The Pressor Response to Water Drinking in Humans
A Sympathetic Reflex?

Jens Jordan, MD; John R. Shannon, MD; Bonnie K. Black, BSN; Yasmine Ali, BS; Mary Farley; Fernando Costa, MD; Andre Diedrich, MD; Rose Marie Robertson, MD; Italo Biaggioni, MD; David Robertson, MD

Background—Water drinking increases blood pressure profoundly in patients with autonomic failure and substantially in older control subjects. The mechanism that mediates this response is not known.

Methods and Results—We studied the effect of drinking tap water on seated blood pressure in 47 patients with severe autonomic failure (28 multiple system atrophy [MSA], 19 pure autonomic failure patients [PAF]). Eleven older controls and 8 young controls served as control group. We also studied the mechanisms that could increase blood pressure with water drinking. Systolic blood pressure increased profoundly with water drinking, reaching a maximum of 33\(\pm\)6 mm Hg in MSA and 37\(\pm\)7 in PAF mm Hg after 30 to 35 minutes. The pressor response was greater in patients with more retained sympathetic function and was almost completely abolished by trimethaphan infusion. Systolic blood pressure increased by 11\(\pm\)2.4 mm Hg in elderly but not in young controls. Plasma norepinephrine increased in both groups. Plasma renin activity, vasopressin, and blood volume did not change in any group.

Conclusions—Water drinking significantly and rapidly raises sympathetic activity. Indeed, it raises plasma norepinephrine as much as such classic sympathetic stimuli as caffeine and nicotine. This effect profoundly increases blood pressure in autonomic failure patients, and this effect can be exploited to improve symptoms due to orthostatic hypotension. Water drinking also acutely raises blood pressure in older normal subjects. The pressor effect of oral water is an important yet unrecognized confounding factor in clinical studies of pressor agents and antihypertensive medications. (Circulation. 2000;101:504-509.)

Key Words: blood pressure ■ norepinephrine ■ water

The mechanisms that maintain water and electrolyte homeostasis in humans are relatively well-understood. Abnormalities in this balance and the physiological consequences of these abnormalities have been the focus of much research. Thus, fluid intake has often been viewed as just one of many regulatory factors in volume- and osmoregulation. Water ingestion increases blood pressure in several animal species.1,2 In humans, however, research on short-term cardiovascular effects of water drinking has been neglected, and the issue is not addressed in major physiology texts. The possibility that water drinking may have short-term cardiovascular effects came to our attention through observations made by patients with severe orthostatic hypotension due to autonomic failure. Several of these patients reported a substantial decrease in the severity of their orthostatic symptoms shortly after drinking water. We showed that drinking 480 mL water increased seated blood pressure 43 mm Hg in patients with autonomic failure and 11 mm Hg in older control subjects.3 This finding prompted us to further investigate the short-term effect of water drinking on blood pressure in patients with autonomic failure and in young and older normal controls. Furthermore, we endeavored to define the mechanism or mechanisms that could contribute to the pressor effect with water drinking.

Methods

Subjects
We studied 47 patients with primary autonomic failure4 referred for disabling orthostatic hypotension. Twenty-eight patients (20 males, 8 females, 66\(\pm\)1 years) had multiple system atrophy (MSA, Shy-Drager syndrome), and 19 (8 males, 11 females, 72\(\pm\)2 years) had pure autonomic failure (PAF, Bradbury-Eggleston syndrome).4 Patients with secondary causes of autonomic failure (eg, diabetes mellitus, amyloidosis) were excluded. In addition, 11 older controls (7 males, 4 females, 57\(\pm\)2.2 years) and 8 younger controls (2 males, 6 females, 25\(\pm\)0.9 years) were recruited. Written informed consent was obtained before study entry. All studies were approved by the Vanderbilt institutional review board.
Protocol
Vasoactive medications and fludrocortisone were discontinued at least 5 half-lives before testing. Studies were conducted at least 2.5 hours after breakfast or lunch. All blood samples were taken from an antecubital heparin lock placed at least 30 minutes before sampling. In patients, supine and upright blood pressure, heart rate, and plasma catecholamines were determined. Patients and controls underwent autonomic reflex testing that included determination of respiratory sinus arrhythmia, a Valsalva maneuver, handgrip testing, and cold pressor testing.\(^3\) In addition, we conducted studies to determine the short-term cardiovascular effects of oral or intravenous water or oral yohimbine.

Oral and Intravenous Water Trials
In all patients and control subjects, the short-term effect of water drinking on seated blood pressure was determined. Subjects were seated in a chair with their feet on the floor. An automated brachial blood pressure cuff (Dinamap, Critikon) was used. After 30 minutes of baseline recording, subjects were given 480 mL tap water and encouraged to drink it as quickly as possible. Seated blood pressure and heart rate were recorded every 5 minutes for the next 90 minutes in patients, and for the next 60 minutes in control subjects. In controls subjects, we obtained venous blood samples for the determination of hematocrit, plasma catecholamines, vasopressin, and plasma renin activity at baseline, and 30 and 60 minutes after water ingestion. In 4 patients, the pressor response to drinking water at 2 different temperatures (9 \(\pm\) 1.2°C) was determined. In 6 patients, the blood pressure effects of drinking 480 mL and 240 mL on separate occasions were compared. In 5 patients, the effect on blood pressure and plasma volume of drinking 480 mL tap water was compared with the blood pressure effect an equal volume of 5% dextrose in water infused intravenously over a 60-minute period.

Oral Yohimbine Trial
Fifteen patients were tested on a separate day with 5.4 mg oral yohimbine with 50 mL tap water; blood pressure was recorded in a manner identical to the oral water trial. The pressor response to yohimbine was compared with that of water.

Oral Water During Ganglionic Blockade
In 2 patients with autonomic failure due to multiple system atrophy and in 7 younger control subjects, the pressor effect of water after complete blockade of the autonomic ganglia was determined. Subjects were studied while supine. In control subjects, an arterial line was placed for continuous blood pressure measurement. \(N^\_\)cholinergic receptors were blocked by continuous infusion of trimethaphan (Arfonad, Hoffmann La-Roche) starting at a rate of 6 mg/min.\(^6\) We defined complete blockade of the efferent arc of the baroreflex as \(< 1\) beat per minute (bpm) change in heart rate with a 25 mm Hg increase or decrease in systolic blood pressure obtained with bolus doses of phenylephrine and nitroprusside, respectively.\(^7\) When this end point was reached, the head of the bed was raised slightly to allow for water drinking. The subjects drank 480 mL tap water. The trimethaphan infusion was continued at a constant rate during the period of recording.

In the autonomic failure patients, trimethaphan was infused starting at a rate of 0.5 mg/min. The infusion rate was doubled every 6 minutes until no further change in blood pressure or heart rate occurred (maximum dose 8 mg/min). When this end point was achieved, the head of the bed was raised slightly, and the subjects drank 480 mL tap water while the trimethaphan infusion was continued at a constant rate.

Analytical Methods
Plasma catecholamines and plasma renin activity were determined by standard methods.\(^8,9\) Plasma vasopressin levels were determined by a radioimmunoassay. Hematocrit was determined in quadruplicate using microcapillary tubes (International Equipment Co, Model MB) centrifuged at 11 500 rpm for 10 minutes. Relative plasma volume changes were determined on the basis of changes in the hematocrit from the baseline value.\(^10\)

Statistics
Results are presented as mean \(\pm\) SEM. Baseline characteristics of subgroups were compared by unpaired 2-tailed \(t\) test. Intraindividual comparisons were tested by paired 2-tailed \(t\) test. ANOVA was used for multiple comparisons. Potential association between parameters was assessed by linear regression analysis. The level of significance was set at \(\alpha = 0.05\).

Results
Autonomic Evaluation
Supine blood pressure was similar in MSA (157 \(\pm\) 5.2/85 \(\pm\) 3.4 mm Hg) and PAF (165 \(\pm\) 11/83 \(\pm\) 6; Table 1). Supine blood pressure was lower in younger (109 \(\pm\) 4.4/70 \(\pm\) 2.5 mm Hg) and older (122 \(\pm\) 4.8/79 \(\pm\) 3.5 mm Hg) patients than in autonomic failure patients (\(P<0.01\) compared

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TABLE 1. Autonomic Reflex Testing

<table>
<thead>
<tr>
<th></th>
<th>MSA</th>
<th>PAF</th>
<th>Older Controls</th>
<th>Younger Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine SBP, mm Hg</td>
<td>157 (\pm) 5.2</td>
<td>165 (\pm) 11</td>
<td>122 (\pm) 4.8</td>
<td>109 (\pm) 4.4</td>
</tr>
<tr>
<td>(\Delta)SBP, mm Hg</td>
<td>(-70\ \pm\ 4.7)</td>
<td>(-82\ \pm\ 9.0)</td>
<td>8 (\pm) 4.8</td>
<td>5 (\pm) 5.1</td>
</tr>
<tr>
<td>(\Delta)HR, mm Hg</td>
<td>13 (\pm) 2.2</td>
<td>10 (\pm) 3.4</td>
<td>8 (\pm) 3.2</td>
<td>7 (\pm) 4.0</td>
</tr>
<tr>
<td>SA ratio</td>
<td>1.08 (\pm) 0.01</td>
<td>1.09 (\pm) 0.09</td>
<td>1.24 (\pm) 0.04</td>
<td>1.42 (\pm) 0.04</td>
</tr>
<tr>
<td>Valsalva II, mm Hg</td>
<td>(-62\ \pm\ 5.6)</td>
<td>(-87\ \pm\ 12)</td>
<td>(-13\ \pm\ 6.3)</td>
<td>2 (\pm) 7.3</td>
</tr>
<tr>
<td>Valsalva IV, mm Hg</td>
<td>(-5\ \pm\ 3.7)</td>
<td>(-7\ \pm\ 8.0)</td>
<td>36 (\pm) 4.2</td>
<td>25 (\pm) 6.0</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.1 (\pm) 0.03</td>
<td>1.2 (\pm) 0.1</td>
<td>1.6 (\pm) 0.12</td>
<td>1.9 (\pm) 0.12</td>
</tr>
<tr>
<td>Hyperventilation, mm Hg</td>
<td>(-21\ \pm\ 4.5)</td>
<td>(-17\ \pm\ 9)</td>
<td>0.5 (\pm) 6.8</td>
<td>(-3\ \pm\ 2.6)</td>
</tr>
<tr>
<td>Cold pressor, mm Hg</td>
<td>6.5 (\pm) 2.0</td>
<td>18 (\pm) 8.0</td>
<td>29 (\pm) 7.6</td>
<td>22 (\pm) 1.9</td>
</tr>
<tr>
<td>Handgrip, mm Hg</td>
<td>10 (\pm) 1.7</td>
<td>2 (\pm) 5.0</td>
<td>18 (\pm) 4.7</td>
<td>15 (\pm) 1.7</td>
</tr>
</tbody>
</table>

Blood pressure responses during phases II and IV of the Valsalva maneuver, hyperventilation, cold pressor testing, and handgrip testing are given as systolic blood pressure (SBP) changes from baseline. A negative value during phase IV of the Valsalva maneuver indicates that blood pressure overshoot was absent.

\(\Delta\)SBP indicates systolic blood pressure change while standing; \(\Delta\)HR, heart rate change while standing; and SA, sinus arrhythmia.
with MSA or PAF). Younger control subjects had lower supine systolic blood pressure than older controls ($P<0.01$); blood pressure decreased $70\pm4.7/28\pm2.6$ in MSA and $82\pm9.0/28\pm3.9$ mm Hg in PAF mm Hg without an adequate increase of heart rate while patients were standing. Patients with MSA had higher plasma norepinephrine levels ($2.2\pm0.57$ nmol/L [370\(\pm96\) pg/mL]) than patients with PAF ($0.88\pm0.29$ nmol/L [150\(\pm49\) pg/mL]; $P<0.05$). Plasma norepinephrine levels increased when patients assumed the upright posture ($3.4\pm1.2$ nmol/L [580\(\pm200\) pg/mL] and $1.3\pm0.29$ nmol/L [217\(\pm49\) pg/mL] in patients with MSA and PAF, respectively). Supine plasma renin activity was relatively low in both patient groups ($0.5\pm0.1$ and $0.4\pm0.1$ ng \(\cdot\) mL\(^{-1}\) \(\cdot\) h\(^{-1}\) in MSA and PAF, respectively) and did not significantly increase with standing ($0.56\pm0.13$ and $0.67\pm0.21$ ng \(\cdot\) mL\(^{-1}\) \(\cdot\) h\(^{-1}\) in MSA and PAF, respectively).

Sinus arrhythmia was markedly reduced in patients with autonomic failure. In both patient groups, blood pressure decreased profoundly during phase II of the Valsalva maneuver, and the blood pressure overshoot during phase IV was absent or blunted. Isometric exercise (handgrip test) and pain (cold pressor test) increased systolic blood pressure less in patients than in normal controls. In most patients, hyperventilation decreased systolic blood pressure. These responses are consistent with severe sympathetic and parasympathetic failure. In older controls, the sinus arrhythmia ratio ($P<0.01$) and Valsalva heart rate ratio ($P<0.05$) were significantly lower than in the younger control group.

### Effects of Water Drinking on Blood Pressure

With water drinking, blood pressure increased $33\pm5/16\pm3$ mm Hg in patients with MSA and $37\pm7/14\pm3$ mm Hg in patients with PAF ($P<0.0001$; Figure 1). The pressor response was evident within 5 minutes after drinking started, reached a maximum after $\approx30$ to 35 minutes, and was sustained for $>60$ minutes. Heart rate decreased $5\pm0.7$ bpm in MSA and $2\pm0.8$ bpm in PAF ($P<0.001$). The pressor response after drinking either cold or warm water was almost identical (Figure 2a). Drinking 480 mL caused a greater pressor response than drinking 240 mL water (Figure 2b). Water drinking also increased systolic blood pressure in healthy older controls, approaching a maximum of $11\pm2.4$ mm Hg $\approx35$ minutes after drinking ($P<0.001$; Figure 3). There was a concomitant decrease in heart rate of $5.4\pm1.8$ bpm below baseline 20 minutes after drinking ($P<0.001$). There was no significant change in blood pressure or heart rate in younger controls. Figure 4 illustrates individual changes in systolic blood pressure in all groups during the 60 minutes after water drinking. Data are expressed as area under the curve.

### Effects of Water Drinking on Plasma Volume

In older controls, plasma volume changed by $-0.1\pm0.9\%$ and $-1.2\pm0.8\%$ 30 and 60 minutes, respectively, after water drinking. In younger controls, plasma volume changed by $-1.0\pm0.9\%$ and $-1.6\pm0.9\%$ 30 and 60 minutes, respectively, after water drinking. Similarly, there was no increase in plasma volume in 5 patients with autonomic failure after water drinking ($-0.2\pm0.7\%$ after 30 minutes). In the same patients, plasma volume increased by $5.3\pm2.0\%$ ($P<0.05$) after intravenous administration of 480 mL 5\% dextrose in water. In these patients, oral water increased systolic blood pressure $52\pm2.0$ mm Hg, but intravenous administration of 480 mL 5\% dextrose in water increased systolic blood pressure only $18\pm14$ mm Hg.

### Effects of Water Drinking on Plasma Catecholamines, Renin, and Vasopressin

Thirty minutes after water drinking, plasma norepinephrine increased in all 11 of the older control subjects (by $0.61\pm0.29$ nmol/L [103\(\pm49\) pg/mL], $P<0.05$) and in 6 of 7 younger controls (by $0.69\pm0.41$ nmol/L [116\(\pm70\) pg/mL], $P=0.14$). In older and younger controls, plasma vasopressin levels and plasma renin activity did not change significantly with water drinking (Table 2). Similarly, plasma vasopressin concentration did not change significantly in autonomic failure patients ($1.6\pm0.2$ pg/mL at baseline, $1.6\pm0.2$ pg/mL 30 minutes after drinking, n=6) after water drinking. Plasma renin activity did not change after water drinking in 2 autonomic failure patients who did have a pressor response.

### Effects of Water Versus Yohimbine on Blood Pressure

The 15 autonomic failure patients who were tested with both water and yohimbine on separate days were stratified according to their response to water (area under the curve) into 3 groups of 5 patients each (small, intermediate, and large
Patients with a greater pressor response to water also had a greater pressor response to yohimbine \((P < 0.01)\); Figure 5). The response to yohimbine was quantified by calculating the area under the curve of systolic blood pressure change between 30 and 90 minutes after the drug was given.

**Effects of Water During Ganglionic Blockade**

In younger normal controls, the infusion rate of trimethaphan that completely abolished baroreflex function was 6.6 ± 0.3 mg/min. Blood pressure decreased from 134 ± 4.2/71 ± 2.6 mm Hg at baseline to 98 ± 3.1/54 ± 2.6 mm Hg, and heart rate increased from 63 ± 3.0 to 83 ± 3.6 bpm with complete ganglionic blockade \((P < 0.0001)\). Blood pressure did not change with water drinking during ganglionic blockade. Plasma norepinephrine concentration decreased from 1.3 ± 0.12 nmol/L (220 ± 21 pg/mL) at baseline to 0.31 ± 0.03 nmol/L (53 ± 5.0 pg/mL) with complete ganglionic blockade \((P < 0.001)\) and did not change with water drinking. The profound pressor response to water drinking in 2 MSA patients was almost completely eliminated with blockade of sympathetic and parasympathetic ganglia (Figure 6).

**Discussion**

These studies demonstrate that water drinking acutely elicits a profound pressor response in patients with autonomic failure. Water drinking also increases blood pressure in older normal control subjects, but it had no effect on blood pressure or heart rate in younger control subjects. Plasma volume, plasma renin activity, and plasma vasopressin concentration did not change with water drinking. If the pressor response to water drinking were mediated through an increase in plasma volume or release of a humoral factor, it should be augmented during complete ganglionic blockade. Ganglionic blockade, a condition which mimics complete autonomic failure,\( ^{6} \) pro-

### TABLE 2. Plasma Renin Activity and Vasopressin Before and After Water Drinking

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 Minutes</th>
<th>60 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal older</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>2.0 ± 0.23</td>
<td>2.9 ± 0.6</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>PRA</td>
<td>0.69 ± 0.4</td>
<td>0.61 ± 0.3</td>
<td>0.4 ± 0.06</td>
</tr>
<tr>
<td><strong>Normal young</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>2.1 ± 0.4</td>
<td>1.7 ± 0.34</td>
<td>1.9 ± 0.32</td>
</tr>
<tr>
<td>PRA</td>
<td>0.92 ± 0.22</td>
<td>0.63 ± 0.14</td>
<td>0.70 ± 0.13</td>
</tr>
</tbody>
</table>

Vasopressin concentrations are given as pg/mL. Plasma renin activity (PRA) is given as ng angiotensin I produced per liter of plasma per hour. Blood samples were obtained after a 30-minute baseline period in the seated position just before water drinking, 30 minutes after water drinking, and 60 minutes after water drinking.
foundly increases the sensitivity to pressor agents\(^7,11\) and to changes in cardiac preload.\(^6\) However, water drinking did not elicit a pressor response in younger controls during ganglionic blockade. Moreover, water drinking did not increase blood pressure in autonomic failure patients when residual autonomic transmission was blocked with trimethaphan.

The demonstration that the pressor response was not enhanced but rather was abolished during interruption of ganglionic transmission indicates that sympathetic or parasympathetic transmission are required. Sympathetic activation is implicated by the observations that \(\alpha\)-adrenoreceptor blockade with phentolamine abolishes the pressor effect of water drinking in animals,\(^1\) and that yohimbine (which acts through sympathetic activation)\(^8,12\) had a greater pressor effect in patients who displayed a pronounced pressor effect to water than it did in patients with a moderate or absent pressor response to water. Finally, in both younger and older controls plasma norepinephrine levels increased after water drinking by a magnitude at least as great as that elicited by smoking 2 unfiltered cigarettes (97 pg/mL increase)\(^13\) or ingesting 250 mg caffeine (102 pg/mL increase)\(^14,15\). The increase in plasma norepinephrine concentrations could be due to sympathetic activation causing increased spillover of norepinephrine from adrenergic synapses into the systemic circulation or to a decrease in norepinephrine clearance.\(^16–18\)

It seems paradoxical that a pressor response driven by sympathetic activation could be exaggerated in patients with severe autonomic failure, a condition that has previously been conceptualized as a deficiency in autonomic function.\(^19,20\) In autonomic failure patients, the loss of sympathetic and parasymathetic function is less complete than that observed during complete ganglionic blockade in normal subjects.\(^6\) Yohimbine, an \(\alpha_2\)-adrenergic antagonist, increases sympathetic activity centrally and augments norepinephrine release from postganglionic adrenergic nerve endings.\(^12\) Yohimbine substantially increases blood pressure in a large subgroup of autonomic failure patients.\(^12,21,22\) It does not elicit a pressor response during ganglionic blockade in normal controls.\(^23\) In contrast, clonidine, an \(\alpha_2\)-adrenergic agonist, decreases blood pressure in some autonomic failure patients and can increase blood pressure in others.\(^24\) Therefore, the loss of sympathetic function, even in patients with severe autonomic failure, is less complete than is commonly believed.

Even though patients with autonomic failure may be able to release norepinephrine, their capacity to do so is less than it is in normal subjects.\(^18\) Thus, in autonomic failure, the smaller amount of norepinephrine released causes a greater increase in blood pressure. This phenomenon could be explained by upregulation of vascular \(\alpha_1\)-adrenoreceptors\(^25,26\) or by impaired baroreflex buffering.\(^7,27\) Impairment of baroreflex function with aging\(^28\) might explain the observation that water drinking increased blood pressure in normal older but not younger controls. The afferent pathways that lead to sympathetic activation with water drinking in humans are not known. In dogs, vagotomy abolishes the pressor effect of moderate gastric distention with fluids or a balloon.\(^2\) Possible factors that might trigger or modulate the pressor response to drinking are distention of abdominal viscera, as well as osmolarity and temperature of the fluids that are given. When different fluids were infused into the stomachs of dogs, distilled water was shown to cause a 2-fold greater increase in blood pressure than normal saline.\(^2\) In humans, infusion of
hypooosmolar solutions through a gastric tube causes a greater increase of sweat production, a sympathetic response, than infusion of isoosmolar solutions.29 In our study, temperature did not affect the pressor response to water.

Drinking water can provide a rapid relief of symptoms resulting from orthostatic hypotension in autonomic failure patients. This intervention is particularly useful in the morning (when orthostatic hypotension tends to be more severe) and can bridge the time required for oral medications to start working. In some patients, water drinking increases systolic blood pressure by >100 mm Hg, which can result in dangerously high blood pressure in the supine position. In these patients, water drinking should probably be avoided for ~1.5 hours before retiring. Another important implication of this study is that oral water intake needs to be controlled in short-term pharmacological studies of pressor agents or antihypertensive medications.

We conclude that drinking water rapidly raises sympathetic activity. In autonomic failure patients, this increase in sympathetic activity coupled with the incapacity to buffer any pressor stimulus profoundly increases blood pressure. It also substantially increases blood pressure in older but not detectably in younger controls. The pressor effect of oral water is an important, unrecognized confounding factor in clinical studies of pressor agents and antihypertensive medications. However, this effect can be exploited to improve symptoms resulting from orthostatic hypotension in patients with autonomic failure.

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