European Heart Journal (1997) **18**, 1890–1896

Effects of pacing-induced myocardial stress and spinal cord stimulation on whole body and cardiac norepinephrine spillover

H. Norrsell*, T. Eliasson*, C. Mannheimer*, L.-E. Augustinsson†, C.-H. Bergh‡, B. Andersson‡, F. Waagstein‡ and P. Friberg§

*From the *Multidisciplinary Pain Centre, Department of Medicine, Östra Hospital, Göteborg, Sweden and the Departments of §Clinical Physiology, ‡Cardiology and †Neurosurgery, Sahlgren's University Hospital, Göteborg, Sweden*

Aims Spinal cord stimulation has been used in the treatment of intractable angina pectoris since the beginning of the 1980s. This study was designed to investigate whether the documented anti-ischaemic effects of spinal cord stimulation are mediated through a decrease in sympathetic activity.

Methods and Results Ten patients with a spinal cord stimulator implanted as anti-anginal treatment were included in the study. Atrial pacing until the patient experienced moderate angina was performed and after 50 min rest the procedure was repeated during spinal cord stimulation. Total body and cardiac norepinephrine spillover was calculated and the former was found to have increased during pacing (47%, $P=0{\cdot}02$). When spinal cord stimulation was applied, total body norepinephrine spillover decreased at a comparable pacing rate (18%, $P=0{\cdot}02$). Cardiac norepinephrine spillover was not affected during the procedure.

Conclusion The results of this study indicate that the anti-ischaemic effect of spinal cord stimulation is not due to reduced cardiac sympathetic activity. However, spinal cord stimulation decreases overall sympathetic activity which may benefit the heart, possibly by reducing oxygen demand. **(Eur Heart J 1997; 18: 1890–1896)**

Key Words: Spinal cord stimulation, sympathetic activity, angina pectoris, atrial pacing.

Introduction

Spinal cord stimulation has been used for several years in the treatment of chronic neuropathic pain[1]. It has been shown to relieve pain, increase local blood flow and promote healing of ulcers in patients with peripheral vascular disease[2]. This treatment has also been used satisfactorily in patients with intractable angina pectoris. The anti-anginal effect appears to be secondary to a decrease in myocardial ischaemia[3–6]. The reduction in the latter seems to be dependent on a decrease in myocardial oxygen consumption[4]. According to a recent study by Haustvat *et al.*, in which positron emission tomography was used to study myocardial blood flow, spinal cord stimulation may redistribute coronary blood flow from unaffected to affected parts of the myocardium[7].

Angina pectoris is a clinical manifestation of transient myocardial ischaemia due to an imbalance between the supply and demand of oxygen in the myocardium. It is generally believed that an increase in sympathetic tone is of crucial importance in the pathophysiology of myocardial ischaemia. Pain, emanating either from myocardial ischaemia or other causes, is thought to elevate both regional and overall sympathetic nerve activity. In one study, Mannheimer *et al.* showed increased time to angina, improved myocardial lactate metabolism and decreased ST segment depression during spinal cord stimulation at comparable pacing frequencies[4]. In another report[8], using transcutaneous electrical nerve stimulation, which is another neuromodulation method, there was a decrease in arterial levels of epinephrine and norepinephrine, both during baseline conditions and during atrial pacing to ischaemia in a group of patients with coronary artery disease, indicating a decrease in efferent sympathetic traffic. Thus, there are reasons to believe that the effects of spinal cord stimulation are mediated through a decrease in sympathetic tone.

Revision submitted 13 June 1997, and accepted 20 June 1997.

Correspondence: Henrik Norrsell, MD, Multidisciplinary Pain Centre, Department of Medicine, Östra Hospital S-416 85 Gothenburg, Sweden.

0195-668X/97/121890+07 S18.00/0

The isotope dilution technique, with infusion of tritium-labelled norepinephrine to steady state, measures norepinephrine spillover and clearance simultaneously[9]. This method allows assessment of both regional and overall sympathetic activity[10]. This is of particular interest, as cardiac norepinephrine spillover represents less than 5% of the total body norepinephrine spillover[11]. A substantial increase in cardiac norepinephrine spillover might thus go undetected if only total body norepinephrine spillover is assessed, and especially if only plasma concentrations of endogenous norepinephrine are measured.

Atrial pacing is a common method to induce and investigate myocardial ischaemia in an experimental setting. The heart rate is increased step by step until the patient reports angina. This makes it possible to induce cardiac stress under stable experimental conditions and, at the same time, to obtain blood samples and monitor haemodynamic parameters.

The aim of the present study was to study the effects of spinal cord stimulation on cardiac and overall sympathetic activity, measured as norepinephrine spillover, during myocardial ischaemia induced by atrial pacing, in order to further clarify the mechanisms of the anti-anginal and anti-ischaemic effects.

Methods

Patients

Ten patients (seven men, mean age 65 years, range 51–79 years) with severe, stable angina pectoris (Canadian Heart Association class III–IV) were included in the study. The anti-anginal medication was considered to be optimal and none of the patients had congestive heart failure. In nine patients, the mean ejection fraction calculated from coronary angiography was 55% (range 35–74%).

All patients had a spinal cord stimulator (Itrel-II, Medtronic, Minneapolis, MN, U.S.A.) implanted for anti-anginal treatment. All stimulators had been implanted by the same surgeon, as described earlier[3]. The time from implantation to study varied from 1 month to 7 years. The stimulation parameters were set individually to ensure good coverage of the area of anginal pain. The parameter settings varied, for pulse width between 210 and 450 μs, for frequency between 45 and 85 Hz and for amplitude between 3 and 7 V. In all patients, the spinal cord stimulation had a satisfactory effect on the anginal symptoms.

Seven patients had suffered a myocardial infarction more than 6 months prior to the study. On electrocardiographic examination during a maximum symptom-limited bicycle ergometer test all patients had chest pain and ST segment depression of the anterior wall. Eight patients had had recurrent angina after a previous coronary bypass operation and two patients were considered unsuitable for coronary revascularization. Seven patients had three-vessel disease and two two-vessel disease. One patient was denied coronary revascularization due to an unfavourable risk profile without previous coronary angiography.

Anti-anginal medication was withheld 12 h prior to the pacing procedure, and spinal cord stimulation treatment was not allowed within 48 h before the study in order to avoid interference from possible long-term effects of the treatment. The patients were studied in the morning in a non-sedated fasting state.

The study protocol was approved by the Ethical Committee at Sahlgren's University Hospital, Göteborg. All patients gave their consent to participate after receiving verbal and written information.

Catheterization

A thermodilution pacing catheter (Wilton–Webster Laboratory, U.S.A.) was placed in or near the great cardiac vein of the coronary sinus, as described earlier[12]. A polyethylene catheter was inserted into the radial artery. Coronary sinus blood flow was measured by thermodilution. Blood samples were drawn simultaneously from catheters in the radial artery and the coronary sinus.

Radio-isotope infusion

A continuous intravenous infusion of tritiated norepinephrine, ([^{3}-H]-L- NE, specific activity 14–20 Ci . mmol^{-1}; New England Nuclear, Boston, MA, U.S.A.) was given via an antecubital vein. The infusate contained acetic acid (2 mmol . l^{-1}) and ascorbic acid (1 mmol . l^{-1}) to prevent degradation. The infusion was continued for at least 30 min prior to blood sampling to ensure that the plasma [^{3}H]NE concentrations reached steady state in the plasma pool[13].

Study design (Fig. 1)

The design of this study was open and non-randomized. The reasons for choosing this design were that the paraesthesias and ECG artefacts during stimulation make a blinded design impossible. In addition, the potential long-term carry-over effect of the stimulation makes a randomized design very difficult.

Blood sampling for analysis of endogenous and tritiated norepinephrine, followed by simultaneous blood pressure and coronary sinus blood flow measurements (R_c) were performed initially. Atrial pacing was then started at a frequency of 80 beats . min^{-1} or 10 beats above the resting heart rate. The pacing rate was increased by 10 beats . min^{-1} every minute, until the patient experienced moderate anginal pain (3 on a four-grade scale where 0 is no pain, 2 is slight pain and 4 is severe pain). The reproducibility and validity of the

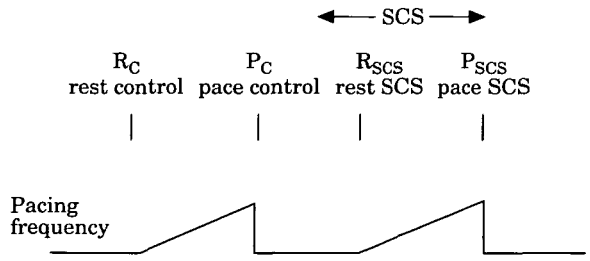

Figure 1 **Study design where the relative pacing levels are shown at the different points of measure. The period marked SCS was the time when spinal cord stimulation was applied. SCS=spinal cord stimulation.**

method have been reported elsewhere[4]. Haemodynamic measurements and blood sampling were then repeated (P_c), after which pacing was stopped and the patient allowed to rest for 30 min. Treatment with spinal cord stimulation was then started and the patient allowed to rest for another 20 min during ongoing stimulation. New baseline haemodynamic measurements were made and blood samples drawn (R_{scs}). The same pacing routine was then repeated during ongoing stimulation. New recordings were made and blood samples drawn at the pacing rate at which angina was produced during the previous control recording (P_{scs}), allowing at least 3 min to reach [^{3}H]NE steady state.

Norepinephrine kinetics

At steady state, the whole body norepinephrine spillover to plasma and whole body norepinephrine clearance were calculated as[14]:

$$\text{Whole body norepinephrine clearance} = \frac{\text{[3H]NE infusion rate (dpm/min)}}{\text{Plasma [3H]NE concentration (dpm/ml)}}$$

and

$$\text{Whole body NE spillover} = \text{Whole body NE clearance} \times NE_A$$

where dpm is the number of disintegrations per minute of tritiated norepinephrine and NE_A is the arterial norepinephrine concentration.

The rate of norepinephrine spillover from the heart was calculated according to the Fick principle. However, as the norepinephrine flux is bi-directional, net spillover calculations tend to underestimate the regional norepinephrine outward flux. Therefore, correction has to be made for norepinephrine uptake, which is determined from the fractional extraction of radiolabelled norepinephrine across an organ[11,14]. Hence, the following formula applies to the heart at steady state:

$$\text{Cardiac norepinephrine spillover} = [(NE_{CS} - NE_A) + NE_A \times EX_{NE}] \times CSPF$$

where NE_{CS} is the plasma norepinephrine concentration in the coronary sinus, NE_A is the arterial plasma norepinephrine concentration, EX_{NE} is the cardiac fractional extraction of radio-labelled norepinephrine (see below) and CSPF is the coronary sinus plasma flow.

$$\text{Cardiac fractional extraction of [}^3\text{H]NE} = ([^3H]NE_A - [^3H]\ NE_{CS})/[^3H]NE_A$$

Catecholamine assays

Blood samples were transferred immediately to ice-chilled tubes containing reduced glutathione and heparin. On completion of each patient, samples were centrifuged at 4 °C and plasma separated for storage at − 80 °C until assayed. Plasma concentrations of endogenous norepinephrine were determined by liquid chromatography with electromechanical detection, a method closely resembling the one used by Medvedev *et al.*[15]. Timed collection of eluate leaving the detection unit, using a fraction collector (Superrac, Kabi-Pharmacia, Sweden), allowed for separation of tritium-labelled norepinephrine and dihydroxy phenyl glycol for subsequent counting by liquid scintillation spectroscopy. The intra-assay coefficient of variation for endogenous as well as tritiated norepinephrine, derived from seven repeated determinations on a single quality control plasma sample, was 6%, whereas the inter-assay coefficient of variation, obtained using the same quality control plasma sample and determined from 21 consecutive extractions and assay runs, was 9%. The coefficient for variation between flow measurements is 8%.

Statistical methods

Results are expressed as means (± 1 SD). Differences were tested for significance using the paired Student's t-test for the haemodynamic parameters and the Wilcoxon paired sign rank test for catecholamine values. All *P* values are two-tailed and when below 0·05 considered as statistically significant. The following comparisons were made (Fig. 1): first, resting values with and without stimulation (R_c vs R_{scs}); secondly, control values with and without pacing (R_c vs P_c); and finally, pacing values were compared (P_c vs P_{scs}).

Results (Tables 1 and 2 and Fig. 2)

No patient had anginal pain during the stimulation period. Mean arterial blood pressure rate pressure product and coronary sinus plasma flow increased with pacing. Heart rate was significantly higher at rest with stimulation than without (P=0·008). Rate pressure product and mean arterial pressure decreased significantly when stimulation was introduced. The extraction of tritium-labelled norepinephrine decreased by 16%

Table 1 Haemodynamic parameters

	Rest control	Pace control	Rest SCS	Pace SCS	Significance of comparisons *P* values		
	R_c	P_c	R_{scs}	P_{scs}	R_c/R_{scs}	R_c/P_c	P_c/P_{scs}
Mean arterial pressure (mmHg)	99 (13)	114 (18)	97 (10)	105 (15)	ns	0·004	0·02
Heart rate (beats . min^{-1})	67 (14)	128 (12)	74 (14)	129 (13)	0·008	<0·0001	ns
Rate pressure product (beats . min^{-1} × mmHg)	9728·3 (2112·0)	19 913·3 (3773·9)	10 241·6 (1989·8)	17 999·3 (2963·1)	ns	<0·0001	0·0085

Values as mean (± 1 SD). *P* values above 0·05 listed as not significant (ns).
SCS=Spinal cord stimulation.

Table 2 Effects of spinal cord stimulation on norepinephrine kinetics

	Rest control	Pace control	Rest SCS	Pace SCS	Significance of comparisons *P* values		
	R_c	P_c	R_{scs}	P_{scs}	R_c/R_{scs}	R_c/P_c	P_c/P_{scs}
Arterial NE (pmol . ml^{-1})	2·73 (1·66)	3·27 (1·28)	2·78 (1·86)	3·28 (1·96)	ns	ns	ns
Total body NE clearance (ml . min^{-1})	2078·95 (430 3)	2348·05 (818·65)	2031·56 (407·33)	2040·51 (432·48)	ns	ns	ns
Total body NE spillover (pmol . min^{-1})	5582·66 (3290·46)	8202·22 (4429 90)	5408·44 (3041·89)	6713·88 (4272·78)	ns	0·02	0·02
Fractional extraction of [^{3}H]NE (%)	70·4 (14·1)	59·0 (16·0)	69·4 (11·3)	57·9 (15·7)	ns	0·02	ns
Coronary sinus plasma flow (ml . min^{-1})	55·9 (18·4)	76·4 (22·2)	47·0 (22·2)	65·0 (21·0)	ns	0·01	ns
Cardiac NE spillover (pmol . min^{-1})	151·06 (102·329)	183·22 (171·97)	139·52 (87·67)	170·70 (119·18)	ns	ns	ns

Values as mean (± 1 SD). *P* values above 0·05 listed as not significant (ns). NE=norepinephrine; [^{3}H]NE=tritiated norepinephrine; SCS=spinal cord stimulation.

from rest control to control pacing (P=0·02), possibly as a consequence of increased coronary blood flow, but was otherwise not affected during the procedure. Total body norepinephrine clearance was not influenced by pacing or stimulation. Likewise, cardiac norepinephrine spillover was not altered by atrial pacing or stimulation (Table 2, Fig. 2(a)). In contrast, total body norepinephrine spillover (Table 2, Fig. 2(b)) increased by 47% during control pacing (R_c vs P_c) (P=0·02). This increase fell by 18% during stimulation (P_c vs P_{scs}) (P=0·02).

Discussion

In the present study, spinal cord stimulation decreased total body norepinephrine spillover during pacing-induced myocardial ischaemia, whereas cardiac norepinephrine spillover was unaffected. This suggests that the positive effects of spinal cord stimulation on the heart[4,16], are not primarily related to a reduction in cardiac sympathetic nerve activity. Neurostimulation of the spinal cord did not affect regional sympathetic activity, measured as cardiac norepinephrine spillover. However, in contrast to total body norepinephrine spillover, cardiac pacing in P_c and P_{scs} did not increase cardiac spillover. Several studies on the effects of transcutaneous electrical nerve stimulation and spinal cord stimulation on cardiac metabolism and haemodynamics have clearly demonstrated that no changes occur under basal conditions, but appear when the heart is stressed[4,12]. This fact might explain why no segmental effect on sympathetic activity was observed.

The isotope dilution technique is an improvement in relation to measurements of plasma catecholamine levels which disregard the influence of norepinephrine clearance[17]. Some reports have measured epinephrine extraction in the heart to estimate norepinephrine extraction. This may be a possible method in a healthy subject but there is no validation for this method in patients with cardiac disease. Another method is to record sympathetic activity intraneurally, which can be done in efferent sympathetic nerves to skin and muscle but not in visceral sympathetic nerves. Since one purpose of this study was to measure specifically cardiac sympathetic activity, the method used here was the only alternative for this study. It is known that the effects of spinal cord stimulation and transcutaneous electrical nerve stimulation depend on stimulation of the

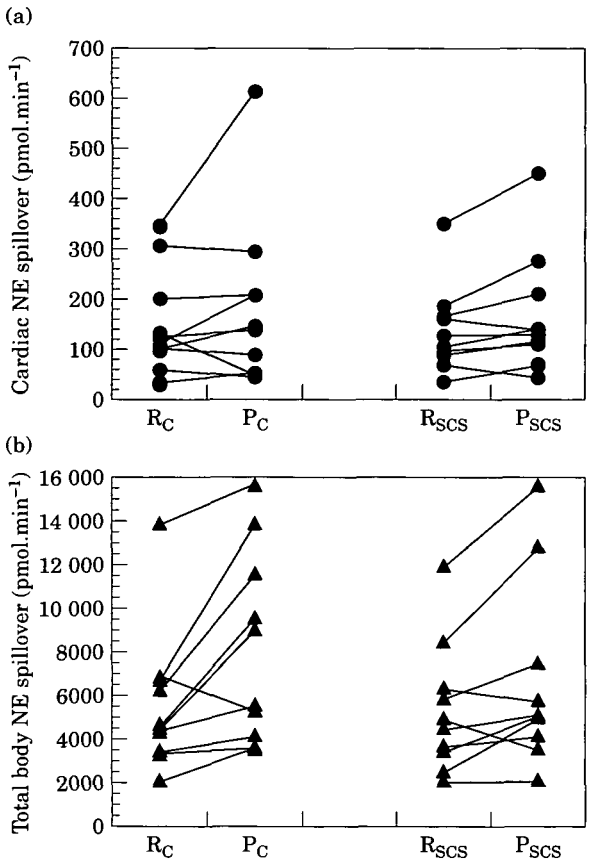

Figure 2 **(a) Individual cardiac norepinephrine spillover values plotted for each and all patients, separately (n=10). NE=norepinephrine; P_c=pace control; P_{scs}=Pace spinal cord stimulation; R_c=rest control; R_{scs}=rest spinal cord stimulation. (b) Individual total body norepinephrine spillover values plotted for each and all patients separately (n=10). NE=norepinephrine; P_c=pace control; P_{scs}= Pace spinal cord stimulation; R_c=rest control; R_{scs}=rest spinal cord stimulation.**

proper spinal cord segments, i.e. that the area of the spinal cord which supplies the ischaemic part of the heart is stimulated[18]. In the clinical setting, it has proved essential that the stimulation paraesthesiae cover the radiation of anginal pain. This fact may indicate that a putative sympathetic modulation of the treatment occurs only in the ischaemic part of the heart. For this reason, such a modulation may be masked in the present study. However, since the patients had a net production of lactate from the myocardium during control pacing, which is abnormal and an indicator of myocardial ischaemia[19], it is reasonable to assume that the blood samples represent ischaemic areas of the myocardium and would therefore also represent areas receiving efferent sympathetic traffic.

The observed increase in heart rate at rest during stimulation was surprising. However, it was small (7 beats . min^{-1}) compared to the differences in heart rate caused by the pacing procedure (61 and 55 beats . min^{-1} respectively) and was therefore not considered to be of biological significance for the purpose of this study, especially since all the other haemodynamic parameters, as well as cardiac and total norepinephrine spillover, did not differ significantly between control and stimulation at rest.

Overall sympathetic activity, measured as total body norepinephrine spillover, increased during pacing. This increase was attenuated during stimulation when compared to the control situation. It has been demonstrated that anginal pain causes a segmental as well as a general increase in sympathetic activity, resulting in local constriction of arteriolae[20]. For example, Kröger *et al.*[21] found that acute somatic pain induced dysfunction distal to a severely stenosed coronary artery by local activation of cardiac sympathetic nerves. Fentanyl, a potent opioid analgesic not only prevented the pain but also reduced the degree of post-stenotic ischaemia. One study that assessed the effects of transcutaneous electrical nerve stimulation on autonomic cardiovascular reflexes found a mild inhibitory effect on the reflexes mediated by the sympathetic nervous system[22]. Other studies have measured catecholamine levels during transcutaneous electrical nerve stimulation treatment. One of these[8] showed a significant decrease in the arterial and coronary sinus levels of epinephrine during stimulation at rest and at the same pacing level as in the control situation. In addition, there was a significant decrease in the arterial levels of norepinephrine when 'transcutaneous electrical nerve stimulation responders' were analysed separately, which was interpreted as a decrease in general sympathetic activity. However, a subsequent study by the same group[23] could not confirm the results. Another study[24] demonstrated a significant decrease in arterial epinephrine concentration at rest but no change in norepinephrine levels, which was interpreted as an inhibiting effect of transcutaneous electrical nerve stimulation on local sympathetic activity. Caution must be observed when these previous results are compared with the present study, as none of the above mentioned studies used the norepinephrine kinetic approach when the effects of neurostimulation on sympathetic traffic were analysed.

There are several tentative explanations for the inhibiting effect of spinal cord stimulation on overall sympathetic activity (Fig. 3). Spinal cord stimulation may have a directly inhibiting effect on efferent sympathetic activity. Furthermore, such stimulation decreases myocardial ischaemia, which may attenuate sympathetic activity, perhaps by an increase in coronary flow, hence reducing activity in cardiac afferents. In addition, spinal cord stimulation decreases pain and anxiety levels and consequently reduces efferent sympathetic traffic. Ischaemia, pain and sympathetic activity are closely related, giving rise to a vicious circle[25]. At our present state of knowledge, it is not possible to explain how spinal cord stimulation acts to interrupt this vicious circle. However, an isolated reduction in cardiac sympathetic activity does not appear to occur.

There are several reports on the relationship between atrial pacing and sympathetic tone. Schwartz

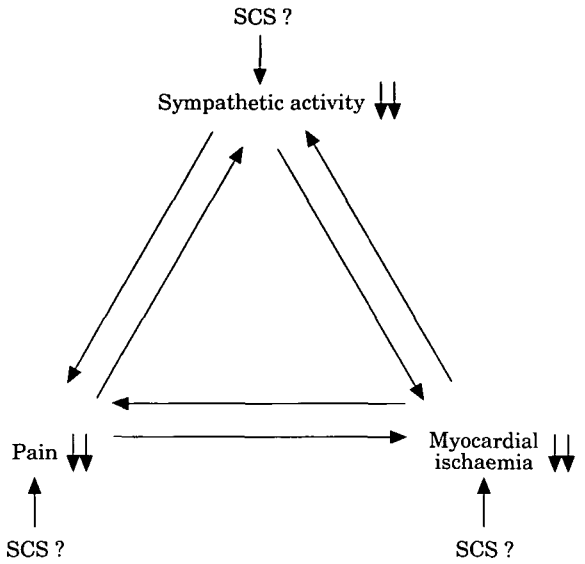

Figure 3 **Possible mechanisms of action for spinal cord stimulation in patients treated for myocardial ischaemia.**

et al.[26] found a higher arterial norepinephrine concentration at rest in a group of patients with myocardial ischaemia. Pacing did not affect the plasma concentration of norepinephrine and the calculated norepinephrine release increased less in patients with myocardial ischaemia compared with control patients. This was interpreted as the peripheral sympathetic tone not being affected by myocardial ischaemia and cardiac sympathetic tone decreased compared to the control situation. In contrast, Emanuelsson *et al.*[27] found a rise in arterial norepinephrine concentration during pacing, which was interpreted as a marker of enhanced general sympathetic activity at the final pacing step. These studies of sympathetic activity during atrial pacing[26,27] have used plasma concentrations as a marker of sympathetic activity, but have ignored the influence of norepinephrine clearance. The isotope dilution technique measures norepinephrine spillover into plasma, which is known to correlate well with sympathetic nerve stimulation[9]. This makes it possible to estimate clearance rate, fractional extraction and bi-directional fluxes of the transmitter simultaneously, and therefore does not underestimate norepinephrine spillover across an organ[9]. In the present study, total body norepinephrine spillover increased significantly during pacing, demonstrating an increase in general sympathetic activity. Cardiac norepinephrine spillover was not affected by atrial pacing, which indicates that cardiac sympathetic activity was not affected. In a study using the same technique and comparing patients with chronic stable angina to patients with a recent episode of unstable ischaemic symptoms[28], there was no increase in cardiac norepinephrine spillover during pacing. This is in accordance with the results of the present study. However, this contradicts the results of Esler *et al.*[17], which showed a modest, but significant, increase in cardiac norepinephrine spillover as a result of cardiac pacing in a group of patients with coronary artery disease. This may be due to higher sympathetic stimulation, i.e. a higher pacing frequency used in this study. Yet another study, using the cold pressor test[29], indicated a large increase in cardiac norepinephrine spillover during stress only in patients with active unstable angina, but not in patients with stable angina pectoris. This suggests involvement of the sympathetic nervous system, especially in unstable angina pectoris.

In summary, spinal cord stimulation decreased overall sympathetic activity during atrial pacing at the same pacing level, whereas cardiac sympathetic activity remained unchanged. The results of this study indicate that spinal cord stimulation decreases overall sympathetic activity which may benefit the heart, possibly by reducing the oxygen demand. The decrease in overall sympathetic activity during spinal cord stimulation may be secondary to a reduction in pain and anxiety as a result of a decrease in myocardial ischaemia as well as a more direct sympatho-inhibitory effect of the stimulation.

Financial support was provided by the Swedish Heart & Lung Foundation and the Swedish Medical Research Council (projects 9047, 11133, B96-19X- 11239-02B).

References

[1] Gybels J, Kupers R. Central and peripheral electrical stimulation of the nervous system in the treatment of chronic pain. Acta Neurochir 1987; 38 (Suppl): 64–75.

[2] Jacobs M, Jörning P, Beckers R *et al.* Foot salvage and improvement of microvascular blood flow as a result of epidural spinal cord electrical stimulation. J Vasc Surg 1990; 12: 354–60.

[3] Mannheimer C, Augustinsson L-E, Carlsson C-A, Manhem K, Wilhelmsson C. Epidural spinal electrical stimulation in severe angina pectoris. Br Heart J 1988; 59: 56–61.

[4] Mannheimer C, Eliasson T, Andersson B *et al.* Effects of spinal cord stimulation in angina pectoris induced by pacing and possible mechanisms of action. BMJ 1993; 307: 477–80.

[5] Sanderson JE, Brooksby P, Waterhouse D, Palmer RBG, Neubauer K. Epidural spinal electrical stimulation for severe angina: a study of its effects on symptoms, exercise tolerance and degree of ischaemia. Eur Heart J 1992; 13: 628–33.

[6] DeJongste M, Haaksma J, Haustvay R *et al.* Effects of spinal cord stimulation on myocardial ischemia during daily life in patients with severe coronary artery disease. Br Heart J 1994; 71: 413–18.

[7] Haustvat R, Blanksma P, DeJongste M *et al.* Effect of spinal cord stimulation on myocardial blood flow assessed by positron emission tomography in patients with refractory angina pectoris. Am J Cardiol 1996; 77: 462–7.

[8] Emanuelsson H, Mannheimer C, Waagstein F, Wilhelmsson C. Catecholamine metabolism during pacing-induced angina pectoris and the effect of transcutaneous electrical nerve stimulation. Am Heart J 1987; 114: 1360–6.

[9] Esler M, Jackman G, Bobik A *et al.* Determination of norepinephrine apparent release rate and clearance in humans. Life Sci 1979; 25: 1461–70.

[10] Esler M, Jennings G, Korner B, Blomberry P, Sacharias N, Leonard P. Measurement of total and organ-specific norepinephrine kinetics in humans. Am J Physiol 1984; 247: E21–E28.

[11] Esler M, Jennings G, Leonard P. Contribution of individual organs to total norepinephrine release in humans. Acta Physiol Scand (Suppl) 1984; 527: 11–16.
[12] Mannheimer C, Carlsson C-A, Emanuelsson H, Vedin A, Waagstein F, Wilhelmsson C. The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris. Circulation 1985; 71: 308–16.
[13] Eisenhofer G, Esler MD, Goldstein DS, Kopin IJ. Neuronal uptake, metabolism, and release of tritium-labelled norepinephrine during assessment of its plasma kinetics. Am J Physiol 1991; 261: E505–15.
[14] Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate and functions. Physiol Rev 1990; 70: 963–85.
[15] Medvedev O, Esler M, Angus J, Cox H, Eisenhofer G. Simultaneous determination of plasma noradrenaline and adrenaline kinetics. Naunyn-Schmiedeberg's Arch Pharmacol 1990; 341: 192–9.
[16] Kujacic V, Eliasson T, Mannheimer C, Jablonskiene D, Augustinsson L-E, Emanuelsson H. Assessment of the influence of spinal cord stimulation (SCS) on left ventricular function in patients with severe angina pectoris: an echocardiographic study. Eur Heart J 1993; 14: 1238–44.
[17] Esler M, Jennings G, Korner P *et al.* Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. Hypertension 1988; 11: 3–20.
[18] Augustinsson L, Linderoth B, Mannheimer C. Spinal cord stimulation in various ischemic conditions. In: Illis L, ed. Spinal cord dysfunction, vol III. Functional stimulation. Oxford: Oxford Medical Publications, 1992. 272–95.
[19] Gertz E, Wisneski J, Neese R, Hooser A, Korte R, Bristow J. Myocardial lactate extraction; multi-determined metabolic function. Circulation 1980; 61: 256–61.
[20] Robertson R, Bernard Y, Robertson D. Arterial and coronary sinus catecholamines in the course of spontaneous coronary artery spasm. Am Heart J 1983; 105: 901–6.
[21] Kröger K, Schipke J, Thämer V, Heusch G. Poststenotic ischaemic myocardial dysfunction induced by peripheral nociceptive stimulation. Eur Heart J 1989; 10 (Suppl F): 179–82.
[22] Sanderson J, Tomlinson B, Lau M *et al.* The effect of transcutaneous electrical nerve stimulation (TENS) on autonomic cardiovascular reflexes. Clin Autonom Res 1995; 5: 81–4.
[23] Mannheimer C, Emanuelsson H, Waagstein F, Wilhelmsson C. Influence of naloxone on the effects of high frequency transcutaneous electrical nerve stimulation in angina pectoris induced by atrial pacing. Br Heart J 1989, 62: 36–42.
[24] Chauhan A, Mullins P, Thuraisingham S, Taylor G, Petch M, Schofield P. Effect of transcutaneous electrical nerve stimulation on coronary blood flow. Circulation 1994; 89: 694–702.
[25] Collins P, Fox K. Pathophysiology of angina. Lancet 1990; 335: 94–6.
[26] Schwartz L, Sole MJ, Vaughan-Neil EF, Hussain NM. Catecholamines in coronary sinus and peripheral plasma during pacing-induced angina in man. Circulation 1979; 59: 37–43.
[27] Emanuelsson H, Mannheimer C, Waagstein F. Changes in arterial levels and myocardial metabolism of catecholamines during pacing-induced angina pectoris. Clin Cardiol 1991; 14: 567–72.
[28] McCance A, Forfar C. Cardiac and whole body (H3) noradrenaline kinetics in ischaemic heart disease: contrast between unstable anginal syndromes and pacing induced ischemia. Br Heart J 1989; 61: 238–47.
[29] Serneri N, Boddi M, Arata L *et al.* Silent ischemia in unstable angina is related to an altered cardiac norepinephrine handling. Circulation 1993; 87: 1928–37.