Acute exercise reduces the response to colon distension in T5 spinal rats

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Collins, Heidi L., and Stephen E. DiCarlo. Acute exercise reduces the response to colon distension in T5 spinal rats. Am J Physiol Heart Circ Physiol 282: H1566–H1570, 2002.—Individuals with spinal cord injuries above thoracic level 6 (T6) experience life-threatening bouts of hypertension, termed autonomic dysreflexia (AD). AD is mediated by peripheral α-adrenergic receptor supersensitivity as well as a reorganization of spinal pathways controlling sympathetic preganglionic neurons. A single bout of dynamic exercise may be a safe therapeutic approach to reduce the severity of AD because mild-to-moderate dynamic exercise reduces postexercise α-adrenergic receptor responsiveness, lowers postexercise sympathetic nerve activity, and reduces the postexercise response to stress. Therefore, this study was designed to test the hypothesis that mild-to-moderate dynamic exercise attenuates the postexercise response to colon distension ( mechanism to elicit AD). To test this hypothesis, six male Wistar rats (406 ± 23 g), 5 wk post-T5 spinal cord transection, were instrumented with an arterial catheter. After recovery, the response to graded colon distension (10, 30, 50, and 80 mmHg, in random order) was determined before and after a single bout of mild-to-moderate dynamic exercise (9–12 m/min, 0% grade for 40 min). After exercise, the pressor response to graded colon distension was significantly attenuated (preexercise change: 2 ± 1, 9 ± 1, 14 ± 1, and 24 ± 2 vs. postexercise change: 2 ± 1, 2 ± 1, 9 ± 1, and 12 ± 3 mmHg). Thus acute exercise is a safe, therapeutic approach to reduce the severity of AD in paraplegic subjects.

autonomic dysreflexia; spinal cord injury

AUTONOMIC REGULATION of the cardiovascular system is abnormal and unstable after spinal cord injury. Hypotension occurs immediately after the injury because of loss of tonic supraspinal excitatory drive to spinal sympathetic neurons (3). Subsequently, resting arterial pressure returns toward normal values; however, episodic bouts of hypertension often develop as part of the condition termed autonomic dysreflexia (AD) (24, 27). AD occurs in as many as 85% of individuals with lesions above thoracic level 6 (T6) and is characterized by severe hypertension. The paroxysmal hypertension can be caused by stimulation of the skin, distension of the urinary bladder or colon, and muscle spasms (4, 23). If not treated promptly, the hypertension may produce cerebral and subarachnoid hemorrhage, seizures, and renal failure and may lead to death (25). The long-term consequence of repeated episodes of severe hypertension has yet to be determined.

Exercise may be a safe therapeutic approach for attenuating the severity of AD by reducing α-adrenergic receptor responsiveness. Several investigators have demonstrated that a single bout of mild-to-moderate dynamic exercise significantly attenuated the postexercise response to α-adrenergic receptor agonists (14–16, 29, 33). For example, a single bout of dynamic exercise significantly attenuated the postexercise response to α-adrenergic receptor activation in the intact conscious rabbit (15), rat (29, 33), and human (14). These data suggest that the ability to increase peripheral vascular resistance after exercise is significantly reduced. Exercise may also be a countermeasure for AD by reducing sympathetic nerve activity because a single bout of mild-to-moderate dynamic exercise often lowers postexercise sympathetic nerve activity for at least 1 h in individuals and animals (10, 13). Therefore, this study was designed to test the hypothesis that a single bout of dynamic exercise attenuates the response to colon distension ( mechanism to elicit AD) in T5 spinal rats.

To test this hypothesis, the response to graded colon distension (10, 30, 50, and 80 mmHg, in random order with at least 5 min between inflations) was determined before and 20 min after a single bout of mild-to-moderate dynamic exercise. All surgical and experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee and con-
formed to the American Physiological Society “Guiding Principles in the Care and Use of Animals.” Six male Wistar rats (406 ± 23 g; age, 93 ± 11 days) underwent T5 spinal cord transection (9). After spinal cord transection, all rats had a motor score of zero, indicating no weight bearing (34). After spinal cord transection, the paraplegic rats were trained to run on a motor-driven treadmill and were familiarized with the experimental procedures (handling, insertion of the balloon, placement in the study box). Four weeks later, the paraplegic rats were surgically instrumented for chronic measurements of arterial pressure and heart rate (HR). In four rats, a Micro-Renathane catheter was placed in the descending aorta via the left common carotid artery for the measurement of arterial pressure, mean arterial pressure (MAP), and HR. In two rats, radiotelemetry devices (model TA11PA-C40; Data Sciences) were implanted in the abdominal cavities with the attached catheter inserted through the femoral artery and advanced into the descending aorta. After recovery (7 days) (20), the response to graded colon distension (10, 30, 50, and 80 mmHg, in random order with at least 5 min between inflations) was determined before and 20 min after a single bout of mild-to-moderate dynamic exercise. Two recent studies investigating mechanisms mediating AD examined the spinal rats 30 days posttransection (19, 21). Thus, to assure that the animals were fully recovered, we studied the spinal rats 36 ± 3 days posttransection.

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 (19). Subsequently, the rat was placed unrestrained in a large Plexiglas box (30.5 × 30.5 × 30.5 cm, 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, preexercise baseline values were recorded over a 15-s interval. Subsequently, the procedure for colon distension was performed. To generate colon distension curves, a hand-held manometer was used to inflate the balloon to pressures of 10, 30, 50, and 80 mmHg (19). Distension pressures were applied in a randomized order, maintained for 60 s, and repeated at 5-min intervals. Control levels of arterial pressure and HR were averaged over 15 s immediately before inflation of the balloon. The responses to colon distension were averaged during the 60 s of balloon inflation. Colon distension produced pressor and bradycardic responses (Fig. 1). Several studies have documented that colon distension is a suitable, less invasive means of producing autonomic dysreflexia in spinal rats (19). In this regard, the rats did not resist insertion of the balloon (possibly because the rats could not feel the procedure), and the rats had minimal movement during the inflations.

After generation of the preexercise colon distension curves, T5 spinal rats had their lower bodies secured onto a small cart and “ran” on a motor-driven treadmill. The paraplegic rats propelled themselves with
their upper bodies at 9–12 m/min for 40 min without the use of aversive stimuli (Fig. 2). Approximately 20 min after exercise (the start of sympathoinhibition and α-adrenergic receptor hyporesponsiveness in intact rats) (18, 29, 30), colon distension curves were generated as described above. Because colon distensions curves were determined before and after a single bout of dynamic exercise, any differences observed could be due to time and not the intervening exercise. Therefore, to control for the effect of time during exercise, colon distension curves were generated in the same rats on an alternate day (>48 h) before and after 60 min (40-min sham exercise plus 20-min postsham exercise) of sitting on the treadmill.

Before generation of the preexercise colon distension curves, baseline MAP and HR averaged 96 ± 2 mmHg and 427 ± 11 beats/min, respectively. After exercise (20 min), baseline MAP (P = 0.039) and HR (P = 0.050) decreased to 88 ± 4 mmHg and 404 ± 10 beats/min, respectively. On the sham exercise day, baseline MAP and HR averaged 97 ± 2 mmHg and 452 ± 15 beats/min, respectively. Twenty minutes after sham exercise, baseline MAP (P = 0.070) and HR (P = 0.460) were not different from preshame exercise values (93 ± 3 mmHg and 442 ± 21 beats/min, respectively).

Exercise produced typical pressor and tachycardic responses (Fig. 2). For example, MAP at rest was 97 ± 3 mmHg. During exercise (30 min), MAP increased to 104 ± 3 mmHg. HR at rest was 441 ± 12 beats/min. During exercise (30 min), HR increased to 486 ± 8 beats/min.

After a single bout of dynamic exercise, the pressor response to colon distension was significantly attenuated (Fig. 3A; two-way ANOVA, P = 0.005). However, the HR response to colon distension was not different postexercise (Fig. 3B; two-way ANOVA, P = 0.087). The postexercise attenuated pressor response to colon distension was due to exercise and not the intervening time because the time control responses were not different (Fig. 3, C and D; P > 0.05).

These results document that a single bout of dynamic exercise attenuates the pressor response to colon distension in T5 spinal rats. Although the mechanisms mediating this effect were not investigated, postexercise α-adrenergic receptor hyporesponsiveness (13, 15, 16, 29, 33) and sympathoinhibition may be the primary factors (10, 14).

Exercise may be a countermeasure for AD by reducing α-adrenergic receptor responsiveness. We demonstrated that a single bout of dynamic exercise significantly attenuated the α-adrenergic receptor-mediated contraction of vascular smooth muscle in the rabbit aorta (16). This in vitro approach provided a direct evaluation of the contractile properties of aortic vascular smooth muscle independent of systemic- and baroreflex-mediated compensatory mechanisms.

Subsequently, we developed a model that allowed us to directly measure agonist-induced changes in responses to graded colon distension (Fig. 3). A single bout of mild-to-moderate dynamic exercise significantly attenuated the pressor response to graded colon distension. The postexercise attenuated pressor response to colon distension was due to exercise and not the intervening time. This is suggested because the changes in mean arterial pressure (C) and heart rate (D) to graded colon distension were not different before and after sham exercise. These data suggest that a single bout of dynamic exercise may be a safe therapeutic approach to reduce the severity of autonomic dysreflexia. *P < 0.05, preexercise vs. postexercise.
gional blood flow independent of baroreflex-mediated compensatory mechanisms in an intact conscious rabbit (15) and rat (29, 30). In these studies, a single bout of treadmill running also attenuated the postexercise vascular response to α-adrenergic receptor activation in the intact conscious rabbit (15) and rat (29, 30), confirming and extending the findings reported for the isolated vessel. The reduced postexercise vasoconstrictor response to α-adrenergic receptor activation was due, in part, to an enhanced buffering of vasoconstriction by nitric oxide (29, 30). These data and those of others (14, 33) suggest that the ability to increase peripheral vascular resistance after exercise is significantly reduced.

Exercise may also be a countermeasure for AD by reducing sympathetic nerve activity (10, 13). Although the current thinking suggests that AD is primarily mediated by peripheral α-adrenergic receptor supersensitivity, morphological changes in sympathetic preganglionic neurons below the level of the lesion may contribute to AD by reflex increases in sympathetic outflow (22). Studies in animals and humans have led to conflicting estimates of the amount of spinally generated sympathetic tone that remains after loss of supraspinal excitation (26, 28, 32, 35). These conflicting results may be due to the presence of anesthetics and the acute effects of surgery (35) or from the fact that visceral sympathetic activity has not been recorded in humans (32, 35). Direct recording of cutaneous and somatic sympathetic activity in individuals with quadriplegia demonstrated very low tonic activity at rest and only moderate increases in response to bladder distension (32, 35). Similarly, individuals with quadriplegia have significantly lower catecholamine levels than intact subjects at rest, and, although norepinephrine increases significantly during episodic hypertension, these levels do not exceed norepinephrine levels in intact subjects at rest. In contrast, Maiorov and colleagues (22) demonstrated low, but stable, basal firing of renal sympathetic nerve activity in conscious rats that increased sixfold during colon distension. The authors concluded that, although spinally generated sympathetic nerve activity makes no apparent contribution to basal arterial pressure, large increases in sympathetic nerve activity during colon distension are adequate to cause substantial increases in arterial pressure. Thus plastic changes in the spinal cord may contribute to AD (22). The relative contribution of spinally generated sympathetic nerve activity and α-adrenergic receptor hyperresponsiveness to AD is questionable. Exercise may be an effective countermeasure for AD because a single bout of dynamic exercise often lowers postexercise sympathetic nerve activity in individuals and animals (10, 13).

Before World War II, 80% of individuals with spinal cord injury died within 3 yr of the injury (17), primarily due to kidney and pulmonary infections (31). However, with the advent of antibiotic drugs and advancements in acute care and rehabilitation, the life expectancy of individuals with spinal cord lesions has increased to near that for able-bodied individuals. However, cardiovascular disease is now the leading cause of death and morbidity for individuals with spinal cord lesions (1, 6). The risk for significant cardiovascular dysfunction is aggravated by the sedentary lifestyle of the typical individual with spinal cord lesions. In fact, individuals with spinal cord injuries are placed at the lowest end of the human fitness spectrum (5, 36). Additionally, individuals with spinal cord injuries have blood lipid profiles characterized by elevated total cholesterol and low-density lipoprotein cholesterol and depressed high-density lipoprotein cholesterol, a lipid profile normally associated with, if not a direct result of, the sedentary lifestyle (2). Therefore, exercise with the arms is often recommended for these individuals, based on studies demonstrating improvements in aerobic capacity and lipoprotein profiles (7, 8, 11, 12). In fact, the Centers for Disease Control (CDC) has recommended further research to evaluate the efficacy of exercise to prevent the development of cardiovascular disease in individuals with spinal cord lesions (7, 8, 11, 12). The results from this study support the recommendation of the CDC in that a single bout of dynamic exercise attenuated thepressor response to colon distension in T6 spinal rats. Furthermore, these results suggest that acute exercise may be a safe, therapeutic approach to reduce the severity of AD in paraplegic subjects. It is interesting to speculate that one mechanism contributing to the improved cardiopulmonary status after exercise in individuals with spinal cord lesions may be a reduced incidence and/or severity of autonomic dysreflexia.

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REFERENCES

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POSTEXERCISE DYSREFLEXIA