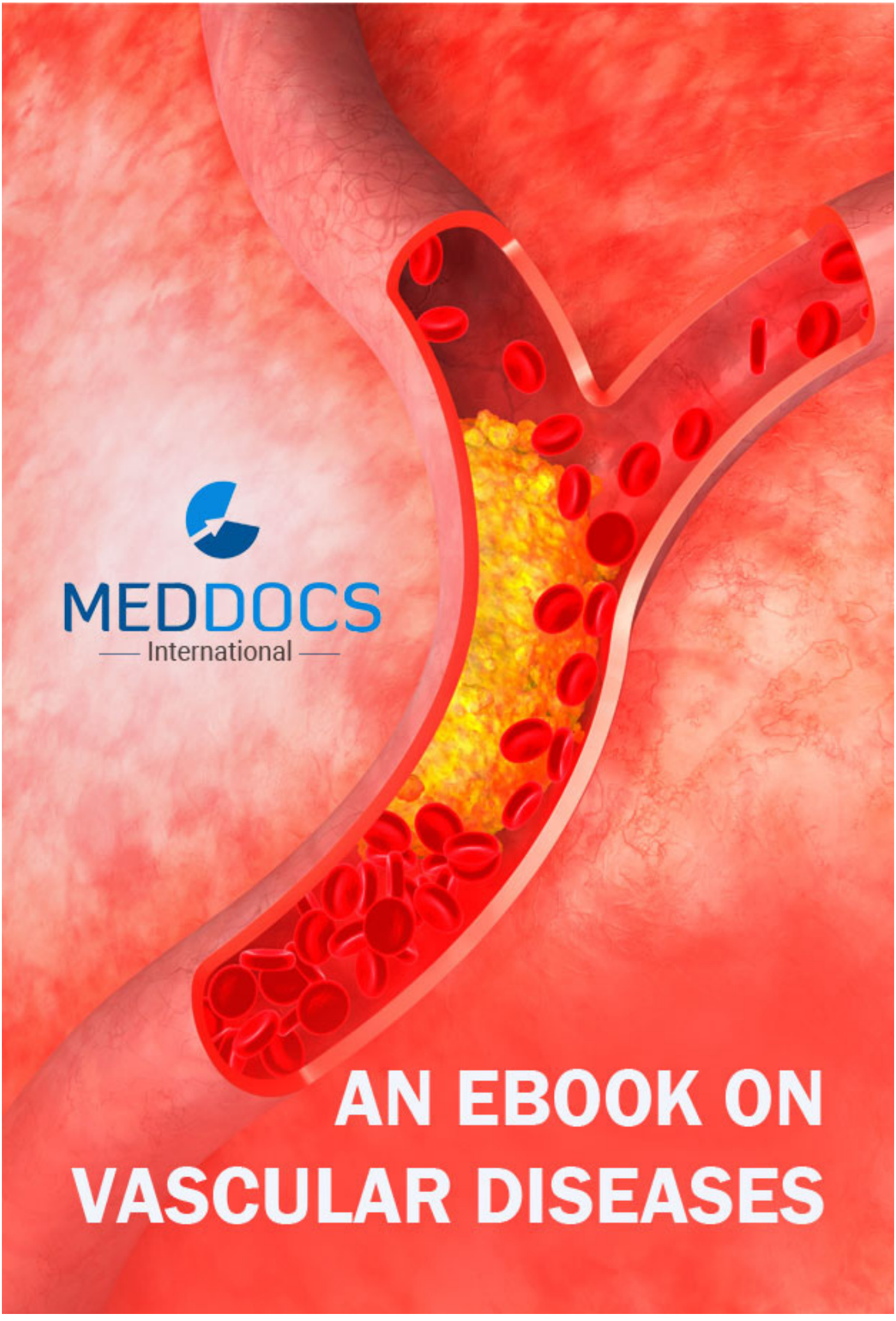

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# AN EBOOK ON VASCULAR DISEASES

# Use of Spinal Cord Stimulation in Peripheral Arterial Occlusive Disease

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## Abstract

Spinal Cord Stimulation is a minimally invasive, reversible therapy implemented with sophisticated techniques and implanted equipment, including different types of electrodes and pulse generators. In medical literature use of SCS to treat peripheral vascular disease since 1976 is well known. Two theories explaining the mechanisms of SCS-induced vasodilation have been proposed based on the results of three decades of clinical and basic science studies: An antidromic mechanism that induced peripheral vasodilation mediated by thin fibers. Sympathetic mechanisms were SCS suppresses sympathetic activity and subsequently produces marked vasodilation. Finally SCS-induced cutaneous vasodilation in the rat hindpaw at 66% of MT was abolished by complete surgical sympathectomy.

## Introduction

Spinal Cord Stimulation (SCS) may be described as the application of electricity to the ascending medial and lateral spinothalamic pathway on the dorsal columns of the spinal cord to modulate the pain signals carried to the brain. The concept of SCS derives its inspiration from the landmark "Gate control theory of Pain" proposed by Melzack and Wall in 1965 [1]. This theory postulated the existence of a "gate" in the dorsal horn of the spinal cord regulating the traffic of neuronal impulses from the sensory afferent neurons to the upper centers in the brain responsible for pain perception.

Aβ fibers (which carry the non-nociceptive stimuli) and C fibers (which carry the painful stimuli) form synapses with the projection neurons of the spinothalamic tract on the dorsal horn of the spinal cord, that are responsible for the transmission of pain signals to the brain. According to the "Gate Control Theory", stimulation of the Aβ fibers in the same region as the C fibers may determine the closure of the "gate", and therefore it can reduce the transmission of pain impulses.

In the spinal cord, these fibers are separated from the motor fibers and are in an accessible location, making the dorsal columns a desirable target for stimulation. Based on this theory, Shealy et al. implanted the first dorsal column stimulator in 1967 for the treatment of pain [2]. However, several decades of research have shown that the mechanism of SCS in the treatment of pain is much more complex [3].

Although the electrical stimulation therapies inspired by the "Gate Control Theory" have succeeded, theory itself remains controversial. Indeed, clinical experience has shown that SCS is more effective for neuropathic pain than for acute or nociceptive pain.

Many theories have been proposed to explain the mechanism of action of SCS.

Wide Dynamic Range neurons (WDR) are found primarily in lamina V and are responsible for much of the information that is transmitted to the brain stem and Thalamus. These neurons

receive not only polymodal inputs from high-threshold mechanical and heat sensitive A-Delta and C fibers nociceptors but also inputs from collaterals of non-nociceptive, low threshold mechanical Aβ afferents and local interneurons of the dorsal horns. They have a moderate threshold for initiating an impulse and are responsible for signals related to itch and flatter. Inputs to the WDR provide the essential segmental framework for the "Gate Control Theory" [4].

Hyperexcitability of the Wide-Dynamic Range (WDR) neurons in the dorsal horn of the spinal cord has been demonstrated in neuropathic pain states [5]. In animal models, SCS frequencies around 50 Hz have shown to induce the release of inhibitory neurotransmitters like GABA resulting in inhibition of the WDR hyperexcitability [6,7].

It has also been suggested that SCS results in release of acetylcholine and its action on muscarinic M4 receptors may be responsible for its analgesic effects [8]. Furthermore, evidence indicates that the pain reduction with SCS may be secondary to stimulation-induced release of serotonin, adenosine, and noradrenaline [9]. Recent evidence suggests the involvement of supraspinal circuitry in mediating the analgesic effects of SCS [10,11].

Today SCS is a minimally invasive, reversible therapy implemented with sophisticated techniques and implanted equipment, including different types of electrodes and pulse generators. SCS does not ablate pain pathways or result in any anatomic changes. It is important to remember the SCS is not meant to eliminate pain but to reduce it, particularly pathological (neuropathic) pain which itself is a disease [4].

Current clinical indications for SCS include the treatment of neuropathic, visceral and ischemic pain.

In medical literature use of SCS to treat peripheral vascular disease appeared for the first time in 1976 [12], since then several studies have been conducted.

Ischemic pain is mostly of nociceptive origin and therefore its responsiveness to SCS is unexpected. Indeed, it seems that in ischemic pain conditions the beneficial effects of SCS are determined by the action on the ischemic condition itself [4].

## Background

### Peripheral arterial occlusive disease

Many ischemic conditions in the limbs are due to Peripheral Arterial Occlusive Disease (PAOD), which is caused by the obstruction of blood flow within an arterial tree, excluding the intracranial or coronary circulations, mostly due to progressive atherosclerosis.

In the early stages PAOD is usually asymptomatic and intermittent claudication is one of tipically referred symptoms. The pathophysiology of arterial claudication is based on a reduction of arterial perfusion to a degree that is inadequate to satisfy working muscles needs.

The quality and pattern of the pain associated with intermittent claudication is quite typical: It is absent at rest and arises after muscle exertion of a specific amount, disappearing quickly with the cessation of exercise. The pain is localized in the working muscles and it is described as "burning", "cramping" or "aching". Inadequate perfusion of the working muscles is proven by the contemporary development of symptoms and the decline in skeletal muscles perfusion as measured by the ankle/brachial index during treadmill walking.

At the cellular level, claudication pain likely results from a combination of ischemic neuropathy (particularly of small unmyelinated A-delta and C sensory fibers) and a localized lactic acidosis deriving from the anaerobic metabolism during ischemia.

One of the main differential diagnoses to be considered in vascular claudication is neurogenic claudication, resulting from whatsoever form of lumbosacral neurospinal compression syndrome. Neurogenic claudication can be recognized because the pain experienced by patients is more often bilateral than that associated with arterial insufficiency. Furthermore, the latter is more diffuse, frequently extending from buttocks to feet, it has a deeper, more aching or burning quality and it is often associated with distal paresthesias or numbness. The severity of symptoms in vascular claudication is determined by the amount of stenosis, presence of collateral circulation and vigor of exercise [4].

The progression of the disease leads to a further decrease in blood flow, therefore rest pain and peripheral trophic lesions occur.

Rest pain is characterized by a diffuse, aching or burning pain in the distal foot and it is initially present at night when the patient is recumbent whereas it disappears when the subject arises and walks around. Its pathophysiology is likely that of an ischemic neuropathy, with positional malperfusion of small sensory nerves at the extremity of the limb.

Arterial ulceration in non-diabetic patients appears as a shallow, pallid, non-healing erosion of the skin in the distal foot. The pain of such ulcerations is unremitting and severe, occasionally refractory even to high dose of oral narcotic agents and it does not only arise from ischemic neuropathy but also from actual necrosis of sensory nerves in the skin at the site of the arterial ulcer. When tissue necrosis occurs, gangrenous changes of the toes or heel can be found; subcutaneous tissue infarction, osteomyelitis and ascending infection may worsen the pain but severe necrosis of the sensory nerves can paradoxically make gangrenous lesions. All patients with rest pain, ischemic ulcers or gangrene will require an operative intervention, either a procedure to restore vascular supply to the affected area or an amputation. Leriche-Fointaine classification is the most widely used system to stage the disease [13].

### SCS: Mechanism of action in PAOD

Sprague-Dawley (SD) rats have been used as animal models to investigate the mechanisms of SCS-induced vasodilation in the lower limbs and feet [14]. SCS stimulation intensity in rats is calculated depending on the Motor Threshold (MT), which is the stimulation required to observe muscle contraction. The experimental SCS is performed at 30%, 60%, 90%, 300% or ten times of MT. The stimulation at 30% of MT is used because it was the closest to the threshold of SCS that produced vasodilation. A stimulation level of 60% of MT is also used because it approximates the parameters of clinical applications of SCS. A stimulation level 90% of MT is used because it is close to but below MT. Stimulation levels at 3 and 10 times of MT are used to observe how SCS at high intensity stimulation affects the peripheral blood flow by mimicking traditional antidromic vasodilation.

Two theories explaining the mechanisms of SCS-induced vasodilation have been proposed based on the results of three decades of clinical and basic science studies:

**Antidromic mechanism**

The idea of an antidromic mechanism for vasodilation was initially proposed by Bayliss [15]. He observed that dorsal root stimulation at high intensity induced peripheral vasodilation mediated by thin fibers.

Administration of high concentration of capsaicin (1%) on the tibial nerves blocks C-fiber conduction, causing the reduction of vasodilation induced by SCS at 90% and 10 times of MT but not at 30 and 60% of MT [16,17].

SCS-induced vasodilation ≤ 60% of MT may be mediated via myelinated fibers, whereas vasodilation at ≥ 90% of MT may also involve unmyelinated C-fibers.

Resiniferatoxin (RTX), an ultrapotent analog of capsaicin and transient receptor potential vanilloid receptor-1 (TRPV1) agonist [18-20] injected intravenously or applied on the spinal cord, peripheral nerves and in the paw abolished vasodilation produced by SCS [21,22].

Thus, these data indicate that SCS-induced vasodilation is predominantly mediated via TRPV1 containing sensory fibers in unmyelinated C-fibers or myelinated Aδ sensory fibers.

Many vasodilators may be found in sensory endings and are released during SCS, CGRP is one of them and it enters vascular smooth muscle layer following the activation of TRPV1 [23].

CGRP is about 10 times more powerful than prostaglandins and 100-1000 times more effective than other well known vasodilators, such as Substance P (SP), Adenosine and Acetylcholine and it acts by binding its receptor CGRP-1 [24].

Nitric Oxide (NO) is another important component involved in SCS-induced vasodilation and it can be released either from TRPV1 conteining nerve endings or from endothelial cells after CGRP activates their intracellular pathways [25].

Another peptide from calcitonin family, Adrenomedullin, is co-localized with CGRP in perivascular nerves and dorsal root ganglia and it seems to be at least partially involved in SCS-induced vasodilation [26].

According to the current evidence, SCS at the spinal L2-L5 segments activates interneurons containing two kinases (ERK; AKT) and possibly other intracellular signaling molecules, which subsequently stimulate spinal terminals of TRPV1 containing sensory fibers. When the neural information reaches the nerve endings in the peripheral tissues provokes a relaxation of vascular smooth muscle cells through CGRP and nitric oxide leading to a local increase in blood flow.

**Sympathetic mechanism**

The sympathetic nervous system causes vasoconstriction via stimulation of alfa-1 and alfa-2 adrenoceptors. SCS suppresses sympathetic activity and subsequently produces marked vasodilation. SCS-induced cutaneous vasodilation in the rat hindpaw at 66% of MT was abolished by complete surgical sympathectomy [27].

Administration of ganglionic blocker, hexamethonium, or neural nicotinic ganglionic blocker, chlorisondamine, had the same effect. High dose of adrenergic receptor blockers phentolamine and prazosine also suppressed SCS-induced vasodilation. Inihibition of vasodilation was not observed after administration of muscarinic receptor antagonists and alfa-2 adrenoceptors blocker [28].

The sympathetic activity and the antidromic theory act in concert to provide pain relief and vasodilation in patients suffering from PAOD. The balance of the dual mechanisms depends on sympathetic activity level, stimulation parameters and patient's personal set of risk factors.

## Management and patient selection

An SCS consists of a power source (IPG) connected to a lead with a cathode (negative electrode) and an anode (positive electrode). The cathode and anode create an electrical field within the bio- logical tissue that can depolarize the target nerves. Stimulation of the dorsal columns fibers effectively reduces pain in many neuropathic and ischaemic pain syndromes.

There are two main types of electrodes used: Surgical or paddle electrodes need a small laminotomy for the introduction into the epidural space and cylindrical electrodes that can be introduced percutaneously. The procedure for percutaneous IPG implant is performed in the operating room under sterile conditions with local anesthesia supplemented by conscious sedation and the access to the epidural space is gained with a Touhy needle, introduced either at L2-L3 or L4-L5 space.

Lead placement is usually performed under fluoroscopy control and an intraoperative stimulation is then carried out. The tip of the electrode position should evoke paresthesias through stimulation; for a better control of pain, the stimulation-induced paresthesias should cover the whole painful area.

Stimulation parameters are adjusted to achieve the best results. The main variables in SCS are the frequency, pulse width, and amplitude. The basic unit is the "pulse", a sustained delivery of a specific amount of current amplitude, for a specific amount of time (pulse width). The amount of charge delivered with each pulse is equivalent to the product of amplitude and pulse width, whereas, frequency determines the number of pulses delivered per second.

The pulse width is generally between 100 and 500 μs. The amplitude is usually 2-8 V. The frequency can vary depending on the stimulation regimen. The stimulation patterns vary among the different diagnostic groups.

Power output or amplitude from the IPG may be in the form of Constant Current (CC) or Constant Voltage (CV). With CC, the voltage is automatically adjusted with changes in the resistance (impedance) to maintain a CC. The amplitude is given in volts (V). With CV, the voltage remains constant and as the impedance varies, the current will change. The amplitude is given in milliamps (mA).

Shorter pulse widths preferentially recruit dorsal roots, and target specific dermatomes. As the pulse width increases, the medial dorsal columns fibers are recruited preferentially, and a greater area of the dorsal columns is stimulated.

The frequency can vary depending on the stimulation regimen [29]:

1. Conventional or tonic stimulation: Uses frequencies of 60– 100 Hz. This produces paraesthesia in the target area. This is the most common mode of stimulation, but in the

last few years, two more modes have gained popularity.

2. Burst stimulation: Involves five pulses in a burst (500 Hz pulse frequency in each burst) with a burst frequency of 40 Hz. Burst stimulation produces little or no paraesthesia.

3. High-frequency stimulatio frequencies of 10 kHz. This pattern does not generate paraesthesia but may produce effective pain relief.

The success of SCS is strongly dependent on appropriate patient selection. To date, RCTs in SCS involved patients with persistent pain (neuropathic or ischaemic) resistant to chronic medical treatment. Patients should have a definite diagnosis or an identifiable pain generator, and a positive trial of stimulation. Patients with major psychiatric disorders, psychological distress, or unreasonable expectations are not suitable. For these reasons, a preoperative psychological assessment is advised. The patient must have the cognitive capacity to give informed consent, demonstrate an ability to understand and use the device properly, and commit to weaning off inappropriate or ineffective medications.

Before inserting the full system, the implanter can site a temporary percutaneous lead under local anaesthetic and connect it to an external pulse generator. Patients may report where they feel paraesthesia, and whether it is covering the painful area. This allows the implanter to position the electrodes over the appropriate area. The temporary lead may be left in situ from one up to four weeks depending on the operator's approach and it allows the patient to experience SCS.

After a successful trial, the temporary lead is removed and a permanent one is placed. The accuracy of the trial in predicting successful implantation has never been fully established. A failed trial is declared if it is not possible to stimulate the painful area, or the patient finds the paresthesia is ineffective or unpleasant; if that occurs, the trial lead is removed.

### Effectiveness of SCS

Critical Leg Ischemia (CLI) is defined as the presence of rest pain or tissue necrosis (ulceration or gangrene) with an ankle systolic pressure of ≤ 50mmHg, or a tie pressure of ≤ 30mmHg, and corresponds to Fontaine Stages III and IV, in addition to the blood pressure criteria [30]. Patients suffering from critical limb ischemia usually undergo vascular reconstructive surgery to improve peripheral circulation in order to relieve pain and avoid amputation. However, revascularization may not be possible or, even if technically feasible, it may not be successful in relieving pain.

Surgically non-reconstructable disease is characterized by ischemia in which angioplasty and bypass grafting is not possible, ABI <0.4, or great toe pressures <30mmHg. In such inoperable cases, a conservative approach with medical therapy is the only remaining option, before an amputation becomes unavoidable.

SCS has been extensively investigated as a possible treatment to relieve pain and prevent the need for amputation.

The main purpose of the studies was to evaluate the clinical outcomes of SCS in a selected group of patients with non-reconstructable peripheral vascular disease. The most common primary endpoint was limb survival; secondary objectives were pain relief, wound healing, quality of life and to assess costs and complication of SCS. An improvement in peripheral blood flow is the most desirable effect to achieve the above mentioned objectives. Transcutaneous oxygen pressure ($TcPO_2$) is a non-invasive method to quantify skin oxygenation and its variation during stimulation is useful to estimate the effects of SCS on microcirculation.

Effectiveness of SCS in patients with Critical Leg Ischemia (CLI) was discussed in a Cochrane systematic review [31] first published in 2003 and later updated in 2005 and 2013. The review included six clinical studies, five of them were randomized trials and the sixth one was a multinational European controlled trial; overall 444 patients have been included in the review. All patients suffered from atherosclerotic non-reconstructable chronic CLI with ischemic rest pain or ulcers smaller than 3 cm in diameter. In all studies, patients received standard control treatment with or without SCS. Standard control treatment consisted of optimal medical conservative therapy, in two trials $TcpO_2$ measurement was used for patients classification and limb salvage was set as a primary endpoint in all the trials. None of the studies showed a significant difference in amputation frequency after 12, 18 or 24 months of follow-up, although all studies showed a trend towards a better amputation-free salvage in the SCS group. This trend was stronger in a subgroup of patients selected depending on their initial $TcpO_2$ as compared to the overall result. In the SCS-EPOS study [32] the difference in cumulative limb salvage was significantly better in patients treated with SCS, in particular in a subgroup selected on their initial $TcpO_2$ and response to trial stimulation. In a subgroup of normotensive patients the amputation rate after 18 months was lower in the SCS group [33]. Pain relief, assessed with the Visual Analogue Scale (VAS) and monitoring of the patient's narcotic and non-narcotic analgesic use, was significantly better in patients treated with SCS after 3 months and after 12 months. However, pain relief in amputated patients was substantially better than in non-amputated patients, irrespective of the treatment. Concerning clinical improvement, two studies [34,35] showed that more patients improved from CLI to claudication in SCS groups than in conservative groups. The healing of ischemic ulcers was reported in two studies: Claeys found SCS had a significantly better effect on wound healing than conservative treatment, whereas Klompt found no significant difference. Pooling resulted in no significant difference between the two treatment modalities.

Quality of life was assessed by using the Nottingham Health Profile (NHP) and the Euroqol questionnaires in both treatment groups in one of the Dutch studies. The overall score of the NHP decreased (i.e. improved) during follow-up in both treatment groups. The mobility score of the NHP was significant better in patients treated with SCS. The Euroqol showed an improvement after 12 months in both groups as well.

No differences in mortality were observed. Usually only the complications of SCS treatment were mentioned. Only in the larger Dutch study, some minor side effect of medical treatment in the conservative group were detailed. Initial implantation problems (technical or anatomical problems causing failure of positioning the electrode in the epidural space), were recorded in two trials. Pooling resulted in a 8% of implantation problems. The risk of surgical reintervention due to changes in stimulation (dislocation of the electrode or fracture of the lead) was 3%. Infections of the lead or subcutaneous pulse generator pocket occurred in 3% of patients. Depletion of the battery within 18 months of follow-up did also occurred: In 5 cases in the SCS-

EPOS study [32], and in three in the ESES study [36]. The overall complication risk was 0.18 (95% CI:0.03-0.32).

Only in the ESES study a cost comparison was made. The average overall costs of hospitalization, rehabilitation, operative procedures, stimulator outpatient care, professional home care, medication and non medical costs at two years were 36.500 Euros in the SCS group and 28.600 Euros in the conservative group. This was a significant difference ($p<0.009$). After adjustment for mortality these figures were 31.340 Euros (SCS), and 23.780 Euros (conservative) ($p<0.002$).

In 2004 Horsch et al. [37] published a retrospective study of data from 258 patients with PAOD who received SCS, whose outcomes were monitored over a period of 18 months.

This report included patients with the following inclusions criteria: $TcPO_2$ baseline value of ≤ 30 mmHg, not candidate for reconstructive surgery, treated with SCS alone and no additional therapies, compliant with a capable of operating the SCS system, no previous major amputation of the target limb, no deep infection, no bacteremia.

The leads had been placed at the level of T11- T12 over the midline under radioscopic control and an intraoperative trial stimulation was performed to ensure that patients experienced adequate paresthesia coverage and pain relief.

$TcPO_2$ measurements were performed with the patient in supine position, using the Hellige $O_2$ monitor. Patients were categorized by their baseline $TcPO_2$ value: Approximately half of the patients (45.7%) had a low $TcPO_2$ value of <10 mmHg at baseline, and the remainder had a medium value of between 10 and 30 mmHg. In an analysis of all 258 patients, limb survival at 18 months was 84.2%. When these data were analyzed by the baseline $TcPO_2$ value, limb survival in the medium baseline $TcPO_2$ group was 89.5% compared with 77.8% in the low baseline $TcPO_2$ group. This was a statistically significant difference ($p=0.014$ log-rank test). $TcPO_2$ was measured at each follow up visit and its value increased gradually over the duration of treatment in the group of patients with a low baseline value. On the other hand, in the group with medium values at baseline, $TcPO_2$ increased mainly in the first month, then it was maintained at approximately 30mmHg for the remainder of follow up period. In both groups, each value of follow up was significantly different from baseline ($p<0.05$ Wilcoxon signed rank test).

## Conclusions

Studies carried out so far provide evidence that in inoperable patients with PAOD, SCS leads to better outcomes than those obtainable with a solely conservative approach with regard to the parameters considered (pain relief, wound healing, quality of life, limb salvage).

However, it emerges that benefits related to SCS (particularly considering limb salvage) are statistically significant only when patients are accurately selected on the basis of tissue microperfusion (assessed using $TcPO_2$) and their responsivity to a trial period.

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