Increased vascular resistance in paralyzed legs after spinal cord injury is reversible by training

MARIA T. E. HOPMAN, JAN T. GROOTHUIS, MARCEL FLENDRIE, KARIN H. L. GERRITS, AND SIBRAND HOUTMAN

Department of Physiology, University Medical Centre Nijmegen, 6500 HB Nijmegen, The Netherlands

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Increased vascular resistance in paralyzed legs after spinal cord injury is reversible by training. J Appl Physiol 93: 1966–1972, 2002; 10.1152/japplphysiol.00897.2001.—The purpose of the present study was to determine the effect of a spinal cord injury (SCI) on resting vascular resistance in paralyzed legs in humans. To accomplish this goal, we measured blood pressure and resting flow above and below the lesion (by using venous occlusion plethysmography) in 11 patients with SCI and in 10 healthy controls (C). Relative vascular resistance was calculated as mean arterial pressure in millimeters of mercury divided by the arterial blood flow in milliliters per minute per 100 milliliters of tissue. Arterial blood flow in the sympathetically deprived and paralyzed legs of SCI was significantly lower than leg blood flow in C. Because mean arterial pressure showed no differences between both groups, leg vascular resistance in SCI was significantly higher than in C. Within the SCI group, arterial blood flow was significantly higher and vascular resistance significantly lower in the arms than in the legs. To distinguish between the effect of loss of central neural control vs. deconditioning, a group of nine SCI patients was trained for 6 wk and showed a 30% increase in leg blood flow with unchanged blood pressure levels, indicating a marked reduction in vascular resistance. In conclusion, vascular resistance is increased in the paralyzed legs of individuals with SCI and is reversible by training.

blood flow; strain-gauge plethysmography; sympathetic nervous system; deconditioning

BLOOD FLOW TO TISSUE IS GOVERNED by perfusion pressure and vascular resistance. Because mean arterial pressure and venous pressure are normally maintained within narrow limits, blood flow control is accomplished in large part by variation in vascular resistance. Vascular resistance is essentially under dual control: 1) systemic control through the autonomic nervous system and humoral factors and 2) local control by the conditions in the immediate vicinity of the blood vessels (myogenic regulation, vasoactive substances like endothelium-derived factors and metabolites produced by the tissue). The importance of sympathetic innervation for vascular resistance has been demonstrated by studies that examined the effect of sympathetic blocking or sympathetic denervation on vascular resistance. Animal research has shown within the first hours and days after sympathectomy a significant decrease in vascular resistance ranging from 20 to 90% (26, 27, 30, 36). Only a few studies investigated the outcome of sympathetic denervation on vascular resistance in humans and showed a significant decrease in vascular resistance shortly after sympathectomy (22, 32), although no changes in vascular resistance were observed after long-term sympathectomy (21, 28).

After spinal cord injury (SCI), the centrally mediated sympathetic control of the circulation may be lacking in the lower part of the body as a result of the disrupted spinal cord. Theoretically, this would lead to vasodilatation of peripheral vessels and, therefore, to a decrease in vascular resistance below the lesion. However, the part of the body below the spinal lesion is paralyzed and extremely inactive, which may affect the vascular properties in this part of the body as well. Previous studies (14, 25) reported a lower blood flow to the paralyzed legs in SCI individuals than in controls (C) patients as measured by echo Doppler ultrasound. However, no blood pressure data were given in these studies, and, with the knowledge that especially tetraplegic individuals often have low blood pressure levels, it is impossible to speculate about changes in vascular resistance in these SCI individuals. Only two studies (5, 17) known to us investigated vascular resistance in the legs of long-term SCI individuals compared with C individuals. In contrast to the previously mentioned studies (14, 25), these studies showed an increase in leg arterial inflow and a decrease in vascular resistance below the level of the lesion in SCI individuals. Nevertheless, there are several reasons to hypothesize that vascular resistance in the legs of long-term SCI individuals will be increased. 1) Animal research has shown that endothelial function changes after long-term sympathectomy with a predominance of endothelin-1 release and a decrease in nitric oxide release (1, 2). As a result of deconditioning of the leg muscles, oxygen demand will be low, and oxygen delivery...
ery will be geared accordingly, which would lead, most likely via flow-dependent mechanisms, to vascular atrophy (14). 3) In long-term SCI patients, the clinically obvious cold and blue-colored legs and the reported poor wound healing (3) are suggestive for a reduced leg blood flow and maybe for an increased vascular resistance. This apparent conflict between reported data on blood flow and vascular resistance in SCI vs. clinical observations and physiological references urged us to perform the present study.

In addition, apart from one study (33) reporting a lower vascular resistance in the arms of SCI compared with C individuals and the study by Karlsson et al. (17) reporting significantly lower vascular resistance in the arms compared with the legs in able-bodied C individuals but not in SCI individuals, we are not aware of any study reporting on vascular resistance below (inactive legs) and above (active arms) the lesion within SCI individuals.

The purpose of this study, therefore, was to assess leg and arm vascular resistance in SCI individuals. To accomplish this goal, we measured resting blood flow in the legs and arms and blood pressure in patients with SCI and compared these values with data obtained in a healthy C group. In addition, leg blood flow and blood pressure were measured in a group of SCI patients before and after 6 wk of electrically stimulated leg muscle training to gain insight into the plasticity of the peripheral vascular system and to distinguish between the effect of loss of central neural control vs. deconditioning on changes in leg vascular resistance. We hypothesize that, in contrast to previously reported results, vascular resistance in the legs of long-term SCI patients has been increased and will decrease by leg muscle training.

METHODS

Subjects. Ten healthy C men and 11 SCI men with no centrally mediated motor, sensor, and sympathetic control of the legs participated in this study (general characteristics are summarized in Table 1). SCI had complete (American Spinal Injury Association ASIA: A) spinal cord lesions of traumatic origin at levels between T4 and T12, and the lesions existed for at least 2 yr (12.8 ± 7.6 yr). All SCI and C individuals exercised between 0 and 4 h/wk, and SCI subjects had never exercised their paralyzed legs by electrical stimulation (ES). C neither smoked nor used medication. Three SCI individuals exercised between 0 and 4 h/wk, and SCI subjects had never exercised their paralyzed legs by electrical stimulation (ES). C neither smoked nor used medication. Three SCI individuals exercised between 0 and 4 h/wk, and SCI subjects had never exercised their paralyzed legs by electrical stimulation (ES). C neither smoked nor used medication. Three SCI individuals exercised between 0 and 4 h/wk, and SCI subjects had never exercised their paralyzed legs by electrical stimulation (ES). C neither smoked nor used medication. Three SCI individuals exercised between 0 and 4 h/wk, and SCI subjects had never exercised their paralyzed legs by electrical stimulation (ES). C neither smoked nor used medication.

Table 1. General characteristics of groups

<table>
<thead>
<tr>
<th></th>
<th>C (n = 10)</th>
<th>SCI (n = 11)</th>
<th>SCI (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>28.8 ± 11.7</td>
<td>40.7 ± 7.2a</td>
<td>38.1 ± 7.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180.2 ± 6.9</td>
<td>182.2 ± 7.1</td>
<td>183.3 ± 6.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.8 ± 6.0</td>
<td>73.5 ± 13.5</td>
<td>67.9 ± 7.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>124 ± 10</td>
<td>112 ± 17</td>
<td>110 ± 15</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76 ± 7</td>
<td>73 ± 11</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92 ± 7</td>
<td>86 ± 13</td>
<td>85 ± 13</td>
</tr>
<tr>
<td>Calf circumference, cm</td>
<td>36.2 ± 2.0</td>
<td>30.3 ± 3.5*</td>
<td>29.8 ± 3.3*</td>
</tr>
<tr>
<td>Forearm circumference, cm</td>
<td>25.6 ± 1.2</td>
<td>28.9 ± 2.3*</td>
<td>28.5 ± 1.3*</td>
</tr>
</tbody>
</table>

Values are means ± SD. C, able-bodied control group; SCI, spinal cord injury group; MAP, mean arterial blood pressure. *Significantly different from C (P < 0.05).
Mean arterial pressure was taken at the time of the flow measurements and calibrated with the manually derived blood pressure.

Maximal calf and forearm circumferences were measured by using a measuring tape.

Data analysis. Arterial inflow (in ml·min\(^{-1}·100\) ml tissue\(^{-1}\)) was calculated as the slope of the volume change over a 5-s interval (Fig. 1). Registrations with artifacts, due to spasms or movement, were excluded. An initial steep rise (tenths of seconds) previously observed and attributed to a cuff inflation artifact (4) was skipped. Averaged values and standard deviations were calculated from the 10 consecutive venous occlusions for each extremity in each individual.

Relative vascular resistance was determined as mean arterial pressure (in mmHg) divided by the relative arterial blood flow (in ml·min\(^{-1}·100\) ml tissue\(^{-1}\)) and expressed in units of resistance (UR; mmHg·min·100 ml tissue·ml\(^{-1}\)).

Training. This part of the study included nine male subjects (5 of them were included in the arm and leg hemodynamic part presented in Experimental design) with motor and sensor complete (ASIA A) thoracic and cervical spinal cord lesions for at least 1 yr up to 22 yr. No vascular changes are to be expected after 1 yr of paralyses, unless a complication or active intervention takes place. The cycle training was performed by using a computer-controlled leg cycle ergometer (Ergys 2, Therapeutic Alliances). This device provides ES to surface electrodes that were placed over hamstring, gluteal, and quadriceps muscles. All subjects trained for 6 wk, three times per week. A training session consisted of 30 min of ES exercise. Before and after the 6-wk training period, resting blood pressure was measured by using a sphygmomanometer and resting longitudinal images, and simultaneous Doppler spectra were obtained from the femoral artery by using a 5-MHz pulsed-wave, color-coded, duplex Doppler ultrasound apparatus (Toshiba SSA-270A, Tokyo, Japan). Resting systolic diameters were measured from three consecutive images and averaged. Furthermore, from the corresponding Doppler spectrum waveforms, the blood velocities were determined, and blood flow was calculated as vessel area times red blood cell velocity. For more details see Gerrits et al. (10).

Statistical analysis. Reproducibility was assessed by calculating the grouped coefficient of variance (CV) (taking the square root of the sum of the squared CV divided by \(n\)) between the two measurements in the healthy C subjects. An unpaired Student’s \(t\)-test was applied to determine differences in physical characteristics, blood pressure, relative blood flow, and vascular resistance between groups. A paired Student’s \(t\)-test was used to assess differences between forearm and leg blood flow and vascular resistance within groups as well as to compare blood pressure, blood flow, and peripheral resistance of the femoral artery before and after training. A \(P\) value of < 0.05 was considered significant.

RESULTS

Three SCI individuals (AL, BH, JL) were on medication, which may have influenced their vascular characteristics; therefore, the results of these subjects were excluded from comparison between SCI and C. A fourth SCI individual (HR) was omitted because he was the only smoker in the group, which left 7 SCI and 10 C for intergroup comparison. The arm arterial inflow data of JE are missing because of a data acquisition problem.

The reproducibility expressed as grouped CV was 9.5% for the blood flow measurements at the leg and 14.5% for the blood flow measurements at the forearm.

Calf and forearm circumferences were significantly different between SCI and C (Table 1). Mean arterial pressure showed no significant differences between both groups (SCI: 85 ± 15 mmHg; C: 92 ± 7 mmHg) (Table 1).

Leg arterial inflow was significantly lower in SCI (0.77 ± 0.48 ml·min\(^{-1}·100\) ml tissue\(^{-1}\)) compared with C (2.13 ± 0.61 ml·min\(^{-1}·100\) ml tissue\(^{-1}\)) (\(P < 0.001\)). The relative vascular resistance in the legs was significantly higher in SCI (159.1 ± 98.8 UR) than in C (47.6 ± 15.1 UR) (\(P = 0.003\); Fig. 2 and Table 2).

No significant differences were observed between leg and forearm arterial inflow and vascular resistance within C (arm flow 1.91 ± 0.80 ml·min\(^{-1}·100\) ml tissue\(^{-1}\); arm resistance 57.8 ± 27.7 UR), whereas within SCI (whole group \(n = 11\), a significantly higher arterial inflow in the arm than in the leg (1.31 ± 0.59 vs. 0.72 ± 0.47 ml·min\(^{-1}·100\) ml tissue\(^{-1}\)) and a significantly lower vascular resistance in the arm than in the leg (68.5 ± 27.7 vs. 166 ± 89.3 UR) was found (Figs. 2 and 3 and Table 2).

All nine subjects completed 18 training sessions, and the mean workload increased from 4 ± 5 kJ at the beginning to 16 ± 14 kJ at the end of the training period. Mean arterial pressure was similar to beginning to 16 ± 14 mmHg). In addition, a significantly larger resting blood flow in the femoral artery was found after training. This was represented by an increase in peak systolic blood flow from 1,330 ± 550 to 1,710 ± 490...
ml/min ($P < 0.01$) and an increase in mean blood flow from 270 ± 120 to 370 ± 160 ml/min ($P < 0.05$). Calculated vascular resistance decreased significantly (~30%) after 6 wk of training.

**DISCUSSION**

The major finding of the present study is the increased vascular resistance in the paralyzed legs after long-term SCI in humans. Although animal research supports and provides explanations for the long-term SCI in humans. Although animal research increased vascular resistance in the paralyzed legs after sympathectomy in rats resulted in an increase in vascular resistance seen after long-term SCI in humans. Additional research is needed to elucidate the role of these different endothelial components in vascular resistance after loss of central sympathetic control. Rodionov et al. (30) showed that 4 wk of sympathectomy in rats resulted in an increase in vascular resistance due to a decrease in density of the vascular network. They hypothesized that this is most likely the result of autoregulatory mechanisms restricting the elevated blood flow after sympathectomy and inducing the closure of some smaller resistance vessels and thereby increasing the structural component of resistance. In accordance with this, previous studies have shown structural adaptations of the vessels in the legs of SCI patients (31), i.e., a decrease in the diameter of the femoral artery (14, 35), a decrease in capillary density (23), and a decrease in venous capacity (9, 15).

In contrast to the findings of the present study, several studies on humans did not report an increase in vascular resistance after sympathetic denervation. In individuals suffering from chronic primary autonomic

Table 2. **Group blood flow and resistance of the forearm and leg**

<table>
<thead>
<tr>
<th></th>
<th>C ($n = 10$)</th>
<th>SCI ($n = 7$)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg blood flow, ml·min⁻¹·100 ml tissue⁻¹</td>
<td>2.13 ± 0.61</td>
<td>0.77 ± 0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Forearm blood flow, ml·min⁻¹·100 ml tissue⁻¹</td>
<td>1.91 ± 0.80</td>
<td>1.14 ± 0.24</td>
<td>0.04</td>
</tr>
<tr>
<td>Leg vascular resistance, UR</td>
<td>47.6 ± 15.1</td>
<td>159.1 ± 98.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Forearm vascular resistance, UR</td>
<td>57.8 ± 27.7</td>
<td>81.6 ± 16.3</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values are means ± SD. UR, unit of resistance (mmHg·min⁻¹·100 ml tissue⁻¹).
failure, vascular resistance in the legs and forearms seemed slightly lower compared with that in C individuals, but not to the point of statistical significance (28). Lepori et al. (21), who measured arterial inflow and relative vascular resistance in six individuals 3–4 yr after they had undergone thoracic sympathectomy for hyperhydrosis, found no significant differences in arm arterial inflow and relative vascular resistance between the sympathectomized and C individuals. However, two important differences between sympathectomized and SCI patients exist that may affect the control of vascular tone. After sympathectomy, the affected limb is denervated, whereas in the SCI patient spinal sympathetic reflex arcs may still be intact and may contribute to the vascular tone below the level of the lesion (6, 12, 24). However, microneurography has shown that sympathetic nerve activity below the lesion in SCI patients is decreased dramatically compared with sympathetic activity seen in healthy C patients (34).

A second major difference between the sympathectomized and SCI patients is that sympathectomized patients have normal voluntary motor control of the affected limb, whereas the sympathetic deprived limbs of SCI patients are paralyzed. As a result of the inactivity and atrophy of the paralyzed muscles below the level of the lesion, oxygen demand is low, and oxygen delivery will be geared accordingly, as has been demonstrated by vascular atrophy in the legs of SCI individuals (9, 14, 15, 25, 35). Langille and O’Donnell (19) demonstrated that a blood flow reduction of 70% resulted in a 21% decrease of the diameter of the vessel in rabbits within 2 wk. The reduction in diameter probably reflects structural (30) as well as functional (1) modifications, and both seem to be endothelium dependent (19).

Regular physical activity may, via similar pathways but in the opposite direction, lead to an increase in diameter of the conduit artery in a number of arterioles and capillaries, leading to a decrease in vascular resistance (11, 18). These pathways may involve an improved endothelial function as assessed by the vasodilator response to acetylcholine before and after training (8) as well as adaptations in the vascular smooth muscle responsiveness after training (37). Along this line, findings of the present study show that the diameter and flow in the femoral artery significantly increased, whereas vascular resistance significantly decreased, after 6 wk of training of the long-term paralyzed legs. This suggests that the increased in vascular resistance in SCI results primarily, if not exclusively, from deconditioning. In addition, Casiglia et al. (5) showed that a rigorous rehabilitation program, including electrically stimulated leg exercise, which all of the SCI patients in their study underwent in the years after their spinal trauma, resulted in a lower leg vascular resistance in these patients compared with C patients. This supports the hypothesis that inactivity, more than a lack of central sympathetic control, is responsible for the increased vascular resistance in SCI patients.

The decrease in leg vascular resistance after SCI as reported by Karlsson et al. (17) is hard to explain. Apart from lack of information on medication, smoking, and leg muscle activity as well as on used cuff pressures and exclusion or inclusion of hand and foot, no explanation can be given for the differences found between the study by Karlsson et al. (17) and the present study. Moreover, the present study revealed that even the patients on medication showed a markedly increased vascular resistance. This may again indicate that changes in the structural component are largely responsible for the increase in vascular resistance.

The finding of the present study that in SCI patients vascular resistance in the arms was significantly lower than in the legs reflects the deconditioned status of the leg muscles and the active status of the arm muscles in SCI patients; the latter was used for ambulation by propulsion of the manually driven wheelchair. In line with this, a lower vascular resistance in the arms of SCI compared with C patients was expected. However, this could not be confirmed in the present study nor in the study by Karlsson et al. (17) that showed a slightly higher vascular resistance in the arms of SCI com-

Fig. 3. Vascular resistance in the forearm (UR) in the SCI group (n = 6) compared with the C group. Values are means ± SD. In addition, the individual values of all participating SCI subjects are presented by their initials. Gray bars represent subjects who were excluded for intergroup comparison because of medication and smoking.
pared with C patients as well. Casiglia et al. (5), however, did show slightly higher forearm blood flows in SCI than in C patients and even reported the highest forearm flow values in the tetraplegic group. Differences in cuff pressures, number of slopes used to calculate the flow, and exclusion or inclusion of the wrist and hand may partly account for the differences among these studies. In addition, marked differences in arm volumes in SCI individuals may strongly influence the calculation of absolute blood flow in the arms.

Limitations. A limitation in this study seems to be the difference in methods used for assessment of blood flow in the legs between the transversal part of the study in which arm and leg blood flow were measured by using plethysmography and the longitudinal part of the study in which leg blood flow was measured before and after training by using echo Doppler. However, venous occlusion plethysmography (16) as well as echo Doppler (7) are well-established and accurate methods of measuring blood flow and, therefore, of calculating vascular resistance in a reliable way. The limitation is related to the fact that absolute values of blood flow and vascular resistance obtained by echo Doppler cannot be directly compared with the relative values obtained by plethysmography. This, however, is not a requirement to answer the main research questions for the present study and will, therefore, not alter the results and conclusion of the present study.

One may question the lack of a C group in the training study. However, all SCI subjects in the training study had a spinal cord lesion for at least 1 year. Because we know that vascular adaptations take place within weeks to months after the injury, no vascular changes are to be expected, unless an intervention takes place.

In conclusion, leg vascular resistance is dramatically enhanced in SCI individuals. This may be caused by structural (a decrease in number of arterioles and capillaries and/or a decrease in the diameter of the resistance vessels) as well as by functional changes (changes in endothelium-derived factors and/or sympathetic vascular regulation). The increased leg vascular resistance is reversible toward normal values by training the paralyzed legs with ES of the muscle.

We acknowledge the enthusiastic participation of all subjects in this study.

REFERENCES


