Preserved α-Adrenergic Tone in the Leg Vascular Bed of Spinal Cord–Injured Individuals

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Background—Supraspinal sympathetic control of leg vascular tone is lost in spinal cord–injured individuals, but this does not result in a reduced leg vascular tone: Leg vascular resistance is even increased. The aim of this study was to assess the α-adrenergic contribution to the increased vascular tone in the lower extremity in patients without central sympathetic control of leg circulation.

Methods and Results—Upper-leg vascular resistance responses to local infusion of incremental doses of phentolamine (a competitive antagonist of the α-adrenoceptor) into the femoral artery were determined in 10 spinal cord–injured individuals (SCI) and 8 healthy age-matched control subjects during local β-adrenergic receptor blockade with propranolol. Basal leg vascular resistance was higher in SCI than in control subjects (41±6 arbitrary units [AU] versus 24±4 AU; P=0.034). The same accounts for minimal leg vascular resistance, assessed during reactive hyperemia, which was higher in SCI compared with control subjects (6.9±1.0 AU versus 2.5±0.2 AU; P<0.01). The maximal phentolamine-induced reduction in leg vascular resistance normalized to each individual’s minimal resistance did not differ between the groups (68±17% and 51±4% for SCI and control subjects, respectively; P>0.1). A decline in mean arterial pressure was observed in both groups with increasing dosage of phentolamine. In response, baroreceptor-mediated vasodisconstriction was observed in the noninfused leg of the control subjects, whereas in SCI individuals this reaction was absent.

Conclusions—These results indicate that the α-adrenoceptor–mediated vascular tone in the leg is preserved in spinal cord–injured individuals without sympathetic supraspinal control. (Circulation. 2003;108:2361-2367.)

Key Words: blood flow ■ vasodilation ■ nervous system, sympathetic ■ receptors, adrenergic, alpha

In healthy humans, the sympathetic nervous system contributes importantly to basal vascular tone as assessed by pharmacological blockade of the α-adrenoceptor or acute denervation in sympathectomized patients. In spinal cord–injured individuals, the supraspinal sympathetic control of leg vascular tone is lost. One would expect a low leg vascular tone and orthostatic intolerance in these individuals. However, the opposite holds true: Leg vascular resistance is increased in spinal cord–injured individuals and orthostatic tolerance seems not to be affected.

In both animal and human research, sympathetic responses have been dramatic increase in blood flow to the denervated part of the body. However, this effect is short-lasting, and presympathectomy levels of blood flow are reached within days in animals to a few months in humans. The underlying mechanism for this biphasic response has not yet been clarified. Apart from partial denervation or reinnervation of sympathetic nerves, circulating catecholamines, other systems regulating vascular resistance such as endothelial factors, the renin-angiotensin system, or denervation-induced upregulation of α-adrenoceptors may substitute for the reduced sympathetic input to vascular tone. In spinal cord–injured individuals, the situation is even more complex because spinal sympathetic reflexes may still be intact. Furthermore, loss of supraspinal control of somatic efferents results in extreme deconditioning of the leg muscles, which is associated with reduced oxygen demand and subsequently with profound functional and structural vascular adaptations. Indeed, leg vascular resistance in spinal cord–injured individuals is even increased in comparison with control subjects, despite the loss of supraspinal sympathetic control.

The purpose of this study was to assess the contribution of α-adrenoceptor–mediated vasoconstriction to the vascular tone in the lower extremity of individuals with central loss of sympathetic control of the leg circulation caused by a spinal cord injury. We hypothesize that the sympathetic contribution to basal vascular tone in spinal cord–injured individuals is reduced in comparison to control subjects.
emptied their bladder in the hour before the test to minimize the

All subjects refrained from caffeine, alcohol, and nicotine for at least 2 years; gender 9; age, 39

The study was approved by the hospital ethics committee. All subjects gave their written informed consent before the study.

**Methods**

Eight healthy control subjects (C), 7 men and 1 woman, and 10 spinal cord–injured individuals (SCI), 8 men and 2 women, participated in the study. Baseline characteristics of the SCI and control subjects are shown in Table 1 and Table 2. The SCI continued their medication throughout the study. The control group was similar with respect to age, gender, and smoking habits. The spinal cord–injured individuals had complete motor and sensor spinal cord lesions of traumatic origin varying from Thoracic 4 to Thoracic 12 (American Spinal Injury Association, ASIA A). The level of the spinal lesion was assessed by clinical examination. After the completion of the study, 8 SCI (6 men and 2 women) were willing to return to the laboratory for assessment of the completeness of the sympathetic profile, 7 men and 2 women). The study was approved by the hospital ethics committee. All subjects gave their written informed consent before the study.

**Experimental Procedures and Protocol**

All subjects refrained from caffeine, alcohol, and nicotine for at least 12 hours and did not eat for 3 hours before testing. All subjects had emptied their bladder in the hour before the test to minimize the influence of any reflex sympathetic activation on peripheral vascular tone.

All tests were performed in the afternoon, with the subjects in supine position in a quiet, temperature-controlled room (22°C to 24°C). Each subject was studied on two different occasions, separated by at least 3 days. On the first day, maximal upper leg blood flow was determined after a 12-minute arterial occlusion period (noninvasive study day). On the second day, phentolamine, a nonselective competitive antagonist of β-adrenergic receptors, was infused into the femoral artery (invasive study day). On both study days, bilateral upper leg blood flow was measured by ECG-triggered venous occlusion plethysmography, using mercury-in-silastic strain gauges (Hokanson EC4, D.E. Hokanson). Strain gauges were placed 10 cm above the patella. The thigh collecting cuffs (12 cm width) were simultaneously inflated with the use of a rapid cuff inflator (Hokanson E-20) to a pressure of 50 mm Hg during 8 heart cycles, with a 10-heart cycles interval between the venous occlusions. The lower legs were supported 10 cm above heart level to facilitate venous outflow between the venous occlusions.23 At least 1 minute before upper leg blood flow measurements were performed, the calf circulation was occluded by inflating cuffs below the knee to suprasystolic values (>200 mm Hg). Calf circulation was excluded from the experimental preparation by a suprasystolic cuff to avoid the use of high dosages with subsequent systemic effects of these drugs (see below). In 9 control subjects, a pilot experiment was performed by using an identical experimental setup, except for the

**TABLE 1. Specific Characteristics of Spinal Cord–Injured Individuals**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, y</th>
<th>Sex</th>
<th>Level of Spinal Lesion</th>
<th>Time Since Injury, y</th>
<th>Sweating Under Lesion</th>
<th>Smoking</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>M</td>
<td>T12</td>
<td>16</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>M</td>
<td>T4</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>M</td>
<td>T4</td>
<td>5</td>
<td>–</td>
<td>Tolterodine, 2 mg BID Baclofen, 10 mg TID</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>F</td>
<td>T10</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>M</td>
<td>T6</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>M</td>
<td>T6</td>
<td>17</td>
<td>–</td>
<td>+ Nitrofurantoine</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>M</td>
<td>T4</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>M</td>
<td>T3</td>
<td>13</td>
<td>+</td>
<td>–</td>
<td>Levothyroxine</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>M</td>
<td>T5</td>
<td>23</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>41</td>
<td>F</td>
<td>T12</td>
<td>9</td>
<td>+</td>
<td>+ Baclofen, 40 mg TID</td>
<td></td>
</tr>
</tbody>
</table>

+ indicates presence; –, absence.

**TABLE 2. Baseline Characteristics (Mean±SEM)**

<table>
<thead>
<tr>
<th></th>
<th>SCI (n=9)</th>
<th>C (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>39±2</td>
<td>36±3</td>
<td>0.36</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>71±4</td>
<td>81±4</td>
<td>0.13</td>
</tr>
<tr>
<td>Thigh volume, L</td>
<td>4.9±0.2</td>
<td>7.6±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125±5</td>
<td>132±5</td>
<td>0.18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73±4</td>
<td>68±2</td>
<td>0.50</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>92±3</td>
<td>90±2</td>
<td>0.63</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67±4</td>
<td>60±4</td>
<td>0.44</td>
</tr>
<tr>
<td>Upper leg blood flow, mL/min per 100 mL</td>
<td>2.7±0.5</td>
<td>4.3±0.6</td>
<td>0.027</td>
</tr>
<tr>
<td>Upper leg vascular resistance, AU</td>
<td>41±6</td>
<td>24±4</td>
<td>0.034</td>
</tr>
<tr>
<td>Maximal upper leg flow, mL/min per 100 mL</td>
<td>14±2</td>
<td>32±3</td>
<td>0.001</td>
</tr>
<tr>
<td>Minimal upper leg vascular resistance, AU</td>
<td>6.9±1.0</td>
<td>2.5±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Epinephrine, nmol/L</td>
<td>0.10±0.01</td>
<td>0.29±0.09</td>
<td>0.17</td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>1.51±0.26</td>
<td>1.34±0.20</td>
<td>0.91</td>
</tr>
</tbody>
</table>
Heart rate was recorded from the ECG. The schedule of the protocol included cannulation of the left femoral artery, so we had to use the right femoral artery. In control subjects, the left femoral artery was cannulated without anesthesia because of the lack of sensibility. In SCI individuals, the femoral artery was cannulated under local anesthesia because of the loss of sensibility under the level of the spinal cord injury. In 2 SCI subjects, we failed to cannulate the left femoral artery, so we had to use the right femoral artery. In control subjects, the left femoral artery was cannulated after local anesthesia (0.4 mL lidocaine 20 mg/mL). Heart rate was recorded from the ECG. The schedule of the protocol is shown in Figure 1. After complete instrumentation and at least 30 minutes after cannulation of the femoral artery, an arterial blood sample was taken to determine norepinephrine and epinephrine concentration. First, baseline leg blood flow was measured during a 5-minute NaCl 0.9% infusion period, followed by infusion of propranolol during 5 minutes in a dose of 2 μg/min per 100 mL of upper leg volume. Upper leg volume was determined by anthropometry as described and validated by Jones et al. Subsequently, phentolamine was infused at incremental doses of 0.375 to 0.75 to 1.5 to 3.0 to 6.0 to 12.0 to 24.0 μg/min per 100 mL of upper leg volume. Previous studies showed complete α-adrenergic blockade in the leg of healthy volunteers at a dose of 12 μg/min per 100 mL. Each dose was given for 5 minutes. During the entire phentolamine infusion, propranolol was coinfused at a dose of 2 μg/min per 100 mL to prevent unopposed β-adrenergic vasodilatation during α-adrenergic blockade. Every 10 minutes, infusions were interrupted and the circulation to the calf was restored by deflating the arterial occlusion cuffs for 5 minutes to prevent discomfort. At the end of the highest dose of phentolamine and propranolol, isoproterenol (15 ng/min per 100 mL) was infused in the controls only to verify β-adrenoceptor blockade. The vasodilator action of this dose of isoproterenol was confirmed in one experiment with a healthy volunteer. In addition, in this pilot study, the propranolol dose used appeared to abolish the vasodilator action of isoproterenol, confirming adequate β-adrenoceptor blockade. During the whole protocol, infusion rate was kept constant at a rate of 20 μL/100 mL per minute.

**Invasive Study Day**

Through the use of a modified Seldinger technique, an intra-arterial cannula (Angiocath 16 gauge, Becton Dickinson) was introduced into the femoral artery of the left leg at the level of the inguinal ligament for blood pressure measurement (Hewlett Packard monitor type 78353B, Hewlett Packard GmbH) and for intra-arterial administration of drugs by an automatic syringe infusion pump (Type STC-521, Terumo Corp). In SCI individuals, the femoral artery was cannulated without anesthesia because of the lack of sensibility under the level of the spinal cord injury. In 2 SCI subjects, we failed to cannulate the left femoral artery, so we had to use the right femoral artery. In control subjects, the left femoral artery was cannulated after local anesthesia (0.4 mL lidocaine 20 mg/mL). Heart rate was recorded from the ECG. The schedule of the protocol is shown in Figure 1. After complete instrumentation and at least 30 minutes after cannulation of the femoral artery, an arterial blood sample was immersed into water of 4°C for 3 minutes. Calf blood flow was measured by means of venous occlusion plethysmography by placing a strain gauge around the thickest part of the calf at baseline and during the 3-minute cold pressor test. Arterial pressure was continuously monitored with Finapress. Calf vascular resistance was calculated by dividing mean arterial pressure by calf blood flow. The mean of the 3 highest values of calf vascular resistance during the cold pressor test was used to calculate the percent change in vascular resistance compared with the mean vascular resistance of the baseline.

**Noninvasive Study Days**

**Reactive Hyperemia**

Maximal upper leg blood flow with the use of venous occlusion plethysmography was determined after a 12-minute arterial occlusion period. A cuff around the left thigh was inflated to >200 mm Hg. Flow measurements were immediately commenced after cuff pressure release. In accordance with previous studies, the highest value of upper leg blood flow was obtained within 30 seconds after cuff release (by the first or second measurement). Simultaneously, arterial blood pressure measurements were performed continuously, at the left third finger using Finapress, to calculate minimal vascular resistance.

**Cold Pressor Test**

To determine the completeness of the sympathetic lesion, the hand was immersed into water of 4°C for 3 minutes. Calf blood flow was measured by means of venous occlusion plethysmography by placing a strain gauge around the thickest part of the calf at baseline and during the 3-minute cold pressor test. Arterial pressure was continuously monitored with Finapress. Calf vascular resistance was calculated by dividing mean arterial pressure by calf blood flow. The mean of the 3 highest values of calf vascular resistance during the cold pressor test was used to calculate the percent change in vascular resistance compared with the mean vascular resistance of the baseline.

**Drugs and Solutions**

Phentolamine (Regitine, 10 mg/mL, Novartis Pharma BV), propranolol (Inderal, 1 mg/mL, Zeneca Farma BV), and isoproterenol (isoprenaline sulfate, 1 mg/mL, Fresenius Kabi Nederland BV) were dissolved in NaCl 0.9% at the beginning of each experiment.

**Data Analysis**

Upper leg blood flow (in mL/min per 100 mL) was calculated as the slope of the volume change curve. Because of a cuff inflation artifact during the first second, the slope from 2 to 6 seconds after cuff inflation was used. Upper leg blood flow values of the last 2 minutes of each infusion were averaged to calculate upper leg blood flow.

Blood pressure significantly changed during the course of the intra-arterial phentolamine infusions. Therefore, upper leg vascular resistance was calculated as mean arterial pressure in mm Hg divided by upper leg blood flow in mL/min per 100 mL and expressed in arbitrary units (AU; mm Hg/min per 100 mL per mL). For these calculations, we assumed that central venous pressure was low and remained constant throughout the protocol.

Since structural differences in the vascular bed of SCI individuals could nonspecifically affect the vasodilator response to phentolamine, the individual responses in vascular resistance to infusion of phentolamine were normalized to each subject’s minimal vascular resistance as assessed during reactive hyperemia. The maximal response (Emax) for each individual was determined by using the maximal observed response to infusion of phentolamine.

**Statistics**

Results are expressed as mean ± SEM. Differences in baseline characteristics and in the maximal effect of phentolamine (Emax) between the groups were tested by means of the Mann-Whitney U test. The effect of propranolol and differences between the last two doses of phentolamine were tested with the Wilcoxon test. Between-group differences in response to infusion of phentolamine were analyzed by means of 2-factor, repeated-measures ANOVA with the phentolamine dose as within-subject factor and the presence of a spinal cord lesion as between-subject factor (Statistical Package for Social Sciences (SPSS), version 10.0). The null hypothesis was formulated, as there were no differences between the groups in response to intra-arterial infusion of phentolamine of upper leg vascular resistance.

A 2-sided probability value of <0.05 was considered to be statistically significant.
Results

Confirmation of the Lack of Supraspinal Sympathetic Control

Individual responses in calf vascular resistance of 8 SCI and 9 control subjects are shown in Figure 2. The increase in calf vascular resistance was significantly less in SCI than in control subjects.

Figure 2. Individual responses of relative calf vascular resistance to cold pressor test of the hand. Subjects 8 and 9 did not participate in this part of the experiment. Dotted line represents subject 4, who is excluded from the analysis.

TABLE 3. Effect of Increasing Dose of Phentolamine on Blood Pressure, Heart Rate, and Vascular Tone of the Infused Leg in SCI and Control Subjects

<table>
<thead>
<tr>
<th>Drug</th>
<th>SCI Subjects (n=9)</th>
<th>Control Subjects (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ULBF</td>
<td>MAP</td>
</tr>
<tr>
<td>NaCl 0.9%</td>
<td>2.7±0.5</td>
<td>92±3</td>
</tr>
<tr>
<td>Prop</td>
<td>2.8±0.5</td>
<td>90±3</td>
</tr>
<tr>
<td>Phe 0.375</td>
<td>3.5±0.6</td>
<td>90±3</td>
</tr>
<tr>
<td>Phe 0.75</td>
<td>3.7±0.6</td>
<td>89±3</td>
</tr>
<tr>
<td>Phe 1.5</td>
<td>4.0±0.6</td>
<td>90±3</td>
</tr>
<tr>
<td>Phe 3.0</td>
<td>4.2±0.6</td>
<td>87±3</td>
</tr>
<tr>
<td>Phe 6.0</td>
<td>4.4±0.6</td>
<td>87±3</td>
</tr>
<tr>
<td>Phe 12.0</td>
<td>4.3±0.6</td>
<td>85±3</td>
</tr>
<tr>
<td>Phe 24.0</td>
<td>4.2±0.6</td>
<td>85±3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

ULBF indicates upper leg blood flow (mL/min per 100 mL); MAP, mean arterial pressure (mm Hg); ULVR, upper leg vascular resistance (AU); HR, heart rate (beats/min); Prop, propranolol in a dose of 2 μg/min per 100 mL; Phe, phentolamine (dose in μg/min per 100 mL). Probability values indicate level of significance for the effect of phentolamine dose on baseline values during propranolol infusion (repeated-measures ANOVA).

Baseline Characteristics

The two groups did not differ with respect to age, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and norepinephrine and epinephrine serum concentration. Body weight and thigh volume were significantly lower in SCI than in control subjects.

Baseline upper leg blood flow was significantly lower and leg vascular resistance was significantly higher in SCI as compared with control subjects.

Maximal leg blood flow was lower and minimal leg vascular resistance was higher in SCI than in control subjects (Table 2).

Response to Drug Infusions in the Infused Leg

Propranolol infusion alone did not affect any of the hemodynamic parameters (Table 3). Isoproterenol, coinfused with phentolamine and propranolol at the end of the protocol in the control group, did not further change upper leg vascular resistance (15.3±4.0 to 15.1±4.7 AU).

Upper leg blood flow increased significantly and upper leg vascular resistance decreased significantly in both groups in response to phentolamine infusion. No difference in upper leg vascular resistance was observed between the doses 12 and 24 μg/min per 100 mL of phentolamine in both groups, indicating that in both groups a maximal effect of phenotamine was observed (P>0.1 for both groups; see Table 3).

The increase in upper leg blood flow in response to infusion of phentolamine was significantly less in SCI compared with control subjects (P<0.001 for the effect of dose in both groups, P<0.05 for the between group effect; see Table 3). However, the relative decrease in vascular resistance did not significantly differ in response to phentolamine infusion between the SCI and control subjects in the infused leg (P>0.1 for the effect of group and the dose by group interaction; see Figure 3A). The maximal responses in vascular resistance, expressed as percent change of baseline normalized to each individual’s minimal resistance (E\text{max}), did not significantly differ between the two groups (68±17% and 73±18% for SCI and control subjects, respectively).
Response to Drug Infusions in the Noninfused Leg

In the noninfused leg, the control subjects showed a maximal increase in upper leg vascular resistance of 23.8±5.1% at a dose of 1.5 μg/min per 100 mL, which decreased slightly to 10.2±5.4% at a dose of 24 μg/100 mL per minute. In contrast, the SCI group upper leg vascular resistance decreased with 22.8±6.2% throughout the incremental doses of phentolamine. (P<0.01 for the effect of group; see Figure 3B).

Discussion

The major observation of the present study is that α-adrenoceptor blockade in the legs of spinal cord–injured individuals decreases the vascular resistance by 68% when normalized to each individual’s maximal vasodilator capacity. The decrease in vascular resistance is of the same magnitude as in control subjects. To our knowledge, this is the first observation that α-adrenergic tone of the leg skeletal muscle vascular bed is preserved in individuals without supraspinal sympathetic control.

Upper leg blood flow is lower and upper leg vascular resistance is higher in SCI than in control subjects. This is in accordance with previous observations in an independent sample of SCI and control subjects, with a different technique used to measure leg blood flow.21 As previously discussed,21 this is most likely due to structural (a decrease in number of arterioles and capillaries and/or a decrease in diameter of the resistance vessels) as well as functional changes. Indeed, previous research,6,25 and the present observation that maximal vasodilation during postischemic hyperemia is reduced in SCI, supports the concept that structural changes in SCI contribute to the reduced baseline leg blood flow.

Phentolamine-induced upper leg vasodilation in SCI, regardless the method of expressing the results (relative or normalized), indicates preserved α-adrenergic vascular tone in these individuals. The absolute upper leg blood flow in response to infusion of phentolamine was less in SCI as compared with control subjects. This is due to structural changes in the leg vascular bed of SCI, since this apparent difference disappeared when results were normalized to the individual maximal vasodilator capacity of the upper leg vascular bed. In control subjects, the vasodilator response to phentolamine was very similar to the response observed by others in a similar group of volunteers.2 Therefore, methodological problems are not likely to explain the lack of difference between the groups in vasodilator response to phentolamine in the present study.

Since upper leg blood flow was lower in SCI than in control subjects, the same dose of phentolamine resulted in higher local plasma concentration of phentolamine in the infused leg in SCI compared with control subjects. However,
in both groups, a maximal vasodilator response to phenolamine was achieved. This is supported by the observed plateau in upper leg vascular resistance in response to infusion of the two highest doses of phenolamine. Therefore, possible differences in plasma phenolamine concentration (these concentrations were not measured) cannot explain the similarity between the two groups in their maximal response in vascular resistance to phenolamine infusion.

In addition, in both groups blood pressure decreased during the course of the phenolamine infusions to a similar extent. This reflects a systemic effect of local vasodilation in a large vascular bed (infused leg). During the course of the experiment a spill of phenolamine into the systemic circulation must have occurred, as reflected by a decrease in upper leg vascular resistance in the noninfused leg in SCI. The drop in blood pressure will engage the baroreflex, resulting in an increase in sympathetic tone to the heart and peripheral circulation. In theory, the baroreflex-mediated increase in sympathetic tone could have limited the vasodilator response to phenolamine in the infused leg of the control subjects. However, this is very unlikely, since a possible reflex vasoconstriction in the infused leg was prevented by the local infusion of phenolamine.

The lack of a baroreflex-mediated increase in heart rate in both groups of volunteers is explained by spill of propranolol into the systemic circulation. Pilot studies clearly showed an increase in heart rate during infusion of phenolamine without simultaneous infusion of propranolol (data not shown). In the present study, subsequent blockade of cardiac β-adrenergic receptors by propranolol prevented the baroreflex-mediated increase in heart rate.

The results observed in this study reject our hypothesis that α-adrenergic tone is reduced in SCI as compared with control subjects. However, the elevated upper leg vascular resistance in spinal cord–injured individuals cannot be explained completely by the preserved α-adrenergic tone, since in both SCI as well as control subjects, the contribution of α-adrenergic stimulation to the leg vascular tone is of the same magnitude. In theory, several mechanisms may be responsible for the preserved α-adrenergic contribution in basal vascular tone in SCI.

First, in the studied subjects, the spinal cord injury may have been incomplete or supraspinal control of sympathetic outflow to the leg may have been restored. This explanation is excluded for several reasons. In 5 of the SCI, sweating was disturbed under the level of the lesion, indicating loss of autonomic control of the skin. Furthermore, the lack of a baroreflex-mediated vasoconstriction in the noninfused leg in SCI as opposed to the control subjects, and the lack of vasoconstriction in the calf during the cold pressor test, indicates a lack of supraspinal control of sympathetic outflow to the leg vasculature in SCI. A second reason for the preserved α-adrenergic tone in SCI may be related to the spinal sympathetic reflex and the local vasoconstrictor reflex. A previous study reported that both spinal sympathetic reflex activity and the vasoconstrictor reflex may contribute to leg muscle vasoconstriction during tilt in tetraplegic subjects, but very low sympathetic activity in cutaneous and muscle postganglionic axons situated below the level of the spinal cord injury was measured in basal supine position.28,29 The vasoconstrictor reflex is elicited by an increase in venous transmural pressure of >25 mm Hg31 and may be mediated by α-adrenoceptors,32 which has not been confirmed by others.33 Thus, although spinal reflexes and vasoconstrictor reflex probably do not explain the preserved α-adrenergic tone, their role cannot completely be excluded.

Finally, α-adrenergic receptor hypersensitivity to circulating catecholamines, the serum concentration of which was similar in both groups, could have preserved the α-adrenergic influence on basal vascular tone. Reduced local release of norepinephrine may have induced a compensatory increase in either the sensitivity or number of α-adrenergic receptors or the efficacy of postreceptor signaling.19,20,34 From the presenting data, it is not possible to assess α-adrenergic sensitivity, since an α-adrenergic antagonist was used, which affinity to the α-receptor is different from the affinity of α-adrenoceptor agonists, such as norepinephrine. Further research should address the question of altered α-adrenoceptor sensitivity in SCI.

A limitation of this study is that we only used α-adrenergic blockade to assess the contribution of the sympathetic nervous system in the control of basal vascular tone below the level of spinal cord injury. Other neurotransmitters, such as adenosine triphosphate and neuropeptide Y, are released simultaneously with norepinephrine by the sympathetic nerve endings and cause vasoconstriction by activating P2X receptors and Y1 receptors, respectively.35 Because of this limitation, we may have underestimated the contribution of the sympathetic nervous system in the regulation of basal vascular tone in control subjects and in individuals with a spinal cord lesion.

In conclusion, α-adrenergic contribution to basal vascular tone is preserved below the level of the lesion in spinal cord–injured individuals and is of the same magnitude as in control subjects. As such, the sympathetic nervous system is still a target for pharmacological intervention to improve the perfusion of the leg in SCI. However, our results do not completely explain the elevated leg vascular resistance in SCI, since the contribution of the sympathetic nervous system to leg vascular tone in SCI is of the same magnitude as in control subjects. Therefore, other factors, such as, for example, impaired endothelium-mediated vasodilation, could be responsible for the observed elevation of leg vascular tone in SCI and should be subject of investigation to further unravel the mechanisms behind the observed increase in leg vascular resistance in SCI.

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References


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