T5 spinal cord transection increases susceptibility to reperfusion-induced ventricular tachycardia by enhancing sympathetic activity in conscious rats

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Lujan HL, DiCarlo SE. T5 spinal cord transection increases susceptibility to reperfusion-induced ventricular tachycardia by enhancing sympathetic activity in conscious rats. Am J Physiol Heart Circ Physiol 293: H3333–H3339, 2007. First published October 12, 2007; doi:10.1152/ajpheart.01019.2007.—We recently documented that paraplegia (T5 spinal cord transection) alters cardiac electrophysiology and increases the susceptibility to ventricular tachyarrhythmias induced by programmed electrical stimulation. However, coronary artery occlusion is the leading cause of death in industrially developed countries and will be the major cause of death in the world by the year 2020. The majority of these deaths result from tachyarrhythmias that culminate in ventricular fibrillation. β-Adrenergic receptor antagonists have been shown to reduce the incidence of sudden cardiac death. Therefore, we tested the hypothesis that chronic T5 spinal cord transection increases the susceptibility to clinically relevant ischemia-reperfusion-induced sustained ventricular tachycardia due to enhanced sympathetic activity. Intact and chronic (4 wk after transection) T5 spinal cord-transected (T5X) male rats were instrumented to record arterial pressure, body temperature, and ECG. In addition, a snare was placed around the left main coronary artery. The susceptibility to sustained ventricular tachycardia produced by 2.5 min of occlusion and reperfusion of the left main coronary artery was determined in conscious rats by pulling on the snare. Reperfusion culminated in sustained ventricular tachycardia in 100% of T5X rats (susceptible T5X, 10 of 10) and 0% of intact rats [susceptible intact, 0 of 10 (P < 0.05, T5X vs. intact)]. β-Adrenergic receptor blockade prevented reperfusion-induced sustained ventricular tachycardia in T5X rats [susceptible T5X 0 of 8, 0% (P < 0.05)]. Thus paraplegia increases the susceptibility to reperfusion-induced sustained ventricular tachycardia due to enhanced sympathetic activity.

cardiovascular risks; arrhythmia; spinal cord injury

AUTONOMIC CONTROL of the cardiovascular system is abnormal and unstable after midthoracic spinal cord injury. For example, individuals with paraplegia have elevated heart rate (20), increased blood pressure variability (48), episodic bouts of life-threatening hypertension as part of a condition termed autonomic dysreflexia (AD) (32), and elevated sympathetic activity above the level of the lesion (24). Paraplegia also alters cardiac electrophysiology and the abundance of Ca2+ regulatory proteins in a manner that increases the susceptibility to ventricular tachyarrhythmias induced by programmed electrical stimulation (PES) (49, 50). Furthermore, cardiovascular morbidity and mortality rates are high for individuals with spinal cord injuries, in part because of a relatively sedentary lifestyle and a higher prevalence of other cardiovascular risk factors including obesity and diabetes (17, 23, 36, 43).

Coronary artery occlusion is the leading cause of death in industrially developed countries. The majority of these deaths result from tachyarrhythmias that culminate in ventricular fibrillation. It is important to note that different mechanisms mediate ischemia-reperfusion-induced and PES-induced arrhythmias (39, 57). Specifically, PES-induced arrhythmias may be mediated by activation of reentrant pathways that respond to class I antiarrhythmic drugs (sodium channel blockers), while ischemia-reperfusion-induced arrhythmias may be mediated by triggered activity that arises secondary to calcium overload and respond to class IV antiarrhythmic drugs (calcium channel blockers) (8, 39, 57). Billman and Hamlin (8) suggested that these differences may explain the fact that electrophysiologically guided antiarrhythmic drug therapy is ineffective in the long-term management of individuals with life-threatening cardiac arrhythmias.

Increased sympathetic activity contributes to cardiac arrhythmias and increases the susceptibility to ventricular fibrillation (44, 53). For example, electrical stimulation of the stellate ganglia or cardiac nerves (46) increases cardiac arrhythmias (9), as does exposure to sympathomimetic amines (41). Conversely, blockade of cardiac sympathetic activity protects against deadly arrhythmias, supporting the wide use of beta-blockers for protection from sudden cardiac death (51, 61). In fact, only β-adrenergic receptor antagonists and amiodarone, a class III antiarrhythmic drug that also blocks β-adrenergic receptors, have been shown to reduce sudden cardiac death (3, 26).

Therefore, we tested the hypothesis that paraplegia increases the susceptibility to clinically relevant ischemia-reperfusion-induced sustained ventricular tachycardia due to enhanced sympathetic activity. We studied conscious, chronically instrumented rats to negate the confounding effects of anesthetic agents and surgical trauma. The ability of anesthesia to influence the susceptibility to ventricular arrhythmias is underrecognized, and there are few studies of reperfusion-induced arrhythmias in conscious animals (27). Furthermore, the use of conscious intact animals avoids the complications associated with isolated hearts, since isolation and denervation of the heart alters autonomic tone and the physiological responses to coronary occlusion.

MATERIALS AND METHODS

Surgical Procedures

Experimental preparations and protocols were reviewed and approved by the Animal Care and Use Committee of Wayne State University. The studies conformed to American Physiological Society guidelines and principles for research involving animals. All surgical procedures were performed with aseptic surgical techniques. Rats (20...
adult Sprague-Dawley males) were anesthetized with pentobarbital sodium (50 mg/kg ip), atropinized (0.05 mg/kg ip), intubated, and prepared for aseptic surgery. Supplemental doses of pentobarbital sodium (10–20 mg/kg ip) were administered if the rat regained the blink reflex or responded during the surgical procedures.

**Surgical Procedures to Implant Telemetry Device**

After anesthesia was induced, a telemetry device (Data Sciences International PhysioTel C50-PXT; pressure, temperature, and electrocardiogram) was implanted in all rats as previously described (12, 50), and a catheter was placed in the intraperitoneal (IP) space for the infusion of fluids. The transmitter body, which contains the thermistor, was placed in the IP space. The pressure sensor of the telemetry device, located within the tip of a catheter, was inserted into the descending aorta for continuous, non-tethered recording of pulsatile arterial blood pressure. The electrical leads from the telemetry device were placed in a modified lead II configuration by placing the negative electrode slightly to the right of the manubrium and the positive electrode at the anterior axillary line along the fifth intercostal space. A minimum of 1 wk was allowed for recovery and for the animals to regain their presurgical weight. During the recovery periods, the rats were handled, weighed, and acclimatized to the laboratory and investigators.

**Spinal Cord Transection**

After all rats had recovered their presurgical weight, animals (n = 10) were anesthetized as described above, intubated, and positioned prone over a thoracic roll that slightly flexed the trunk. The fourth thoracic vertebra was exposed via a midline dorsal incision, and the spinous process and laminae were removed. Two ligatures (6.0 silk) were tightened around the underlying spinal cord between the fifth and sixth thoracic segments, and the spinal cord was completely transected by cutting between the ligatures with scissors. In this way there was minimal bleeding. Sym pathetic innervation to the heart is derived from preganglionic fibers that exit the spinal cord at the first through fourth thoracic levels (10). Transection between the fifth and sixth thoracic levels of the spinal cord preserves supraspinal control of cardiac sympathetic activity. The completeness of the transection was confirmed by visual inspection of the lesion site. During the acute recovery period (~10 days), all rats were handled at least six times daily. During these periods, visual inspections and physical manipulations were performed to detect and prevent pressure sores. During the acute recovery period, rats required only daily inspection and bladders did not require manual compression. At posttranssection day 7, the rats received a motor activity score according to criteria described previously (58). The motor activity score was assessed by placing the animal on a paper-covered table and observing spontaneous motor activity for 1 min. Motor scores ranged from 0 to 5. A motor score of 5 indicates normal walking, whereas a score of 0 indicates no weight bearing or spontaneous voluntary movement in the hindlimbs. All rats had a motor score of 0, which indicates no weight bearing. On completion of the studies, the site of the spinal transection was confirmed by autopsy (29). Intact rats (n = 10) underwent similar surgical procedures; however, the spinal cord was not transected. All rats were allowed to recover at least 4 wk.

**Thoracotomy Procedures**

After the 4-wk recovery period, the animals were anesthetized as described above and the hearts were approached via a left thoracotomy through the fourth intercostal space. A coronary artery occluder, made from an atraumatic needle holding 5.0-gauge prolene suture (8720H, Ethicon), which passed through a PE-10 polyethylene guide tubing (Clay Adams), was passed around the left main coronary artery 2–3 mm from the origin by inserting the needle into the left ventricular wall under the overhanging left atrial appendage and bringing it out high on the pulmonary conus (13, 14). The guide tubing with the other end of the occluder was then exteriorized and secured at the back of the neck. The tubing was filled with a mixture of vaseline and mineral oil to prevent a pneumothorax. At least 1 wk was allowed for recovery. During the recovery periods, the rats were handled, weighed daily, and acclimatized to the laboratory and investigators. Three separate surgeries (telemetry, spinal cord transection, and thoracotomy) were performed because the animals recover significantly better than when two major surgeries are conducted during one session.

**Experimental Procedures**

*Susceptibility to reperfusion-induced sustained ventricular tachycardia.* Conscious, unrestrained rats were studied in their home cages (~13,350 cm³) for all experiments. Rats were allowed to adapt to the laboratory environment for ~1 h to ensure stable hemodynamic conditions. After the stabilization period, beat-by-beat, steady-state preocclusion hemodynamic variables were recorded over 10–15 s. Subsequently, the left main coronary artery was temporarily occluded for 2.5 min by use of a prolene suture as previously described (13, 14). Specifically, acute coronary artery occlusion was performed by pulling up on the suture that was around the left main coronary artery and holding the occlusion for 2.5 min. We selected a duration of 2.5 min for the occlusion because we recently documented that reperfusion after 3 min of coronary artery occlusion culminated in sustained ventricular tachycardia in 56% of male rats [Ref. 38; susceptible 9 of 16]. On the basis of these previous results, we hypothesized that reperfusion after 2.5 min of coronary artery occlusion would not culminate in sustained ventricular tachycardia in intact male rats but would in the more susceptible T₁2-transected rats. During the occlusion, rapid changes in ECG (peaked T wave followed by ST segment elevation), arterial pressure, and heart rate occurred within seconds of pulling on the suture (Fig. 1) (14). On release, there was a gradual reduction in the ST segment, and the animals had either normal sinus rhythm (Fig. 1, top) or an episode of sustained ventricular tachycardia (Fig. 1, bottom). Sustained ventricular tachycardia was defined as sustained ventricular rate (absence of P wave, wide bizarre QRS complex) >900 beats/min with a reduction in arterial pressure below 40 mmHg. When sustained ventricular tachycardia developed, normal sinus rhythm appeared with gentle compression of the thorax. Without compression of the thorax, the sustained ventricular tachycardia progressed to ventricular fibrillation. Ventricular fibrillation was defined as a ventricular rhythm without recognizable QRS complex, in which signal morphology changed from cycle to cycle, and for which it was impossible to estimate heart rate. In the event when the animal did not resume normal sinus rhythm, cardioversion was achieved (after the rat lost consciousness) with the use of one shock (10 J) of DC current.

On an alternate day (at least 1 wk later) the protocol was repeated in susceptible rats (rats that experienced sustained ventricular tachycardia in the control condition) with cardiac β₁-adrenergic receptor blockade [metoprolol (MT) 10 mg/kg (30)]. Cardiac β₁-adrenergic receptor blockade was achieved by infusion of the specific β₁-adrenergic receptor antagonist MT into the intraperitoneal catheter. Ten minutes after MT administration, coronary artery occlusion and reperfusion were performed as described above.

**Determination of ischemic zone.** After the experiments, the rats were euthanized with an overdose of pentobarbital sodium. To determine the size of the ischemic zone, the heart was excised with the occluder intact and perfused via the aorta with 30 ml of 0.9% saline to wash out the blood. Subsequently, the left main coronary artery was occluded by tying the suture. Evans blue dye (100 µl, 0.5%) was perfused via the aorta, allowing the dye to infuse into the nonischemic area of the heart and leaving the ischemic regions unstained. The heart was trimmed, leaving only the right and left ventricles, rinsed to remove the excess blue dye, and weighed. The heart was trimmed
again, leaving only the ischemic region. The weight of the ischemic zone was expressed as a percentage of total ventricular weight (13, 14).

To determine whether the occlusion produced a myocardial infarction, the heart was sliced transversally into 1.0-mm sections and incubated in a 1% 2,3,5-triphenyltetrazolium chloride solution (TCC, Sigma) at 37°C for 20 min. The heart sections were placed between two glass slides and immersed in 10% formalin overnight to enhance the contrast of the stain. TCC staining differentiates viable tissue by reacting with myocardial dehydrogenase enzymes to form a red brick stain. Necrotic tissue that has lost its dehydrogenase enzymes does not form a red stain and shows up as pale yellow. This stain has been shown to be a reliable indicator of myocardial infarction (19). As shown by the TCC staining, no animal sustained an infarct.

Data Analysis

All recordings were sampled at 2 kHz, and the data are expressed as means ± SE. A Student’s unpaired t-test was used to compare the ischemic zone between intact and T5 transected (T5X) rats. A χ²-analysis was used to compare the percentage of animals sustaining ventricular tachycardia in intact and T5X rats, as well as T5X rats with β-adrenergic receptor blockade. A two-way ANOVA with repeated measures on one factor (condition: preocclusion and prerelease) with post hoc Student-Newman-Keuls method was used to compare mean arterial blood pressure and heart rate immediately before the occlusion (preocclusion) and immediately before the release of the occluder (prerelease) in intact and T5X rats, as well as T5X rats with β-adrenergic receptor blockade. Preocclusion and prerelease data were the average of every beat during the last 10–15 s of the period. Finally, two separate one-way ANOVAs were used to compare ST segment elevation and rate-pressure product between groups. The rate-pressure product, an index of myocardial oxygen demand, was calculated as systolic blood pressure × heart rate/1,000 (28). The ECGs were analyzed off-line to measure the ST segment elevation (voltage difference between the baseline and J point) with the ECG analysis software for Chart (ADInstruments) (54).

RESULTS

Figure 2 presents the incidence (%) of reperfusion-induced sustained ventricular tachycardia in intact and T5X rats as well as T5X rats with β-adrenergic receptor blockade. Reperfusion after a brief period (2.5 min) of cardiac ischemia culminated in sustained ventricular tachycardia in 0% of intact rats (susceptible 0 of 10) but 100% of T5X rats [susceptible 10 of 10 (P < 0.05, intact vs. T5X)]. Only data from the susceptible rats (rats that experienced sustained ventricular tachycardia in the control condition) were included in the β-blockade analysis. β-Adrenergic receptor blockade prevented sustained ventricular tachycardia in all T5X rats [susceptible 0 of 8, 0% (P < 0.05)]. Only eight T5X rats were studied with β-adrenergic blockade because one of the T5X rats could not be revived and one T5X rat died 4 days after the control experiment from an unknown cause.
and T5X rats, as well as T5X rats with β-adrenergic receptor blockade. Mean arterial pressures were not different between intact and T5X rats. Within the T5X with β-blockade condition, prerelease MAP was lower compared with preocclusion. In contrast, heart rate was significantly higher in T5X rats, and β-adrenergic receptor blockade in T5X rats normalized heart rate. Finally, there were no significant differences in the ischemic zone between intact and T5X rats (intact 55 ± 1% vs. T5X 59 ± 1%).

DISCUSSION

In this study, we tested the hypothesis that T5 spinal cord injury (paraplegia) increases susceptibility to reperfusion-induced sustained ventricular tachycardia by enhancing cardiac sympathetic activity. Specifically, we recorded the susceptibility to sustained ventricular tachycardia induced by myocardial ischemia and reperfusion in conscious intact and T5X rats. The major findings of this study include the following: 1) T5X increased the susceptibility to reperfusion-induced sustained ventricular tachycardia (Figs. 1 and 2); 2) β-adrenergic receptor blockade (in the susceptible rats) prevented reperfusion-induced sustained ventricular tachycardia; and 3) the cardio-protective effect of β-adrenergic receptor blockade in the susceptible T5X rats may be due to an anti-ischemic mechanism since β-adrenergic receptor blockade normalized the elevation in rate-pressure product and ST segment elevation (Fig. 3). This conclusion is consistent with a recent study that documented that β-adrenergic receptor blockade prevented reperfusion-induced sustained ventricular tachycardia when the heart rate was paced at nonblockade levels in female but not male intact rats (38), supporting the suggestion that the cardio-protective effect of β-adrenergic receptor antagonism results secondarily from a reduced metabolic demand (less of an ischemic insult) than reductions in cardiac sympathetic drive directly. The data from the present study confirm and extend previous reports that paraplegia alters cardiac electrophysiology and increases the susceptibility to ventricular tachyarrhythmias induced by PES (49, 50) by documenting that paraplegia also increases the susceptibility to the clinically relevant reperfusion-induced sustained ventricular tachycardia in conscious animals. Furthermore, the increased susceptibility to the clinically relevant reperfusion-induced sustained ventricular tachycardia was mediated, in part, by enhanced sympathetic activity. These are important considerations because patients with high-level spinal cord injuries prioritize the recovery of autonomic functions such as cardiovascular and sexual function and bowel and bladder control, above the ability to walk (4). As stated profoundly by Christopher Reeve (47): “Spinal cord injury is a ferocious assault on the body that leaves havoc in its wake.

Figure 3 presents the ST segment elevation (Fig. 3, top) and rate-pressure product (Fig. 3, bottom) immediately before release of the occluder in intact and T5X as well as T5X with β-adrenergic receptor blockade groups. As expected, coronary artery occlusion increased ST segment elevation and rate-pressure product in all groups. The increase in ST segment elevation and rate-pressure product were greater in T5X vs. intact rats. β-Adrenergic receptor blockade reduced both ST segment elevation and rate-pressure product to levels seen in the intact rats.

Table 1 presents resting mean arterial pressure and heart rate immediately before the occlusion (preocclusion) and immediately before the release of the occluder (prerelease) in intact and T5X rats and T5X rats with β-adrenergic receptor blockade.

Table 1. Mean arterial pressure and heart rate immediately before occlusion and immediately before release of occluder in intact and T5X rats and T5X rats with β-adrenergic receptor blockade

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg</th>
<th>HR, Beats/min</th>
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<tr>
<td></td>
<td>Intact</td>
<td>T5X</td>
</tr>
<tr>
<td>Preocclusion</td>
<td>114 ± 2</td>
<td>118 ± 4</td>
</tr>
<tr>
<td>Prerelease</td>
<td>118 ± 4</td>
<td>121 ± 4</td>
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Values are means ± SE. MAP, mean arterial pressure; HR, heart rate; T5X, T5 transected; β-block, β-adrenergic receptor blockade; preocclusion, immediately before occlusion; prerelease, immediately before release. *P < 0.05 intact vs. T5X; †P < 0.05 T5X vs. T5X β-block; ‡P < 0.05 preocclusion vs. prerelease.
Paralysis is certainly part of its legacy, but there are other equally devastating consequences including autonomic dysfunction: comprised cardiovascular, bowel, bladder, and sexual function. Treatments and cures for these losses would greatly improve the quality of life for all of us living with spinal cord injury” (September 30, 2004).

The results from this study are clinically and scientifically relevant because acute coronary artery occlusion is the leading cause of death for both men and women in industrially developed countries and will be the major cause of death in the world by the year 2020 (42). The majority of these deaths result from tachyarrhythmias that culminate in ventricular fibrillation (6, 21, 42, 56). The arrhythmias are triggered by the ischemic insult directly (ischemia-induced arrhythmias) or during the reperfusion phase (reperfusion-induced arrhythmias). The mechanisms mediating the arrhythmias during ischemia and reperfusion are related but distinct (7, 39, 45, 56). Ischemia is a more common trigger of sudden death than reperfusion; however, life-threatening reperfusion arrhythmias are observed during relief of coronary spasm, during angioplasty or thrombolysis, and after cardiac surgery with ischemic arrest (16). Reperfusion may also precipitate deadly arrhythmias that account for some cases of sudden cardiac death (45) in individuals without known cardiac disease (39, 56). Despite the clinical relevance of reperfusion-induced arrhythmias, this is the first report of reperfusion-induced arrhythmias in spinal cord-injured subjects. This is especially relevant because morbidity and mortality from cardiovascular disease in individuals with chronic spinal cord injury exceeds that caused by renal and pulmonary complications, the primary cause of mortality in previous decades (43). Furthermore, Lee and colleagues (33) evaluated the prevalence of coronary artery disease in individuals with paraplegia and reported that a staggering 54.5% of individuals with paraplegia have coronary artery disease. These data contrast sharply with the estimated prevalence of coronary artery disease in the general population (men 6.9%, women 6.0%) (55). Understanding the mechanisms responsible for the increased susceptibility to cardiovascular disease has the potential to impact the lives of millions of individuals and families with spinal cord injury (4, 47).

It is well documented that changes in the ST segment are a valid marker of the severity of myocardial ischemia (34). Specifically, the ST segment shift correlates with both metabolic and contractile parameters of myocardial ischemia (35). Because of these findings, ST segment changes are widely used as an index of myocardial injury resulting from ischemia (40). Other indirect indexes of myocardial oxygen consumption, e.g., tension-time index, double product, and triple product, are also used in clinical and experimental studies (5). These indirect indexes are highly correlated with direct measurements of myocardial oxygen consumption. We used ST segment shifts and double product (rate-pressure product; Fig. 3) as an index of the severity of myocardial ischemia. ST segment elevation and rate-pressure product were significantly greater in T5X vs. intact rats, and β-adrenergic receptor blockade normalized these metabolic parameters in T5X rats. In addition, heart rate was significantly higher in T5X rats compared with intact rats and was normalized after β-adrenergic receptor blockade. Together, these data suggest that a higher level of sympathetic activity in T5X rats increased the susceptibility to sustained ventricular tachycardia.

The sympathetic nervous system affects cardiac electrophysiology by activating β-adrenergic receptors (for review see Ref. 1). β-Adrenergic receptor stimulation increases intracellular cAMP, heart rate, atrioventricular nodal conduction, and contractile force and shortens atrial and ventricular refractoriness. In addition, β-adrenergic receptor stimulation enhances the plateau phase of the action potential by increasing current through L-type Ca2+ channels (ICa). Repolarization is also accelerated because of an increase in both the delayed cardiac rectifier current (IK) and the chloride current (ICl). Thus the effects of β-adrenergic receptor stimulation may shorten or prolong action potential duration depending on whether effects on ICa or IK/ICl predominate. β-Adrenergic receptor blockade and enhanced parasympathetic tone are protective against ventricular arrhythmias and sudden death (18, 52, 60, 62). However, overactivity in the cardiac parasympathetic nerves can contribute to a variety of bradyarrhythmias, whereas overactivity of the cardiac sympathetic nerves can contribute to a variety of tachyarrhythmias (25); thus spinal cord injury, depending on the specific site of the lesion, may effect sympathetic and parasympathetic activity in a manner that promotes arrhythmias. Specifically cardiac parasympathetic fibers never pass through the spinal cord; thus spinal cord injury does not interrupt cardiac parasympathetic activity. However, sympathetic preganglionic neurons located in the first to fourth thoracic spinal cord segments contribute sympathetic innervation to the heart (10), and spinal cord injury above the first thoracic segment disrupts central control of preganglionic cardiac sympathetic activity. In this situation, cervical and upper thoracic spinal cord injury disrupts the interaction of cardiac sympathetic and parasympathetic innervation. Disruption of this balance has profound effects on cardiac rate, performance, and rhythm. Similarly, when the spinal cord is injured at or below T4 (as performed in this study), cardiovascular control is markedly unbalanced because the heart and blood vessels innervated by upper thoracic segments remain under brain stem control whereas the vasculature of the lower body is affected by unregulated spinal reflexes. These unfettered reflexes lead to episodes of hypertension in a syndrome termed autonomic dysreflexia (AD), a condition that has received considerable attention in recent years (11, 12). Thus spinal cord injury at T5 (as performed in this study), by maintaining central control of cardiac sympathetic preganglionic neurons, promotes higher cardiac sympathetic activity and lower cardiac parasympathetic activity and contributes to tachyarrhythmias.

It is important to note that the enhanced cardiac sympathetic activity is not part of the well-characterized syndrome called AD. AD occurs in as many as 85% of individuals with spinal cord injuries above thoracic level 6 (T6) and is characterized by severe hypertension, sweating, dizziness, nausea, and severe headaches. AD can be caused by stimulation of the skin, distension of the urinary bladder or colon, and muscle spasms. The afferent stimulation below the level of the injury results in massive sympathetic activity that causes vasoconstriction of most vascular beds below the injury and baroreflex-mediated bradycardia due to parasympathetic activation and sympathetic withdrawal above the lesion with resultant vasodilatation that mediates headaches and skin flushing. Since our lesion was at T5 and spinal segments T1–T4 provide sympathetic control to the heart, the enhanced cardiac sympathetic activity cannot be mediated by AD.
Limitations

It is important to note that the β-adrenergic receptor antagonist reduced the metabolic consequences of the coronary occlusion and suppressed the formation of arrhythmias. Thus the cardioprotective effect of β-adrenergic receptor antagonism appears to result secondarily from a reduced metabolic demand (less of an ischemic insult) than reductions in cardiac sympathetic drive directly. Because we did not measure sympathetic activity, we should use caution with regard to the role of enhanced sympathetic activity in the induction of arrhythmias during ischemia. To distinguish the metabolic effects of sympathetic activation from direct actions (i.e., enhanced calcium entry) of β-adrenergic receptor activation on the ventricular myocardium, we recently used cardiac pacing to increase heart rate to nonblockade levels during ischemia-reperfusion in the presence of β-adrenergic receptor antagonism in intact male rats (38). In this study, β-adrenergic receptor blockade failed to prevent reperfusion-induced sustained ventricular tachycardia when heart rate was paced at nonblockade rates (38). These data support the suggestion that the protective effect of β-adrenergic receptor blockade was due to a reduction in heart rate (anti-ischemic effect).

We used a relatively high dose of MT that may block both β1- and β2-adrenergic receptors, and we did not confirm the selectively of this agent. Thus we are unable to determine the receptor subtype responsible for the cardioprotection. This is an important consideration because nonselective β-adrenergic blockade may be more effective than selective β1-adrenergic receptor blockade in reducing mortality in individuals with congestive heart failure (31). Previous studies demonstrated enhanced β2-adrenergic receptor responsiveness in animals susceptible to ventricular fibrillation (1). Activation of β2-adrenergic receptors promotes increased calcium currents without altering calcium reuptake by the sarcoplasmic reticulum (2). The resulting elevations in intracellular calcium could provoke oscillations in membrane potential and trigger ventricular arrhythmias, particularly when calcium regulation is further altered by myocardial ischemia and sympathetic activation (22). In this context, future studies must be designed to determine the relative contribution of specific β-adrenergic receptor subtypes in the cardioprotection of individuals with mid thoracic spinal cord injury.

Finally, we should have included a time control for the second occlusion to confirm the reproducibility of the results, because it is possible that the absence of arrhythmias with β-adrenergic receptor blockade reflects some nonspecific adaptation to the control occlusion. However, we do not think that the control occlusion affected the response to the subsequent occlusion ≥1 wk later, because recent studies using identical ischemia-reperfusion protocols with randomized interventions (i.e., β-adrenergic receptor blockade or electroacupuncture) failed to document an effect of an occlusion on subsequent occlusions (37, 38).

Conclusions

Cardiovascular disease is a growing concern for individuals with spinal cord injury. In fact, the prevalence of coronary artery disease in individuals with paraplegia is a reported staggering 54.5% (33), which contrasts sharply with the estimated prevalence of coronary artery disease in the general population (men 6.9%, women 6.0%) (55). Furthermore, morbidity and mortality from cardiovascular disease exceeds that caused by renal and pulmonary complications, the primary cause of mortality in previous decades (43). Cardiovascular morbidity and mortality are high for individuals with spinal cord injuries, presumably because of a relatively sedentary lifestyle and a higher prevalence of other cardiovascular risk factors, including obesity and diabetes (17, 23, 36). In fact, individuals with spinal cord injury are at the lowest end of the human fitness spectrum (15, 59). Furthermore, autonomic control of the cardiovascular system is abnormal and unstable after midthoracic spinal cord injury, which increases the susceptibility to PES-induced (49, 50) and reperfusion-induced ventricular arrhythmias.

GRANTS

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