Water Ingestion as Prophylaxis Against Syncope

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Background—Water ingestion raises blood pressure substantially in patients with perturbed autonomic control and more modestly in older subjects. It is unclear whether prophylactic water drinking improves orthostatic tolerance in normal healthy adults.

Methods and Results—Twenty-two healthy subjects, 18 to 42 years of age, with no history of syncope underwent head-up tilt-table testing at 60° for 45 minutes or until presyncope or syncope occurred. In their initial test, participants were randomized to either 16 oz (473 mL) of water drinking 5 minutes before tilt-table testing or tilt-table testing alone, with the alternative in a second test on a different day. During the first 30 minutes of tilt, 8 of 22 subjects without water experienced presyncope but only 1 of 22 who had ingested water (P=0.016). Water drinking attenuated the heart rate increase associated with tilt (P<0.001) while accentuating the increase in total peripheral resistance (P=0.012). The average time study participants tolerated head-up tilt was 26% longer after water (41.1±8.1 versus 32.6±14.3 minutes, mean±SD), with a pairwise mean difference of 8.5±14.0 minutes (95% CI, 2.3 to 14.7 minutes; P=0.011).

Conclusions—Water enhances tolerance of upright posture. The effect of water is mediated by increased peripheral vascular resistance. Water ingestion may constitute a simple and effective prophylaxis against vasovagal reactions in healthy subjects, such as those associated with blood donation. (Circulation. 2003;108:2660-2665.)

Key Words: syncope ■ water ■ test, tilt table ■ hypotension, orthostatic ■ norepinephrine

Syncope, the sudden brief loss of consciousness caused by diminished cerebral blood flow, occurs at least once in almost 22% of the population, and 9% have recurrent syncope.1 It occurs in both children2 and adults and is responsible for ≈6% of emergency room visits and 3% of hospitalizations.3 Most syncopal events are triggered by standing or emotion and are often referred to as vasovagal reactions.4 Under certain circumstances, such as blood donation, syncope has important medical and societal significance. More than 150 000 people experience syncope or near-syncope each year at the time of blood donation to the American Red Cross.5 Reducing such syncopal reactions could have a beneficial impact on donor convenience, safety, and desire to donate again. Currently, in blood donation facilities, the major preventive strategies against syncope focus on postdonation food and beverage, with little emphasis on predonation factors, such as water drinking.

When vasovagal syncope occurs frequently, pharmacological agents and pacemakers6,7 are used, but therapy is expensive, efficacy is questionable, and adverse effects are common.8 We have shown previously that water ingestion raises blood pressure ≈30 mm Hg in patients with abnormal autonomic control9 and more modestly in older normal subjects.10 Tilt-table testing provides a means of calibrating orthostatic tolerance and assessing factors that influence it.11,12 We tested the hypothesis that water ingestion would enhance orthostatic tolerance. We also aimed to address the underlying physiology of this effect.

Methods

Subjects

The study was approved by the Institutional Review Board of Vanderbilt University and conducted in the General Clinical Research Center. We studied 22 healthy, normal adults (11 male and 11 female) with no history of syncope and not currently using any prescription or over-the-counter medication except for oral contraceptives.

Study Protocol

We used a randomized, crossover study design. Each subject underwent the study protocol twice on separate days. Subjects received either tilt test with water or tilt test without water in their initial study, with the alternative in their second test. Room-temperature tap water (16 oz [473 mL]) was ingested 5 minutes before head-up tilt. Analysis of the water demonstrated 5.1 mg/L sodium, 7.6 mg/L chloride, and 76 mg/L calcium, with a pH of 7.2.
Caffeine-containing beverages, nicotine, and alcohol were prohibited for 1 week before the study. Subjects were placed on a calculated diet containing 150 mmol sodium and 70 mmol potassium for ≥3 days before testing. The volunteers took no food or beverage from midnight until the testing session on the subsequent morning. Study sessions took place in a quiet, dimly lit room at a comfortable ambient temperature (70°F to 75°F; 21°C to 24°C).

**Instrumentation**

An antecubital venous catheter for blood sampling was inserted ≥15 minutes before the beginning of the test, with the patient in the supine position. Heart rate and blood pressure were monitored by finger volume-clamp method (Finapres, 2300, Ohmeda), which provided continuous, noninvasive heart rate and pressure measurements. Baseline Finapres blood pressures were calibrated against cuff pressure from a Dinamap vital signs monitor (Critikon Company LLC) before data collection. Thoracic bioimpedance was monitored continuously for cardiac output, respiration, and peripheral vascular resistance (Thrim model 2994D, UFI).

**Head-Up Tilt-Table Test**

All studies began at 8:30 AM and finished by 10:30 AM. Data acquisition began after a 30-minute supine adaptation. After a further resting period of 10 minutes in the supine position, subjects were tilted at angles chosen to graduate orthostatic stress. Head-up tilt was stepwise (0°, 15°, 30°, 45°, 60°) at 3-minute intervals (Tilt Table, BETA plus, Berne Manufacturing Co). Subjects then remained tilted for 45 minutes or until presyncope symptoms were observed. Syncope was defined as a systolic pressure <70 mm Hg and heart rate <50 bpm. Presyncope was defined as a fall in blood pressure of ≥30 mm Hg with a concomitant fall in heart rate of ≥10 bpm, or a fall in heart rate of ≥30 bpm with a concomitant fall in blood pressure of ≥10 mm Hg. These hemodynamic end points were assessed from tracings by 2 independent evaluators not involved in the protocol itself and blinded to the intervention group.

**Analytical Methods**

Blood samples for catecholamines were obtained and assayed as previously described.13 Samples were collected at −5, 0, 10, 15, 30, and 45 minutes of the study. In addition, blood was taken for assay 1 minute after the onset of presyncope or syncope for estimation of plasma volume change.13–15 Signals for blood pressure, the ECG, and bioimpedance were sampled at 500 Hz using Dataq model DI-220 and visualized using Windaq Pro software (Visual Numerics Inc). Total recordings of R-R interval, finger blood pressure, and bioimpedance were sampled at 500 Hz using Dataq model DI-220 and visualized using Windaq Pro software (Visual Numerics Inc). Complete recordings of R-R interval, finger blood pressure, and respiration were analyzed offline with a program based on PV-wave software (Visual Numerics Inc). Total peripheral resistance was calculated from the mean brachial blood pressure and cardiac output.

**Statistics**

Our primary end point was time until presyncope. The null hypothesis was that this time would not be statistically different between the tilt-table study after water ingestion and the study without water. A sample size of 22 was estimated to have 80% power to detect an effect size (difference between the means divided by the SD of the difference) of 0.6 with a paired t test with a 2-sided significance level of 0.05.15 A Pearson χ² test or Fisher’s exact test was used to assess categorical baseline comparisons. McNemar’s test was used to compare the pairwise presyncope concordance during the water and no-water phases. Differences between group means for continuous measurements were tested by Student’s t test or the Mann-Whitney U test. Before-and-after comparisons were analyzed with the paired t test or the Wilcoxon signed-rank test. A general linear model repeated-measures ANOVA was used to assess changes from baseline between the 2 phases of the study while adjusting for and assessing covariates such as the day order of the study. Cox proportional-hazards analysis was used to determine the effect of water on time to presyncope.17 Assumptions of proportional hazards were assessed by use of Schoenfeld’s residuals.18 The log-rank test was used to compare survival curves.19 Values are reported as means and SDs unless otherwise noted. Probability values of P = 0.05 were considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed with SPSS (version 11.0, SPSS).

**Results**

**Water Ingestion and Orthostatic Tolerance**

Resting baseline control data for study subjects are shown in Table 1. There were no significant baseline pairwise differences. Subjects receiving water tolerated head-up tilt-table testing 26% longer (41 ± 8 versus 33 ± 14 minutes, P = 0.011). Water increased the time by an average of 8.5 ± 14.0 (SD) minutes (95% CI, 2.3 to 14.7 minutes). Twelve participants tolerated tilt longer during the water phase, whereas only 3 had a longer tilt duration without water, but in all 3, water ingestion increased the duration by an average of 14.0 (SD) minutes (95% CI, 2.3 to 14.7 minutes).

We also examined the order effect of the 2 studies on duration of head-up tilt. Duration of tilt on the first day was 29.9 ± 14.7 minutes without water and 38.2 ± 10.4 minutes with water. On day 2, the durations were 35.3 ± 14.2 minutes without water and 44.0 ± 3.3 minutes with water. The effect of

| TABLE 1. Characteristics of the 22 Subjects Studied at Baseline (Time 0) |
|-----------------|-----------------|-----------------|-----------------|
| Age, y          | 26.6 ± 7.7      | 18–42           |
| Sex, M/F        | 11/11           | -               |
| Weight          | 160.6 ± 33.0    | 121.1–237.9     |
| kg              | 72.9 ± 15.0     | 55–108          |
| Height          | 167.3 ± 4.1     | 161.8–77        |
| inches          | 172.3 ± 10.5    | 158–197         |
| Body mass index, kg/m²* | 24.6 ± 3.5 | 19.5–31.7 |
| Blood pressure, mm Hg  | 114.0 ± 12.9 | 96–138          |
| Systolic        | 62.2 ± 6.8      | 48–76           |
| Diastolic       | 62.2 ± 6.8      | 48–76           |
| Heart rate, bpm | 65.2 ± 9.7      | 49–78           |
| Cardiac output, L/min | 5.0 ± 1.1 | 3.1–6.9          |
| Peripheral resistance, dyne · s · cm⁻⁵ | 1903 ± 514 | 1031–3165        |
| Stroke volume, mL | 74.8 ± 16.9 | 38.2–102.8       |
| Hematocrit, %   | 37.5 ± 3.3      | 31.5–42.3       |
| Epinephrine, pg/mL | 15.0 ± 8.8 | 5.9–28.1         |
| Norepinephrine, pg/mL | 151.7 ± 58.0 | 68–274           |
| Plasma DHPG, pg/mL | 809.1 ± 181.1 | 385–1191         |
| Plasma dopa, pg/mL | 1389.8 ± 298.9 | 884–1921         |

*Body mass index is weight in kilograms divided by the square of the height in meters.
water ingestion was significant ($P=0.066$), the effect order had on water (the order–water interaction) was borderline ($P=0.059$), and the order itself was nonsignificant ($P=0.964$).

**Effects of Water Ingestion on Hemodynamic Variables**

Systolic blood pressure, heart rate, cardiac output, and peripheral vascular resistance for head-up tilt with and without water were all altered significantly by tilt. Water-by-time interactions were significant for attenuation of heart rate increase associated with tilt ($P<0.001$). Heart rate rose from $65.0 \pm 10.0$ bpm at baseline to $87.2 \pm 11.2$ bpm in subjects not receiving water and from $65.7 \pm 10.9$ bpm to $80.1 \pm 9.8$ bpm in the same subjects 20 minutes after ingestion of water (Figure 3). Peripheral vascular resistance rose sharply with tilt. It then gradually declined in subjects who ingested no water but remained elevated in those who ingested water ($P<0.001$, Figure 4).

With upright posture or head-up tilt, hemoconcentration occurs as plasma volume enters the extravascular space in a gravity-dependent manner. Thus, under many circumstances, hematocrit may reflect this acute change in plasma volume. In this study, hematocrit increased significantly with head-up tilt. After 45 minutes of head-up tilt, there was a $16.7 \pm 4.8\%$ increase in hematocrit without water and $13.8 \pm 4.2\%$ increase in hematocrit with water ($P=0.065$).

**Plasma Catecholamines**

In the supine position, concentrations of plasma norepinephrine and epinephrine were within normal range. With gradual tilting, both increased and were significantly raised between 15 and 45 minutes ($P<0.001$). No significant difference in norepinephrine concentration with water versus without water was noted 15 minutes after tilt ($305 \pm 108$ versus $275 \pm 130$ pg/mL; $P=0.211$). Plasma epinephrine rose significantly in response to head-up tilt ($P<0.01$), with increases in epinephrine of $43 \pm 4.5$ pg/mL without water and $41.3 \pm 4.1$ pg/mL with water at the 30-minute time point. Plasma dihydroxyphenylglycol (DHPG) rose significantly with upright posture. In the supine position, the average plasma dopa levels were similar in subjects receiving water or tilt alone. With water ingestion and tilt, however, there was a smaller decrease in dopa at 10 and 15 minutes after head-up tilt ($P=0.041$, Figure 5).

**Discussion**

The most important new finding in this study is that water ingestion significantly improves orthostatic tolerance during head-up tilt in normal healthy adults. Whereas 8 of 22 subjects experienced hypotension/bradycardia in the first 30 minutes with tilt alone, only 1 of 22 subjects experienced these symptoms in the first 30 minutes with water ingestion and tilt. The protection afforded by water was strongly correlated with an increase in peripheral vascular resistance. Water increased tolerance time to head-up tilt by 26%. Among subjects who experienced hypotension/bradycardia, both with water and without water, all had better orthostatic tolerance with water than without.

Water ingestion itself has a large pressor effect in autonomic failure. This effect is also present in older normal subjects, is antagonized by ganglionic blockade, and is associated with increases in plasma norepinephrine and in muscle sympathetic nerve activity. Water ingestion also benefits orthostatic intolerance. We hypothesized that this effect of water ingestion might also provide a margin of protection against syncope during orthostatic stress in normal subjects.

Water ingestion interacted with the cardiovascular response to orthostatic stress by attenuating the heart rate increase induced by head-up tilt testing in our study. Although the mechanism of the lesser heart rate increase after water ingestion is unclear, a trend toward reduced heart rate after water ingestion has been observed in our previous studies of water ingestion in other conditions and indeed has been applied to reduce the orthostatic tachycardia in patients with orthostatic intolerance. Our understanding of this heart rate reduction with water is limited.

Vasovagal syncope is associated with a vasodilatation and a reduction in muscle sympathetic nerve activity together with an increase in plasma epinephrine in patients who
The potentiation of the total peripheral resistance that the resistance-enhancing effect of water was greater in the subgroup that did not have presyncope during either trial, in responses. The effect of water is especially remarkable in the faint and in patients with recurrent vasovagal syncope. The potentiation of the total peripheral resistance increase in our study subjects in response to water might suggest that water somehow abrogates these vasodilator responses. The effect of water is especially remarkable in the subgroup that did not have presyncope during either trial, in that the resistance-enhancing effect of water was greater in them.

An important factor contributing to interindividual variation in response to upright posture is orthostatic loss of plasma volume. In this study, hematocrit changes during tilt were substantial. The magnitude of this response may affect autonomic and cardiovascular mechanisms involved in the maintenance of homeostasis during upright posture. There was a trend toward less tilt-induced plasma loss among the 7

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Table 2. Individual Hemodynamic Responses to Head-Up Tilt

**Figure 3.** Heart rate (HR) during head-up tilt. Water ingestion blunts increasing heart rate response during upright tilt. *P*<0.05.

**Figure 4.** Total peripheral resistance (TPR) during head-up tilt. Water ingestion accentuated increasing TPR during tilt-table testing. *P*<0.001.
subjects who did not experience presyncope during the study. This may contribute to the stability of hemodynamics in subjects given water before the orthostatic challenge. Hematocrit slopes with tilt were steeper early in the study and less steep 30 minutes after head-up tilt. Similar observations of blood density and hematocrit measurement after water were noted by Endo et al.\textsuperscript{26} They found a biphasic change in plasma volume. Initially, there was early hemocoencentration, which they ascribed to sympathetic activation. This was followed by hemodilution, presumably because of a postabsorptive effect of the water. Together with these observations, our study results suggest that volume effects of water might become important, especially late in our head-up tilt protocol.

Previous studies have shown evidence for increased plasma norepinephrine\textsuperscript{19} or increased muscle sympathetic activity\textsuperscript{27} in response to water ingestion. We assessed plasma catecholamines and their metabolites in an effort to address the concomitant effects of water and upright posture intertwined. Plasma norepinephrine and epinephrine both rose with tilt, as did plasma DHPG. DHPG is produced predominantly intraneuronally by the action of monoamine oxidase on cytoplasmic norepinephrine. Because the DHPG is then available for release into plasma, plasma levels of this metabolite often reflect sympathetic activation and norepinephrine transporter function. The half-life of catecholamines in plasma is very short, \textasciitilde 60 to 120 seconds. Although plasma norepinephrine rose significantly with tilt, the presence or absence of water in the protocol did not seem to alter the plasma levels significantly. Similarly, plasma epinephrine levels, which rose even more dramatically, especially with presyncope, did not show significant differences with water. Dopa levels were significantly greater in patients who had received water than in those who had not. Plasma dopa levels often indicate level of activation of the enzyme tyrosine hydroxylase, which converts tyrosine to dopa in neurons. In addition, the gastrointestinal circulation is a major source of dopa production.\textsuperscript{28} The difference in dopa in this study may reflect an enhanced sympathetic activity.

The fact that heart rate was lower after water ingestion in the setting of upright tilt raises the possibility of a readjustment of baroreflex modulation of heart rate in our subjects. Such an effect could lead to lower cardiac sympathetic drive. Such a targeted decrease in sympathetic activity to the ventricles might improve tilt tolerance, in keeping with the so-called “ventricular theory” of the pathophysiology of syncope. However, the increase in plasma norepinephrine and the increase in muscle sympathetic nerve traffic in the peroneal nerve after water ingestion would be at variance with this unless the sympathetic suppression were targeted specifically to the heart.

The thorniest problem we faced in the design, conduct, and interpretation of this study was the placebo effect. All our previous studies of therapeutic interventions in autonomic disorders over the past 20 years have included a placebo. In preparation to include a placebo in this study, we undertook ancillary studies in autonomic failure patients and were able to demonstrate that 50 mL of water did not significantly raise pressure. We considered using 50 mL of water as a sort of placebo control for the 500 mL of water. Ultimately, we rejected this because, although it would technically be a placebo, in reality American study subjects would not accept 3 tablespoons of water as a true placebo because they “know” from their health classes in school that the dose of water is an 8-oz glass. However, our colleagues in Berlin and Leeds did undertake a somewhat analogous study using 50 mL of water as placebo and obtained nearly identical results in a small number of subjects.\textsuperscript{29} This strengthens the view that our results are not a result of placebo alone. However, the fact that it is perhaps impossible to provide an adequate placebo arm in our study certainly does not imply that no placebo response could occur.

Ascertainment of hemodynamic criteria assignment was validated by 2 individuals blinded to the intervention. Thus, observer bias is unlikely to be a factor in our findings. In studies of autonomic cardiovascular regulation, meticulous control of study variables is crucial. Only healthy subjects abstaining from caffeine, alcohol, and nicotine were included. We randomized the order of interventions to avoid the confounding effect of a training effect and to minimize other potential biases.

It seems remarkable that a measure as simple as water ingestion could have such a large effect on orthostatic tolerance. The important role of sodium in blood pressure control mechanisms and orthostatic intolerance is firmly entrenched in the physiological literature and is of unquestioned importance in the chronic control of blood pressure. An acute effect of water on blood pressure in human subjects, however, is not mentioned in modern texts of human physiology. Yet our previous studies in older normal subjects showed that systolic pressure rose as much as 11 mm Hg in response to water; such a change means that water ingestion most likely represents a major unrecognized source of blood pressure fluctuation from visit to visit in older subjects. Furthermore, the blunted increase in heart rate during tilt and the increase of total peripheral resistance after water ingestion will need to be taken into account in future clinical research whenever drugs are ingested with water because of the potential confounding effects of water on human hemodynamics.
The fact that acute ingestion of water exerts such profound effects may be exploited in situations in which prophylaxis against syncope is possible. In blood donation programs, a period of enhanced vulnerability to syncope occurs during and immediately after phlebotomy. Water prophylaxis against syncope might benefit blood donors. In our studies of the effect of water on blood pressure in autonomic failure, the large (30 mm Hg) increases in blood pressure observed after water ingestion were not replicated by the intravenous infusion of comparable volumes of dextrose solution.2 Thus, the caloric fluids and food usually available at blood donation centers might paradoxically be less prophylactic against syncope than the administration of water alone. Another situation in which acute administration of water might be helpful is in astronauts on return from the microgravity environment, because it might attenuate their orthostatic intolerance on return to earth.

Acknowledgments

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References

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The corrected version of this article is available online at http://circ.ahajournals.org/cgi/content/full/111/3/369. (The previous version, if needed, can be accessed by selecting the “Previous Version of This Article” link.)

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In the article by Lu et al, “Water Ingestion as Prophylaxis Against Syncope,” which appeared in the November 25, 2003, issue of the journal (Circulation. 2003;108:2660–2665), Figure 4 was not the correct figure; a duplicate of Figure 5 was inadvertently placed above the Figure 4 legend. The correct Figure 4 appears below. Its legend was correct as originally printed. We regret this error.

Figure 4. Total peripheral resistance (TPR) during head-up tilt. Water ingestion accentuated the increasing TPR during tilt-table testing. \( P < 0.001. \)

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In the March 21, 2005, online posting of the article by Bennett et al, “The Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): A Science Advisory From the American Heart Association” (Circulation. 2005;111:1713–1716; DOI: 10.1161/01.CIR.0000160005.90598.41), the discussion of the Adenoma Prevention with Celecoxib (APC) trial contained some unclear text about the results of the trial. The printed version as it appears in this issue has been changed to improve clarity, as has the online version.

DOI: 10.1161/01.CIR.0000164587.06064.83
In the article by Urbich et al, “Relevance of Monocytic Features for Neovascularization Capacity of Circulating Endothelial Progenitor Cells,” which appeared in the November 18, 2003, issue of the journal (Circulation, 2003;108:2511–2516), the authors have identified incorrect representative laser Doppler images in Figure 4. The representative images were inadvertently mixed up during electronic compilation of the original laser Doppler recordings for composition of the representative figure. The quantitative data shown in the analysis are not affected because quantitative analysis was performed using the original recordings. The corrected images for Figure 4A and 4B appear below. The authors regret this error.