Pressor Effect of Water Drinking in Tetraplegic Patients
May Be a Spinal Reflex

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Abstract—Water drinking elicits a profound sympathetically mediated pressor response in patients with autonomic failure. To further elucidate the mechanism of the response, we assessed the acute effect of drinking water on supine blood pressure and heart rate in 13 tetraplegic patients (12 men, 1 woman; 39 ± 4 years of age; body mass index, 25 ± 1 kg/m²) with complete spinal cord injury (C2 to C7). Heart rate and finger blood pressure were recorded continuously. Brachial blood pressure was measured every 5 minutes. Baroreflex sensitivity was assessed by the sequence method. Stroke volume was calculated by use of transthoracic bioimpedance. Patients were placed in the supine position with the upper body elevated by 15°. After 30 minutes, supine patients ingested 500 mL of water and the following 60 minutes were monitored. Finger blood pressure at baseline was 123 ± 8/65 ± 4 mm Hg. Water drinking elicited a pressor response that was apparent within 5 minutes and reached a maximum of 138 ± 8/73 ± 4 mm Hg after 35 to 40 minutes (P < 0.05). Heart rate decreased from 64 ± 2 bpm at baseline to 60 ± 2 bpm (P < 0.001). The mean area under the curve for brachial systolic blood pressure changes differed significantly from zero (364 ± 151 mm Hg/min). Total peripheral resistance increased by 15 ± 4% (P < 0.05). Baroreflex sensitivity increased from 18 ± 5 ms/mm Hg at baseline to 23 ± 6 ms/mm Hg at 35 minutes after water drinking (P < 0.01). Water drinking elicits a pressor response even if the direct connection between brain stem cardiovascular centers and spinal sympathetic neurons is interrupted. This observation might suggest that water drinking activates postganglionic sympathetic neurons either directly or through a spinal reflex mechanism.

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Key Words: blood pressure ■ autonomic nervous system ■ pressoreceptors ■ reflex

Water drinking elicits a profound increase in blood pressure in many patients with severe orthostatic hypotension from autonomic failure. Seated blood pressure increases after water drinking within 5 minutes, reaches a maximum after ~35 minutes, and is sustained for >60 minutes.1,2 Water drinking increases blood pressure moderately in older but not younger control subjects.2,3 The pressor response is probably mediated through an increase in sympathetic tone rather than a change in plasma volume.2,3 Indeed, water drinking increases plasma norepinephrine levels in younger and older normal control subjects.2,3 Water drinking also increases sympathetic nerve traffic to the vasculature.3 The time course of both sympathetic nerve traffic and plasma norepinephrine response corresponds to the time course of the water pressor response. Ganglionic blockade with trimethaphan almost completely abolished the pressor response to water in patients with autonomic failure.2 Furthermore, patients with residual autonomic function have a greater pressor response, whereas the pressor response is moderate or absent in patients with little or no residual autonomic function.2 Patients with high spinal cord injuries provide an opportunity to further elucidate the mechanism of the sympathtic activation with water. In these patients, functioning efferent sympathetic neurons in the spinal cord are disconnected from brain stem input.4 Were the water-induced pressor response explained by a brain stem mechanism, these patients should not have a pressor response. In contrast, a response that is mediated through a spinal reflex mechanism should be exaggerated in these patients.5

Methods

Subjects
We studied 13 tetraplegic patients (12 men, 1 woman; 39 ± 4 years of age; body mass index, 25 ± 1 kg/m²) who underwent a rehabilitation program. None of the patients was in spinal shock. The level and the completeness of spinal cord injury were assessed according to standard clinical guidelines.6 All patients presented with a complete spinal cord lesion between C2 and C7. The study was approved by the Institutional Review Board of the Humboldt University, and informed consent was obtained from patients before study entry.

Protocol
Vasoactive medications were discontinued at least 5 half-lives before testing. One patient continued to ingest ipratropium bromide for the treatment of symptomatic sinus bradycardia. Studies were conducted...
at least 2.5 hours after breakfast or lunch. Patients were not permitted to drink for at least 1.5 hours before testing and were asked to empty the bladder before the study. We assessed the effect of drinking 500 mL of tap water at room temperature (20°C) in less than 5 minutes on blood pressure, heart rate, heart rate variability, baroreflex sensitivity, and on hemodynamic parameters (stroke volume, cardiac output, total peripheral resistance). Subjects were studied in a comfortable supine position with the upper body elevated by 15°. Brachial blood pressure was determined every 5 minutes with the use of an automated blood pressure cuff (Dinamap, Critikon). Electrocardiograms, continuous finger arterial blood pressure (Finapres, TNiO), and impedance cardiograms (Cardioscreen, Medis GmbH) were recorded on a beat-to-beat basis. Patients underwent autonomic testing including determination of respiratory sinus arrhythmia (deep breathing, breathing rate 6/minute) and a Valsalva maneuver.7 Respiratory sinus arrhythmia was calculated as the coefficient between the longest and shortest R-R intervals during the best of 8 respiratory cycles. The Valsalva ratio was calculated as the coefficient between the longest R-R interval during phase IV and the shortest R-R interval during phase II of the Valsalva maneuver. Both coefficients are related to parasympathetic heart rate control. After 30 minutes of baseline recording, subjects drank 500 mL of noncarbonated table water (Aquanori) in <5 minutes, and the recordings were continued for the next 60 minutes.

Data Acquisition and Data Analysis
The data were digitized with 14-bit resolution and sample frequency of 500 Hz, with the use of the WINDAQ data acquisition system (DI220, DATAQ). R-R intervals, diastolic and systolic blood pressure values, and respiration were defined off-line for the complete records with the use of a program written by one of the authors, which is based on PV-wave software (Visual Numerics Inc). Stroke volume (SV), cardiac output, and total peripheral resistance (TPR) were calculated by use of the 8-electrode transthoracic bioimpedance technique as described elsewhere.8 SV was calculated according to the Sramek-Bernstein equation. Mean finger arterial blood pressure was used for the beat-to-beat calculation of TPR.

Spectral Analysis and Baroreflex Sensitivity
Power spectral density was estimated with the FFT-based Welch algorithm. The power in the frequency range of low frequencies (0.04 to <0.15 Hz) and high frequencies (0.15 to <0.40 Hz) were calculated according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology recommendations.9 The spontaneous baroreflex sensitivity was calculated as the slope of the linear regression lines between the R-R intervals and the systolic blood pressure values by means of the sequence technique.10,11 Sequences with at least 3 intervals, 0.5 mm Hg blood pressure changes, and 5-ms R-R interval changes were analyzed only if the correlation coefficients were >0.85. Baroreflex sensitivity was calculated as the mean value of the significant slopes obtained during 15-minute baseline (−25 to −10 minutes before drinking water) and from 30 to 45 minutes after drinking water.

Statistics
If not otherwise indicated, results are presented as mean±SEM. Individual areas under the curve (systolic blood pressure changes over time) were determined between 5 minutes and 60 minutes after water ingestion.2 Intraindividual comparisons were made by the paired t test. One-way ANOVA for repeated measurements was used for multiple comparisons. A value of P<0.05 was considered to be statistically significant.

Results
Clinical Characteristics
The clinical characteristics of the study population are given in Table 1. Respiratory sinus arrhythmia ratio (1.27±0.06) and Valsalva ratio (1.68±0.09) were within the normal range.

## Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Gender</th>
<th>Age, y</th>
<th>Injury Level</th>
<th>Time After Injury, mo</th>
<th>Orthostatic Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>M</td>
<td>37</td>
<td>C7</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>T2</td>
<td>M</td>
<td>37</td>
<td>C5</td>
<td>223</td>
<td>–</td>
</tr>
<tr>
<td>T3</td>
<td>M</td>
<td>17</td>
<td>C6</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>T4</td>
<td>F</td>
<td>27</td>
<td>C7</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>T5</td>
<td>M</td>
<td>31</td>
<td>C5</td>
<td>65</td>
<td>–</td>
</tr>
<tr>
<td>T6</td>
<td>M</td>
<td>25</td>
<td>C4</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>T7</td>
<td>M</td>
<td>68</td>
<td>C4</td>
<td>4</td>
<td>+</td>
</tr>
<tr>
<td>T8</td>
<td>M</td>
<td>54</td>
<td>C4</td>
<td>7</td>
<td>+</td>
</tr>
<tr>
<td>T9</td>
<td>M</td>
<td>36</td>
<td>C5/6</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>T10</td>
<td>M</td>
<td>28</td>
<td>C2–C7</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>T11</td>
<td>M</td>
<td>22</td>
<td>C4</td>
<td>6</td>
<td>+</td>
</tr>
<tr>
<td>T12</td>
<td>M</td>
<td>48</td>
<td>C4</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>T13</td>
<td>M</td>
<td>61</td>
<td>C4–C6</td>
<td>8</td>
<td>+</td>
</tr>
</tbody>
</table>

During phase II of the Valsalva maneuver, blood pressure decreased 33±8/6±4 mm Hg. The blood pressure overshoot during phase IV of the Valsalva maneuver was absent or markedly blunted in all patients (−4±2/−2±2 mm Hg). These findings are consistent with intact parasympathetic control of heart rate and impaired sympathetic function.

## Hemodynamic Effects of Water
Figure 1 illustrates changes in finger blood pressure and R-R intervals after water ingestion. Presented are the averaged beat-to-beat values for every 60 seconds. The time during which the patients drunk water was excluded. There was a marked increase in brachial and finger arterial blood pressure after drinking 500 mL of tap water in tetraplegic patients. Before water drinking, supine finger blood pressure was 123±8/65±4 mm Hg. Within 5 minutes after patients drank water, blood pressure started to increase and reached a maximal value of 138±8/73±4 mm Hg after 40 minutes. Heart rate decreased from 64±2 bpm at baseline to 60±2 bpm (P<0.001) after water drinking. Brachial blood pressure at baseline was 114±5/67±3 mm Hg and 125±9/71±4 mm Hg after 35 minutes. Individual data on the brachial blood pressure response to water quantified as area under the curve are shown in Figure 2. The mean area under the curve of the change in systolic blood pressure was 36±151 mm Hg/min. The effect was significantly different from zero (P<0.05). However, there was large interindividual variability in the sensitivity to water, and not all patients featured a pressor response. The pressor response was greater in older subjects (r=0.725, P<0.01) and was correlated with the change in TPR (r=0.788, P<0.01). Compared with baseline values, SV (104±4%; NS) and cardiac output (99.9±3%; NS) were similar at 35 minutes after drinking water. Systemic vascular resistance increased 15±4% (P<0.05) with water drinking (Figure 3).

Heart Rate and Blood Pressure Variability and Baroreflex Function
Heart rate variability in the time and frequency domain increased after drinking 500 mL of tap water and reached
maximal values at \( \approx 35 \) to 40 minutes after water ingestion. Figure 4 illustrates the dynamic of R-R intervals and systolic arterial finger blood pressure for an individual patient. According to the results of spectral analysis of heart rate variability, the changes were mainly due to an increase in the high frequency band. Power spectral density of heart rate and blood pressure variability in the low frequency band did not change after water drinking (Table 2). However, baroreflex sensitivity calculated with the use of the sequence technique increased moderately after water drinking (Table 2). The number of significant sequences for upslopes and downslopes was similar after water drinking.

Discussion
The main finding of this study was that water drinking elicits a substantial pressor response in patients with chronic high spinal cord injury. On average, systolic blood pressure increased by \( \approx 15 \) mm Hg. In individual patients, the increase was \( >30 \) mm Hg. The changes in diastolic and mean arterial blood pressure were less pronounced but nonetheless significant. This finding is in agreement with the literature showing more pronounced changes in systolic blood pressure than in diastolic blood pressure with water drinking in patients. One possible explanation for this observation may be that the ejection of a similar left ventricular stroke volume into a less compliant vascular bed leads to the more substantial increase in systolic blood pressure compared with mean pressure. The
pressor response in patients with high spinal cord injury was associated with a small but significant decrease in heart rate and an increase in heart rate variability. The ability of the baroreflex to elicit rapid adjustments in heart rate was improved with water drinking.

The water pressor response in our patients was markedly greater than the response in healthy subjects of similar age. Water drinking did not change blood pressure in younger healthy subjects (mean age, 25 years). In older subjects (mean age, 57 years), systolic blood pressure increased 11 mm Hg after water drinking. Patients with pure autonomic failure or patients with central autonomic dysfunction caused by multiple system atrophy have a greater response than patients with high spinal cord injury. Systolic blood pressure increased 33 mm Hg in multiple system atrophy and 37 mm Hg in patients with pure autonomic failure.

The possibility that a change in volume status is the crucial mechanism explaining the water pressor response is unlikely for several reasons. First, in a previous study in patients with autonomic failure, we did not find changes in plasma volume.

**TABLE 2. Heart Rate Variability, Systolic Blood Pressure Variability, and Baroreflex Sensitivity**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>35 Minutes After Drinking Water</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV, %</td>
<td>5.08±0.85</td>
<td>6.05±0.96</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RMSSD, msec</td>
<td>81±22</td>
<td>100±26</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>HF-RR, msec</td>
<td>272±74</td>
<td>351±87</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LF-RR, msec</td>
<td>415±167</td>
<td>484±141</td>
<td>NS</td>
</tr>
<tr>
<td>LF-SBP, mm Hg</td>
<td>1.98±0.61</td>
<td>1.77±0.50</td>
<td>NS</td>
</tr>
<tr>
<td>LF-DBP, mm Hg</td>
<td>5.1±1.5</td>
<td>4.2±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>BRSup, msec/mm Hg</td>
<td>1.5±0.4</td>
<td>1.8±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>BRSDown, msec/mm Hg</td>
<td>18±5</td>
<td>23±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sequences up×min⁻¹</td>
<td>3.4±0.6</td>
<td>2.9±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sequences down×min⁻¹</td>
<td>4.2±0.8</td>
<td>4.1±0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Measurements were conducted at baseline and 35 minutes after drinking 500 mL water. CV indicates coefficient of variation of RR intervals; RMSSD, root mean square of successive differences of RR intervals; HF-RR, RR variability in the high frequency range; LF-RR, RR variability in the low frequency range; LF-SBP and LF-DBP, blood pressure variability in the low frequency range; BRSup, baroreflex sensitivity determined using the sequence technique (for upslopes of systolic blood pressure); and BRSDown, baroreflex sensitivity for downslopes of systolic blood pressure.

with water drinking. Yet, intravenous infusion of the same volume of 5% dextrose in water caused a marked change in plasma volume but only a moderate change in blood pressure. Second, in the present study in patients with high spinal cord injury, thoracic impedance did not change with water drinking. Thoracic impedance is highly correlated with intrathoracic blood volume. Finally, solute-free water is distributed throughout the extracellular and intracellular space. If one assumes that a water load (500 mL) is absorbed but not excreted, total body water would change by 1% in a person weighing 175 lbs. Plasma volume would increase by ≈35 mL. Moreover, a substantial part of the ingested water is likely to be excreted at the time the maximal pressor effect of water is observed.

The pressor response in our patients mainly resulted from an increase in systemic vascular resistance. Similarly, the pressor response in patients with autonomic failure was associated with an increase in systemic vascular resistance.

Even though blood pressure does not change in healthy young subjects, calf vascular resistance increases. However, in the same subjects, systemic vascular resistance did not change. Thus, water drinking appears to elicit an increase in vascular tone that contributes to the pressor response. To conclude that an increase in vascular resistance is the sole mechanism of the water pressor response would be premature.

There is strong evidence that the water pressor response is mediated through sympathetic activation. The observation that water drinking elicited a pressor response in patients with high spinal cord injury may give important clues as to the potential mechanism of the sympathetic response. Our observation suggests that the sympathetic activation does not require neural connections between brain stem and spinal sympathetic neurons, which are lost in our patients. Clearly, the pressor response cannot be fully explained by brain stem or cortical activation. Instead, the sympathetic nervous system may be activated by a spinal mechanism. Patients with high spinal cord injury are exquisitely sensitive to stimuli that cause sympathetic activation at the spinal level. Bladder distention, for example, increases sympathetic activity and dramatically increases blood pressure (“autonomic dysreflexia”). Catastrophic hypertensive episodes associated with intracranial bleeding have been observed in these patients.

One important question that arises from our study is why the response to water drinking differs quantitatively be-
tween patients with high spinal cord injury and patients with autonomic failure, as well as control subjects. The phenomenon may be explained by differences in the ability of the baroreflex to buffer changes in vascular tone elicited by water. Indeed, in healthy subjects, an increase in vascular tone is followed by a baroreflex-mediated decrease in heart rate and sympathetic vasomotor tone. The compensatory adjustment attenuates the pressor response. In patients with high spinal cord injury, the baroreflex cannot restrain sympathetic efferent neurons to the heart or to the vasculature. Therefore, water drinking may elicit a greater response in these patients than in healthy control subjects.

Baroreflex control of parasympathetic innervation of the heart is intact in patients with high spinal cord injury. In particular, in younger patients, parasympathetic activation can provoke severe bradycardia. In contrast, in patients with autonomic failure, baroreflex control of sympathetic and parasympathetic efferent neurons is almost lost. The preserved parasympathetic baroreflex regulation in the patients with spinal cord injury may have attenuated the pressor response, compared with patients with autonomic failure. Indeed, with every mm Hg increase in systolic blood pressure with water, heart rate decreased 0.4 bpm in patients with spinal cord injury. The decrease in heart rate with water was only 0.15 bpm/mm Hg in patients with multiple system atrophy and 0.05 bpm/mm Hg in patients with pure autonomic failure. The improvement in baroreflex sensitivity with water may further attenuate the pressor response. The hypothesis that a baroreflex-mediated increase in parasympathetic traffic to the heart attenuated the pressor response in spinal cord injury patients is supported by the heart rate variability data. Heart rate variability determined in the time and in the frequency domain increased with water drinking. The increase was evident in the high-frequency domain of heart rate variability, which is strongly modulated by the parasympathetic nervous system. A central sympathetic activation of the heart is unlikely, given the level of the spinal cord lesion. The afferent signal that activates the sympathetic nervous system after water drinking is not known. Water temperature did not have an effect on the response to water. Possibly, visceral stretch causes sympathetic activation. However, water doses as low as 120 mL increase blood pressure in susceptible patients. Another possible explanation is that local changes in osmolarity are contributory. Studies in animals demonstrated the presence of osmoreceptive afferent nerve fibers. The pressor effect of water drinking can be exploited to treat orthostatic hypotension in a large subgroup of patients with autonomic failure. Indeed, water is as potent or even more potent than some of the commonly used pressor agents. Water drinking also improves orthostatic tolerance in healthy subjects. One particular advantage of water is the fact that the onset of its effect is very rapid. Water drinking also attenuates postprandial hypotension in patients with autonomic failure. Orthostatic hypotension is very common in patients with high spinal cord injury, even in the seated position. However, only a smaller subgroup of these patients requires treatment of orthostatic hypotension. Water drinking might be a useful and essentially cost-free intervention to attenuate orthostatic hypotension in these patients.

Perspectives
The mechanisms that could mediate water-induced sympathetic activation are still not fully understood. Our studies may suggest spinal mechanisms. It is even less understood how water or other gastrointestinal stimuli might activate the sympathetic nervous system in humans. In animals, mechanical and chemical stimulation of gastrointestinal organs can induce sympathetic activation. The sympathetic activation profoundly changes cardiovascular regulation. In humans, the interaction of the gastrointestinal tract and the cardiovascular system has been neglected. The observation of a water-induced pressor response might help to renew the interest in this important physiological interaction.

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