Spinal cord stimulation suppresses bradycardias and atrial tachyarrhythmias induced by mediastinal nerve stimulation in dogs

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CLINICAL EVIDENCE INDICATES that delivering high-frequency, low-intensity electrical stimuli to the dorsal aspect of the cranial thoracic spinal cord can alleviate symptoms associated with chronic refractory angina of cardiac origin (6, 7, 11). We have proposed that a primary mechanism of such spinal cord stimulation (SCS) therapy may be due to its capacity to modulate the intrinsic cardiac nervous system in the presence of excessive afferent neuronal inputs arising from the ischemic ventricle (2, 8).

Increasing extrinsic neuronal inputs to the intrinsic cardiac nervous system can initiate self-terminating episodes of atrial tachyarrhythmia/fibrillation in intact hearts without the need for concomitant programmed electrical stimulation of atrial muscle (3, 4, 14, 16). Atrial tachyarrhythmias can be induced experimentally by electrical stimulation of mediastinal nerves during the refractory period of atrial muscle to avoid local muscle capture (4, 14). The initial beats of the tachyarrhythmias thus elicited appear to be of focal origin (4). It is possible that this may account, in part, for the fact that select mediastinal nerve ablation can suppress paroxysmal atrial fibrillation (13).

We have proposed that a primary mechanism of such SCS therapy may reside in its capacity to modulate the intrinsic cardiac nervous system in the presence of excessive afferent neuronal inputs arising from the ischemic ventricle (2, 5, 8, 9). In this study, we investigated the possibility that SCS therapy might suppress neuronally induced atrial tachyarrhythmia formation via its capacity to stabilize excessive inputs to the intrinsic cardiac nervous system.

METHODS

Animals

A total of 21 adult mongrel dogs (either sex), weighing 15–27 kg, were used in this study. Experiments were performed in accordance with guidelines for animal experimentation (17) and approved by the institutional animal care committee. Animals were anesthetized with sodium thiopental (25 mg/kg iv, supplemented as required), intubated, and maintained under positive-pressure ventilation.

Implantation of Spinal Cord-Stimulating Electrodes

With animals lying in the prone position, a small incision was made in the caudal, dorsal thoracic skin. The epidural space of the midthoracic spinal column was penetrated percutaneously with a Touhy needle, using ventral-dorsal positional fluoroscopy and loss-of-resistance technique (6). A quadrupolar electrode catheter with 1.5 cm interelectrode distance (QUAD Plus Model 3888, Medtronic, Minneapolis, MN) was introduced, and its tip was advanced under fluoroscopy to the T1 level of the dorsal surface of the spinal column, slightly to the left of the midline. The rostral pole (cathode) and caudal pole (anode) selected for subsequent use were connected to a constant current generator (WPI model A385, 50 Hz, 0.2-ms duration) controlled by a stimulator (model S88, Grass Instruments, Quincy, MA). Threshold intensity for motor responses (proximal forepaw and shoulder muscle contraction) was determined. After a satisfactory electrode position was obtained, the external portion of that electrode catheter was covered with a protective silicone sleeve that was fixed to the...
interspinous ligament. Thereafter, the animals were placed in the supine position, and the motor threshold was rechecked. Spinal cord stimulus intensity was set at 90% of motor threshold (8), varying between 0.21 and 0.86 mA (mean 0.39 mA) among animals.

**Instrumentation for Electrophysiological Study**

Left ventricular chamber and aortic pressures (Millar electronic pressure sensors) along with a lead II ECG were recorded on a rectilinear pen recorder (Nihon Kohden, Tokyo, Japan). With the animal remaining in the supine position, a sternotomy was performed, the pericardium was incised, and the heart was exposed. Atrophicventricular (AV) block was induced by formaldehyde injection (37%, 0.1 ml) into the AV node to separate atrial from ventricular electrical events. Right ventricular pacing (50–60 beats/min) was instituted to assure adequate cardiac output. After this surgery, the anesthetic agent was changed to α-chloralose (50 mg/kg iv bolus, supplemented with 25 mg/kg doses as required). Silicone plaques carrying 191 unipolar recording contacts (4.6–5.9 mm spacing) were positioned on the ventral, lateral, and dorsal surfaces of the right and left atria and attached with sutures (4). The unipolar leads and lead II ECG were connected to a multichannel recording system (EDI 12/256, Institut de Génie Biomédical, École Polytechnique de Montréal) controlled by custom-made software (Cardiomap III, www.crhc.umontreal.ca/cardiomap) using a PC computer. Unipolar electrograms (measured with reference to Wilson’s central terminal derived from the four limb leads) were amplified by programmable-gain analog amplifiers (0.05–450 Hz) and converted to digital format at 1,000 samples/s/channel. Data were stored on hard disk, from which files were subsequently retrieved for detailed analysis.

**Electrical Stimulation of Mediastinal Nerves**

In all of the experiments, the right-sided mediastinal nerves studied were located on the ventral and ventrolateral surfaces of the superior vena cava, either in its caudal portion (intrapерicardial sites) or in the first centimeter of the superior vena cava cranial to the pericardial reflection (extrapericardial sites). Individual nerve branches coursing over the superior vena cava arise from the intrathoracic right vagosympathetic nerve complex, some of which can be identified by their accompanying blood vessels (3, 4). In five experiments (conducted according to protocol A; see below), electrical stimuli were also delivered to left-sided mediastinal nerves that arise from the left vagosympathetic nerve complex, coursing intrapericardially cranial to the pulmonary veins (3).

A train of five electrical stimuli (1–2 mA, 1-ms duration, 5-ms pulse interval) was delivered to selected mediastinal nerve sites once per cycle of spontaneous atrial activity during the refractory period of adjacent atrial tissues (~30 ms after excitation of a reference electrogram) to avoid muscle capture. Active sites were identified functionally such that, when exposed to focal electrical stimuli, changes in atrial rhythm were elicited (4). The most frequently identified response was atrial tachyarrhythmias by an episode of spontaneously terminating atrial tachyarrhythmia/fibrillation with an average cycle length of ~120 ms (4). No response was elicited from the adjacent atrial tissues (30 ms after excitation of a reference electrogram) to avoid muscle capture. Active sites were identified functionally such that, when exposed to focal electrical stimuli, changes in atrial rhythm were elicited (4). The most frequently identified response was atrial tachyarrhythmias by an episode of spontaneously terminating atrial tachyarrhythmia/fibrillation with an average cycle length of ~120 ms (4). No response was elicited from other intrapericardial or extrapericardial sites tested, despite periods of stimulation lasting for up to 20 s. Each active locus was marked with ink for repeat stimulation. Electrical stimuli were delivered focally via bipolar electrodes (1.5-mm spacing) mounted on a probe that was connected to a battery-driven current source controlled by a programmable stimulator (Bloom Associates, Philadelphia, PA). Contact between the bipolar electrodes and tissue was interrupted immediately after the onset of an episode of atrial tachyarrhythmia.

**Protocol A: Effects of Spinal Cord Stimulation (11 Animals)**

This protocol was performed in four steps. 1) In control states, multiple (six or more) active neural sites were identified and then restimulated to confirm reproducibility of responses (5-min recovery period between successive stimulations). 2) After the identification of active sites, SCS was applied for 20 min (3). 3) Thirty minutes after discontinuing SCS (2, 5), the previously identified active sites were restimulated twice. 4) When sites were identified at which atrial tachyarrhythmias could still be initiated post-SCS, atropine (0.1 mg/kg iv) was administered and those mediastinal nerve sites were restimulated a final time.

**Protocol B: Reproducibility**

In five other animals, a protocol similar to protocol A was used but without SCS stimulation in step 2. Protocol B allowed us to verify that, in the absence of SCS, the functional responses were reproducible in a similar time frame.

**Protocol C: Effects of Spinal Cord Stimulation in Animals With Bilateral Stellectomy**

In five other animals, the right and left stellate ganglia were extirpated before determining the responses to electrical stimulation of mediastinal nerves in control states and after SCS (as in protocol A).

**Data Analysis**

Analyzing unipolar electrograms with Cardiomap III software, we identified activation times as the moment the atrial activation complex at which the slope of the negative potential displacement (−dV/dt_{max}) was maximal (4). During basal states (i.e., sinus rhythm), the atrial cycle length determinations were derived from 10 atrial cycles. With respect to bradycardia or sinus tachycardia elicited by mediastinal nerve stimulation, atrial cycle length was assessed by means of the maximum interval recorded during two consecutive atrial electrograms. The reference electrogram for these determinations was recorded from the right atrial free wall. Threshold for cycle length change in response to mediastinal nerve stimulation was set at >2% variation. The duration of the episodes of tachyarrhythmia/fibrillation was calculated as the interval between the atrial premature depolarization initiating the arrhythmia and the last arrhythmia beat. Atrial cycle lengths recorded during neurally induced atrial tachyarrhythmias were averaged over 50-s periods when the arrhythmias lasted for 50 s or more. When shorter-duration arrhythmias were elicited, that index was averaged from data collected throughout the arrhythmia period. The earliest 10-ms epicardial breakthrough area was determined from isochronal maps (10-ms interval) before being computed automatically by linear interpolation from activation times at all 191 electrode sites of the biatrial silicon plaque electrodes.

For each protocol, Student’s paired t-test was used for comparisons of continuous variables measured in the responses to electrical stimulation at a given nerve site in control states (step 1) vs. post-SCS or sham (step 3). The numbers of sites from which atrial arrhythmias were elicited when individual loci were stimulated electrically before and after SCS application were compared using the χ²-test. The level of certainty for rejecting the null hypothesis was P < 0.05. Data are presented as means ± SD.

**RESULTS**

**Protocol A: Effects of Spinal Cord Stimulation**

Mediastinal nerve stimulation in control states. In 11 anesthetized animals, focal electrical stimuli were delivered to multiple sites on the superior vena cava and, in five of them, cranial to the ventral left atrium during basal states (i.e., sinus rhythm). A total of 86 “active” sites were identified that, when subjected to focal electrical stimulation, elicited bradycardia alone (12 sites: 11 right-sided, 1 left-sided), bradycardia fol-
Table 1. Spinal cord stimulation: bradycardia responses to mediastinal nerve stimulation

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Before SCS (control)</th>
<th>After SCS</th>
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<tbody>
<tr>
<td>Protocol A: SCS (11 animals)</td>
<td># sites 62/86</td>
<td>47/86*</td>
</tr>
<tr>
<td></td>
<td>Sinus CL, ms 416 (42)</td>
<td>435 (47)†</td>
</tr>
<tr>
<td></td>
<td>Bradycardia CL, ms 535 (83)</td>
<td>534 (98)</td>
</tr>
<tr>
<td></td>
<td>CL prolongation, % 30 (24)</td>
<td>23 (20)†</td>
</tr>
<tr>
<td>Protocol B: testing reproducibility (without SCS) (5 animals)</td>
<td># sites 27/28</td>
<td>25/28</td>
</tr>
<tr>
<td></td>
<td>Sinus CL, ms 403 (25)</td>
<td>397 (22)</td>
</tr>
<tr>
<td></td>
<td>Bradycardia CL, ms 541 (72)</td>
<td>524 (75)</td>
</tr>
<tr>
<td></td>
<td>CL prolongation, % 35 (20)</td>
<td>33 (22)</td>
</tr>
<tr>
<td>Protocol C: SCS after bilateral stellectomy (5 animals)</td>
<td># sites 27/31</td>
<td>27/31</td>
</tr>
<tr>
<td></td>
<td>Sinus CL, ms 529 (71)</td>
<td>521 (60)</td>
</tr>
<tr>
<td></td>
<td>Bradycardia CL, ms 712 (166)</td>
<td>724 (157)</td>
</tr>
<tr>
<td></td>
<td>CL prolongation, % 34 (23)</td>
<td>39 (26)</td>
</tr>
</tbody>
</table>

Data are presented as means (SD). # sites, proportion of total active sites from which bradycardias were elicited by mediastinal nerve stimulation. Atrial cycle length (CL) measurements were made during baseline “sinus” rhythm (i.e., before mediastinal nerve stimulation) and during bradycardia; their difference is expressed as percent CL prolongation. These variables were measured before (control) and after spinal cord stimulation (SCS) (protocol A), in reproducibility experiments without SCS (protocol B), and in animals with bilateral stellectomy (protocol C). Differences between control and trial data were tested using t-test for paired data (continuous variables) or χ² (incidence). *P < 0.03 and †P < 0.006 error rejecting the null hypothesis.

Episodes of atrial tachyarrhythmia/fibrillation displayed average cycle lengths of 118 ± 12 ms. Moderate “sinus” tachycardia occurred in response to stimulation of only three nerve sites, as a shortening of sinus cycle length from 392 ± 41 to 306 ± 55 ms (22 ± 6% shortening). Among the total of 62 initial bradycardias thus elicited (with or without a subsequent tachycardia), there was a 30 ± 24% prolongation in atrial cycle length (i.e., sinus cycle length changed from 416 ± 42 to 535 ± 83 ms; Table 1, protocol A). Similar atrial responses were elicited by repeat stimulation of any active site in control states.

As illustrated in Figs. 1A and 2A, the sequence of events elicited from the majority of active sites consisted of a bradycardia phase (1–4 atrial cycles) that was interrupted, after a latency of 0.5–3 s, by a spontaneous atrial premature depolarization initiating an episode of atrial tachyarrhythmia/fibrillation. The arrhythmia persisted, on average, for 16 ± 10 s beyond cessation of nerve stimulation before terminating spontaneously (Table 2, protocol A).

Mediastinal nerve stimulation after preemptive SCS. Baseline sinus cycle length increased by 5% after applying SCS (Table 1, protocol A: from 416 ± 42 to 435 ± 47 ms, P < 0.006). After SCS, repeat electrical stimuli initiated tachyarrhythmia/fibrillation from only 29 of the 71 previously identified active sites (Table 2, protocol A). Bradycardias (alone or followed by tachyarrhythmia/fibrillation) were also elicited from significantly fewer sites after SCS (Table 1; protocol A: reduced from 62 to 47, P < 0.03). The maximum cycle length prolongations elicited during the bradycardias induced after SCS (23 ± 20%) were significantly reduced vs. the bradycardias elicited from these sites in control states (30 ± 24%, P < 0.006). Electrical stimulation applied to seven nerve sites caused slight sinus tachycardia during which cycle length shortened from 432 ± 47 to 411 ± 47 ms (this 5 ± 4%

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**Fig. 1.** Complete suppression of atrial tachyarrhythmia/fibrillation elicited by mediastinal nerve stimulation after spinal cord stimulation (SCS). Atrial electrical activity recorded from a unipolar electrode on the ventral, midregion of the right atrial free wall in a canine preparation with atrioventricular block: note the presence of dissociated ventricular (V) complexes. Bursts of electrical stimuli were applied to a caudal right-sided mediastinal nerve during the atrial refractory period (arrows above) before (A) and after (B) preemptive SCS. In control states (A), 2 bursts of electrical stimuli (2 arrows above) were sufficient to induce a paroxysm of atrial tachyarrhythmia/fibrillation that lasted for 16 s. Note that these atrial arrhythmias persisted throughout the 12.5 s not shown. When burst stimuli were applied to the same site for 34 atrial cycles after SCS (B), there was an initial bradycardia but tachyarrhythmias were not elicited. CL, atrial cycle length.
shortening was significantly smaller than the 22 ± 6% shortening seen in three such responses in control states).

Figure 1 illustrates an example of a tachyarrhythmia that was elicited from an active site in control state (A) but not after SCS (B), despite the repeated applications of focal electrical stimuli for up to 20 s. The incidence of tachyarrhythmias was reduced after SCS, whether focal electrical stimuli were applied to right (from 55 to 28 sites) or left (from 16 sites to 1 site) mediastinal nerves.

Of the tachyarrhythmias still induced from 29 nerve sites by repeat electrical stimulation after SCS, 24 tachyarrhythmias were preceded by bradycardia, and 5 were elicited without a preceding bradycardia. The durations of the tachyarrhythmia/fibrillations were reduced in 16 episodes (20/4 to 7/4 s) and increased in 10 others (9/5 to 17/4 s). In the three remaining episodes, the tachyarrhythmia duration exceeded 100 s in control states but were reduced to an average of 41 s after SCS (since duration exceeded the mean duration by several SDs, the data from these three episodes were not included in the statistics presented in Table 2). Thus duration was not significantly affected overall (16/10 to 11/7 s; Table 2, protocol A). The latency from beginning mediastinal nerve stimulation to tachyarrhythmia onset was not affected by SCS (control: 1.7 ± 1.9 s, post-SCS: 1.6 ± 1.0 s).

Epicardial Mapping

Classically, the sites of earliest epicardial activation and areas of earliest 10-ms activation occurred in the superior portion of the right atrial free wall during all basal beats (“sinus” rhythm) and shifted toward the inferior right atrial regions during the bradycardias (not shown) (4, 12, 15). As reported previously (4), the earliest 10-ms epicardial breakthrough areas during the initial tachyarrhythmia beats induced by right-sided mediastinal nerve stimulation were localized in the right atrial free wall, Bachmann bundle region, or adjacent
base of the medial right atrial appendage (Fig. 3A). These epicardial breakthrough points were consistent with focal activity arising from endocardial sites of origin in the right atrial subsidiary pacemaker complex, that is, the crista terminalis and dorsal locations that include the right atrial aspect of the interatrial septum (4, 15). The earliest epicardial breakthrough loci identified in the initial beats of the tachyarrhythmias elicited following SCS were distributed similarly as in control states (Fig. 3B).

Atropine administration. Any residual atrial arrhythmias that were elicited by mediastinal nerve stimulation following SCS (protocol A) were eliminated following subsequent atropine administration, even when identified sites were restimulated for periods of up to 20 s.

Protocol B: Reproducibility

The induction of the bradycardias, as well as the cycle length prolongation during bradycardia, were reproducible between control and repeat stimulation in protocol B (Table 1). Likewise, the incidence of atrial tachyarrhythmias/fibrillations was not significantly different between control and repeat stimulations in protocol B (Table 2). The tachyarrhythmia/fibrillation cycle length and duration were reproducible as well.

Protocol C: Acute Bilateral Stellectomy

The baseline sinus cycle length was significantly longer among the five animals of the stellectomy group (Table 1, protocol C: 529 ± 71 ms) than in the animals with intact stellate ganglia (protocol A: 416 ± 42 ms). The sinus cycle length was not affected by SCS in the animals with stellectomy (after SCS: 521 ± 60 ms).

In the five animals of the stellectomy group, 31 active nerve sites were identified which, when stimulated electrically in control states, elicited bradycardia alone (five nerve sites), bradycardia followed by atrial tachyarrhythmia/fibrillation (22 sites), tachyarrhythmia/fibrillation without preceding bradycardia (1 site), or a moderate acceleration of sinus rate (3 sites). The induction of bradycardias in response to nerve stimulation (with or without subsequent tachyarrhythmias) and the attendant cycle length prolongation were unaffected after SCS (Table 1, protocol C: control: 34 ± 23%, post-SCS: 39 ± 26%). Contrasting with protocol A, in animals with bilateral stellectomy, SCS did not alter the ability of mediastinal nerve stimulation (when applied to 23 nerve sites) to evoke atrial tachyarrhythmia/fibrillation. Furthermore, tachyarrhythmia durations were similar between control states and after SCS (Table 2, protocol C).

DISCUSSION

The main finding reported herein is that thoracic spinal cord neurons, when stimulated electrically, can obtund the induction of atrial tachyarrhythmias/fibrillation associated with excessive, asymmetric activation of the intrinsic cardiac nervous system. Given that “active” sites were defined as the ones from which neuronally induced atrial rate responses (bradycardia and/or tachyarrhythmia/fibrillation) were elicited in control states, the proportion of total active sites from which tachyarrhythmias/fibrillation were elicited by mediastinal nerve stimulation was reduced from 71/86 in control states to 29/86 when repeat stimulation was applied to the previously identified nerve sites after SCS, i.e., a 60% reduction. The cycle length and duration of the residual tachyarrhythmias were not, overall, significantly affected after SCS. However, there was a tendency for shortening of duration, as seen in the majority of the episodes elicited after SCS (19/29). Removal from the statistics of data concerning the tachyarrhythmias with durations longer than 100 s in control state may have contributed to the conclusion that there were no changes in duration.

Interestingly, the initial tachyarrhythmia beats elicited after SCS displayed early epicardial breakthroughs that were localized in areas similar to those identified in control states. Taken together, the data suggest that, once elicited, the foci involved in the tachyarrhythmias induced after SCS were similar to the ones that were elicited in control states. Any residual atrial tachyarrhythmia evoked after SCS was eliminated by atropine, as previously shown in this model in the absence of SCS (4, 16). It is classical knowledge that cholinergic efferent neuronal inputs to the atria reduce atrial refractory periods in a spatially heterogeneous manner (1, 10), in addition to inducing bradycardia.

The proportion of total responsive sites from which bradycardias were elicited by mediastinal nerve stimulation was
reduced from 62/86 in control states to 47/86 when repeat stimulation was applied to the previously identified nerve sites after SCS, that is, a 25% reduction. Moreover, there was a significant reduction in the magnitude of the Bradycardias that were still elicited after SCS. Minor prolongation of baseline sinus cycle length also occurred after SCS, as reported by others (9). The reproducibility experiments support the notion that these differences were not related to changing conditions within the time frame of the protocol.

We thus conclude that the data reported herein support SCS effects in the form of 1) significant reductions in the inductions of both the tachyarrhythmia/fibrillations and the Bradycardias elicited in response to electrical stimulation of mediastinal nerves, 2) significant reductions in the magnitude of neurally induced cycle length prolongation during the Bradycardias. We were thus able to demonstrate an effect of SCS on the induction of the tachyarrhythmia/fibrillation episodes but without statistically significant change in their dynamics (cycle length) once elicited.

Linkage between enhanced spinal cord neuronal inputs and inhibition of neurally induced atrial tachyarrhythmias was further demonstrated by the fact that the antiarrhythmic effect of SCS did not occur after extirpation of both stellate ganglia before SCS. This is consistent with previous data indicating that the capacity of SCS to modulate the intrinsic cardiac nervous system, even when transducing excessive afferent inputs from the ischemic ventricle, occurs primarily via axons coursing in the subclavian ansae and stellate ganglia (8).

It is also important to note that the blunting effect of SCS on the Bradycardia responses to nerve stimulation was not elicited in the presence of bilateral stellpectomy (Table 1). Thus the ability of SCS to obliterate both the Bradycardias and the neurally induced atrial tachyarrhythmias can be eliminated by bilateral stellpectomy. Because the parasympathetic efferent preganglionic inputs to the intrinsic cardiac nervous system remained intact in the stellpectomy preparations, it is unlikely that such medullary neurons play a significant role in SCS-induced modulation of neurally induced atrial arrhythmias. We propose that neural inputs from the spinal cord modulate cardiac efferent postganglionic neurons, presumably via the effects of such inputs on intrinsic cardiac local circuit neurons (2).

That activated thoracic spinal cord neurons can modulate neurally induced atrial tachyarrhythmias secondary to overloading the intrinsic cardiac nervous system has implications with respect to suppressing such untoward atrial events in a clinical setting. These data are in accord with the observation that enhanced spinal cord neuronal inputs to the intrinsic cardiac nervous system obviate the latter’s capacity to transduce the ischemic myocardium (8) and thereby stabilize neurally induced ventricular electrical alterations in such a state (5, 9).

They also support previous findings indicating that SCS neuromodulation therapy exerts its cardioprotective effects without compromising cardiac function, either at rest or during induced stress (2, 5, 7, 8).

**Perspectives**

SCS obviate the induction of atrial tachyarrhythmias resulting from excessive activation of intrinsic cardiac neurons, indicating that the intrinsic cardiac nervous system may be a target for SCS therapy in the management of atrial tachyarrhythmias. It is known that neurally induced tachyarrhythmias can be acutely obviated by local mediastinal neuronal ablation (3, 4, 14); however, that approach may represent temporary therapy due to the capacity of intrathoracic neurons to sprout neurites to innervate other intrinsic cardiac neurons and cardiomyocytes. Although much more research needs to be performed to understand how inputs from the spinal cord stabilize the intrinsic cardiac nervous system in the presence of cardiac pathology, our current data delineate this component of the cardiac neuronal hierarchy as a potential target for antiarrhythmic therapy.

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