



# Neuromodulation for chronic refractory angina

**Roger Moore and Michael Chester**

*National Refractory Angina Centre, Mersey Regional Cardiothoracic Centre, Liverpool, UK*

Neuromodulation is the use of therapies which alter the relationship between the heart, its autonomic innervation and the central nervous system with the objective of reducing the ischaemic burden and diminishing the perception of angina.

Despite rapid innovations in percutaneous and surgical revascularisation techniques, increasing numbers of refractory angina patients are presenting to cardiologists with advanced coronary disease, which is unsuitable for further revascularisation. Such patients are often severely disabled by chronic angina pectoris, which often correlates poorly with the degree of observable ischaemia. It is with the background of this burgeoning group of patients, 'refractory' to revascularisation, that has led to increasing interest in the alternative strategies of neuromodulation.

Neuromodulation owes its origins to Melzack and Wall's gate theory of pain<sup>1</sup> that predicted that stimulation of vibratory afferent nerves would reduce or gate the transmission of pain traffic relaying through the cord at the same point. Transcutaneous electrical nerve stimulation (TENS)<sup>2</sup> was specifically designed to make use of this predicted effect and was used to treat a variety of pain conditions, before it was shown to be effective in angina. Spinal cord stimulation (SCS) was also used to good effect in non-cardiac pain conditions before being found to be effective in relieving angina in a patient implanted for cancer pain control.

The UK Pain Society Angina Special Interest Group and the Angina Special Interest Group of the International Association for the Study of Pain and the British Cardiovascular Interventional Society have endorsed the recommendation of the UK National Refractory Angina Group that neuromodulation should be offered as part of a multidisciplinary angina management programme based on the current guidelines (see <[www.angina.org](http://www.angina.org)> for details).

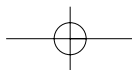
*Correspondence to:*  
Dr M R Chester, Director,  
National Refractory  
Angina Centre, Mersey  
Regional Cardiothoracic  
Centre, Thomas Drive,  
Liverpool L14 3PE, UK

## **Transcutaneous electrical nerve stimulation**

### *Clinical evidence for TENS treatment in angina*

Early studies conducted on limbs compromised by peripheral vascular disease demonstrated improved microcirculatory blood flow as well as a





direct analgesic effect<sup>3</sup>. These anti-ischaemic properties provoked interest in the possibility of treating coronary artery insufficiency, which led to Mannheimer *et al*<sup>4</sup> producing the first reports of successful application of TENS for chronic angina pectoris in 1982. Several similar small randomised controlled studies<sup>5-8</sup> followed this publication, demonstrating that TENS could improve symptom control, reduce nitrate usage, increase exercise tolerance and extend walking times to ischaemia in chronic angina patients. In common with routine revascularisation strategies, none of the TENS trials attempted to evaluate the placebo effect of the treatment. There have been major difficulties in designing placebo studies because the treatment appears to require paraesthesia for efficacy and so blinding the patient is impossible.

TENS has also been shown to reduce the number of ischaemic episodes in patients presenting to the coronary care ward with unstable angina<sup>9</sup> (Borjesson 1999 5 /id).

There have been no studies published looking at long-term effects of TENS on prolonged symptom improvement or impact on quality of life in the treatment of chronic angina. Although our own experience of a large series of 150 chronic refractory angina patients indicates significant and sustained improvement is possible in some patients and a randomised controlled study is underway.

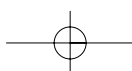
### *TENS application*

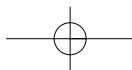
The electrodes are placed on the chest either side of the maximal area of perceived pain. The electrodes are then connected to the generator and output set at a frequency of 70 Hz and a pulse width of 0.2 ms. The intensity is then increased from zero until the perceived sensation is just less prominent than the patient's typical angina episode<sup>5</sup>.

Patients are advised to activate the TENS device for 1 h, three times per day for background control and also to use it prophylactically during acute angina attacks like GTN. A higher intensity level is required for prophylactic treatment during an acute angina episode with output increased to until the discomfort is relieved. In many patients, the analgesic effect is almost immediate with conversion of the pain to a less noxious sensation, which then gradually subsides. If the pain does not improve within 15 min, or sooner if associated with nausea, vomiting or sweating, patients are advised to attend hospital to exclude an acute coronary event.

### *Complications*

There are few complications in TENS therapy apart from interactions with pacemaker technology. Contact dermatitis is occasionally troublesome





and can be avoided by rotating the electrode positions. If it does recur, varying the type of electrode and contact jelly can resolve the problem. In extreme cases a 'holiday' with local steroid treatment is helpful.

### *Safety*

TENS therapy is safe in the majority of patients. Permanent cardiac pacemakers are not a contra-indication and problems of abnormal sensing are rare<sup>10</sup>. Any misinterpretation can be avoided by reprogramming the device to a bipolar sensing configuration or altering sensing thresholds<sup>11</sup>.

The TENS electrodes should not be placed directly over the pacemaker can.

There is a single case report of an implanted ventricular defibrillator misconstruing a TENS output as ventricular fibrillation resulting in an inappropriate shock. Care, therefore, must be taken when using TENS therapy in this situation.

## **Spinal cord stimulation**

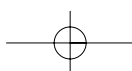
### *Clinical evidence*

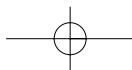
The first stimulator was implanted for intractable angina in Australia in 1987<sup>12</sup>. Subsequently, there has been extensive scrutiny of SCS in 'refractory' patients, with over 70 publications to date. SCS has been shown to diminish angina, reduce the frequency of hospital admissions and improve patients' quality of life<sup>13-16</sup>. These improvements appear to be persistent without generating additional risks for the patients.

Spinal cord stimulation was compared to high-risk non-prognostic coronary artery bypass surgery in the ESBY<sup>17</sup> randomized trial. Both groups displayed a significant reduction in angina frequency and short-acting nitrate requirements, whilst only the surgical group showed significant improvement of exercise induced ischaemia at 6 months. However, the surgical arm had a high procedural mortality rate which compared to no deaths in the SCS group.

### *SCS implantation*

Prior to implantation, it is essential that there is a clear understanding between the patient and carer and the medical team about the aims and objectives of therapy. Fear and anxiety are major problems in chronic refractory angina and SCS is not an anxiolytic nor is it implantable psychotherapy.





The device consists of three different components: the implanted pulse generator (IPG), the epidural electrode and a connecting lead. With the awake-patient placed in the prone or sitting position, a Touhy needle is placed in the epidural space using a paramedian approach at the T3–T5 level. Once in position, the electrode is advanced to the appropriate level under fluoroscopy guidance (tip at C6–T1). The electrode is connected to an external generator and the final electrode level adjusted with reference to the patient's pattern of stimulatory anaesthesia. Once satisfied that the paraesthesia is pleasant and covers the area of referred pain, the patient is anaesthetized and the IPG is implanted subcutaneously on the anterior abdominal wall. The two units are then connected by a tunneled lead.

The majority of implanters prefer to complete the entire procedure at one sitting to reduce cost and infection risk (1-stage procedure). If the initial on-table trial is unconvincing, then it is reasonable to externalise the trial lead and implant a few days later if appropriate (2-stage procedure).

### Complications

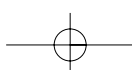
The main risk for patients is infection, which usually requires explantation of the entire system (viz. permanent pacemakers). All procedures are undertaken with sterile technique and covered with prophylactic antibiotics. Because with the percutaneous approach the lead is free within the epidural space, lead displacement is relatively common and requires re-exploration of the epidural electrode. Lead fracture is relatively uncommon.

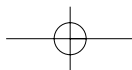
The most serious potential complication is epidural haemorrhage but is rare (approximately 1:2000), whilst an inadvertent dural tap though usually self-limiting can be quite distressing to the patient and occasionally requires a dural patch.

### Safety

Clinicians are naturally concerned over the potential risks of masking myocardial ischaemia. Cardiologists have been apprehensive, fearing that SCS might lead to an increase in the extent of silent ischaemic episodes and also affect the patient's ability to detect an acute coronary event<sup>20</sup>.

Research, however, has established that with SCS the overall ischaemic burden is diminished, myocardial infarction is not disguised<sup>21</sup> and that mortality rates are similar to matched cohorts within the general population of coronary artery disease patients<sup>19</sup>.





## General mechanisms of action

The precise method by which neuromodulation alleviates symptoms and reduces ischaemia has not yet been defined. Several possible mechanisms have been proposed.

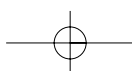
### Placebo effect

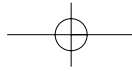
Attempts to explain the clear clinical benefits of neuromodulation in terms of 'placebo' versus 'physiological' is impossible as both TENS and SCS produce a clearly perceived sensation when activated<sup>22</sup>. Any credible sham device would, therefore, be required to produce a discernible stimulus, which could then be criticized for providing neurostimulation. This creates an irresolvable dilemma.

The placebo effect relates to the psychological influence of a therapeutic agent based on the subject's own belief of the efficacy of the treatment rather than any direct physiological impact of the therapy. The reality is that placebo is a good thing and will influence the outcome from any therapy including angioplasty and bypass surgery. Although its influence is purely psychological, it has also been shown to be capable of eliciting a physiological response. The placebo response has been thought of as a transient phenomenon, but landmark trials in angina have demonstrated that the benefit of placebo can be long lasting<sup>23,24</sup>

### Gating theory

Melzack and Wall<sup>1</sup> proposed that the stimulation of large diameter type A (proprioceptive) fibres leads to attenuation of transmission from activated small unmyelinated type C fibres from the periphery to the central pain receptors via inhibitory interneurons, at the level of the dorsal horn of the spinal cord. Therefore, theoretically, either stimulation of peripheral nerves with TENS or stimulation at the level of the dorsal horn with SCS could lead to attenuation of incoming angina signals travelling along sympathetic efferent pathways. Investigation with SCS has revealed a generalized 'field effect' with reduced neural activity mediated by alteration in the balance of inhibitory and excitatory neurotransmitters. Linderoth *et al*<sup>25</sup> assayed dorsal horn neurotransmitter levels, demonstrating rises in the inhibitor  $\gamma$ -aminobutyric acid (GABA) and reduced level of excitatory amino acids (aspartate and glutamate) after SCS in rats. In addition, intrathecal administration of GABA antagonists and adenosine agonists have been shown to increase the effectiveness of SCS in the rat model<sup>26</sup>. This





suggests that SCS may act, in part, by up-regulating the natural spinal GABAergic inhibitory interneurons. The GABA system is likely, however, merely to be an example, with the complete pattern of action liable to include the contribution of other messengers and involve their subtle and complex interactions.

### *Endogenous opioids*

It has been proposed that part of the effect of neurostimulation is mediated through heightening of endogenous endorphin activity both at the spinal and cardiac level. Administration of opiates has been shown to be clinically effective in this patient group and SCS has been demonstrated to increase spinal endorphin levels. Mannheimer *et al*<sup>27</sup> investigated the impact of SCS on cardiac  $\beta$ -endorphin levels using coronary sinus sampling in patients undergoing right atrial pacing. He established that SCS results in elevated cardiac  $\beta$ -endorphin levels, but interestingly also showed that the addition of the endorphin antagonist, naloxone, failed to diminish the benefit of SCS. It is, therefore, not clear as to whether endorphins play a central role in the mechanism of neurostimulation or is just a peripheral phenomenon.

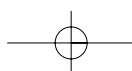
### *Sympathetic nervous system*

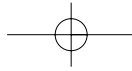
Increasing intrinsic cardiac sympathetic activity results in increased myocardial workload and, therefore, elevated oxygen demand. The epicardial and arteriolar coronary vessels are innervated by the sympathetic system, which has a pivotal role in vasomotor control through  $\alpha$ -adrenergic receptors<sup>28</sup>. There are no consistent data on whether the sympathetic system exerts a resting vasoconstrictor tone on the resting coronary circulation, but clear evidence of sympathetic influence during exercise. It is, therefore, evident that any therapy that acts to minimize sympathetic activity will reduce the circumstances likely to potentiate ischaemia in patients with significant coronary artery disease.

In addition to its role in exacerbation of ischaemia, it is also becoming clear that the sympathetic system is also the main conduit in the transmission of angina, from ischaemic myocardium to the central nervous system<sup>29</sup>.

#### **Sympathetic pathways**

The heart has wide-spread sympathetic nerve endings, which coalesce to form the cardiac sympathetic plexus and collateral ganglia. Cardiac nerves link these structures to adjacent swellings within the cervical region of the paravertebral sympathetic ganglion chain<sup>30</sup>. These structures





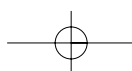
are termed the stellate and middle cervical sympathetic ganglia. The sympathetic pathways connect with the intermediolateral grey column of the upper thoracic spinal cord (T1–T4) through the white and grey rami communicantes. The sympathetic pathway extends upward in the posterolateral brainstem terminating in the hypothalamus.

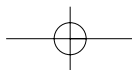
Studies have revealed that angina reaches consciousness not solely via the hypothalamus but by excitation of the upper thoracic spinothalamic tract, which relay through the ventroposterolateral thalamus and continue upward to the higher brain centres<sup>31</sup>, although no anatomical relationship between the sympathetic pathway and the STT has been demonstrated.

The sympathetic/parasympathetic balance has been investigated by Hautvast *et al*<sup>32</sup> who failed to show any alteration in heart rate variability with SCS. However, Meglio *et al*<sup>33</sup> did find a decrease in resting heart rate and features suggestive of a functional sympathectomy in 25 patients with stimulators, and several investigators have demonstrated a small fall in systolic blood pressure during neurostimulation with both TENS and SCS<sup>34</sup>. Recent work by Foreman *et al*<sup>35</sup> has cast some light on the mechanism by which neurostimulation may alter cardiac sympathetic drive. They observed that spinal cord stimulation in dogs undergoing coronary artery ligation had a suppressive effect on intrinsic cardiac sympathetic activity. Furthermore, they also discovered that this effect could be neutralised by interrupting the afferent and efferent sympathetic tract in the subclavian anseae. This provides evidence that SCS may act through the influence of spinal cord neurons communicating with the intrinsic cardiac nervous system via intrathoracic cardiac nerves.

#### Coronary blood flow and myocardial perfusion

Chauhan *et al*<sup>35</sup> used intracoronary Doppler wires to analyse the effect of TENS on coronary blood flow in CAD, Syndrome X and cardiac transplant patients. There was an increase in coronary flow at rest in all but the transplanted patients, which implied a sympathetic mediated mechanism. However, Sanderson<sup>37</sup> and Jessurun<sup>38</sup> were unable to verify these results in follow-up studies with Syndrome X and CAD patients, respectively. Likewise, Norsell *et al*<sup>39</sup> did not see an increase in coronary flow velocity in patients undergoing pacing stress with spinal cord stimulation. The coronary resistance vessels are, however, thought to consist of two resistance compartments in series. The first section consists of  $\alpha$ -adrenergically constrained arterioles and the second section consisting of smaller vessels autoregulated by local metabolic factors. It is, therefore, possible that, whilst sympathectomy may reduce resistance in the first compartment, it may simultaneously, by reducing overall myocardial oxygen demand, increase resistance in the second. As a consequence, there may be no overall alteration in vasomotor tone and, therefore, no increase in coronary blood flow.





The effect of neuromodulation on myocardial perfusion during exercise has been investigated using positron emission tomography (PET)<sup>40</sup> in patients with ischaemic heart disease. The investigators found that although SCS failed to alter the overall blood flow, there was a redistribution of blood to previously ischaemic area producing a more homogeneous pattern.

## Algorithm

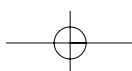
It is important to realize that, for the majority of patients, neuro-modulation will lessen the intensity of their chest pain and reduce the frequency of attacks rather than completely eradicate symptoms. We have, therefore, found it necessary in our own department to provide the patient with education, counselling, help with relaxation and cognitive behaviour therapy as part of an integrated care algorithm<sup>41</sup>. This pathway is commenced prior to neurostimulation in order for the patients to gain maximum benefit from TENS and SCS. It provides an opportunity to reassure, change life-style patterns, such as minimal physical activity, and gain agreement with patients to realistic treatment goals.

## Conclusions

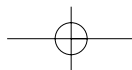
Neuromodulation has been shown to improve anginal symptoms and reduce ischaemia without placing the patient at significant risk. The exact mechanism of action remains unclear, but is likely to be a complex interaction involving placebo effect, nociceptive gating and cardiac sympathetic modulation.

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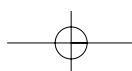
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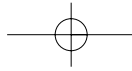






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### Ischaemic heart disease: therapeutic issues

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