Mechanism of expiratory muscle activation during lower thoracic spinal cord stimulation

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DiMarco, A. F., K. E. Kowalski, G. Supinski, and J. R. Romaniuk. Mechanism of expiratory muscle activation during lower thoracic spinal cord stimulation. J Appl Physiol 92: 2341–2346, 2002. First published February 1, 2002; 10.1152/japplphysiol.01231.2001.—Lower thoracic spinal cord stimulation (SCS) may be a useful method to restore an effective cough mechanism. In dogs, two groups of studies were performed to evaluate the mechanism of the expiratory muscle activation during stimulation at the T9-T10 level, which results in the greatest changes in airway pressure. In one group, expiratory muscle activation was monitored by evoked muscle compound action potentials (CAPs) from the internal intercostal muscles in the 10th, 11th, and 12th interspaces and from portions of the external oblique innervated by the L1 and L2 motor roots. SCS, applied with single shocks, resulted in short-latency CAPs at T10 but not at more caudal levels. SCS resulted in long-latency CAPs at each of the more caudal levels, and also resulted in a fall in airway pressure generation. In the second group, sequential spinal root sectioning was performed to assess their individual mechanical contribution to pressure generation. Section of the ventral roots from T8 through T10 resulted in negligible changes, whereas section of more caudal roots resulted in a progressive reduction in pressure generation. We conclude that 1) SCS at the T9-T10 level results in direct activation of spinal cord roots within two to three segments of the stimulating electrode and activation of more distal roots via spinal cord pathways, and 2) pathway activation of motor roots makes a substantial contribution to pressure generation.

Electrical stimulation; expiratory muscles; cough

Patients with spinal cord injury lack of an adequate cough mechanism as a result of loss of expiratory muscle function. Because the innervation of the expiratory muscles is usually intact in these patients, the expiratory muscles can potentially be activated by magnetic and electrical stimulation techniques (8–11, 13, 19–21, 26). In recent studies, we found that lower thoracic electrical spinal cord stimulation (SCS) with a single electrode lead placed on the dorsal epidural surface of the spinal cord results in positive changes in airway pressure generation at all sites between the T8 and L2 spinal cord levels (8–11). The greatest changes in airway pressure result from stimulation applied at the T9-T10 spinal cord level. Although the motor roots innervating the expiratory muscles extend to the L2 level, we previously demonstrated that electrical stimulation with modest current levels (15 mA) results in direct activation of motor roots only in the vicinity of the stimulating electrode (8, 9). Because stimulation at the T9-T10 level results in large positive changes in airway pressure generation, we postulated that activation of more caudal motor roots via spinal cord pathways might also contribute to the observed responses.

Therefore, the purpose of the present study was to assess the potential effects of activation of spinal cord pathways on expiratory muscle activation during lower thoracic SCS at the T9-T10 level. This was accomplished by monitoring evoked muscle compound action potentials (CAPs) from the expiratory intercostal and abdominal muscles during SCS. In addition, we evaluated the effects of spinal cord transection on airway pressure generation and, in a separate group of animals, the changes in airway pressure generation before and after sequential sectioning of the spinal roots.

METHODS

Studies were performed in 15 mongrel dogs (weight, 15–23 kg; mean of 18.2 ± 0.6 kg). All animals were anesthetized with pentobarbital sodium. A dose of 30 mg/kg was given intravenously; additional doses were provided as needed. Animals were tracheostomized and intubated with a cuffed endotracheal tube (10-mm ID). Catheters were placed in the femoral vein and artery for administration of intravenous fluids and anesthetic and to monitor arterial blood pressure (model P23XL, Spectramed, Statham Instruments, Hato Rey, PR), respectively. A homeothermic blanket (Harvard Apparatus, Cambridge, MA) was used to maintain body temperature at 38 ± 0.5°C. End-tidal Pco2 was monitored with a rapidly responding CO2 analyzer (O.R. SARAcap, PPG Biomedical Systems, Lenexa, KS) at the tracheal opening. Tracheal pressure was measured with differential pressure transducer (model MP-45, Validyne, Northridge, CA) during

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airway occlusion and recorded on an eight-channel recorder (model DASH8, Astro-Med, Warwick, RI). Electrical stimulation was applied with a Grass two-channel electrical stimulator (model S88, Grass Instruments, Quincy, MA) with single shocks or trains of 50 Hz, 1- to 2-s train duration, 0.2-ms pulse duration. In previous studies, we determined that a stimulus current of 15 mA was optimal because it resulted in near maximal changes in airway pressure without causing significant activation of nonrespiratory musculature (9). This stimulus current therefore was employed in the present studies.

Protocol 1. In one group of animals (n = 4), the spinal cord was exposed via laminotomies at the T8 and T11-T12 levels. A platinum-iridium stimulating electrode (model 3586, Medtronic, Minneapolis, MN) was inserted epidurally and positioned on the dorsal surface at the T9-T10 spinal cord region to activate the expiratory muscles. Single-shock electrical stimulation (15 mA, 0.2-ms pulse duration) was applied to determine CAPs before and after sequential sectioning of the spinal cord. The skin over the lower thorax and upper abdominal wall was reflected to expose the expiratory muscles. Electromyographic electrodes (bipolar stainless steel wires) were implanted in the posterior axillary line into the intercostal muscles (10th, 11th, and 12th interspaces) and external oblique (dermatome regions innervated by L1 and L2 motor roots). Recordings of CAPs were amplified (model BMI-830, Charles Ward Enterprises, Ardsmore, PA) and recorded on an oscilloscope (model 5223, Tektronix, Beaverton, OR). The latencies of CAPs were determined from the stimulus artifact and the onset of CAPs. The spinal cord was sequentially sectioned (dorsal columns, lateral funiculi, and then ventral funiculi) with watchmaker’s forceps at the T11-T12 level. Pressure generation during SCS (15 mA, 50 Hz, 0.2-ms pulse duration) was measured in separate trials after each spinal sectioning.

Protocol 2. In another group of animals (n = 11), a laminectomy was performed extending from the T7 to the L2 spinal levels. A stimulating electrode was inserted onto the epidural surface of the spinal cord at the T9-T10 level. The effects of bilateral sequential root sectioning was assessed at each spinal cord level from a cephalad to caudal direction. Root activation. In contrast, CAPs recorded from muscles innervated from T12, L1, and L2 had substantially longer latencies of 3.6 ± 0.1, 4.1 ± 0.1, and 4.6 ± 0.2 ms, respectively. After sectioning of the dorsal columns, CAPs from T10 to T11 were unaffected, whereas those from T12 to L2 were abolished (Fig. 1, right). This phenomenon occurred in each of the animals studied.

Effects of sequential spinal cord sectioning on pressure generation. Because our previous electromyographic studies suggested that only the motor roots T8 through T11 are activated directly by SCS at the T9-T10 level, we evaluated the influence of spinal cord pathways on pressure generation after spinal cord section at the T11-T12 level (8, 9). The effect of sequential spinal cord sectioning for one animal and group mean effects (means ± SE) are shown in Fig. 2. Sectioning of

**RESULTS**

**Effects of single-shock stimulation on muscle activation.** As in previous studies, we found that the optimum site for pressure generation with a single electrode was at the T9-T10 region of the spinal cord (11). The CAPs resulting from SCS in this region are shown in Fig. 1. The latencies of CAPs evoked in the internal intercostal muscle from the 10th and 11th interspaces ranged from 1.6 to 2.0 ms with a mean of 1.7 ± 0.1 and 1.8 ± 0.1 ms, respectively, consistent with direct motor root activation. In contrast, CAPs recorded from muscles innervated from T12, L1, and L2 had substantially longer latencies of 3.6 ± 0.1, 4.1 ± 0.1, and 4.6 ± 0.2 ms, respectively.

**Data analysis.** Latency measurements of the CAPs were calculated to obtain information related to the characteristics of the fibers stimulated and an estimate of the number of synapses involved in muscle activation. Latency of the CAPs were determined from the stimulus artifact and onset of the CAP. Mean control pressures were compared with pressures developed after sequential sectioning of the spinal cord. Significant change in pressure generation after sectioning was taken to indicate the involvement of specific spinal cord pathways in the activation of more caudal expiratory muscles. In experiments involving spinal cord root sectioning, mean control pressures were compared with pressures developed after bilateral sequential sectioning of the ventral roots at each spinal cord level.

Statistical analysis was performed by using a one-way analysis of variance and the Newman-Keuls test, where applicable. A P value of < 0.05 was taken as significant.
the dorsal columns resulted in large decrements in pressure generation from 58 ± 2 to 31 ± 4 cmH2O (P < 0.001). After subsequent sectioning of the lateral funiculi and complete spinal cord, pressure generation fell further to 26 ± 3 and 23 ± 2 cmH2O, respectively (not significant for each compared with postdorsal column section).

**Effects of sequential bilateral spinal root sectioning on pressure generation.** The changes in airway pressure generation from one animal and mean data after root sectioning in the cephalad to caudal direction are shown in Fig. 3. Mean control airway pressure during SCS was 55 ± 2 cmH2O. Sectioning of the spinal roots from T8, T9, and T10 resulted in negligible changes in pressure generation at 55 ± 2, 54 ± 1, and 51 ± 3 cmH2O, respectively (not significant for each, compared with control), whereas sectioning of more caudal roots resulted in progressive reductions in airway pressure generation. After sectioning of roots T11, T12, T13, L1, and L2, pressure fell to 39 ± 3, 33 ± 4, 21 ± 2, 13 ± 1, and 10 ± 2 cmH2O, respectively (P < 0.05 compared with control for each).

The effect of sequential sectioning of the spinal roots in the caudal to rostral direction on airway pressure generation in the one animal and mean effects are shown in Fig. 4. Mean control airway pressure during SCS was 52 ± 2 cmH2O. Sectioning of the L2, L1, T13, T12, and T11 roots resulted in substantial decrements in airway pressure generation (to 43 ± 4, 33 ± 4, 25 ± 3, 17 ± 2, and 12 ± 2 cmH2O, respectively; P < 0.05 compared with control for each). Subsequently, root sectioning of T10 through T8 resulted in negligible changes in pressure generation to 11 ± 2, 10 ± 1, and 11 ± 2 cmH2O, respectively (not significant for each, compared with post T11 section).

**DISCUSSION**

The major finding of the present study is that the mechanism by which SCS at the T9-T10 level results in expiratory muscle activation involves both direct spinal root activation in the vicinity of the stimulating electrode and also activation of more caudal motor roots via spinal cord pathways. Moreover, activation of
the more caudal roots makes a substantial contribution to airway pressure generation.

**Mechanisms of motor root activation via SCS.** In a previous investigation, we systematically evaluated direct motor root activation at various spinal cord levels by monitoring the short-latency (2–3 ms) muscle CAPs resulting from SCS (8, 9). With modest levels of current employed (15 mA), only motor nerves within two to three segments of the stimulating electrode are activated by direct stimulation. The results of the present study confirm short-latency activation of motor roots within two to three segments of the spinal cord and also demonstrate activation of more distal motor roots (T11–L2) but with longer latencies. The long-latency, but not the short-latency, CAPs were eliminated by spinal cord section at T11-T12 level (just below the level of direct activation), indicating activation of spinal cord pathways as the mechanism of more caudal motor root activation.

The results of the present study also define the separate mechanical correlates of direct and pathway activation of motor roots during electrical stimulation at the T9-T10 level. This was accomplished by two separate, but complementary, methods. In association with the elimination of the long-latency CAPs by spinal cord section, airway pressure generation fell to 40% of control values. In the second, potential spinal pathway activation of more caudal spinal nerves was eliminated by bilateral sectioning of the motor roots between T8 and L2. After rostral to caudal and caudal to rostral root section, pressure generation fell to 18 and 21% of control values, respectively. Importantly, pressure generation was reduced only by section of roots T11 through L2; section of roots T8 through T10 had no effect on pressure generation, consistent with their direct activation via close proximity to the stimulating electrode. The results of both studies indicate that activation of more caudal motor roots (T11 through L2), via spinal cord pathways, plays a major role in the generation of large airway pressures during stimulation at the T9-T10 spinal cord level. Conversely, direct stimulation alone, which results in activation of only those motor roots in the immediate vicinity of the electrode (T8 through T11), results in substantially less pressure generation.

**Critique of method.** We evaluated the potential contribution of pathway activation of motor roots caudal to the stimulating electrode because the bulk of expiratory muscles are innervated by the lower thoracic and upper lumbar roots. However, it is possible that stimulation of pathways projecting to motoneurons located cephalad to the electrode may have also contributed to the observed changes in airway pressure (9). The T7 and T8 roots, which predominantly innervate expiratory muscles, were most likely activated by direct stimulation based on our previous CAPs studies (9). Stimulation of the upper thoracic roots innervate predominantly inspiratory muscles, the possible activation of which may have reduced pressure generation. The fact that the actual pressures generated remained strongly positive, however, suggests that there was modest, if any, inspiratory muscle activation.

Isolation and section of each pair of roots is a lengthy and tedious procedure with the potential to damage motor axons, thereby reducing the effects of electrical stimulation to roots activated by direct activation. Close analysis of our results, however, suggests that potential axonal injury distal to the site of sectioning was minimal. Section of the T8, T9, and T10 roots (both in the cephalad and caudal directions, in separate trials) had no significant impact on pressure generation. Significant mechanical injury, however, would have been expected to reduce muscle activation and pressure generation. Because this did not occur, significant mechanical injury appears unlikely.

We assessed the mechanical contribution of motor root activation via changes in pressure generation. It should be noted, however, that these pressure changes do not necessarily reflect the agonistic action of each portion of the expiratory muscles. It is possible, for example, that the lower portions of the expiratory muscles function predominantly as fixators, rather than making a major direct contribution to pressure generation, whereas the upper portion of the abdominal muscles represent the major agonists. In this scenario, contraction of the upper abdominal muscles alone, as occurred after spinal cord section, would be much less effective in terms of pressure generation due to dissipation of pressure across the flaccid lower abdominal wall.

**Comparison to previous studies.** Application of electrical current in the T2 region of the spinal cord results in inspiratory intercostal muscle activation and the generation of large inspired volumes (5–7, 12). This technique, in combination with unilateral diaphragm stimulation, has been shown to be a clinically useful method of providing ventilatory support in ventilator-dependent tetraplegic individuals (6, 7). Our laboratory previously evaluated the mechanism of inspiratory intercostal motor root activation during upper thoracic SCS (8, 25). Bilateral section of the spinal roots (T1–T6) does not affect negative inspiratory pressure generation during SCS at the T2 level, indicating that the motor roots are activated directly during SCS (distal to the site of section) and that spinal cord pathways are not involved. Our laboratory also compared latencies of intercostal nerve CAPs resulting from SCS with that resulting from direct motor root stimulation (25). The latencies of direct motor root activation were not significantly different from those occurring during SCS, indicating that upper thoracic SCS results in intercostal muscle activation via direct motor root activation. As discussed above, the mechanism of expiratory muscle activation is quite different, involving both direct motor root and spinal cord pathway activation.

**Spinal cord pathway activation via SCS.** Dorsal column section had the greatest impact on pressure generation, implicating pathways in this region of the spinal cord as the major mechanism of activation of more caudal thoracic and lumbar motor roots. Of in-
terest, previous studies have demonstrated that thick fibers in the dorsal columns have the lowest activating threshold, followed by large axons in the lateral funiculi and ventral funiculi, during epidural SCS. Because pressure generation fell an additional 16 and 12% after section of the lateral and ventral funiculi, respectively, it is possible that the spinocerebellar, corticospinal, rubrospinal, and/or propriospinal tracts also made a small contribution to the observed responses.

The dorsal columns contain cutaneous, joint, and primary muscle afferent fibers (1–4, 14, 15, 17, 22, 24). The cutaneous and joint afferents have segmental collaterals projecting to the dorsal horn of the gray matter, and their minimum linkage with motoneurons is bi- and trisynaptic. The long-latency CAPs, however, occurred as early as 3.6 ms (at the T12 spinal cord level). Assuming synaptic delays, distance between the stimulating and recording electrodes, and maximum fiber conduction velocity of 60–70 m/s, antidromic activation of more caudal roots could not have involved cutaneous and joint afferents. Consequently, antidromic activation of primary muscle afferents that produce monosynaptic facilitation of lower thoracic and upper lumbar motoneurons (innervating expiratory muscles) in the lower portion of the spinal cord are most likely responsible for the observed effects.

In support of this conclusion, previous studies in cats indicate that motoneurons in the more caudal portion of the spinal cord can be activated by epidural SCS at the T7 level via stimulation of fibers in the dorsal columns. Niznik et al. (23) demonstrated that late multiphasic evoked potentials from the L7 ventral nerve root, resulting from epidural SCS at T7, were abolished by dorsal column lesions caudal to the stimulating electrode. This conclusion is also in agreement with the results of Hunter and Ashby (18) in which the segmental effects of epidural SCS were studied in human subjects. These investigators implanted stimulating electrodes over the dorsum of the thoracic cord for the management of pain. They demonstrated that SCS applied with a dorsal epidural electrode generates action potentials in more caudal motor roots. They also surmised that these responses involved antidromic activation of primary afferents in the dorsal columns. Finally, Haghighi et al. (16) and Su et al. (27) each demonstrated that nerve CAPs were generated in caudal motor roots during thoracic epidural SCS. In both studies, the responses were abolished by dorsal column transection and loss of spinal-evoked potentials was observed at low levels of stimulation, suggesting the responses involved recruitment of large-diameter fibers at the site of stimulation.

Clinical significance. Concerning the potential use of this device in patients with spinal cord injury, elucidation of the mechanism of expiratory muscle activation via SCS and, more specifically, the specific neural structures involved, is necessary for optimal electrode placement and design. An appropriately designed electrode can maximize the activation of neural structures responsible for expiratory muscle activation and resultant positive changes in airway pressure. Consequently, the magnitude of current injected and potential for side effects could be minimized.

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REFERENCES


