Effects of autonomic disruption and inactivity on venous vascular function

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Veterans Affairs Medical Center, Spinal Cord Damage Research Center and Medical Services, Bronx 10468; Departments of Medicine and Rehabilitation Medicine, Mount Sinai School of Medicine, New York 10029; Department of Rehabilitation Medicine, College of Physicians and Surgeons, Columbia University, New York 10032; and University of Osteopathic Medicine and Health Sciences, Des Moines, Iowa 50312

Wecht, Jill M., Ronald E. De Meersman, Joseph P. Weir, William A. Bauman, and David R. Grimm. Effects of autonomic disruption and inactivity on venous vascular function. Am. J. Physiol. Heart Circ. Physiol. 278: H515–H520, 2000.—The effects of autonomic disruption and inactivity were studied on the venous vascular system. Forty-eight subjects, 24 with spinal cord injury (SCI) and 12 sedentary and 12 active able-bodied controls, participated in this study. Peripheral autonomic data were obtained to estimate sympathetic vasomotor control (low-frequency component of systolic blood pressure (LF_{SBP})). Vascular parameters were determined using strain-gauge venous occlusion plethysmography: venous capacitance (VC), venous emptying rate (VER), and total venous outflow (VO_{t}). An additional vascular parameter was calculated: venous compliance ([VC/occlusion pressure] × 100). VC and VO_{t} were significantly different (SCI < sedentary < active). VER adjusted for VC was not different for any group comparison, whereas venous compliance was significantly lower in the SCI group than in the able-bodied groups and in the sedentary group compared with the active group. Regression analysis for the total group revealed a significant relationship between LF_{SBP} and venous compliance (r = 0.64, P < 0.0001). After controlling for LF_{SBP} through analysis of covariance, we found that mean differences for all venous vascular parameters did not change from unadjusted mean values. Our findings suggest that in subjects with SCI, the loss of sympathetic vasomotor tone contributes more than inactivity to reductions in venous vascular function. Heightened VC, VO_{t}, vasomotor tone, and venous compliance in the active group compared with the sedentary group imply that regular endurance training contributes to optimal venous vascular function and peripheral autonomic integrity.

spinal cord injury; vasomotor tone; venous occlusion plethysmography; autonomic nervous system

The venous system contains ~60% of total blood volume and acts as a low-resistance conduit for blood flow from tissue to the heart. In the systemic circulation, the force driving venous return is the pressure differential between the peripheral veins and the right atrium (central venous pressure). When variations in blood volume occur, the total capacity can be altered to maintain venous pressure, assuring blood return to the heart. Thus the pressure-volume relationship of the veins is an integral part of cardiovascular homeostasis.

The autonomic nervous system, specifically efferent sympathetic modulation, causes contraction of smooth muscle of the vessel walls and, along with activation of the skeletal muscle pump, contributes to control of vascular compliance, central venous pressure, and venous return. In individuals with spinal cord injury (SCI) autonomic disruption, immobility, and inactivity play critical roles in affecting peripheral vascular circulation (15). Immobility can be defined as chronic confinement to a wheelchair or prolonged bed rest, and in healthy subjects immobility has been reported to induce orthostatic hypotension (13, 14). Similarly, individuals with chronic SCI demonstrate increased orthostatic hypotension and intolerance (16). The degree and relative contribution of autonomic disruption and inactivity on peripheral vascular function as well as the underlying mechanisms responsible for orthostatic dysfunction have not been addressed.

Venous occlusion plethysmography is a noninvasive technique for estimating total limb blood flow (2, 8, 20) and has been used as a means to study human venous vascular control (3, 7, 11). The aims of this investigation were to determine the specific contribution of autonomic disruption and inactivity on venous vascular function in persons with tetraplegia and paraplegia and both sedentary and active able-bodied controls.

METHODS

Subjects. Forty-eight individuals from the New York City metropolitan area were recruited for the study. The subjects consisted of 12 males with tetraplegia (cervical cord lesion C4-C7), 12 males with paraplegia (thoracic vertebrae 10 and below), and 12 sedentary and 12 active able-bodied controls. Of the individuals with SCI, 71% were classified as incomplete (ASIA Impairment Scale B and C), and the other 29% were classified as complete (ASIA A). The sedentary control subjects were males who had never been involved in regular physical activity. The active control subjects included 10 males and 2 females who were involved in regular endurance training programs for at least 6 mo before the investigation; an arm maximal exercise test was performed to verify fitness status (mean peak O_{2} consumption = 108 ± 14% predicted of

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maximal leg O\textsubscript{2} consumption). All subjects were between the ages of 30 and 50 yr without known cardiovascular or pulmonary diseases or diabetes mellitus. Subjects with SCI were all healthy outpatients, a minimum of 2 yr postinjury, and capable of maintaining an independent lifestyle. The Institutional Review Board for Human Studies of the Bronx Veterans Affairs Medical Center granted approval for the study, and informed consent for each subject was obtained before investigation.

Subjects reported to the laboratory between 10:00 AM and 1:00 PM at least 3 h postprandial and refrained from caffeine and heavy exertion 12–24 h before testing began. Autonomic data and strain-gauge venous occlusion plethysmography measures were collected in a thermoneutral environment (21–23°C) after subjects sat quietly for 20 min in their wheelchair or a comfortable chair.

Autonomic data acquisition. Five minutes of resting data were collected. Beat-to-beat heart rate, systolic blood pressure (SBP), and respiration were acquired at a sampling rate of 200 Hz/channel with a 12-bit analog-to-digital converter (DAQcard-700, National Instruments, Austin, TX). Resting SBP was measured with the left arm supported in a horizontal position at the height of the right atrium, using a photoplethysmograph (Finapres, Ohmeda, CO) attached to the middle phalanx of the middle finger. Respiration was measured from respiratory-induced temperature changes in the mouth using a thermistor (YSI temperature probe, Yellow Springs, OH) inserted in a mouthpiece.

Autonomic data analysis. The low-frequency component of SBP (LF\textsubscript{SBP}) was used to estimate sympathetic vasomotor control (17, 21). Data were analyzed with a customized program created using LabVIEW software (National Instruments, Austin, TX). All signals were visually inspected for artifact and anomalies, peak detection was performed on all systolic peaks, and systolic peak oscillations (mmHg) were linearly interpolated to provide continuous waveforms. The data were then transformed into frequency spectra using discrete Fourier transform algorithms. Spectral estimates were smoothed by applying a Hanning window function to produce the power spectrum, and the spectral bandwidth for the LF\textsubscript{SBP} was between 0.04 and 0.15 Hz. Venous occlusion plethysmography. The left leg was elevated and supported in a horizontal position with the foot approximately level with the heart. Pressure cuffs were placed on the leg at midthigh, distal to the calf. While the cuff distal to the calf was inflated to a suprasystolic pressure (160–180 mmHg), venous occlusion was performed by rapidly inflating the thigh cuff (within 2 s) to a pressure just below arterial systolic pressure (160–180 mmHg). Venous occlusion plethysmography was performed by inflating the thigh cuff (within 2 s) to a pressure just below arterial systolic pressure (160–180 mmHg) and deflating it at a rate of 10 mmHg/s. The change in limb volume from unimpeded arterial inflow while venous outflow was arrested (23). All measurements were determined based on a calibration spike marked 10 s before cuff inflation representing the change in volume at 1% change in volume (4). Three occlusion maneuvers were performed on each subject, and the vascular parameters were averaged. Simultaneous measurement of beat-to-beat blood pressure, heart rate, and respiration were recorded.

Three venous vascular parameters were determined from the occlusion curve: 1) venous capacitance (VC, %change) defined as the change in limb volume from the start of the occlusion cycle to peak occlusion; 2) venous emptying rate (VER, %change/s) calculated as the first derivative of the venous outflow curve obtained 0.5 s after cuff release, and 3) total venous outflow (VO\textsubscript{T}, %change) determined as the integral of the outflow curve from maximal venous distension to maximal venous emptying. Additionally, venous compliance was calculated using the formula [(VC/occlusion pressure) x 100] (6).

Statistical analysis. All data are reported as means ± SD. A natural logarithmic transformation was applied to the LF\textsubscript{SBP} data. An ANOVA was used to determine significant mean differences for LF\textsubscript{SBP} and all venous vascular parameters among the four groups, and Fisher post hoc analysis was applied to determine significant differences among group comparisons (P < 0.05). Analysis of covariance (ANCOVA) was used to determine differences in VER and VO\textsubscript{T} when controlling for VC. ANCOVA was also applied to determine differences in all vascular parameters by controlling for LF\textsubscript{SBP}. Simple regression analyses were used to describe the relationship between venous compliance and LF\textsubscript{SBP} for the total group.

RESULTS

Subject characteristics and mean cardiovascular and autonomic data are reported by group (Tables 1 and 2). A typical venous occlusion graph for subjects in each group is presented (Fig. 1), depicting differences among the four groups for the entire venous occlusion maneuver. Mean venous vascular data are reported (Table 3). No significant differences in VC were found when the tetraplegia group was compared with the paraplegia group, but both of these groups were significantly lower than the sedentary and active groups (P < 0.0001). Furthermore, VC in the sedentary group was reduced relative to the active group (P < 0.001). Significant mean differences for VER were determined when the tetraplegia and paraplegia groups were compared with the sedentary and active able-bodied groups (P < 0.01); however, using ANCOVA and controlling for differences in VC, we found that adjusted mean differences for VER were no longer evident among the groups. VO\textsubscript{T} was not significantly different in the SCI groups, but was significantly lower in the SCI relative to the able-bodied groups (P < 0.001), and the sedentary group had significantly reduced VO\textsubscript{T} compared with the active group (P < 0.05). Unlike VER, after controlling for VC, we found that mean values for VO\textsubscript{T} did not differ from unadjusted means.

Venous compliance was significantly lower in the groups with SCI compared with both able-bodied groups (P < 0.0001). Venous compliance was also significantly reduced in the sedentary compared with the active group (P < 0.05). Mean differences for LF\textsubscript{SBP} among all group comparisons were directly related to functional ability (tetraplegia < paraplegia < sedentary < active).

Table 1. Characteristics of subjects

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Tetraplegia</th>
<th>Paraplegia</th>
<th>Sedentary</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>40 ± 5</td>
<td>42 ± 6</td>
<td>40 ± 7</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178 ± 6</td>
<td>179 ± 7</td>
<td>176 ± 10</td>
<td>172 ± 11</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 ± 16</td>
<td>90 ± 23</td>
<td>83 ± 12</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>DOI, yr</td>
<td>13 ± 9</td>
<td>14 ± 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comp., % (n)</td>
<td>17 (2)</td>
<td>42 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inc., % (n)</td>
<td>83 (10)</td>
<td>58 (7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SD; n, number of subjects. DOI, duration of injury; Comp., complete injury; Inc., incomplete injury; Parap, paraplegia; Act, active; Tetra, tetraplegia. 1, Para vs. Act; 2, Tetra vs. Para.
Simple regression analysis revealed a significant relationship between LFSBP and venous compliance for the total group ($r = 0.64$, $P < 0.0001$) (Fig. 2). After controlling for LFSBP with ANCOVA, we found that mean differences for all venous vascular parameters did not change from the unadjusted mean values. No differences were found for any of the venous vascular parameters between the tetraplegia and paraplegia groups and, therefore, is presented as one group (SCI) in the discussion.

**DISCUSSION**

Vascular compliance is dependent on the combined effects of neurohumoral and mechanical influences. Enhancement of vascular compliance has been described in highly trained individuals as heightened vessel responsiveness to various exogenous stimuli (5). Venous compliance, calculated as the ratio of venous capacitance and occlusion pressure, is dependent on both neural and mechanical mechanisms for its expression. Venous emptying rate depicts the mechanical (elastic recoil) aspect of vessel compliance, whereas LFSBP estimates neural (sympathetic) vasomotor control. The degree to which these mechanisms affect optimal venous compliance can be better understood by our comparison of subjects with partial to complete sympathetic interruption and immobility with able-bodied sedentary or active controls.

Venous capacitance was defined as the maximal venous distension at a specific pressure and was characterized as the change in limb blood volume from initial to peak occlusion (19). During the occlusion procedure the leg was elevated to the height of the atrium, reducing the pressure gradient in an attempt to standardize initial venous volumes before occlusion. Although baseline venous volume was not quantified, we believe that elevation of the limb was not sufficient to fully empty the veins in the groups with SCI, and we postulate that blood was pooled in the vessels, partially explaining their reduced venous capacitance. Maximal distention, however, was evident in all subjects based on a plateau in the occlusion curve. Our results demonstrated an approximate 70% reduction in venous capacitance in both groups with SCI compared with that of the able-bodied groups. Hopman and co-workers (12) reported similar findings in individuals with paraplegia, demonstrating a 50% reduction in venous capacitance relative to able-bodied controls. It appears, there-

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**Table 2. Cardiovascular and autonomic results**

<table>
<thead>
<tr>
<th></th>
<th>Tetraplegia</th>
<th>Paraplegia</th>
<th>Sedentary</th>
<th>Active</th>
<th>$P &lt; 0.05$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>74 ± 11</td>
<td>71 ± 13</td>
<td>66 ± 8</td>
<td>58 ± 8</td>
<td>3, 5</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>91 ± 14</td>
<td>131 ± 15</td>
<td>120 ± 16</td>
<td>123 ± 22</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>59 ± 16</td>
<td>76 ± 13</td>
<td>73 ± 11</td>
<td>65 ± 10</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>67 ± 14</td>
<td>92 ± 12</td>
<td>89 ± 12</td>
<td>88 ± 14</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>LFSBP, mmHg²/Hz</td>
<td>4.2 ± 0.9</td>
<td>5.7 ± 1.0</td>
<td>6.7 ± 0.8</td>
<td>7.6 ± 0.6</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
</tbody>
</table>

Data are means ± SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LFSBP, low-frequency systolic blood pressure. Sed, sedentary. 1, Tetra vs. Para; 2, Tetra vs. Sed; 3, Tetra vs. Act; 4, Para vs. Sed; 5, Para vs. Act; 6, Sed vs. Act.
Venous vascular function

Table 3. Venous vascular results

<table>
<thead>
<tr>
<th></th>
<th>Tetraplegia</th>
<th>Paraplegia</th>
<th>Sedentary</th>
<th>Active</th>
<th>P &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC, %Δ</td>
<td>24.4 ± 8</td>
<td>36.6 ± 15</td>
<td>161 ± 77</td>
<td>207 ± 56</td>
<td>2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>VER, %Δ/s</td>
<td>9.01 ± 5.4</td>
<td>15.4 ± 6.3</td>
<td>33.6 ± 19.2</td>
<td>44.1 ± 19.4</td>
<td>2, 3, 4, 5</td>
</tr>
<tr>
<td>VERadj, %</td>
<td>23.1 ± 3.8</td>
<td>27.1 ± 3.5</td>
<td>17.6 ± 4.1</td>
<td>20.9 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Outflow time, s</td>
<td>5.3 ± 2.5</td>
<td>5.2 ± 2.0</td>
<td>4.9 ± 1.6</td>
<td>5.3 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>VO2, %Δ/s</td>
<td>2.5 ± 1.2</td>
<td>3.4 ± 1.3</td>
<td>38.0 ± 19</td>
<td>66.7 ± 45</td>
<td>2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Compliance, %</td>
<td>0.34 ± 0.11</td>
<td>0.51 ± 0.21</td>
<td>2.23 ± 1.07</td>
<td>2.87 ± 0.77</td>
<td>2, 3, 4, 5, 6</td>
</tr>
</tbody>
</table>

Data are means ± SD. VC, venous capacitance; VER, venous emptying rate; VERadj, adjusted venous emptying rate (VER/VC); VO2, total venous outflow; 1, Tetra vs. Para; 2, Tetra vs. Sed; 3, Tetra vs. Act; 4, Para vs. Sed; 5, Para vs. Act; 6, Sed vs. Act.

Therefore, that the combination of sympathetic denervation and the absence of regular orthostatic challenge contributed substantially to the loss of venous capacitance.

In our study, as previously reported (22), lower venous capacitance was observed in the sedentary group compared with the active group, suggesting that the level of activity contributes to the magnitude of venous distensibility by enhancing vasodilatory responsiveness of the vessels. Using venous occlusion plethysmography, Snell and co-workers (22) observed an increased vasodilatory capacity in a group of athletes relative to sedentary controls, enabling the athletes to use a larger fraction of their maximal vascular conductance. These investigators (22) hypothesized that enhanced conductance in athletic able-bodied individuals is the result of mechanical rather than regulatory mechanisms; however, no marker of neural vasomotor tone was reported.

Venous emptying rate was significantly lower in the SCI than in the able-bodied groups, similar reductions have been observed (12) in individuals with paraplegia relative to able-bodied controls with lower venous emptying rate associated with higher flow resistance. We believe, however, that venous capacitance must be controlled to accurately assess venous emptying rate, because with increased capacitance the amount of pressure exerted on the vessel walls will be substantially higher, resulting in greater elastic recoil and a higher absolute venous emptying rate. Accordingly, we found that mean differences in venous emptying rate were no longer present independent of venous capacitance, indicating that venous emptying rate is dependent on the distensibility of the vessels. Although the venous vasculature of the able-bodied groups was capable of greater distention, the adjusted venous emptying rate was similar to that of the groups with SCI, suggesting that the elastic recoil mechanism responsible for emptying rate does not rely on peripheral sympathetic innervation but rather on mechanical properties.

As expected from our findings for venous capacitance, total venous outflow was significantly lower in the SCI than in the able-bodied groups, and it was also reduced in the sedentary compared with the active able-bodied group. The venous emptying curves (Fig. 1) display clear differences in individual outflow slopes among the groups. A passive and active phase of venous emptying was first described by Pointel and co-workers (18), who characterized the differences between these phases as distinct shifts in the outflow curve from a steep descent to a more gradual descent separated by a plateau. The steep descent (passive phase) has been hypothesized to represent elastic recoil of the vessel wall, whereas the more gradual descent (active phase) depicts venous constriction. Before our report herein, the absence of an active phase in subjects with SCI had not been described. We postulate that this is due to partial to complete peripheral sympathetic disruption, reflecting the loss of both contractile properties of the vessel walls and vasomotor control. Further support comes from the absence of differences in venous emptying rate when differences in capacitance are controlled statistically, suggesting that the passive phase of venous emptying relies solely on mechanical influences, whereas total venous emptying depends on both mechanical and neural mechanisms. Similar values for venous emptying rate (passive phase) and differences in total venous outflow between the two able-bodied groups suggest that the active phase of venous emptying is responsible for group differences, thus emphasizing the role of regular endurance training in improving active venous constriction, venous smooth muscle tone, peripheral and central venous pressures, and venous return.

The walls of the veins contain smooth muscle innervated by the sympathetic nervous system. Excitation of efferent sympathetic nerves results in contraction of the venous smooth muscle, increasing the stiffness of the vessel walls and making it less distensible, thus increasing the pressure of the blood within the vein (1).
This pressure change facilitates return of blood to the heart and helps preserve central venous pressure. From the number and complexity of mechanisms regulating vascular tone, one must exercise caution when interpreting results obtained from beat-to-beat systolic blood pressure variability (represented by LF_{SBP}). Though other indexes of peripheral sympathetic activity were not obtained in this study, the relationship between group membership and LF_{SBP} was strong, indicating varying degrees of autonomic disruption and activity.

The measurable levels of LF_{SBP} in the SCI subjects reflect the high percentage of incomplete injury; however, others (9, 10) have suggested, in neurologically complete quadriplegia, that observed heart rate and arterial blood pressure variability may represent excitation of supraspinal reflexes or potentially an upregulation of receptor function. Moreover, higher levels of LF_{SBP} in the active group imply that regular physical activity may heighten the dynamic nature of arterial blood pressure and resting sympathetic vasomotor tone. Alternatively, augmented LF_{SBP} in the active group may be residual sympathetic modulation resulting from a previous exercise bout or higher daily activity levels, such as stair climbing rather than elevator riding, in individuals inclined to regular physical activity. We demonstrated that group means for all vascular parameters did not change when statistically controlling for differences in LF_{SBP}, suggesting that group membership and LF_{SBP} are closely related. Thus any attempt to distinguish the specific contribution of resting sympathetic vasomotor tone to venous vascular function is confounded in the present study design.

Adaptations to pressure changes within the vasculature, represented by the venous compliance, are largely modulated by neural and mechanical influences and result from vessel distensibility, elastic recoil, and smooth muscle contraction. Venous compliance therefore is a measure of the responsiveness of the venous vascular system and was approximately sixfold greater in the able-bodied groups than in the SCI groups. Venous compliance was also significantly different when the sedentary group was compared with the active groups, signifying the importance of regular physical activity in the maintenance of optimal vascular function. Among all subjects, a moderate relationship was established between LF_{SBP} and venous compliance, indicating that autonomic innervation contributed to resting venous compliance, accounting for 41% of the variability. Thus in the SCI population, diminished sympathetic vasomotor tone may contribute more substantially to reductions in venous compliance than either immobility or inactivity.

Using venous occlusion plethysmography, we have described the response of veins in the lower extremity to change in blood volume through several measures of venous compliance that delineate the mechanisms regulating resting venous vascular function. Differences among the groups in these variables reflected the degree to which various physiological conditions alter peripheral circulation. Autonomic disruption, immobility, and inactivity combined cause considerable reduction in vessel compliance and vasomotor tone. In subjects with SCI, it appears that loss of sympathetic vasomotor tone contributed more than inactivity to reductions in vascular integrity. Heightened venous capacitance, total outflow, compliance, and vasomotor tone in the active group illustrate that regular endurance training enhances vessel response to provocation, confirming the general assumption that both mechanical and neural adaptations are necessary for optimal vascular function. The clinical implications of these findings are that orthostatic intervention and/or regular physical activity may improve vascular compliance and, potentially, peripheral and central venous pressure in individuals with SCI.

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