JESSICA de VRIES, MD*
Department of Cardiology, Thoraxcenter
University Medical Center of Groningen
University of Groningen
The Netherlands

ROBERT D. FOREMAN, PhD*
Department of Physiology
University of Oklahoma Health Sciences Center
Oklahoma City, OK

MIKE J.L. DeJONGSTE, MD, PhD, FESC*
Department of Cardiology, Thoraxcenter
University Medical Center of Groningen
University of Groningen
The Netherlands

The anti-ischemic effects of electrical neurostimulation in the heart

In 2001, the American College of Cardiology and the American Heart Association introduced electrical neurostimulation (ENS) in their joint guidelines for the treatment of angina pectoris. The introduction of this therapy was supported by many (mainly small) articles examining the beneficial effects of ENS for patients with treatment-refractory angina. Even though ENS is considered to be an antianginal therapy, many physicians question the anti-ischemic benefit that ENS is frequently suggested to confer. This review briefly summarizes the antianginal effects of ENS, with a focus on the therapy's anti-ischemic outcomes.

THE ROLE OF ISCHEMIA IN ANGINA PECTORIS

The complex neurochemical cascades that are responsible for the sensation of angina are initiated by myocardial ischemia. The latter develops when myocardial oxygen demand exceeds oxygen supply, as depicted in **Figure 1**.

Ischemia results in a reduction in the formation of adenosine triphosphate (ATP). As a result, acidosis develops and chemical substances are released, including lactate, serotonin, bradykinin, histamine, reactive oxygen species, and adenosine.[1,2] These substances primarily stimulate chemosensitive receptors of unmyelinated nerve fibers terminating within cardiac muscle fibers and around the coronary vessels.[3] Adenosine can induce angina via stimulation of the A1 adenosine receptor.[4,5] The nerve fibers travel in the sympathetic afferent pathways from the heart and enter the lower cervical and upper thoracic spinal cord (C7 to T4) via the dorsal root ganglia of these segments. Impulses are then transmitted via ascending spinal pathways to the thalamus and ultimately the cerebral cortex, where the angina is "felt" as generally orginating from the chest, the arms, and sometimes the neck and jaw.

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TWO MAIN TYPES OF ELECTRICAL NEUROSTIMULATION FOR ANGINA

The treatment of chronic stable angina pectoris has involved applying electrical current to various sites of the body (ganglion, nerve, spinal cord, skin, subcutis). To date, ENS is most often applied either to the spinal cord (spinal cord stimulation, or SCS) or to the skin (transcutaneous electrical nerve stimulation, or TENS). For details on the implant procedure involved in SCS, see DeJongste et al.[6]

Patients who are referred to the hospital and fulfill the inclusion criteria for SCS **(Table 1)** may be considered candidates for SCS. A team of clinicians—typically consisting of anesthesiologists, cardiologists, neurosurgeons, nurse practitioners, and psychologists—makes the final decision to implant an SCS device, apply TENS, or consider other alternatives. To achieve a successful outcome, it is essential to first perform cardiac, neurologic, surgical and psychological examinations and provide essential information to the patient up front. In this respect, TENS application may be used before implantation of an SCS device to allow the patient to get acclimated to the paresthesias. Although randomized studies comparing SCS with TENS are lacking, observational studies lead to the conclusion that SCS is more effective than TENS in the treatment of refractory angina.

ANTIANGINAL PROPERTIES OF ELECTRICAL NEUROSTIMULATION

Patients are candidates for ENS if they suffer from chronic stable angina pectoris that is refractory to conventional antiaginal therapies despite maximal tolerable dosing and if coronary revascularization is not an option.[7] ENS has been used for these "no option" patients for years—by means of stellate ganglion stimulation since 1967,[8] by TENS since 1982,[9] and by SCS since 1987.[10]

Both observational and randomized studies of ENS for angina have demonstrated long-term beneficial effects, including a reduction in severity of angina

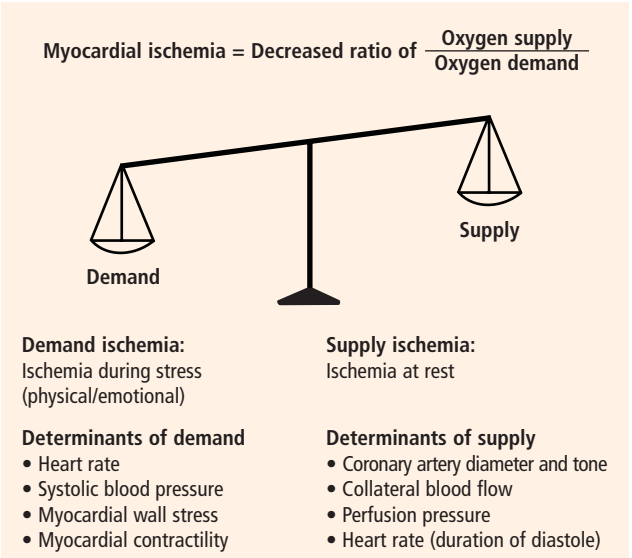

FIGURE 1. Schematic of myocardial ischemia and the determinants of the oxygen ratio. Myocardial ischemia occurs when the ratio of oxygen supply to oxygen demand decreases—as a result of a decreased oxygen supply, an increased oxygen demand, or both.

TABLE 1
Inclusion and exclusion criteria for spinal cord stimulation

Inclusion criteria
Stable angina pectoris (Canadian Cardiovascular Society scale III to IV), despite optimal medical treatment, resulting from documented significant coronary artery disease
Patient is not suitable for revascularization
Patient understands the therapy and is able to use the device
Exclusion criteria
Cardiac pacemaker dependence/implantable cardioverter defibrillator
Likelihood of magnetic resonance imaging in the future
Psychological instability
Insurmountable technical and anatomic problems (specifically in the spine)

complaints, a decreased intake of short-acting nitrate tablets, and an improved quality of life, in conjunction with an improvement in exercise capacity.

There has been concern over the safety of SCS out of fear that it might deprive the patient of an important angina "warning signal." However, fear of an inability to experience angina during ischemic events seems unjustified. Rather than abolishing angina, ENS is thought to enhance the angina threshold. As a result, patients report an increase in exercise capacity and a reduction in angina severity. There is abundant literature dealing with "natural occurrence" of angina, specifically during acute myocardial infarction, in patients treated with ENS. This is congruent with the absence of an adverse effect on mortality as demonstrated in prospective and retrospective studies. Moreover, SCS was not able to suppress the conduction of cardiac nociceptive signals to the cerebrum during cardiac distress.[11]

ANTI-ISCHEMIC PROPERTIES OF ELECTRICAL NEUROSTIMULATION

Many diagnostic tests are available to assess myocardial ischemia, each with its own limitations.[12] Because the different measures of ischemia are found to be independent, it is recommended that efficacy be assessed separately for each clinical end point before appropriate treatment is considered.[13]

One of the major problems with studies of ENS is their design. Patients feel the paresthesias, so they cannot be blinded, and the physician sees the stimulation artefacts on the electrocardiogram (ECG). Nevertheless, randomization and crossover designs are still feasible. In this review we will specifically address the anti-ischemic studies performed with ENS in patients with chronic refractory angina.

Studies of (neuro)chemicals

A very accurate test for ischemia involves measuring lactate metabolism. Mannheimer et al used atrial pacing to show that TENS improved lactate metabolism during atrial pacing, in conjunction with less-pronounced ST-segment depression,[14] and later showed that these effects were seen both in the presence and in the absence of treatment with the endorphin blocker naloxone.[15] The latter study further demonstrates that the heart is capable of producing endorphins following ENS.[15]

Another study found that ENS decreased total body norepinephrine by 18% (P = .02).[16] Moreover, total body norepinephrine levels increased during pacing by 47% (P = .02), whereas total cardiac norepinephrine spillover remained unchanged during pacing and active SCS. These findings suggest that the anti-ischemic effects of ENS are not exerted via cardiac sympathetic activity, even though the overall sympathetic activity is decreased. The authors concluded that the heart may benefit from ENS through a reduction in oxygen demand.[16]

TABLE 2
Improvements in exercise stress test parameters with electrical neurostimulation*

	Improvement in maximum exercise†	Increase in time to angina (sec)	Reduction in ST-segment depression at maximum workload (mm)	Reduction in ST-segment depression at comparable workload (mm)	Improvement in rate-pressure product‡ at maximum workload
Mannheimer et al, 1985[14]	73 W	NA	NA	0.6	3.6
Mannheimer et al, 1988[19]	28 W	216	0.3	0.6	0.57
Sanderson et al, 1992[20]	64 sec	NA	1.5	0.9	0.5
De Jongste et al, 1994[21]	168 sec	171	0.4	NA	0.9
Hautvast et al, 1998[22]	80 sec	69	0.3	0.4	1.5
Mannheimer et al, 1998[23]	1.6 W	NA	0	0	–0.2
Murray et al, 2004[25]	35 sec	30	0.1	0.4	0.4

* Results are the differences between baseline and follow-up after electrical neurostimulation (either transcutaneous or spinal cord stimulation), except for the study by Murray et al, for which results are the differences between the treatment group and the control group.
† Expressed as workload (watts) or as duration (seconds).
‡ Rate-pressure product = systolic blood pressure × heart rate × 10^3.
NA = not available

Cardinal et al concluded that ENS appears to counteract the deleterious effects that stressors—particularly stressors with effects on the intrinsic cardiac nervous system, such as angiotensin II—exert on ischemic myocardium.[17] Further, it has been shown that ENS modulates these intrinsic cardiac neurons, which contain many substances, and thus may prevent deleterious consequences of myocardial ischemia.[18]

Exercise stress testing

The most frequently used method to demonstrate myocardial ischemia is exercise stress testing. Since the magnitude of ST-segment depression on the ECG is considered a quantitative measure of myocardial ischemic burden, exercise stress testing may also be used to quantify the reduction of myocardial ischemia. **Table 2** summarizes the effects of ENS on exercise stress test parameters from seven different studies.

Mannheimer et al found in 1985 that TENS increased work capacity and reduced ST-segment depression,[14] and in 1988 these same researchers found comparable results with SCS.[19] Subsequent studies are in agreement with these early observations **(Table 2)**.[20–22]

One of the larger randomized controlled trials was the ESBY (Electrical Stimulation versus Coronary Artery Bypass Surgery) study, which was designed to compare SCS with coronary artery bypass graft surgery (CABG) in patients with no proven prognostic benefit from CABG and an increased surgical risk.[23] The primary objective was to examine symptoms, survival, and myocardial ischemia after 6 to 60 months of therapy. Anginal symptoms improved significantly in each group, with no significant difference between the groups. Mortality was significantly lower in the SCS group, but exercise stress tests showed significant increases in maximum workload capacity and in rate-pressure product with CABG, as well as significant decreases in ST-segment depression at comparable workload and maximum workload with CABG, although exercise was performed with SCS off. These effects were maintained after 5 years of follow-up.[24]

The carry-over effect of TENS was studied in a randomized, placebo-controlled, crossover trial in which exercise stress testing was performed at baseline and after 2 and 4 weeks.[25] After 2 weeks of inactive TENS, patients were switched to active TENS, and vice versa. TENS increased total exercise time and time to maximum ST-segment depression. There was no significant difference in the maximum degree of ST-segment depression or in the rate-pressure product at maximum exercise.

Ambulatory ECG monitoring

Monitoring the magnitude of ST-segment depression on ECG during daily activities provides quantitive evidence of ischemia during submaximal efforts. The ECG also provides information about the status of the autonomic nervous system by assessing heart rate variability.

Di Pede et al studied myocardial ischemia and heart rate variability using a Holter monitor for 48 hours in 15 patients who were already being treated with SCS for 9 to 92 months.[26] Active SCS showed a 50% reduction in the number and a 45% reduction in the duration of ischemic episodes, decreasing the total ischemic burden. Since the heart rate variability parameters were unchanged,[26] SCS possibly exerted anti-ischemic effects over a long period of time by increasing myocardial blood flow. Similar findings have been reported by others.[6,22,27]

Moore et al assessed the effect of three different output settings of SCS (zero, half-maximum, and maximum) on short-term heart rate variability in 16 patients.[28] They found that heart rate variability parameters changed with maximum SCS and half-maximum SCS compared with zero SCS, which did not change heart rate or arterial blood pressure.

Noninvasive perfusion (imaging)

As early as 1990 it was suggested that the anti-ischemic effects of ENS may be related to changes in regional myocardial blood flow.[29] With positron emission tomography (PET), it is possible to quantify myocardial perfusion noninvasively.

De Landsheere et al used PET to perform quantitative analysis of regional myocardial perfusion at rest and after exercise, before and during SCS, in eight patients who had been undergoing SCS for at least 2 months.[30] SCS increased regional myocardial clearance significantly in nonaffected segments but not in the affected segments. However, ST-segment depression decreased during SCS treatment.

Hautvast et al evaluated myocardial blood flow with PET in nine patients, at baseline and after 6 weeks of SCS.[31] SCS was associated with a reduction in ST-segment depression during stress testing with the adenosine reuptake inhibitor dipyridamole. The distribution of myocardial blood flow was more homogeneous during SCS. However, SCS may also have blunted the effect of dipyridamole.

Mobilia et al studied myocardial blood flow with PET in 11 patients who had undergone SCS treatment for 2 to 48 months.[32] The first PET scan was taken on day 1 with SCS deactivated, and the second scan was taken on day 2 with SCS activated. Regional myocardial perfusion increased in nine patients, but the mean value of myocardial flow did not change.

Diedrichs et al demonstrated an improved quality of life and physical fitness after 3 months of SCS, with maintenance of these results at 1-year follow-up.[33] Physical fitness was measured using a 6-minute walk test and bicycle ergometry; quality of life was measured with the Seattle Angina Questionnaire. Additionally, MIBI-SPECT (single-photon emission computed tomography) imaging showed myocardial perfusion to be unchanged after 3 months, whereas there was a shift toward improved myocardial perfusion after 1 year. The researchers hypothesized that analgesia is the main effect of SCS and that changes in myocardial ischemia are secondary and might be due to increased physical activity.

Invasive coronary blood flow measurements/ atrial pacing

Chauhan et al measured the effect of TENS on coronary blood flow in 34 patients with syndrome X, 15 patients with coronary artery disease (CAD) affecting the right coronary artery, and 16 heart transplant patients.[34] A Doppler flow wire was used to measure coronary blood flow in the left coronary artery at rest and after 5 minutes of TENS. Coronary blood flow increased significantly in patients with syndrome X and in those with CAD, but no change was observed in the heart transplant patients. No significant changes were seen in the diameter of the left coronary artery or in hemodynamics. Additional assessment of catecholamine levels showed a significant reduction of epinephrine levels in patients with syndome X and in those with CAD, whereas levels were unchanged in the heart transplant patients. Norepinephrine levels were unchanged in all patients.

Norrsell et al measured the effect of SCS on coronary blood flow velocity in eight patients with CAD and four patients with syndrome X.[35] All patients underwent pacing that increased in frequency until they experienced moderate angina, at which point pacing continued for 7 minutes and SCS was begun after 2 minutes. During pacing the average peak velocity increased significantly (53%, $P = .02$), without differences in average peak velocity during pacing when SCS was activated.

Jessurun et al studied the effect of TENS on coronary blood flow using two flow wires, with one wire positioned in an affected artery and the other in a patent artery.[36] They found that TENS increased flow in the patent artery, with a decrease of flow in the affected area and a decrease in ST-segment depression of the ischemic area. This result may be attributable to the flow of blood through collateral pathways from the patent artery toward the ischemic region, bypassing the stenosis in the affected area.

Mechanisms of anti-ischemic effects

Coronary blood flow is influenced by coronary artery

diameter and tone (resistance) as well as by collateral blood flow.[37,38] Coronary atherosclerosis reduces coronary blood flow, leading to a reduction of myocardial oxygen supply, which in turn can lead to angina.

Anti-ischemic effects can be established by improving myocardial blood flow or by reducing the oxygen requirements of the heart. The latter can result from reduced sympathetic activity, by afterload reduction following reduced systemic vascular resistance, and by reduction of myocardial contractility, which also reduces the heart's oxygen needs.

Different outcomes have been reported regarding sympathetic activity and ENS, with some groups finding no differences in parameters of heart rate variability[6,22,26,27] while other groups have reported findings that could be due to decreased sympathetic activity.[14,16,28] Changes in myocardial blood flow were assessed with invasive measurements, SPECT, and PET.[30–36]

CONCLUSIONS

In addition to having an antianginal effect, ENS is thought to exert beneficial effects on myocardial ischemia by improving ischemic tolerance. Ischemic tolerance is the result of both preconditioning and collateral recruitment in the heart. Studies have reported the effect of ENS on adenosine and caffeine handling.[18,39] Furthermore, the heart appears to produce endorphins.[15] Additionally, ENS affects the alpha-receptor. All three of these factors are involved in the upregulation of protein kinase C that subsequently opens the ATP-dependent potassium channels and leads to preconditioning. At the same time, a recent pilot study by our group demonstrated a trend in collateral recruitment by ENS.[40] Moreover, another recent study found that preemptive SCS reduces the size of infarcts via cardiac adrenergic neurons.[41] We therefore hypothesize that ENS improves myocardial ischemia by mobilizing the mechanisms that produce preconditioning and by recruiting collaterals.

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Address: *Mike J.L. DeJongste, MD, PhD, FESC, Thoraxcenter, Department of Cardiology, University Hospital of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands; M.J.L.De.Jongste@Thorax.UMCG.nl.*