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Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris

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Abstract

Objective: Electrical stimulation of the dorsal aspect of the upper thoracic spinal cord is used increasingly to treat patients with severe angina pectoris refractory to conventional therapeutic strategies. Clinical studies show that spinal cord stimulation (SCS) is a safe adjunct therapy for cardiac patients, producing anti-anginal as well as anti-ischemic effects. However, little information is yet available about the underlying mechanisms involved. **Methods:** In order to determine its mechanism of action, the effects of SCS on the final common integrator of cardiac function, the intrinsic cardiac nervous system, was studied during basal states as well as during transient (2 min) myocardial ischemia. Activity generated by intrinsic cardiac neurons was recorded in 9 anesthetized dogs in the absence and presence of myocardial bipolar electrodes (50 Hz; 0.2 ms; parameters within the therapeutic range used in humans). **Results:** The SCS suppressed activity generated by intrinsic cardiac neurons. No concomitant change in monitored cardiovascular indices was detected. Neuronal activity increased during transient ventricular ischemia (46%), as well as during the early reperfusion period (68% compared to control). Despite that, activity was suppressed during both states by SCS. **Conclusions:** SCS modifies the capacity of intrinsic cardiac neurons to generate activity. SCS also acts to suppress the excitatory effects that local myocardial ischemia exerts on such neurons. Since no significant changes in monitored cardiovascular indices were observed during SCS, it is concluded that modulation of the intrinsic cardiac nervous system might contribute to the therapeutic effects of SCS in patients with angina pectoris. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Autonomic nervous system; Ischemia; Reperfusion

1. Introduction

Patients who suffer from severe angina pectoris following coronary artery revascularization or whose clinical status render them inappropriate candidates for such a procedure can obtain relief from their angina by spinal cord stimulation (SCS) [1,2]. High frequency, low intensity electrical stimuli delivered to the dorsal aspect of the T_1-T_2 thoracic spinal cord suppresses the pain associated with myocardial ischemia while not affecting awareness of the symptoms from a possible myocardial infarction [3–6]. Application of SCS does not seem to induce any adverse effects in patients experiencing transient ischemia of the myocardium [7], patients retaining their capacity to sense angina during increased workload [8].

The effects of SCS have been attributed to improved

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myocardial perfusion and/or alterations in the oxygen demand and supply ratio as reflected in a reduction in stress-induced alterations in the ST segment of the ECG [7]. Spinal cord stimulation also improves myocardial lactate metabolism [8]. Spinal cord stimulation has recently been suggested as an adjunct to coronary artery bypass surgery in high-risk patients [9]. The mechanisms whereby this mode of therapy produces its beneficial effects are, as yet, poorly understood.

Spinal cord stimulation has been shown to influence information processing within the central nervous system [10,11]. This treatment modality has also been demonstrated to influence peripheral blood flow [12–16]. In order to understand the mechanisms underlying SCS in cardiac control, we studied the effects of SCS upon the intrinsic cardiac nervous system. Intrinsic cardiac neurons receive constant inputs from spinal cord neurons to regulate regional cardiac function on a beat-to-beat basis [17–19]. Transient regional ventricular ischemia can markedly increase the activity generated by intrinsic cardiac neurons [20]. Furthermore, excessive activation of limited populations of intrinsic cardiac neurons may induce cardiac dysrhythmias, even in normally perfused hearts [21].

The objective of the present study was to determine whether SCS, applied with clinically employed electrical stimulation parameters, modifies the activity generated by intrinsic cardiac neurons in situ. Secondly, these experiments were designed to determine whether SCS changes cardiac dynamics. Thirdly, effects of SCS on intrinsic cardiac neural activity were characterized during coronary arterial occlusion as well as during the subsequent reperfusion period to determine if SCS modifies intrinsic cardiac neuronal function in the presence of myocardial ischemia. Results obtained in the present experiments indicate that SCS influences the behavior of intrinsic cardiac neurons markedly, changes that might be involved in the clinically observed effects of SCS during acute myocardial ischemia.

2. Methods

2.1. Animal preparation

Experiments performed in the present study were approved by the Institutional Animal Care and Use Committee of the OUHSC and followed the guidelines outlined by the International Association for the Study of Pain and in the NIH Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC, 1996). Nine adult male dogs of mixed breed weighing between 15 and 25 kg were used. Animals were kept under standard laboratory conditions in a light-cycled environment (12 h/12 h) with free access to water at all times and to food at regular intervals.

For the duration of the surgery, dogs were first anesthetized with sodium thiopental (20 mg/kg, iv) and maintained with sodium thiopental administered in boluses (5 mg/kg i.v.) to effect every 5-10 min. Animals were intubated and then artificially ventilated using a Harvard respirator (Palm Springs, CA). After the surgical preparation was completed, anesthesia was changed to alpha chloralose. An initial bolus dose of alpha chloralose (75 mg/kg, i.v.) was administered, with repeat doses (20 mg/kg) given as required during the remainder of the experiment. The level of anesthesia was checked throughout each experiment by observing pupil reaction, monitoring jaw tension and squeezing a hindpaw to determine if blood pressure and heart rate changed. This anesthetic regimen has been demonstrated to produce adequate anesthesia without suppressing autonomic neural responses [19]. Electrodes inserted into the forelimbs and the left hind limb were connected to an Astro-Med, Inc. (West Warwick, RI) model MT 9500 eight channel rectilinear recorder to monitor a modified Lead II electrocardiogram.

2.2. Implantation of spinal cord stimulation electrodes

After induction of anesthesia, animals were placed in the prone position and the epidural space of the mid-thoracic spinal column was penetrated percutaneously with a Touhy needle using A-P fluoroscopy and loss-of-resistance technique, as is routinely done in the clinic. A four-pole catheter (Medtronic QUAD Plus Model 3888; Medtronic Inc., Minneapolis, MN) was introduced through the cannula and its tip was advanced to the T1 level of the spinal column and placed slightly to the left of the midline [12]. The two poles of this stimulating lead chosen for subsequent use (inter-electrode distance of 1.5 cm) were placed at the level of the T1 and T4 vertebrae. Final placement was aided by delivering electrical current to induce motor responses using the rostral or caudal poles as cathodes, respectively. Rostral stimulation just above motor threshold resulted in proximal forepaw and/or shoulder muscle contractions while caudal electrode stimulation induced contractions in the lower trunk. Once the appropriate electrode positions were obtained, the lead was fixed to the intraspinous ligaments with a suture surrounding a Silicone protective sleeve. Extension wires were tunneled subcutaneously to the ventral surface of the animal where they were connected to a stimulator. Motor responses were rechecked after the animal had been turned to the supine position to make sure the electrodes had not moved during this maneuver and to establish the appropriate stimulus intensities for the subsequent SCS.

2.3. Cardiac instrumentation

After placing the animal on its back, a bilateral thoracotomy was made in the fifth intercostal space to expose the heart. The subclavian ansae on both sides of the thorax were exposed and silk ligatures were placed around them so that each could be easily sectioned later in the experiments to decentralize the intrinsic cardiac nervous system. The ventral pericardium was incised and retracted laterally to expose the heart and the ventral right atrial deposit of fat containing the ventral component of the right atrial ganglionated plexus [19]. Neurons in this ganglionated plexus are representative of those found in the various intrinsic cardiac ganglionated plexuses.

Left atrial chamber pressure was measured via a PE-50 catheter inserted directly into the left atrial chamber via its appendage. Left ventricular chamber pressure was monitored via a Cordis (Miami, FL) #6 French pigtail catheter, which was inserted into that chamber through a femoral artery. Systemic arterial pressure was measured using a Cordis #7 French catheter placed in the descending aorta via the other femoral artery. These catheters were attached to Bentley (Irvine, CA) Trantec model 800 transducers.

2.4. Neuronal recording

Activity generated by ventral right atrial neurons was recorded in situ, as has been done in previous studies [19]. To minimize epicardial motion during each cardiac beat, a circular ring of stiff wire was placed gently on the fatty epicardial tissue overlying the ventral surface of the right atrium containing the right atrial ganglionated plexus. A tungsten microelectrode (30-40 µm diameter and exposed tip of 1 µm; impedance of 9–11 M at 1000 Hz), mounted on a micromanipulator, was lowered into this fat using a microdrive. Exploration was done by driving the electrode tip through this tissue beginning at the surface of this fat, penetrating to regions adjacent to cardiac musculature. Proximity to the atrial musculature was indicated by increases in the amplitude of the ECG artifact. The indifferent electrode was attached to mediastinal connective tissue adjacent to the heart. Signals recorded via the electrode were led to a CWE BMA-831 differential preamplifier with a high impedance head stage (bandpass filters set at 300 Hz and 10 kHz), and were processed by a signal conditioner (bandpass 100 Hz-2 kHz). Signals were amplified further via a Princeton Applied Research (Princeton, NJ) battery driven amplifier (300 Hz-2 kHz) and were displayed on an Astro-Med, Inc. (West Warwick, RI) MT 9500 8 channel rectilinear recorder along with the cardiovascular variables described above. Data were stored via a Vetter (Rebesburg, PA) M3000A digital tape system for later analysis. Action potentials generated by neurons in one site of a right atrial ganglionated plexus were recorded using extracellular recording electrodes, individual units being identified by their amplitudes and configurations. As established previously [18], extracellular action potentials so generated are derived from somata and/or dendrites rather than axons of passage. Amplitudes of identified action potentials varied by less than 25 µV over several minutes. Each potential retained the same configuration over time. Action potentials recorded in a given locus with the same configuration and amplitude ($\pm 25 \ \mu V$) were considered to be generated by a single unit.

2.5. Protocols

Five different protocols were employed in each animal (cf. Fig. 1). The order in which each protocol was applied was randomized among animals.

2.5.1. Protocol A-spinal cord stimulation

The parameters used to electrically stimulate the thoracic spinal cord were similar to those used clinically [6]. Stimuli were delivered to the dorsal aspect of the thoracic spinal cord via a Grass model S48 stimulator connected to the quadripolar electrode via a stimulus isolation unit (Grass model CCU1) via a constant current unit (Grass SIU1). With the animal placed in the supine position for all subsequent experimentation, the current intensity used to evoke detectable skeletal muscle motor responses was determined as the motor threshold (MT). Stimuli (50 Hz and 0.2 ms duration) were delivered at two intensities (66 and 90% of MT). An intensity of 66% of MT has been shown to recruit low threshold, rapidly conducting axons (A-beta), whereas higher intensity stimuli (90%) activate fast A-delta fibers as well as the other axonal populations [16,22]. The current measured at MT varied among animals likely because of the varied anatomy of the thoracic spinal space among animals. The stimulus intensity was found to vary between 30 and 50 µA when current was set to 66% of MT. When the stimulus current was 90% of MT, it varied between 80 and 210 µA among different animals. The MT was rechecked periodically and remained stable over time in individual animals. With respect to protocol A, cardiac indices and intrinsic cardiac neural activity were monitored immediately before, during and for 30-45 s after 4 min of SCS at 90% of MT (Fig. 1A).

2.5.2. Protocol B-regional ventricular ischemia

A silk (3–0) ligature was placed around the left anterior descending coronary artery and another around the circumflex coronary artery, approximately 1 cm from their respective origins. Each ligature was led through a short segment of polyethylene tubing in order to occlude these arteries later in the experiments while leaving the arterial blood supply (right coronary and sino-atrial arteries) patent to the ventral right atrial neurons that were being investigated. For protocol B, cardiac indices and neuronal activity were monitored before, during and immediately after occluding the two coronary arteries concurrently for 2 min (Fig. 1B).

2.5.3. Protocols C, D and E in which SCS and regional ventricular ischemia were combined

The effects of 2 min of myocardial ischemia on intrinsic cardiac neuronal activity and regional cardiac indices were



Fig. 1. Average neuronal activity data derived from all animals during each of the five protocols utilized in this study. When SCS was applied alone (A) neuronal activity was suppressed, a change which persisted for a short time after terminating the SCS (SCS off). (B) Coronary artery occlusion (CAO) enhanced neuronal activity. (C) SCS suppressed neuronal activity before, during and after coronary artery occlusion. Data obtained for the other protocols (SCS and CAO) are presented in panels D and E. * Represents data which was significantly different from control values (P < 0.05).

studied in the presence of SCS (at 90% of MT for 4 min) applied at different times during the myocardial ischemia. Protocol C: The spinal cord was stimulated for 4 min and the 2 min of coronary artery occlusion began 1 min after the onset of the SCS (in the middle of the SCS; Fig. 1C). Protocol D: Spinal cord stimulation was initiated 1 min after coronary artery occlusion began (staged occlusion with overlapping stimulation) (Fig. 1D). Protocol E: In this protocol, spinal cord stimulation began immediately after finishing 2 min of coronary artery occlusion (Fig. 1E). The order in which each of these protocols was applied was randomized among dogs.

After all of the protocols described above were completed, the right and left subclavian ansae were sectioned in five of the dogs, thereby eliminating spinal cord afferent and efferent communications with neurons in intrathoracic ganglia. After this maneuver, the five SCS and transient coronary occlusion protocols described above were repeated.

2.6. Data analysis

Individual action potentials, which maintained their configurations over time, were analyzed. Activity generated by the somata and/or dendrites of neurons within the right atrial ganglionated plexus was averaged during successive 30-s periods before, during and after each intervention. At the same time, heart rate, left ventricular wall (intramyocardial) and chamber systolic pressures were measured, as was aortic pressure. Neuronal activity and cardiovascular indices recorded immediately before each intervention and during the steady state response to intervention were averaged and presented as an means±S.E.M. Fluctuations in the amplitude of action potentials generated by a unit varied by less than 50 µV over several minutes, action potentials retaining the same configurations over time. Thus, action potentials recorded in a given locus with the same configuration and amplitude $(\pm 50 \text{ }\mu\text{V})$ were considered to be generated by a single

unit. Action potentials with signal-to-noise ratios greater than 3:1 were analyzed. The threshold for neuronal activity changes was taken as a change of more than 20% from baseline values. Neuronal activity responses elicited by each intervention were evaluated by comparing activity generated immediately before each intervention with data obtained at the point of maximum change during the intervention. Data were expressed as means \pm S.E.M. Oneway ANOVA and paired *t*-test with Bonferroni correction for multiple tests were used for statistical analysis. A significance value of *P*<0.05 was used for these determinations.

3. Results

3.1. Identification of active sites

Action potentials were identified in 1-3 loci within the ventral right atrial ganglionated plexus of each animal. Based on the different amplitudes and configurations of the recorded action potentials within these loci, ongoing activity was generated by an average of 5.1 ± 0.9 (range 3-9) neurons. Identified neurons generated, on average,

 496 ± 112 impulses per minute (ipm) during control conditions throughout the duration of these experiments. Multiple neurons at each identified active site generated action potentials that were altered in a similar fashion by each of the different interventions tested.

3.2. (Protocol A) effects of spinal cord stimulation

Only the effects of SCS employed at 90% of MT will be presented in the Results section since 66% MT elicited minimal changes in the activity generated by the intrinsic cardiac neurons. The average activity generated by identified right atrial neurons in all animals (n=9) fell from 496 ± 112 to 150 ± 71 ipm (P<0.01) during SCS at 90% MT (Fig. 1A). Neuronal activity remained depressed for 10-20 s after SCS ceased (142 ± 61 ipm), returning to control levels by about 1 min after cessation of stimulation (Fig. 2A). SCS did not change monitored cardiac indices overall. For instance, SCS did not change heart rate (155 ± 8 vs. 159 ± 8 beats per minute) or left ventricular chamber systolic (124 ± 8 vs. 131 ± 8 mmHg) and diastolic pressures. SCS did not change aortic pressure ($124\pm8/$ 99 ± 6 vs. $122\pm5/95\pm4$ mmHg).



Fig. 2. Initiation of coronary artery occlusion (arrow below) resulted in an increase in the activity generated by right atrial neurons (individual units identified by action potentials greater than the small atrial electrogram artifacts). From above down are the ECG, aortic pressure (AP), left ventricular chamber pressure (LVP) and neuronal activity. Horizontal timing bar=30 s.

3.3. (Protocol B) effects of transient myocardial ischemia

When ventricular ischemia was induced by occluding both the left anterior descending and circumflex coronary arteries for 2 min in neurally intact preparations, the activity generated by right atrial neurons increased in each animal (Fig. 2). Neuronal activity increased, on average, by 46% (370±126 to 539±91 ipm; P<0.01) (Figs. 2B and 3) despite the fact that the blood supply of identified neurons was unaffected. Neuronal activity remained elevated immediately after reperfusion began (621±175 ipm, +68% compared to control values; P < 0.05). Monitored cardiac indices did not change significantly during the 2 min of coronary artery occlusion or during the reperfusion period. For instance, heart rate was similar at the end of ventricular ischemia episodes (140 ± 10 beats per minute) as before these episodes began (142 ± 9 beats per minute). Even though left ventricular chamber systolic pressure underwent minor reductions in a few instances, this index remained unchanged overall $(121\pm 6 \text{ vs. } 121\pm 6 \text{ mmHg})$. Left ventricular diastolic pressure and aortic pressure were also unaffected. No serious dysrhythmias were induced during the brief periods of coronary artery occlusion. During the early reperfusion phase, minor S-T segment elevation and terminal QRS slurring was evident in each animal.

3.4. SCS modulated responses to transient myocardial ischemia

Neuronal activity was not enhanced by coronary artery occlusion induced in the presence of SCS, irrespective of

whether SCS was applied during (Fig. 1C and D) or immediately after (Fig. 1E) the ischemic period. Monitored cardiovascular variables did not change significantly when the combined coronary artery occlusion and SCS protocols were instituted.

3.4.1. (Protocol C) occlusion in the middle of stimulation

When the 2-min period of myocardial ischemia occurred in the middle of the SCS (1 min after SCS began), the neurosuppressor effects of SCS persisted during the ischemic period (Fig. 3). For instance, intrinsic cardiac neuronal activity was reduced from that of control states (511±197 ipm) during SCS (169±99 ipm, P<0.01 compared to control), neuronal activity remaining suppressed when the stimulation occurred in conjunction with the occlusion (164±74, P<0.01 compared to control; Fig. 1C). Suppression of neuronal activity persisted after terminating the occlusion while the SCS was maintained (166±84 ipm, P<0.01 compared to control). Only after discontinuing the SCS did neuronal activity gradually return to control values.

3.4.2. (Protocol D) occlusion overlapped by stimulation

During this protocol (Fig. 1D), the activity generated by intrinsic cardiac neuronal activity was enhanced by 42% (388 ± 155 to 555 ± 211 ipm; P<0.01) during the initial coronary artery occlusion period. When SCS was applied 1 min after the occlusion began, neuronal activity was suppressed by 46% (activity of 211 ± 134 ipm) even though the myocardial ischemia persisted (Fig. 3C). In this protocol, neuronal activity remained suppressed during the reperfusion period (227 ± 134 ipm) while the SCS per-



Fig. 3. Influence of SCS on the ECG, left ventricular chamber pressure (LVP=145 mmHg) and intrinsic cardiac neuronal activity (lowest line) before and during coronary artery occlusion. (A) Multiple neurons generated action potentials, represented by their differing heights, at a rate of 132 impulses per minute (ipm) during control states. (B) Once SCS was initiated (note stimulus artifacts in the neuronal tracing), neuronal activity decreased to 34 imps/min (no activity generated during the record). ECG alterations were induced thereby. (C) Neuronal activity continued at that rate (39 ipm) in the presence of SCS even though coronary artery occlusion had been maintained for over 1.5 min.

sisted. Neuronal activity returned to control values only after SCS ceased $(394 \pm 142 \text{ ipm})$.

3.4.3. (Protocol E) occlusion followed by stimulation

In this protocol (Fig. 1E), coronary artery occlusion alone enhanced neuronal activity $(403\pm150 \text{ to } 701\pm315$ ipm; P < 0.01). When SCS was started immediately following termination of 2 min of coronary occlusion (that is during the early reperfusion period), neuronal activity fell to 173 ± 95 ipm (P < 0.01 compared to the ischemia period). Neuronal activity remained suppressed throughout this stimulation period, being 244 ± 98 ipm (P < 0.01compared to control values) after 4 min of SCS. This is in distinct contrast to the finding that neuronal activity remained elevated (~70% of control values) during the early reperfusion period immediately after SCS was terminated (Fig. 1B).

3.5. Acute decentralization

After all of the experimental protocols described above were completed, the spinal cord was stimulated in 5 animals at 90% of MT before and after sectioning the right and left ventral and dorsal subclavian ansae. After surgically disconnecting intrinsic cardiac neurons from the spinal cord neurons, ongoing neuronal activity decreased from 378 ± 34 to 162 ± 72 ipm (P<0.01). SCS did not modify the activity generated by identified intrinsic cardiac neurons thereafter (162 ± 72 vs. 147 ± 61 ipm); nor did SCS affect recorded cardiac indices.

4. Discussion

Results of the present experiments demonstrated that the activity generated by intrinsic cardiac neurons is modulated when the dorsal aspect of the thoracic spinal is stimulated electrically. That suppression of the ongoing activity generated by intrinsic cardiac neurons induced by SCS persisted for at least 30 s following termination of 4 min of SCS implies that the effects of this intervention last beyond the stimulation period. Interruption of afferent and efferent nerves traveling in the subclavian ansae eliminated the suppressor effects that SCS exerted on intrinsic cardiac neurons. These data indicate that the influence of spinal cord neurons on the intrinsic cardiac nervous system occur primarily via axons coursing in the intrathoracic sympathetic nervous system.

Based on results obtained when SCS was applied to the lumbosacral spinal cord, it is likely that both sympathetic afferent and efferent fibers contributed to suppression of intrinsic cardiac activity so identified. Four minutes of SCS at 66% of MT was much less effective in suppressing neuronal activity than when the spinal cord was stimulated at 90% of MT. Spinal cord stimulation at 90% MT antidromically activates sensory afferent fibers that release calcitonin gene-related peptide (CGRP) from their afferent terminals, an action that may be dependent on the presence of nitric oxide; such local release of CGRP from sensory afferent nerve terminals produces vasodilation of the rat hind paw [16]. It is known that endorphins are released into the coronary circulation of humans during SCS [23]. The release of neuropeptides by antidromic activation of sensory neurites [16] may also act to change the activity generated by intrinsic cardiac neurons [24].

Activation of sympathetic efferent preganglionic axons suppresses many intrathoracic reflexes that are involved in cardiac regulation [25] as well as the activity generated by populations of neurons within intrathoracic extracardiac [26] and intrinsic cardiac [18,19] ganglia, thereby reducing the capacity of intrathoracic sympathetic efferent neurons to influence cardiodynamics [27]. This effect may in part be due to activating inhibitory synapses within intrathoracic ganglia, including those on the heart such as occurs when intracranial pressure raises [28]. Such suppression of neuronal activity has been demonstrated in sympathetic efferent neurons controlling the peripheral vasculature as well [14,22].

As has been shown previously [20], the activity generated by right atrial neurons increased in the presence of regional ventricular ischemia (Fig. 2), remaining elevated during the early reperfusion phase (Fig. 1B). This may have clinical relevance since excessive activation of limited populations of intrinsic cardiac neurons can lead to the induction of ventricular arrhythmias [21] or even ventricular fibrillation [29]. Application of SCS before and during the induction of transient coronary artery occlusion prevented ischemia-induced changes in neuronal activity (Fig. 3), including that identified during the reperfusion period (Fig. 1C). In other words, although intrinsic cardiac neuronal activity was enhanced during regional ventricular ischemia, SCS returned intrinsic cardiac neuronal activity to base line levels during these ischemic episodes. It is important to note that the two coronary arteries that were occluded did not supply arterial blood to identified right atrial ventral neurons [20]. The transient periods of regional ventricular ischemia were of short enough duration to induce minor or no alterations in recorded cardiac variables. Thus, the effects of transient coronary artery occlusion on intrinsic cardiac neuronal activity most likely were the result of altered inputs to intrinsic cardiac neurons arising from distant ischemia-sensitive afferent neurites. SCS was effective in reducing such inputs. These neurosuppressor effects occurred whether SCS was applied immediately before or during coronary artery occlusion, or during the early reperfusion phase (Fig. 1). These data support the notion that SCS suppresses intrinsic cardiac neurons responsiveness to regional ventricular ischemia as well as during the subsequent reperfusion period.

The data obtained in this study are in accord with clinical findings indicating that improvement of cardiac function and symptoms can occur when SCS is applied to patients with angina pectoris [30]. Since modification of the intrinsic cardiac nervous system can lead to alterations in ventricular regional flow [31], perhaps some of the responses elicited by SCS involved subtle changes in the redistribution of coronary artery blood flow given that no detectable changes in cardiodynamics were identified with the methods used in these experiments. Thus, the effects that SCS induces in a clinical setting may, in part, reside in the capacity of such therapy to stabilize this final common regulator, even in the presence of ventricular ischemia. Since the intrinsic cardiac nervous system receives inputs arising from cardiac sensory neurites as well as from central neurons [28], SCS may exert multiple effects on this local neuronal circuitry. Heterogeneous activation of intrinsic cardiac neurons can destabilize cardiac neuronal regulation that, in turn, can lead to the genesis of ventricular tachydysrhythmias [21]. Data obtained in the present experiments indicated that SCS reduces the excitability of intrinsic cardiac neurons, even in the presence of ventricular ischemia and, as such, may help to stabilize cardiac function.

In summary, electrical stimulation of the thoracic spinal cord may influence the function of the final common neuronal regulator of cardiac function, the intrinsic cardiac nervous system, even in the presence of myocardial ischemic challenge. Thus, SCS may act in part to protect the heart from some of the deleterious consequences resulting from myocardial ischemia that produces angina pectoris via altering the function of the intrinsic cardiac nervous system.

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