Thoracic Spinal Cord Stimulation Reduces the Risk of Ischemic Ventricular Arrhythmias in a Postinfarction Heart Failure Canine Model

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Background—Thoracic spinal cord stimulation (SCS) is a promising therapy in treating refractory angina. This study was designed to investigate SCS with regard to the risk of arrhythmias during myocardial ischemia and its cardiac electrophysiological effects.

Methods and Results—We studied 22 dogs with healed anterior myocardial infarction (MI) and superimposed heart failure (HF) induced by rapid ventricular pacing. SCS was applied at the dorsal T1–T2 segments of the spinal cord (at 50 Hz, 0.2 ms) for 15 minutes. Transient (2-minute) myocardial ischemia was induced on 2 separate occasions (no SCS and SCS) to provoke ventricular arrhythmias (ventricular tachycardia/ventricular fibrillation; VT/VF). Ischemic episodes were separated by 90 minutes, and dogs were randomly assigned to receive SCS or no SCS before the first or second ischemic episode. SCS reduced the occurrence of VT/VF from 59% to 23% when SCS was applied during transient myocardial ischemia (odds ratio, 0.36; 95% confidence interval, 0.1626 to 0.5646; \(P = 0.0009\)). SCS also decreased sinus rate by 7.5 \(\pm\) 14 bpm (\(P = 0.048\)), increased the PR interval by 11.1 \(\pm\) 14.7 ms (\(P = 0.009\)), and reduced systolic blood pressure by 9.8 \(\pm\) 13.6 mm Hg (\(P = 0.02\)).

Conclusions—Thoracic SCS appears to protect against ischemic VT/VF in a canine model of healed MI and HF. SCS reduced sinus rate and systolic blood pressure, changes consistent with the previously known antisympathetic effect of SCS, which may have contributed to the antiarrhythmic benefits. (Circulation. 2005;111:3217-3220.)

Key Words: spinal cord • electric stimulation • arrhythmia • ischemia • nervous system, autonomic

Ventricular arrhythmias account for the majority of causes of sudden cardiac death.1 The autonomic nervous system plays an important role in sudden cardiac death and ventricular arrhythmias.2 Sympathetic activation appears to predispose to ventricular arrhythmias, whereas parasympathetic activation appears to be protective.3–6 Thus, modulation of autonomic tone has been a target for attempts at reducing the risk of ventricular arrhythmias.

Thoracic spinal cord stimulation (SCS) has recently been used to treat intractable angina pectoris.7–11 Although the precise mechanism(s) by which thoracic SCS exerts its effects are unknown, current evidence suggests that SCS has a sympatholytic effect.12,13 SCS has been shown to decrease sympathetic tone, as shown by norepinephrine kinetics, tests of sympathetic reflexes, and the use of ganglionic blockers. Prior studies showed that SCS reduced peripheral sympathetic drive induced by right atrial pacing14 and suppressed activity generated by intrinsic afferent sensory cardiac neurons related to sympathetic excitation.15 Furthermore, in a canine model, SCS slowed the sinus rate, prolonged atrioven-

    ventricular nodal conduction time, and increased the ventricular refractory period, with the effect mediated by the vagus.16 These findings would suggest that thoracic SCS might be protective against ventricular arrhythmias through its effects on autonomic tone. The present study tested the hypothesis that thoracic SCS has antiarrhythmic effects during myocardial ischemia as well as autonomic modulation on cardiac electrophysiology (EP) and hemodynamics.

Methods

Animal Model Preparation

All procedures were approved by the Indiana University Institutional Animal Care and Utilization Committee. The study was performed in a canine model of healed myocardial infarction (MI) and pacing-induced heart failure (HF) that was shown to have a high incidence of spontaneous ischemic ventricular arrhythmias.17 Twenty-seven mongrel dogs (weighing 17 to 29 kg) were tranquilized with thiopental sodium (15 to 20 mg/kg IV), intubated with a cuffed endotracheal tube, and ventilated with room air with a Harvard model 607 volume-cycled respirator, with subsequent anesthesia with 1.0% to 2.0% isoflurane.
A bipolar lead was inserted fluoroscopically through the right jugular vein into the right ventricular apex and connected to a pacemaker (Thera, Medtronic Inc) implanted in the neck. By cardiac catheterization, 0.2 to 0.3 mL of polyvinyl alcohol foam embolization particles (Cook Inc) was injected through the angiographic catheter into the proximal left anterior descending coronary artery. Two weeks after recovery from MI, rapid ventricular pacing at 200 ppm was started and was continued for 2 to 3 weeks to induce HFr,19,20

An acute testing protocol was scheduled 5 weeks after MI creation and 3 weeks after completion of the rapid-pacing protocol. Acute instrumentation included placing an SCS lead, EP leads, and a coronary angioplasty balloon. After baseline EP testing, dogs underwent induction of transient (2-minute) cardiac ischemia induced by inflating an angioplasty balloon placed within the left circumflex coronary artery. Complete occlusion of the proximal left circumflex coronary artery was confirmed angiographically.

Spinal Cord Stimulation
Initially, after induction of anesthesia, the dog was laid prone on the table with the dorsal side exposed. A spinal needle was used to access the epidural space at T5–T6 level, through which the Pisces Quad (Medtronic, Inc) SCS lead was introduced into the epidural space. The lead electrodes were introduced under fluoroscopic guidance to the T5–T6 level. The lead extender was attached and the lead position tested by obtaining muscle thresholds for both polarities. A Grass stimulator (Grass Instruments) was used. Shoulder motion and spinal twitching were used as evidence for muscle contraction to determine the stimulation threshold. Threshold was chosen as the lowest output required for a muscle response. SCS was performed at 90% of this motor threshold. The stimulation parameters used for SCS were tailored to be similar to those used clinically. SCS was delivered with monophasic pulses (50 Hz; pulse width, 0.2 ms).

EP Evaluation
Standard 6F quadrupolar mapping catheters were introduced via the femoral veins and positioned in the right atrial appendage, right ventricular apex, and His bundle region under fluoroscopic guidance. Six surface ECG leads and bipolar recordings from the intracardiac electrodes were recorded on a digital EP system (Prucka Cardio Laboratory, GE Medical Systems) and analyzed with digital calipers at a sweep speed of 200 to 400 mm/s. The sinus cycle length, surface ECG (PR, QRS, QT), and intracardiac conduction (AH, HV) intervals were measured during sinus rhythm.13 The anterograde Wenckebach cycle length was determined, and the effective refractory periods (ERPs) of the right atrium and right ventricle were measured after pacing drives at a 300-ms cycle length, as previously reported.21,22

Experimental Protocol
Blood pressure, ECG, and EP measurements were performed at baseline (no SCS) and during SCS. After baseline measurements were obtained, SCS was started at 90% of motor threshold. Fifteen minutes after beginning SCS and before ischemia induction, EP testing was repeated during continued SCS. The dogs then underwent induction of myocardial ischemia twice. Ischemic episodes were separated by a 90-minute recovery period, and dogs were randomly assigned in a crossover fashion to receive SCS (for 15 minutes) or no SCS before the first or second ischemic episode. Cardiac rhythm was monitored for sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) (defined as VT or VF lasting >30 seconds or associated with hemodynamic compromise). SCS was performed in the assigned dogs for 15 minutes immediately before and was continued during the session of transient ischemia.

Statistical Analysis
Data are expressed as mean ± SD. Statistical analysis of the comparison between the incidence of VT/VF with and without SCS during myocardial ischemia was performed with the asymptotic Wald

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BP indicates blood pressure; HR, heart rate.
*Statistically significant P value.

2-sided test for paired data (Asymptotic Wald Statistic, NCSS User Guide V1). A Student t test of the paired data was used to compare various hemodynamic and EP parameters measured during the control period (just before SCS) and those measured during SCS. A value of P < 0.05 was considered significant for the differences tested.

Results
An anterior MI was produced in 27 dogs. Two thirds of the dogs developed acute ST-segment elevation, whereas one third developed ST-segment depression or T-wave inversion. The perioperative mortality rate was 19% (5 of 27 dogs). Most (4 of 5 dogs) of the mortality was attributed to sudden cardiac death that occurred during the first 24 hours after MI creation. After 2 to 3 weeks of rapid ventricular pacing, transthoracic echocardiograms showed severe left ventricular systolic dysfunction (left ventricular ejection fraction <35%) in all surviving dogs. The spinal stimulation lead was successfully placed in all animals, with acceptable stimulation thresholds.

Hemodynamic and EP Parameters
Fifteen minutes of SCS significantly decreased heart rate by 7.5 ± 14 bpm (P = 0.048), increased the PR interval by 11.1 ± 14.7 ms (P = 0.009), and reduced systolic blood pressure by 9.8 ± 13.6 mm Hg (P = 0.02). There was a trend toward a reduction of diastolic blood pressure (P = 0.06) and right ventricular ERP (P = 0.09). SCS did not produce significant changes in QRS duration, QT interval, HV interval, atrial ERP, or Wenckebach cycle length (Table).

Ventricular Arrhythmias
The Figure shows the incidence of ventricular tachyarrhythmias (VT/VF) in no-SCS and SCS study groups. Of 22 dogs, 9 never developed VT/VF during ischemia with or without SCS, whereas 5 dogs developed VT/VF regardless of whether they received SCS or not. In 8 of 22 dogs, VT/VF occurred in the absence of SCS but was prevented by SCS. None of the 9 dogs in which ischemia alone did not induce VT/VF developed VT/VF while SCS was being performed. Thoracic SCS reduced the overall incidence of VT/VF during transient myocardial ischemia from 59% to 23% (odds ratio [P2–P1], 0.36; 95%
confidence interval, 0.1626 to 0.5646; $P=0.0009$), and this effect was consistent when SCS was applied during either the first or second ischemic episode. The overall incidence of VT/VF was equal during the first and second sessions of ischemia (59%).

**Discussion**

SCS was first used in the mid-1980s to treat patients with refractory angina pectoris. Several studies have demonstrated the efficacy of SCS in improving exercise tolerance, decreasing the frequency of anginal episodes, and prolonging time to ECG signs of ischemia. It does not mask new anginal pain or signs of myocardial ischemia, and there is no increase in the incidence of ventricular arrhythmias.

Although the exact mechanisms of these reported clinical effects have not been clearly elucidated as yet, they are likely related not only to inhibition of pain transmission but also to the antischismic properties of this therapy. Available scientific data suggest a complex mechanism of action of SCS that likely involves a unique interplay of pain relief, changes in myocardial blood flow, and modulation of sympathetic activity. Several previous studies have shown that SCS modulates the autonomic nervous system; withdrawal of sympathetic tone and/or enhancement of vagal tone may underlie the observed effects of SCS. Either effect can theoretically produce beneficial effects on ventricular arrhythmias. However, this application of SCS has not been studied before.

**Major Findings**

This study demonstrated that in a canine model with healed MI and superimposed pacing-induced HF, thoracic SCS significantly reduced susceptibility to ischemic ventricular arrhythmias. No proarrhythmic effects of SCS were observed, as all the dogs that had no ventricular arrhythmias during ischemia without SCS were also arrhythmia-free when ischemia was induced while receiving SCS.

The mechanism(s) underlying this effect of SCS is unclear yet, but we hypothesize that such an effect is related to the influence of SCS on autonomic tone. Previous work showed that the activity generated by right atrial neurons increased in the presence of regional ventricular ischemia. Such excessive activation of limited populations of intrinsic cardiac neurons can lead to the induction of ventricular arrhythmias. Application of SCS before and during the induction of transient coronary artery occlusion prevented ischemia-induced changes in neuronal activity. Such suppression of intrinsic cardiac neuron responsiveness to regional ventricular ischemia may help stabilize cardiac function and protect the heart from the deleterious consequences resulting from myocardial ischemia, including ischemia-provoked ventricular arrhythmias.

In addition, thoracic SCS appears to protect against ischemic VT/VF possibly as a result of enhanced vagal and/or withdrawal of sympathetic tone. SCS reduced sinus rate and systolic blood pressure, changes consistent with the previously known antisympathetic effect of SCS, which may have contributed to the antiarrhythmic benefits. However, the present study, which did not include the use of $\beta$-adrenergic or vagal blockade, could not prove a relation between antiarrhythmic effects and cardiac neuronal modulation of SCS. The present study also could not solve the question of whether the reduction in VT/VF incidence was caused by a direct cardiac effect of SCS or was a result of heart rate slowing during SCS. Thus, more research is warranted to elucidate the underlying mechanism behind the antiarrhythmic effects of SCS.

**Limitations**

We evaluated the effects of SCS on ventricular arrhythmias in a canine model with healed MI and superimposed pacing-induced HF. The mechanism of MI and HF induction in this model is different from that responsible for cardiac disease in the majority of patients in whom SCS is being used clinically. Thus, this model is at best an approximate simulation of the clinical disease, and results of this study will need to be confirmed in coronary patients.

The study was conducted in anesthetized animals, which might have influenced the results. However, anesthesia was
held constant during the study and was conducted in a similar fashion in both the no-SCS and SCS-treated animals. Effects in nonseated, ambulatory animals are still to be evaluated. Moreover, this study did not address the long-term effects of SCS on ventricular arrhythmias, and evaluation of more extended periods of SCS is warranted.

Another point of concern is the factor of ischemic preconditioning. Differences in susceptibility to ventricular arrhythmias between the first versus the second ischemic episode might be due to ischemic preconditioning rather than the intervention used. To address this possibility, we randomly assigned the animals to receive SCS or no SCS before the first or second ischemia session, and SCS reduced the occurrence of VT/VF when used before either the first or the second episode of ischemia.

Conclusion
SCS has been increasingly used and studied for the treatment of patients with severe coronary artery disease and refractory angina. The results of the present study indicate that, in a canine model with healed MI and HF, thoracic SCS protects against ischemia-provoked ventricular arrhythmias. If these results can be extrapolated to coronary patients receiving SCS for refractory angina, SCS may offer an antithrombotic benefit.

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