TENS attenuates response to colon distension in paraplegic and quadriplegic rats

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Collins, Heidi L., and Stephen E. DiCarlo. TENS attenuates response to colon distension in paraplegic and quadriplegic rats. Am J Physiol Heart Circ Physiol 283: H1734–H1739, 2002; 10.1152/ajpheart.00253.2002.—Individuals with spinal cord injuries above thoracic level 6 experience episodic bouts of life-threatening hypertension as part of a condition termed autonomic dysreflexia (AD). The hypertension can be caused by stimulation of the skin, distension of the urinary bladder or colon, and/or muscle spasms. Transcutaneous electrical nerve stimulation (TENS) may reduce the severity of AD because TENS has been used to inhibit second-order neurons in the dorsal horn. Therefore, we tested the hypothesis that TENS attenuates the hemodynamic responses to colon distension. Eleven Wistar rats underwent spinal cord transection between thoracic vertebrae 4 and 5 (paraplegic, n = 6) or between cervical vertebra 7 and thoracic vertebra 1 (quadriplegic, n = 5). After recovery, all rats were instrumented with a radiotelemetry device for recording arterial pressure. Subsequently, the hemodynamic responses to graded colon distension were determined before and during TENS. During TENS the hemodynamic responses to colon distension were significantly attenuated. Thus TENS may be a preventive approach to reduce the severity of AD in paraplegic and quadriplegic individuals.

AUTONOMIC DYSREFLEXIA (AD) occurs in as many as 85% of individuals with spinal cord injuries (SCI) above thoracic level 6 (T6) and is characterized by severe hypertension. If not prevented or treated promptly, the hypertension may produce cerebral and subarachnoid hemorrhage, seizures, or renal failure and may lead to death (24). AD is the second most common long-term secondary medical complication associated with SCI and thus is a major health concern (25). In fact, AD is the most prominent life-threatening situation for individuals with SCI (4). The long-term consequence of repeated episodes of severe hypertension has yet to be determined; however, it is well documented that increased blood pressure variability is a significant cardiovascular disease risk factor (3).

Early interventions designed to prevent AD involved invasive methodologies such as subarachnoid alcohol blocks, anterior rhizotomies, and sacral extradural neurotomies and cordectomies; however, these procedures often disrupt sexual, bladder, and bowel function (4, 27). Currently, chronic pharmacological blockade of components of the autonomic nervous system are used to prevent AD; however, these interventions are associated with similar side effects (27). Thus noninvasive, nonpharmacological interventions designed to attenuate the severity of AD have the potential to improve the quality of life for individuals with SCI and their families.

Transcutaneous electric nerve stimulation (TENS) has been used successfully to manage pain for a variety of clinical conditions (31). Spinal cord stimulation and TENS have also been used to reduce spasticity in individuals with chronic SCI (32). These results suggest that TENS may be a noninvasive, nonpharmacological approach to reduce the severity of AD.

Therefore, this study was designed to test the hypothesis that TENS attenuates the hemodynamic responses of AD in chronic paraplegic and quadriplegic rats. To test this hypothesis, hemodynamic responses to graded colon distension were determined in conscious, freely moving paraplegic and quadriplegic rats before and during TENS (paraspinal electrodes from T12 to S3, 60 Hz, 2-μs duration, ~600 μA producing a minimal visible contraction). These parameters were chosen to enhance activation of large-diameter afferent fibers (7, 13). The first colon distension was performed 20 min after TENS started, and TENS remained on during generation of the colon distension curves. Twenty minutes is a standard TENS treatment duration, although TENS is often applied for hours or chronically for days (8). All surgical and experimental procedures were reviewed and approved by the Insti...
tutional Animal Care and Use Committee and conformed with the American Physiological Society’s Guiding Principles in the Care and Use of Animals. Six Wistar rats (4 female, 278 ± 24 g; 2 male, 370 ± 42 g) underwent a spinal cord transection between thoracic vertebrae 4 (T4) and 5 (T5). The T4 and T5 vertebrae were exposed via a midline dorsal incision. The underlying spinal cord was completely transected through the intervertebral space (2). The paraplegic rats were allowed to recover for 58 ± 14 days. Five additional Wistar rats (3 female, 222 ± 50 g; 2 male, 225 ± 15 g) underwent a spinal cord transection between cervical vertebra 7 (C7) and thoracic vertebra 1 (T1). The underlying spinal cord between C7 and T1 was completely transected through the intervertebral space (29). The quadriplegic rats were allowed to recover for 62 ± 8 days. During the recovery period, all rats were familiarized with the experimental procedures (handling, insertion of the balloon, etc.). After recovery, all rats were surgically instrumented for chronic measurements of arterial pressure and heart rate. Radiotelemetry devices (model TA11PA-C40; Data Sciences International) were implanted in the abdominal cavity with the attached catheter inserted through the femoral artery and advanced into the descending aorta. In addition, the quadriplegic rats were instrumented with three subcutaneous electrodes for recording of the electrocardiogram. Seven days later (22), hemodynamic responses to graded colon distension (10, 30, 50, and 80 mmHg, in random order with at least 5 min between inflations to allow arterial pressure and heart rate to return to baseline levels) were determined in conscious, freely moving rats before and during TENS (8). To ensure that the animals were fully recovered, we studied the paraplegic rats 64 ± 13 days and the quadriplegic rats 70 ± 8 days after transection.

All rats had a motor score of zero, indicating no weight bearing (36). On the day of the experiment, a latex balloon attached to a Tygon catheter (fashioned in our laboratory) was inserted 7–8 cm into the colon through the anus and secured by taping the catheter to the base of the tail (2). Conducting gel was placed on standard TENS electrodes, and the electrodes were placed bilaterally from T12 to S3 and secured with an elastic bandage. Subsequently, the rats were placed unrestrained in their home cage (with free access to water). The animals were allowed to adapt to the laboratory environment for 1 h to ensure a stable hemodynamic condition. After all variables obtained a steady state, pre-TENS baseline values were recorded.
over a 15-s interval. Subsequently, the procedure for colon distension was performed. Colon distension curves were generated before and during TENS on the same day. To generate colon distension curves, a handheld manometer was used to inflate the balloon to pressures of 10, 30, 50, and 80 mmHg (2). These pressures are well within the physiological range of pressures recorded in conscious humans (30). Distension pressures were applied in a randomized order, maintained for 60 s, and repeated twice at each pressure level at 5-min intervals. Control levels of arterial pressure and heart rate were averaged over 15 s immediately before inflation of the balloon. The hemodynamic responses to colon distension were averaged during the 60 s of balloon inflation for each level of pressure. It is important to note that colon distension produces pressor and bradycardic responses in paraplegic and quadriplegic rats (Fig. 1; Refs. 2, 21, 29). In contrast, colon distension produces pressor and tachycardic responses in intact rats (21, 28). Thus in this report we examined autonomic dysreflexic responses. Colon distension is a suitable, less invasive means of producing AD in spinal rats (21). In this regard, the rats did not resist insertion of the balloon (possibly because the rats could not feel the procedure) and they had minimal movement during the inflations.

Because colon distension curves were determined before and 20 min after TENS started, any differences observed could be due to time and not the intervening TENS. Therefore, to control for the effect of time (time control), the procedures were repeated on four of the same paraplegic rats and four of the same quadriplegic rats on an alternate day (>48 h) without turning the TENS unit on (sham TENS).

Individuals with SCI have significantly different levels of tonic and reflex activation of sympathetic activity to the heart and vasculature based on the level of the injury. For example, individuals with injury between C7 and T1 have reduced tonic sympathetic activity without supraspinal or arterial baroreflex control of sympathetic activity to the heart. In contrast, individuals with injury between T4 and T5 have elevated levels of tonic sympathetic activity with supraspinal and arterial baroreflex control of sympathetic activity to the heart and upper body vasculature. However, sympathetic activity below T5 is reduced. Thus the tonic level and reflex control of sympathetic activity are dependent on the site of the injury. For these reasons, the responses for the paraplegic and quadriplegic rats are presented separately. Table 1 presents baseline arterial pressure and heart rate before generation of the colon distension curves in control conditions (pre-TENS), after 20 min of TENS (during TENS), and before and 20 min after sham TENS (time control) conditions for paraplegic and quadriplegic rats. Neither TENS nor time significantly altered resting hemodynamic parameters (Table 1).

A two-way analysis of variance revealed that TENS significantly attenuated the pressor and bradycardic responses to colon distension in paraplegic (Fig. 2, A and B) and quadriplegic (Fig. 3, A and B) rats. Furthermore, the attenuated hemodynamic responses to colon distension were due to TENS and not the intervening time because the time control responses were not different in paraplegic (Fig. 2, C and D) and quadriplegic (Fig. 3, C and D) rats. Of additional interest are the arrhythmias produced by colon distension before TENS (Fig. 1, Pre-TENS, inset). After TENS the arrhythmias were virtually eliminated (Fig. 1, During TENS, inset).

The results of this report document that TENS reduced the hemodynamic responses to graded colon distension in paraplegic and quadriplegic rats. These results are consistent with previous studies documenting that TENS reduces spasticity in individuals with chronic SCI. Furthermore, TENS application to somatic receptive fields decreased the activity of spontaneously firing second-order dorsal horn cells and decreased the activity of noxiously evoked dorsal horn neurons (10, 11). Interestingly, these results are also consistent with the large number of studies documenting that acupuncture, an invasive surrogate for TENS, suppresses visceral reflexes (9).

The hypertension associated with AD is markedly underrecognized. Thus AD must be listed in the differential diagnosis of hypertension. Furthermore, individuals teaching health care providers about hypertension must include AD in the discussion and provide a thorough understanding of the entity (4). Importantly, 50 million Americans have elevated blood pressure or are taking antihypertensive medications (17). A continuous, strong, graded, independent and etiologically significant relationship between elevated blood pressure and cardiovascular and cerebrovascular risk has been described (35). Thus early intervention for all individuals with hypertension is recommended based on studies documenting that antihypertensive therapy reduces mortality and ameliorates symptoms of hypertension in individuals with hypertension is recommended based on studies documenting that antihypertensive therapy reduces mortality and ameliorates symptoms of hypertension in individuals with hypertension is recommended based on studies documenting that antihypertensive therapy reduces mortality and ameliorates symptoms of hypertension in

| Table 1. Baseline arterial pressure and heart rate in paraplegic and quadriplegic rats |
|-------------------------------|-------------------------------|
| Paraplegic | Quadriplegic |
| | Pre-TENS | During TENS | Pre-TENS | During TENS |
| No. of animals | 6 | 5 |
| AP, mmHg | 106 ± 2 | 105 ± 10 | 94 ± 4 | 96 ± 8 |
| HR, beats/min | 427 ± 23 | 412 ± 27 | 380 ± 38 | 385 ± 42 |

<table>
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<tr>
<th>Paraplegic</th>
<th>Quadriplegic</th>
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<tr>
<td>Pre-time control</td>
<td>Time control</td>
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<td>No. of animals</td>
<td>4</td>
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<tr>
<td>AP, mmHg</td>
<td>97 ± 4</td>
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<tr>
<td>HR, beats/min</td>
<td>455 ± 14</td>
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Values are means ± SE for n rats. Paraplegic rats recovered for 64 ± 13 days and quadriplegic rats for 70 ± 8 days after spinal cord injury before experiments. Arterial pressure (AP) and heart rate (HR) were measured before and during generation of colon distension curves with transcutaneous electrical nerve stimulation (TENS) and before and after sham TENS (time control).
individuals with accelerated hypertension as well as individuals with so-called benign hypertension. These results suggest that reducing the hemodynamic response to AD may have long-term beneficial consequences in individuals with SCI.

Although the mechanisms mediating the TENS effect were not investigated, TENS may have reduced the hemodynamic responses to graded colon distension by the “gate control theory” (26). The gate control theory proposes that stimulation of large-diameter afferent fibers inhibits second-order neurons in the dorsal horn and prevents impulses carried by small-diameter fibers from being transmitted. Specifically, the paroxysmal hypertension and exaggerated vasoconstrictor responses associated with AD can be caused by stimulation of the skin, distension of the urinary bladder or colon, and/or muscle spasms (5, 24). Unmyelinated C fibers and thinly myelinated Aδ fibers from these areas transmit information to the spinal cord, resulting in stimulation of reflex sympathetic vasoconstrictor activity (23, 33). The electrical parameters of the TENS used for the present study activate larger Aβ fibers. Input from large-diameter Aβ fibers can block the transmission of impulses from small-diameter, thinly myelinated fibers in the dorsal horn (10, 11). Alternatively, TENS may be effective in reducing the hemodynamic responses to graded colon distension by stimulating the release of endogenous opioids (34). Specifically, the electrical current may stimulate the release of endogenous opioids that block the transmission of small-diameter afferent fibers in the dorsal horn (34). Opioid peptides enkephalin and dynorphin are contained in spinal dorsal horn neurons (12, 16). Similarly, opioid receptors are located on primary afferent fibers as well as dorsal horn neurons (20). Low-frequency TENS stimulates the release of spinal endogenous opioids (1, 14, 34), and activation of µ- and δ-opioid receptors inhibits the release of substance P and

Fig. 2. Mean arterial blood pressure (A) and heart rate (B) responses to graded colon distension before and during TENS in conscious, paraplegic rats (n = 6). Graded colon distension produced typical pressor and bradycardic responses. TENS application significantly attenuated the pressor and bradycardic responses to colon distension. The attenuated pressor and bradycardic responses were caused by TENS and not the intervening time, because the responses at Pre-Time Control and Time Control were not different (C and D; n = 4 paraplegic rats). *P < 0.05, Pre-TENS vs. During TENS.
calcitonin gene-related peptide from primary afferent fibers (15). Thus the effects of TENS may be due to blockade of primary afferent fibers via an opioid mechanism.

An area of potential importance contributing to the severity of AD as well as the mechanisms mediating the TENS-induced attenuation of the hemodynamic responses to colon distension may involve the morphological changes that occur in the spinal cord after injury (18, 19, 37). For example, Krenz and Weaver (19) documented sprouting of myelinated and unmyelinated primary afferent fibers caudal to a midthoracic spinal cord lesion. Subsequently, Krenz and colleagues (18) attenuated the sprouting and reduced the hemodynamic response to colon distension with an antibody to nerve growth factor. At this point, it is unclear how these anatomic changes contribute to AD or the mechanisms of TENS; however, this potentially important area merits further investigation.

Clinical Implications

Before World War II, 80% of individuals with SCI died within 3 years of the injury. However, with the advent of antibiotic drugs and advancements in acute care and rehabilitation, the life expectancy of individuals with SCI has increased to near that of able-bodied individuals. Importantly, cardiovascular disease is now a leading cause of death and morbidity for individuals with SCI (6). The long-term consequence of repeated episodes of severe hypertension has yet to be determined. However, it is well known that increased arterial pressure variability is a significant cardiovascular disease risk factor (3). Thus interventions designed to reduce episodic bouts of hypertension may prevent end-organ damage, cerebral and subarachnoid hemorrhage, seizures, and renal failure and may prevent death. TENS may be a noninvasive, nonpharmacological approach to reduce...
the severity of AD in individuals with SCI. This potentially clinically important area merits further investigation.

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REFERENCES


