And/or skin lesions (ulcerations or gangrene) in the region of the feet or toes, which surface may not exceed 3 cm^2.
3. Doppler ankle systolic pressure $\leq$50 mm Hg or ankle/brachial pressure index $\leq$35%. For patients with diabetes mellitus and incompressible ankle arteries, absence of arterial ankle pulsations on physical examination.
4. Patient's written informed consent.

Exclusion criteria

1. Vascular disorders other than atherosclerotic disease.
2. No rest pain (e.g., only intermittent claudication) and no gangrene or ulceration.
3. Ulcerations deeper than the fascia or gangrene with a diameter larger than 3 cm^2.
4. Intractable existing infection of the ulceration o gangrene area
5. Neoplastic or concomitant disease restricting life expectancy to less than a year.
6. Presence of a cardiac pacemaker
7. Inadequate patient compliance due to psychological or social incompetence.

Table 3. *Characteristics of patients (n = 120) included in a Dutch randomized trial (Klomp et al.* [41])

Characteristics	*Standard* % (n)	*SCS* % (n)
Female	38% (23)	45% (27)
Age (mean + SD)	72 ± 10.6	73 ± 9.8
Diabetes	38% (23)	37% (22)
Contralat.leg		
– symptomatic	48% (29)	32% (19)
– amputated	12% (7)	15% (9)
Smoking		
– not for >1year	27% (16)	37% (22)
– still smoking	44% (26)	30% (18)
CVA/TIA	27% (16)	22% (13)
Myocardial infarction	37% (22)	38% (23)
Angina pectoris	25% (15)	20% (12)
Ulcerations/gangrene	68% (41)	63% (38)
Gangrene		
– dry	38% (23)	40% (24)
– wet	8% (5)	13% (8)
Previous vascular surgery		
– none	18% (11)	25% (15)
– 1 or 2	48% (29)	42% (25)
– >3	33% (20)	32% (19)
Sympathectomy (randomized leg)	32% (19)	35% (21)
Ankle pressure (mean + SD)	41.6 ± 21.8	35.2 ± 24.8
Ankle-brachial index (mean + SD)	0.28 ± 0.1	0.23 ± 0.1
$TcpO_2$ (mm Hg)	10	10

Clinical studies/level of evidence

Spincemaille *et al.* [65] published a systematic review on patients with CLI and SCS. Characteristics of patients treated for PAOD (Peripheral Arterial Obstructive Disease) were very similar in non-randomised studies and randomised controlled studies (RCTs). In the randomised studies standard treatment resulted in a limb salvage of 40–50% after two years follow-up. More specific treatments, such as prostaglandins or spinal cord stimulation (SCS) had slightly higher limb salvage ranging from 55 to 65%. The transcutaneous oxygen pressure ($TcpO_2$) was the parameter most frequently used to evaluate skin microcirculation. Limb survival of patients with an intermediate $TcpO_2$ value was 76% for SCS

treatment compared to 52% in the conservative treated patients ($p = 0.08$). A limb salvage of 88% was found in patients treated with SCS if the difference between the supine and sitting $TcpO_2$ baseline values ($\Delta TcpO_2$) was ≥ 15 mm Hg. A rise in $TcpO_2$ after trial stimulation of at least 15% resulted in a limb salvage of 77% at 18 months ($p < 0.01$).

A recent systematic review and meta-analysis of the available controlled trials was done by Ubbink *et al.* [73]. He reported: "main endpoints were limb salvage, pain relief and clinical situation. Eighteen reports were found of which 5 RCTs. Nine studies were used for the analysis. The 12 month survival appeared significantly greater in the SCS group (risk difference (RD) -0.13, 95% CI -0.04 to -0.22)) Significant pain relief occurred in both treatment groups, but patients who received SCS required significantly less analgesia and reached Fontaine stage II more often than those who did not have SCS (RD 0.33 (95% CI 0.19–0.47)) This article however does not stress the importance of the initial $TcpO_2$. Further selection on the basis narrows the targeted population but clearly select the patients who will benefit from SCS. Amann *et al.* [1] reported at 12 months follow up a cumulative limb survival of patients treated with SCS which was significantly better than the control group. Their selection criteria were a baseline forefoot $TcpO_2$ of <30 mm Hg and both sufficient pain relief and paresthesia coverage ($>75\%$) after test stimulation for 72 h. This kind of selection was already discussed and proposed in two other articles mentioned in this paragraph. $TcpO_2$ seems the best promising way of selecting patients for SCS treatment.

Implantation technique

In most cases, local anaesthesia is used to position the lead in the epidural space. General anaesthesia makes a correct placement of the electrode nearly impossible, because patients cannot provide information on the exact area where paraesthesia are felt. An epidural or a good regional block with complementary sedation even makes it possible to perform a laminectomy. These paraesthesia are phantom sensations created by SCS which activates the dorsal column neurones. When treating patients with critical limb ischemia, it is essential to obtain/produce paraesthesia in the painful region of the limb, but the same is true for several other chronic pain conditions. The site of puncture of the epidural space with a Touhy needle is two or three levels below the area where the tip of the lead will finally be positioned (T10). The best technique is an oblique (45° to the surface) and paramedian route in order to avoid sharp angles of the lead when perforating the ligamentum flavum of the epidural space (Fig. 7). The lead is always positioned medially or slightly lateral to the midline in the dorsal part of the epidural space. Fluoroscopic control during the procedure is mandatory. Positioning of the lead in the epidural canal is the most important part of the procedure. One should be careful to avoid migration of the lead during the subsequent stage of the procedure. Fixation of the lead at the level of the superficial fascial layer is

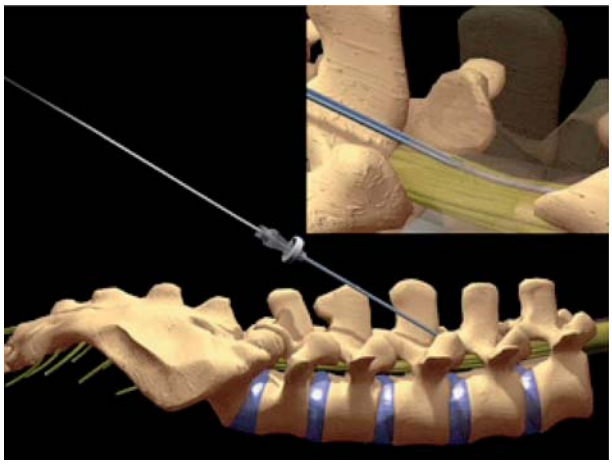

Fig. 7. Diagram showing insertion of epidural lead

necessary. The lead is connected to an extension cable, which in turn is connected to the pulse generator. The whole system is implanted subcutaneously in the same way as a pacemaker. The patient obtains an external programmer which allows the generator to be switched on and off. Another feature is the possibility of changing amplitude, pulse width and pulse rate; usually only the option of changing amplitude is activated. The physician can, however, fully control and programme the pulse generator using a remote external programmer.

Cost effectiveness

In the Dutch randomized study a cost calculation was performed [41]. At that time costs were calculated in Dutch guilders which are equivalent to 0.5€. The study was performed almost 10 years ago. Most of the costs derived from staying in hospital and in rehabilitation facilities. These costs were similar for both groups: mean *f*25957 and *f*14870 per patient in the spinal-cord-stimulation group vs *f*27153 and *f*16465 in the standard group. The mean cost for operative procedures per patient was *f*18428 in the stimulator group and *f*918 in the standard group. The cost of implanting the stimulator was *f*15900. Costs for professional care at home and in homes for the elderly, were similar. Outpatient cost, medications, medical supplies, and non-medical costs were a small part of the cost. Total cost at 2 years was *f*80439 per patient in the spinal-cord stimulator group, *f*17376 (28%) higher than in the standard group ($p = 0.009$). Adjusted for mortality, the mean cost per patient was *f*69066 in the stimulator group and *f*52407 in the standard group, $p = 0.002$.

Ubbink calculated the costs for SCS in case of CLI in his review article [73] and stated: "pooled data but not the individual RCTs revealed a significant beneficial effect in terms of limb salvage, at the cost of a significantly higher number

of correctable complications and apparently higher costs. The finding that eight patients need to be treated to save one more leg, together with the higher cost of SCS treatment (about 8000€ for 2 years), suggests that about 64000€ extra needs to be spent to achieve this end. This should be weighted against any improvement in quality adjusted life years and the eventual cost of a major amputation, itself accompanied by ongoing high costs and high mortality rate".

Both studies give about the same differences in costs for both treatments. However regarding a better selection procedure the superiority of SCS must be easier to prove.

Conclusions

It seems from the available literature that SCS in CLI with a good selection algorithm is able to select those patients able to respond to SCS thereby reducing the number of amputations under SCS treatment. This group of patients with chronic CLI has a 50% survival of 5 years. So if amputation can be avoided and quality of life is enhanced, the short life expectancy for these patients is considerably ameliorated. The best recent reference is the Cochrane report of Ubbink giving all information on the effectiveness of SCS in PVD [74].

Suggestions for further reading

Electrical stimulation and the relief of pain. (2003) In: Simpson BA (ed), Pain research and clinical management, vol 15. Elsevier, Amsterdam.

Operative neuromodulation vol 1 (2006) In: Sakas D, Simpson B, Krames E (eds), Functional neuroprosthetic surgery. An introduction. Acta Neurochir Suppl 97/1

For more practical information

http://www.ans-medical.com/
http://www.medtronic.com/neuro/paintherapies/pain_treatment_ladder/neurostimulation/neuro_neurostimulation.html
http://www.neuromodulation.com/

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