Water Drinking Acutely Improves Orthostatic Tolerance in Healthy Subjects

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Background—Orthostatic symptoms and syncope are common, even in apparently healthy subjects. In patients with severe autonomic dysfunction, water drinking elicits an acute pressor response and improves orthostatic hypotension. We tested the hypothesis that water drinking also improves orthostatic tolerance in healthy subjects.

Methods and Results—In a randomized, controlled, crossover fashion, 13 healthy subjects (9 men, 4 women, mean age 31 ± 3 years of age) ingested 500 mL and 50 mL of mineral water 15 minutes before head-up tilt on two separate days. Finger blood pressure, brachial blood pressure, heart rate, thoracic impedance, and blood flow velocity in the brachial artery and the middle cerebral artery were measured. Orthostatic tolerance was determined as the time to presyncope during a combined protocol of 20 minutes of 60° head-up tilt alone, followed by additional increasing steps of lower body negative pressure (−20, −40, and −60 mm Hg for 10 minutes each or until presyncope). Drinking 500 mL of water improved orthostatic tolerance by 5 ± 1 minute (range, −1 to +11 minutes, P < 0.001). After drinking 500 mL of water, supine mean blood pressure increased slightly (P < 0.01) as the result of increased peripheral resistance (P < 0.01). It also blunted both the increase in heart rate and the decrease in stroke volume with head-up tilt. Cerebral blood flow regulation improved after water drinking.

Conclusions—Water drinking elicits an acute hemodynamic response and changes in cerebrovascular regulation in healthy subjects. These effects are associated with a marked improvement in orthostatic tolerance. (Circulation. 2002;106:2806-2811.)

Key Words: hemodynamics • vasodilation • syncope • cerebrovascular disorders

At least 3.5% of women and 3% of men have syncope during their lifetime.1 Neurovascular syncope is the most common form.2 The syncope can be explained by reflex-mediated vasodilation and bradycardia.3 This response can be induced in most otherwise healthy subjects exposed to a sufficiently severe orthostatic stress.4 Most patients have syncope infrequently and do not require aggressive treatment; however, some patients with frequent syncopal episodes do require therapeutic measures. Unfortunately, most pharmacological treatments do not result in sufficient symptomatic improvement.5 Cardiac pacemaker implantation does not prevent the vasodilation during a syncopal episode, which limits its usefulness.5 Alternative treatment approaches are needed, both for otherwise healthy “occasional fainters” and for patients with frequent syncopal episodes. Water drinking may be such a treatment.5,7 This hypothesis originated from studies in rare patients with severe orthostatic hypotension caused by autonomic failure. In these patients, water drinking elicits a large, acute pressor response and has been successfully used therapeutically.5–11 In patients with orthostatic intolerance (ie, postural orthostatic tachycardia syndrome), water drinking blunts the orthostatic tachycardia but has only a modest effect on blood pressure.11 Water drinking also has effects on blood pressure and heart rate in normal subjects, although the actions are more subtle 9,12 and appear to be mediated through sympathetic activation.9,13 In a human model of neurally mediated syncope, we tested the hypothesis that water drinking improves the hemodynamic and neural adjustment to upright posture and improves the ability to withstand orthostatic stress. We used a combination of head-up tilt testing and lower body negative pressure to induce neurally mediated presyncope in healthy subjects because this has been shown to provide a quantitative and reproducible measure of orthostatic tolerance.4 Regular tilt testing is less useful as a method to induce neurally mediated syncope in healthy subjects because it exerts a weaker orthostatic stimulus.

Methods

Subjects

Thirteen healthy volunteers (9 men, 4 women, mean age 31 ± 3 years of age range, 21 to 48 years), body mass index, 24 ± 1 kg/m^2 were included in the study. The subjects were taking no regular medication with the exception that 3 of the female subjects were taking oral...
contraceptives. The local research ethics committee had approved the trial. Written informed consent was obtained before study entry.

Protocol
In a randomized, crossover design, every subject underwent the determination of orthostatic tolerance twice on separate days between 9 and 12 AM. Participants abstained from alcohol drinking for 24 hours and did not smoke on testing days. After an overnight fast, subjects were placed on a tilt table with the right arm at heart level. Finger blood pressure (Finapres, Ohmeda), brachial blood pressure (Hewlett Packard 78325C), and ECG were measured continuously. Thoracic bioimpedance was monitored continuously by means of a 2-MHz ultrasound probe (Cardioscreen, Medis GmbH). Forearm blood flow velocity on the right arm was monitored by an 8-MHz ultrasound device (Multi-Dop X4, TCD-8.01, DWL), kept in place by a headset. End-tidal CO2 was measured continuously (Binos 1, Leybold-Heraeus).

Signals of finger blood pressure and thoracic impedance were analyzed off-line. Cardiac stroke volume was calculated according to Sramek’s formula. Mean cerebral and brachial velocity values were averaged over a minimum of 10 beats. Mean cerebral blood pressure was calculated as arterial blood pressure – (1.36 × h) (h=height difference in cm between brachial cuff and ultrasound probe). Changes in cerebrovascular resistance were calculated as described previously.

Spectral Analysis and Baroreflex Sensitivity
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, using the sequence technique. Heart rate and blood pressure variability in the high-frequency (0.15 to 0.4 Hz) and in the low-frequency (0.04 to 0.15 Hz) band and baroreflex sensitivity were determined by means of spectral and cross-spectral analysis.

Statistics
All data are expressed as mean ± SEM. Intrarandom and interindividual differences were compared by paired and unpaired t tests, respectively. ANOVA testing for repeated measures was used for multiple comparisons. Relations between parameters were assessed by linear regression analyses. A value of P < 0.05 was considered significant.

Results
Water Drinking and Orthostatic Tolerance
After drinking 50 mL of water, one subject tolerated the procedure for the maximum period tested (end of lower body negative pressure at −60 mm Hg phase), and his orthostatic tolerance was taken as 50 minutes (Table 1). In 12 subjects, the test was terminated sooner. Orthostatic tolerance (time to presyncope) was 31 ± 3 minutes (range, 11 to 50) after drinking 50 mL of water. Drinking 500 mL of water prolonged the time to presyncope in 11 subjects. The mean time increased to 36 ± 3 minutes (range, 21 to 50) (P < 0.001...

<p>| TABLE 1. Individual Hemodynamic Responses to Combined Head-Up Tilt and Lower Body Negative Pressure |
|---------------------------------|-----------------|----------------|----------------|----------------|----------|</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Duration, min</th>
<th>Last SBP, mm Hg</th>
<th>ΔSBP, mm Hg</th>
<th>Last HR, HR</th>
<th>ΔHR, bpm</th>
<th>End Point</th>
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<tr>
<td>1</td>
<td>m</td>
<td>43</td>
<td>79</td>
<td>−50</td>
<td>62</td>
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<tr>
<td>2</td>
<td>m</td>
<td>50</td>
<td>111</td>
<td>−6</td>
<td>138</td>
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<td>completed</td>
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<tr>
<td>3</td>
<td>m</td>
<td>33</td>
<td>33</td>
<td>−3</td>
<td>161</td>
<td>11</td>
<td>tachycardia</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>21</td>
<td>21</td>
<td>−3</td>
<td>28</td>
<td>−54</td>
<td>cardioinhibitory</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>39</td>
<td>16</td>
<td>−4</td>
<td>67</td>
<td>−46</td>
<td>vasodepressor</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>44</td>
<td>58</td>
<td>−4</td>
<td>135</td>
<td>−4</td>
<td>vasodepressor</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>23</td>
<td>55</td>
<td>−3</td>
<td>55</td>
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<tr>
<td>9</td>
<td>m</td>
<td>50</td>
<td>101</td>
<td>0</td>
<td>110</td>
<td>−13</td>
<td>completed</td>
</tr>
<tr>
<td>10</td>
<td>f</td>
<td>36</td>
<td>106</td>
<td>−3</td>
<td>150</td>
<td>−10</td>
<td>tachycardia</td>
</tr>
<tr>
<td>11</td>
<td>f</td>
<td>24</td>
<td>98</td>
<td>−59</td>
<td>125</td>
<td>5</td>
<td>vasodepressor</td>
</tr>
<tr>
<td>12</td>
<td>f</td>
<td>36</td>
<td>110</td>
<td>−15</td>
<td>129</td>
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<td>mixed</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>36.3</td>
<td>82</td>
<td>0</td>
<td>104</td>
<td>−18</td>
<td>...</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>3</td>
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<td>12</td>
<td>6</td>
<td>...</td>
</tr>
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</tr>
</tbody>
</table>

Duration refers to time to termination of the tilt test. Last SBP indicates systolic blood pressure at the end of the test; last HR, heart rate at the end of the test; ΔSBP, change in systolic blood pressure in the last 90 seconds of the test; ΔHR, change in heart rate in the last 90 seconds of the test. The end point was classified according to current guidelines on the diagnosis of syncope as orthostatic tachycardia indicates tachycardia; type 1, mixed; type 2A, cardioinhibitory; type 3, vasodepressor, or completion of the whole protocol.
compared with 50 mL of water) (Figure 1). The three subjects who had symptoms of presyncope during the phase of head-up tilting alone (50 mL of water) all showed large improvements after drinking 500 mL of water, which took them into the lower body suction phase. Older and younger subjects received a similar benefit.

Supine Hemodynamic Effects of Water Drinking

Supine heart rate was 62 ± 3 bpm before drinking 50 mL of water and 60 ± 2 bpm before drinking 500 mL of water (P = NS; Figure 2, top). Supine brachial blood pressure was 121 ± 3/70 ± 2 mm Hg before drinking 50 mL and 118 ± 2/70 ± 2 mm Hg before drinking 500 mL of water (P = NS; Figure 2, middle and bottom). Fifteen minutes after drinking, blood pressure was 120 ± 3/67 ± 2 mm Hg with 50 mL of water and 119 ± 2/73 ± 2 mm Hg with 500 mL of water (P < 0.01 for diastolic and mean arterial pressure, NS for systolic values; Figure 2, middle and bottom). Heart rate 15 minutes after drinking water was 62 ± 3 bpm with 50 mL of water and 60 ± 2 bpm with 500 mL of water (P = NS; Figure 2, top). Water drinking (either quantity) did not change stroke volume or cardiac output in the supine position. However, supine total peripheral resistance measured by impedance cardiography increased after drinking 500 mL of water to 106 ± 1% of baseline value (compared with 100 ± 1% after 50 mL of water, P < 0.01; Figure 3, bottom). Supine forearm blood flow velocity decreased 2.4 ± 1.2 cm/s after drinking 500 mL of water (P < 0.01) but not after drinking 50 mL of water.

Effects of Water Drinking on Hemodynamic Responses to Head-Up Tilting

After 10 minutes of 60° head-up tilt, heart rate was 78 ± 3 bpm with 50 mL of water and 69 ± 2 bpm with 500 mL of water (P < 0.001; Figure 2, top). Brachial blood pressure was 121 ± 3/75 ± 2 mm Hg after 50 mL of water and 123 ± 2/79 ± 2 mm Hg after 500 mL of water (P < 0.05 for diastolic blood pressure; P = NS for systolic blood pressure; Figure 2, middle and bottom). The decrease in stroke volume with head-up tilting was blunted after drinking 500 mL of water (−45 ± 2% with 50 mL, −38 ± 3% with 500 mL of water; P < 0.01; Figure 3, top). The tilt-induced changes in cardiac output and total peripheral resistance were similar during both interventions (Figure 3, middle and bottom). Supine thoracic impedance and the change in thoracic impedance with upright posture were also similar after drinking 50 mL or 500 mL of water (Figure 4).

Cerebral Blood Flow Velocity and Cerebral Autoregulation

Water drinking had no effect on supine blood flow velocity (change in blood flow velocity, −1.8 ± 2.6 cm/s with 50 mL of water and −6.6 ± 4.0 cm/s with 500 mL of water). With head-up tilt, blood flow velocity decreased 19 ± 3% with 50 mL of water and 12 ± 4% with 500 mL of water (P = NS). Calculated cerebral blood pressure decreased with tilting, but no difference was found between the two tests. Cerebral
vascular resistance also showed no significant differences between the two tests. The autoregulation index was lower after the 500-mL water drink (0.7±0.1 to 0.5±0.1, P<0.03) (Figure 5). We found a correlation between the autoregulation index and orthostatic tolerance for all data combined (P<0.05), but only a trend when analyzed separately for the two treatment groups.

Water drinking had no influence on end-tidal CO₂ concentrations, neither while supine nor during the tilt test.

Heart Rate and Blood Pressure Variability and Baroreflex Sensitivity
In the supine position there was no significant effect after water drinking on heart rate or blood pressure variability (Table 2). Drinking 500 mL of water attenuated the decrease in heart rate variability with head-up tilt. In particular, water drinking blunted the decrease in heart rate variability in the high-frequency range. The baroreflex sensitivity during head-up tilt tended toward higher values after water (Table 2).

Discussion
To give people who fainted "a glass of water" may be common sense. Our study shows that drinking 500 mL of water increases orthostatic tolerance in most healthy subjects within 15 minutes. The test subjects were able to withstand the severe orthostatic stress of a combination of head-up tilt...
tilting and lower body negative pressure for an average of 5 additional minutes. The combination of head-up tilting with lower body negative pressure exerts a much greater orthostatic stimulus than regular standing. Therefore, the ability to withstand the test for ≥5 minutes represents a major improvement in orthostatic tolerance. Changes of this magnitude in patients with attacks of syncope or presyncope are associated with considerable symptomatic improvements.19 Subjects with lower orthostatic tolerance had the greatest improvement in orthostatic tolerance. In an earlier study, cardiovascular and hematologic responses to tilt testing were examined after 26 hours of dehydration and after oral rehydration.7 After dehydration, 2 of 6 subjects had severe presyncopal symptoms during head-up tilt. After rehydration, symptoms occurred in none of the subjects. Dehydration and hydration were assessed in a sequential fashion in that study, which is a potential weakness. The risk for neurally mediated syncope decreases markedly with repeated tilt testing, so which is a potential weakness. The risk for neurally mediated syncope decreases markedly with repeated tilt testing, so dehydration and intake. Drinking 500 mL9 or even 1000 mL12 of water does not change plasma volume more than 1% to 2%. Finally, thoracic impedance in the supine and upright positions was not influenced by water drinking.23 Therefore, it is highly unlikely that the improvement of orthostatic tolerance after water drinking is merely a volume effect.

Water drinking led to hemodynamic changes that are not related to changes in plasma volume. In the supine position, water drinking induced a small increase in peripheral resistance. Other studies have shown that water drinking also increased leg vascular resistance in healthy young subjects.13 Mean arterial pressure was slightly increased compared with the control intervention. Similarly, in previous studies, water drinking caused little or no change in resting blood pressure in young healthy subjects.9,24,25 In healthy young subjects, the change in vascular tone in the limbs with water may be in part compensated by opposing changes in other vascular beds. In contrast, patients with impaired baroreflex buffering function caused by autonomic failure have a profound pressor response to water drinking.8,21 The change in vascular tone is presumably related to sympathetic activation. The pressor effect of water in patients with autonomic failure is almost completely abolished with ganglionic blockade.9 Furthermore, water drinking increases venous plasma norepinephrine concentrations.9,13 Finally, sympathetic nerve traffic to the leg increases with water drinking.13

The water drinking–induced change in sympathetic vasoconstrictor tone may have improved the hemodynamic response to upright posture in our study. Drinking 500 mL of water decreased upright heart rate moderately and attenuated the orthostatic decrease in heart rate variability. Furthermore, baroreflex sensitivity was better maintained with standing. The predominant effect of water drinking on upright heart rate variability in the high-frequency range may suggest a baroreflex-mediated increase in parasympathetic tone.24 The effect of water drinking on upright heart rate is even more pronounced in patients with idiopathic orthostatic intolerance.11 Treatment with α-adrenoreceptor agonists results in a similar reduction in upright heart rate.27 Interestingly, the

### Table 2. Heart Rate Variability, Blood Pressure Variability, and Baroreflex Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Head-Up Tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500 mL</td>
<td>50 mL</td>
</tr>
<tr>
<td>Rmssd, ms</td>
<td>96±13</td>
<td>83±11</td>
</tr>
<tr>
<td>pnn50, %</td>
<td>31±4</td>
<td>31±5</td>
</tr>
<tr>
<td>HF_RRI, ms²</td>
<td>970±200</td>
<td>860±200</td>
</tr>
<tr>
<td>LF_RRI, ms²</td>
<td>2000±420</td>
<td>1700±610</td>
</tr>
<tr>
<td>LF/HF_RRI</td>
<td>2.5±0.4</td>
<td>1.9±0.3</td>
</tr>
<tr>
<td>HF_SBP, mm Hg²</td>
<td>3.3±0.9</td>
<td>3.3±1.3</td>
</tr>
<tr>
<td>LF_SBP, mm Hg²</td>
<td>11±3</td>
<td>11±3</td>
</tr>
<tr>
<td>BRS_LF, ms/mm Hg</td>
<td>18±3</td>
<td>19±3</td>
</tr>
<tr>
<td>BRS+, ms/mm Hg</td>
<td>22±2</td>
<td>24±3</td>
</tr>
<tr>
<td>BRS–, ms/mm Hg</td>
<td>21±3</td>
<td>22±3</td>
</tr>
</tbody>
</table>

Measurements were obtained 15 minutes after drinking 50 mL or 500 mL (supine) and again after 10 minutes of 60° head-up tilt. Rmssd indicates square root of the mean squared differences of successive normal-to-normal intervals; pnn50, proportion of successive normal-to-normal interval differences >50 ms; HF_RRI and LF_RRI, R-R variability in the high- and low-frequency ranges; HF_SBP and LF_SBP, blood pressure variability in the high- and low-frequency ranges; BRS_LF, baroreflex slope in the low-frequency range; BRS+ and BRS–, baroreflex slope for upsloping and downsloping blood pressure sequences.
α-adrenergic receptor agonist midodrine is one of the few drugs that reduces the occurrence of neurally mediated syncope.\textsuperscript{26,29} The improvement in orthostatic tolerance with water drinking may be related to a similar mechanism.

Our experiments indicate that cerebral vascular autoregulation may also be improved after water drinking, since cerebral blood flow was maintained stable over a broader range of blood pressure values in our subjects. The change in cerebral autoregulation may contribute to the increase in orthostatic tolerance with water drinking. Indeed, we found a trend toward a relation between autoregulation index and orthostatic tolerance.

The main limitation of our study is the open design. However, it is almost impossible to test the effect of water drinking in a double-blind fashion. It could be suggested that the decision to terminate the tilt study may have been influenced by the treatment status. Therefore, the hemodynamic responses at the end of the tilt study were evaluated independently by two blinded investigators who were not present during the experiments. At the end of the tilt study, all subjects exhibited a rapid decline in blood pressure and/or heart rate or substantial orthostatic tachycardia. Blood pressure and heart rate at the very end of the tilt protocol were similar with 50 and 500 mL of water drinking. Thus, the difference in orthostatic tolerance between interventions cannot be explained by differences in the termination of the study.

We conclude that drinking 500 mL of water substantially increases orthostatic tolerance in healthy subjects. In particular, water drinking delays the onset of neurally mediated presyncope. This effect appears to be mediated by an improvement in both systemic and cerebral hemodynamics with orthostatic stress. The effect cannot be explained by increasing plasma volume alone. Thus, water drinking may serve as an adjunctive treatment in patients with neurally mediated syncope. We usually recommend that the daily fluid intake should be in the range of 2 to 3 liters in such patients. However, the timing of the water intake is of major importance. Patients should drink most of the water before a situation that might precipitate syncope, such as prolonged standing or heat exposure.

Acknowledgments
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References