

Electrical Neuromodulation and Ischemic Heart Disease

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Introduction

Despite an increase in the knowledge of the pathophysiology of cardiovascular diseases in conjunction with improved therapies and diagnostics, cardiovascular diseases remain the main cause of illness in Western societies. Cardiovascular diseases encompass a large number of syndromes of which ischemic heart disease is one of the most important, concerning morbidity and mortality.¹ Attributed to improved primary prevention measures, such as lifestyle changes and treatment of risk factors for cardiovascular diseases, advances in pharmacotherapeutical and surgical treatment strategies, the quality of life of patients suffering from ischemic heart disease has been improved. In addition, mortality from cardiovascular disease drops since three decades. Subsequently, more patients survive their heart disease longer, however ultimately without options for further treatment.² So, in general, notwithstanding the therapeutic merits usually supplying appropriate symptom relief in the majority of patients,³ in an increasing number of patients with ischemic heart disease the major goal the control of angina pectoris⁴ is not met. These patients, with an unmet medical need, have severe disabling angina, occurring during minimal exercise or even at rest. They are subsequently suffering from chronic angina pectoris that is therapeutically refractory to standard therapies. The term “chronic stable refractory angina pectoris” has been designated to patients with severe chest pain, resulting from coronary artery disease that is uncontrollable by both antianginal medication (aspirins, β -blocking agents, calcium-channel blockers, long-acting nitrates etc.) and revascularization procedures (Percutaneous Transluminal Interventions [PTI] and Coronary Artery Bypass Surgery [CABS]).⁵ However, the severity of anginal symptoms is to the judgement of the patients. Therefore, the European Study Group on the Treatment of Refractory Angina Pectoris has recently redefined this 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 reversible myocardial ischemia should be clinically established to be the cause of symptoms.”⁶ Patients enduring this condition are usually characterized by a long history of coronary artery disease, have been treated with CABS and PTI procedure(s), previously, are in the beginning of the sixties, predominantly male, have a slightly reduced left ventricular ejection fraction, and an elevated fibrinogen.^{7,8} With regard to the latter the increased fibrinogen is most likely to be an epi-phenomenon, related to chronic inflammation induced by coronary artery disease.⁹ In addition, as a result of an acute worsening of their coronary artery disease, these patients frequently need hospital admissions.¹⁰ Therefore, the search for and evaluation of adjunct therapies has to be encouraged in order to identify novel strategies which are capable to reduce the angina burden 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 angina pectoris, refractory to conventional therapies such as pharmacological approaches and revascularization procedures, adjunct therapies have become available, recently. One of the most promising adjunct 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.

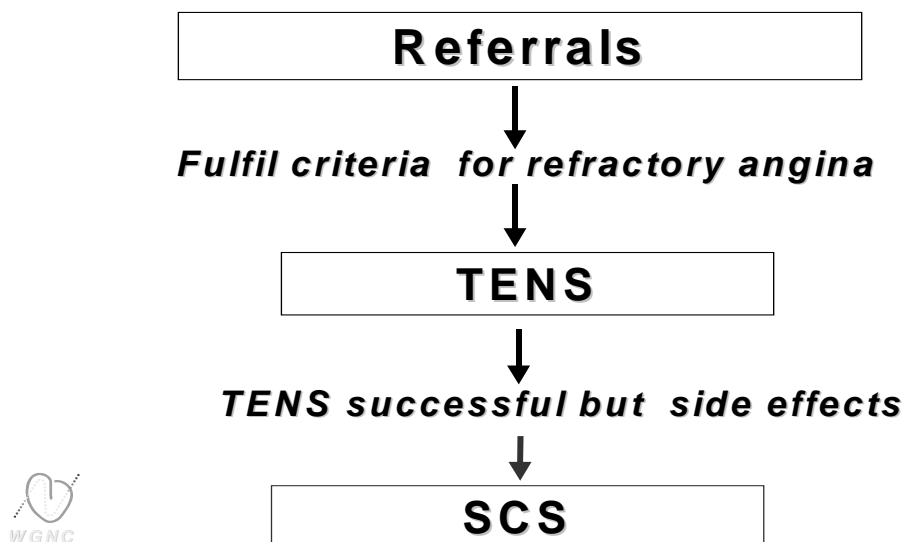
It is the purpose of this review to discuss the literature and provide practical guidelines. In this respect it is worth to notify that electrical neuromodulation has become incorporated in the ACC/AHA guidelines since 2002.¹¹

Neuromodulatory therapies.

To obtain an antianginal effect, modulation of the nervous system has been performed for many years and may be executed through vagal stimulation,¹² by creating a temporary sympathetic block through injections with local anesthetics into the stellate ganglion,¹³ through application of electrical current, (i.e. 'electrical neuromodulation'), through destructive therapies applied via denervation of the stellate ganglion,¹⁴ or by means of modulation of the extrinsic cardiac nervous system. The latter can be applied through transthoracic,¹⁵ or endoscopic sympathectomy.^{16,17} Electrical neuromodulation is either applied 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 angina pectoris resistant to conventional strategies.^{18,19}

Information, rehabilitation and neurostimulation

All patients who are referred to our hospital and fulfil the inclusion criteria will receive transcutaneous electrical nerve stimulation (TENS) for 2-3 days (Figure 1). Extensive information and training the patients to let them adequately manage the device, making use of a rehabilitation program, is essential for a beneficial outcome. TENS application before implanting a spinal cord stimulator (SCS) is not used for screening but merely for getting the patients get used to the SCS. Clinically we often have observed patients who are upset when confronted with a device that has to be implanted. So, to get the patients used to the therapy we start with TENS. Some patients however remain on TENS therapy, sometimes they fear to receive an implanted device. Others later proceed to SCS, mainly for reasons of an ortho-ergic reaction, which rather frequently is observed when TENS is applied onto the chest.



Implantation

The implantation procedure of SCS, being a reversible non-destructive therapy, has been described elsewhere.²³ The key to the success of SCS is an accurate placement of the stimulating electrode in the dorsal epidural space. The procedure is performed under local anesthetics, with the patient in prone position. The paresthesias induced by the stimulator have to correspond with the area where most of the patients experience the angina pain.

When the tip of the electrode is correctly positioned, usually at the C7-T1 level, the lead is anchored and connected to a pulse generator, generally placed in a subcutaneous pocket in the upper abdominal wall. The stimulator can be activated (or deactivated) by the patient, either through application of a magnet or by making use of the patient programmer.

History of neuromodulation for angina pectoris

In 1965 Braunwald was the first to observe antiangina and antiischemic effects when applying electrical current through a self-made device to the stellate ganglion.²⁰ The first report on antiangina effect of SCS in patients with chronic refractory angina pectoris was published by Murphy and Giles, in 1987.²¹ 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.²² Since the nineties many authors have advocated SCS as an effective additional approach for patients chronically disabled by their angina.^{3,5,6,7,8,18,19,23,24,25,26,27,28,29,31} To date, in selected patients, SCS may even be considered as an alternative to bypass surgery.²⁸ 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, in the last years research has been performed to determine whether the observed electro-analgesic effect of SCS is accompanied by an antiischemic effect.

The antianginal effect of electrical neuromodulation

Both observational and randomized studies on SCS have demonstrated beneficial effects, expressed in a reduction in angina complaints and use of short acting nitrates, and perceived quality of life²⁹, in conjunction with an improvement in exercise capacity.^{25,27,30} In approximately 80% of patients the beneficial effects of SCS last for at least one year^{5,7,25,26,30} and in nearly 60% of these patients improvement in exercise capacity and quality of life has been reported for up to 5 years.³¹ 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.^{7,25,28,31,32} 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.^{25,31,32,33} 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. In addition, SCS was not able to suppress the conduction of cardiac pain signals to the cerebrum during cardiac distress.³⁴

Spinal cord stimulation and myocardial ischemia

In addition to the antianginal effect, SCS exerts antiischemic effects. In many publications on these patients, the suggested antiischemic effect has been demonstrated by making use of different tools, such as exercise stress testing^{25,27,28} and ambulatory ECG monitoring.^{23,27} These 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, one study showed an increased tolerance to atrial pacing and delayed onset of anginal complaints during SCS.³⁵ All patients ultimately experienced angina pectoris. Chauhan *et al*³⁶ demonstrated an increase in coronary flow velocity, using Doppler flow catheters during neuromodulation. The raise 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.³⁷ Therefore, the reduction in ischemia is thought to be related to homogenization of myocardial blood flow. In contrast to the favorable influence of SCS on anginal complaints, many concerns remain with regard to the potential risk on an increase in

myocardial ischemia with serious ensuing sequelae, 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. In addition, since SCS appears to employ an antiischemic effect, without increasing mortality^{5,7,28} and without concealing the anginal warning signal during an acute myocardial infarction,^{25,26,31,32,33,34} neuromodulation is considered as a safe therapy for patients invalidated by refractory angina.

Mechanisms of action of spinal cord stimulation at the central nervous system

In 1965, Melzack and Wall published the ‘gate-control theory’.³⁸ The model was based on the theory that stimulation of myelinated relatively fast conducting A-fibers modulate the processing of pain in the non-myelinated slower conducting C-fibers in the dorsal horn. In higher brain centers, both angina pectoris and neuromodulation have been found to affect areas involved in cardiovascular control.^{34,39} Intra cardiac neurons (ICN) are considered as the final common integrator of the nervous system in the heart.⁴⁰ 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.⁴¹ In addition to these putative actions at different levels in the central nervous system (CNS), a variety of neurotransmitters and vasoactive compounds, like adenosine and endorphins, are thought to link shifts in the activity in CNS’ centers to control cardiovascular state.

Mechanisms of action of spinal cord stimulation 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.³⁴ Initially, the antiischemic effect of SCS was subscribed to modulation of the autonomic nervous system, more specifically, to the sympathetic branch. However, clinical data do not support this hypothesis, since no change in heart rate variability, or in (nor)-epinephrine metabolism has been found during spinal cord stimulation.^{23,27,42,43}

The raise 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.³⁷ 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 collaterals⁴⁴ or that other mechanisms are involved such as angiogenesis⁴⁵ or preconditioning⁴⁶ 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.²² During SCS the anginal threshold was higher, maybe secondary to an 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. 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 opioids 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, dipyridamole, an adenosine re-uptake inhibitor, has been found to blunt the effect of SCS.⁴¹ Finally, the intake of caffeine, which influences the adenosine handling via xanthine metabolism, has been observed to impair the effects of neuromodulation.⁴⁷

Own Experience

Since 1986 we collaborate in a multidisciplinary team to select, implant and carefully follow-up patients treated with electrical neuromodulation for refractory angina pectoris. Since SCS is not reimbursed in our country we start with TENS and if TENS is successful but has to be withheld for reasons of side effects, we continue with SCS (Figure 1). In retrospect, we analyzed all the patients with refractory angina pectoris referred to our hospital for electrical neuromodulation.

Since 1986, 665 patients have been treated at the University Medical Center Groningen for refractory angina pectoris. TENS has been applied in 540 (81,2%) and SCS in 111 (16,7%) of the patients. The rest have been treated with angiogenesis⁴⁵ and stellate blockade. Since 1986 a total of 125 patients died, 94 in the TENS group (17,4%) of whom 48 were cardiac deaths (51,1%) and 31 in the SCS group (27,9%) of whom 9 (29,0%) were registered as cardiac deaths. The average patient treated with TENS was 62 (range 28-85) years and 59 (range 38-79) years for SCS. The patients were predominantly male (64%), suffering for 12 years from coronary artery disease, had a left ventricular ejection fraction of 49% (entire population), used 24 tablets short-acting Nitroglycerine per week, had experienced 0.76 myocardial infarctions, underwent 0.75 CABG procedures, and 0.89 PTI-procedures. Only 8% of our patients had single vessel disease. The majority of patients with refractory angina had multi vessel disease i.e. 2-vessel disease (12%) and 3-vessel disease (36%). 199 patients had a diffuse affliction of their coronary arteries (30%). In addition, 13% of the patients had cardiovascular syndrome X. The results (Figure 2) show that SCS is still effective in 80% of the patients after a period of 4 years. After that same period, TENS was effective in 55% of the patients. Regarding the predictors of outcome no statistical significant relations were found with efficacy of the therapy. However, although hard clinical evidence is lacking, SCS is thought to be more effective than TENS in the treatment of patients with chronic refractory angina pectoris. Application of current through the (high resistant) skin with TENS provokes in 28% of our patients' side effects, such as ortho-ergic reactions. These patients were subsequently considered for SCS.

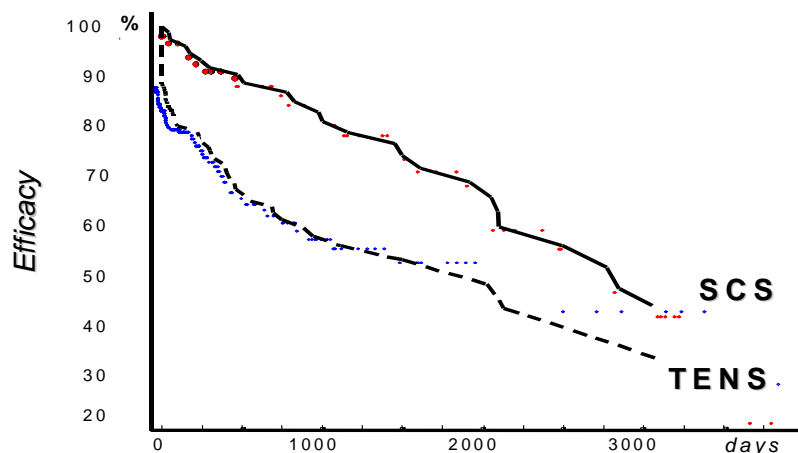


Figure 2: Spinal Cord Stimulation (SCS: n=111) and Transcutaneous Electrical Nerve Stimulation (TENS: n=540).

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 likely to be multi-factorial and are thought to take place at different levels in the heart and the brain.

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