

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 \pm 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 $\approx 6\%$ 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 pacemakers^{6,7} 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 auto-

nomous 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.

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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, β ETA 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 (Dataq Instruments Inc). Complete recordings of R-R interval, finger blood pressure values, 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 0.05.¹⁶ A Pearson χ^2 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

TABLE 1. Characteristics of the 22 Subjects Studied at Baseline (Time 0)

	Mean \pm SD	Range
Age, y	26.6 \pm 7.7	18–42
Sex, M/F	11/11	...
Weight		
lb	160.6 \pm 33.0	121.1–237.9
kg	72.9 \pm 15.0	55–108
Height		
inches	67.3 \pm 4.1	61.8–77
cm	172.3 \pm 10.5	158–197
Body mass index, kg/m ^{2*}	24.6 \pm 3.5	19.5–31.7
Blood pressure, mm Hg		
Systolic	114.0 \pm 12.9	96–138
Diastolic	62.2 \pm 6.8	48–76
Heart rate, bpm	65.2 \pm 9.7	49–78
Cardiac output, L/min	5.0 \pm 1.1	3.1–6.9
Peripheral resistance, dyne \cdot s \cdot cm ⁻⁵	1903 \pm 514	1031–3165
Stroke volume, mL	74.8 \pm 16.9	38.2–102.8
Hematocrit, %	37.8 \pm 3.3	31.5–42.3
Epinephrine, pg/mL	15.0 \pm 8.8	5.9–28.1
Norepinephrine, pg/mL	151.7 \pm 58.0	68–274
Plasma DHPG, pg/mL	809.1 \pm 181.1	385–1191
Plasma dopa, pg/mL	1389.8 \pm 298.9	884–1921

*Body mass index is weight in kilograms divided by the square of the height in meters.

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).²⁰

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 \pm 8 versus 33 \pm 14 minutes, $P=0.011$). Water increased the time by an average of 8.5 \pm 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. Seven completed 45 minutes of tilt during both phases. During the first 30 minutes of tilt, 64% (14 of 22) of those without water tolerated the study. This increased to 96% (21 of 22) tolerating the tilting after water ingestion (Figure 1). Water ingestion increased the cumulative proportion tolerating the tilt test significantly, from 45% to 68% ($P=0.036$; Figure 2). Three subjects experienced presyncope both with and without water, but in all 3, water ingestion increased the duration of head-up tilt (11 versus 7, 35 versus 25, and 34 versus 12 minutes; Table 2).

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 \pm 14.7 minutes without water and 38.2 \pm 10.4 minutes with water. On day 2, the durations were 35.3 \pm 14.2 minutes without water and 44.0 \pm 3.3 minutes with water. The effect of

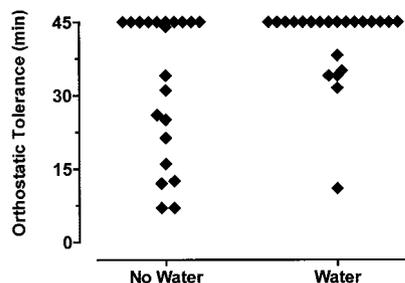


Figure 1. Duration of head-up tilt after drinking 16 oz (473 mL) of water vs no water. Mean improvement of duration of head-up tilt was 8.5 ± 14.0 minutes. $P=0.011$ by Wilcoxon signed-rank test.

water ingestion was significant ($P=0.006$), 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 ± 10.0 bpm at baseline to 87.2 ± 11.2 bpm in subjects not receiving water and from 65.7 ± 10.9 bpm to 80.1 ± 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

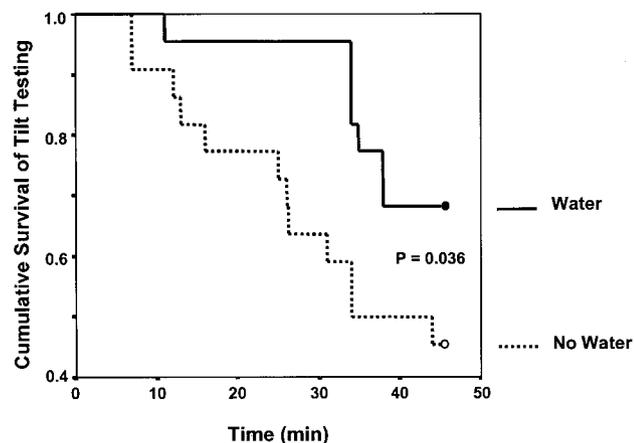


Figure 2. Kaplan-Meier curves of cumulative proportion with orthostatic tolerance (remaining free of presyncopal episodes) with and without water. At 30 minutes, 95% of those with water compared with 63% of those without water were able to tolerate tilt. At completion of study (45 minutes), 69% with water compared with 45% without water were able to tolerate tilt. $P=0.036$ by log-rank test.

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 ± 108 versus 275 ± 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 ± 4.5 pg/mL without water and 41.3 ± 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.¹⁰ Water ingestion also benefits orthostatic intolerance.²¹ 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.²¹ 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

TABLE 2. Individual Hemodynamic Responses to Head-Up Tilt

Pt. No.	Group	Sex	Water Order	With Water					Without Water				
				Duration, min	Last SBP, mm Hg	SBP Change	Last HR, bpm	HR Change	Duration, min	Last SBP, mm Hg	SBP Change	Last HR, bpm	HR Change
1	1	M	2	45.0	108	...	90	...	45.0	107	...	100	...
2	1	F	2	45.0	113	...	98	...	45.0	110	...	108	-32
3	1	M	1	45.0	114	...	84	...	45.0	117	...	98	-25
4	1	M	1	45.0	105	...	76	...	45.0	110	...	80	...
5	1	F	2	45.0	95	...	74	...	45.0	93	...	83	...
6	1	F	2	45.0	115	...	88	...	45.0	94	...	114	-30
7	1	M	1	45.0	131	...	79	...	45.0	131	...	80	-71
8	2	F	1	38.2	55	-42	60	-40	45.0	110	...	98	...
9	2	M	1	34.0	65	-64	50	-18	45.0	126	...	72	...
10	2	F	1	32.5	57	-49	50	-65	45.0	110	...	108	...
11	3	F	1	45.0	126	...	106	...	44.0	50	-70	50	...
12	3	M	2	45.0	120	...	87	...	34.0	50	-64	45	-39
13	3	M	2	45.0	113	...	90	...	31.0	45	-33	40	0
14	3	M	2	45.0	120	...	74	...	31.0	60	-43	56	-70
15	3	M	1	45.0	130	...	85	...	26.0	65	-65	40	-49
16	3	F	2	45.0	109	...	112	...	21.3	60	-45	87	...
17	3	F	1	45.0	98	...	89	...	16.0	50	-65	75	...
18	3	M	2	45.0	135	...	128	...	12.5	82	-40	58	-36
19	3	F	2	45.0	99	...	89	...	7.0	40	-61	50	-24
20	4	F	1	35.0	56	-30	54	-51	25.0	66	-32	60	-36
21	4	F	2	34.0	65	-27	55	-32	12.0	65	-68	67	...
22	4	M	1	11.0	45	-86	51	-47	7.0	55	-81	72	-32

Pt. No. denotes a patient identification No. but not the order in this study. Group 1 never experienced presyncope during either tilt-test. Group 2 experienced presyncope only during the water phase. Group 3 experienced presyncope only during the phase without water. Group 4 experienced presyncope during both phases. Water order of 1 indicates subjects who received water at the first tilt-test; 2, those who received water at the second test. Duration denotes the time from baseline to presyncope or until the end of the study (45 minutes) if presyncope did not occur. Last SBP denotes the last systolic blood pressure at the end of the test. SBP change denotes the changes in the systolic blood pressure in the last 120 seconds of the test. Last HR indicates the last heart rate in beats per minute. Change in HR indicates the change in heart rate in the last 120 seconds.

faint^{22,23} and in patients with recurrent vasovagal syncope.^{24,25} 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

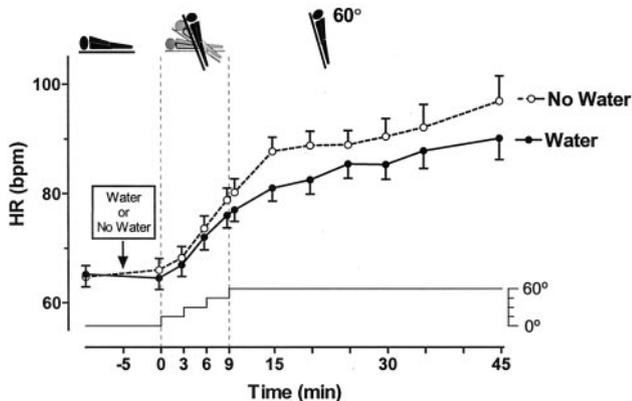


Figure 3. Heart rate (HR) during head-up tilt. Water ingestion blunts increasing heart rate response during upright tilt. $P < 0.05$.

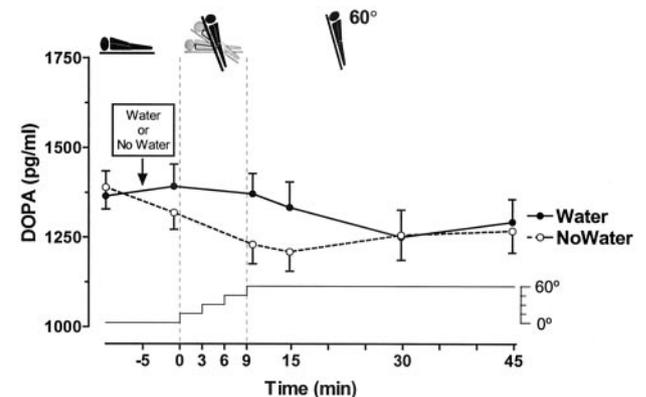


Figure 4. Total peripheral resistance (TPR) during head-up tilt. Water ingestion accentuated increasing TPR during tilt-table testing. $P < 0.001$.

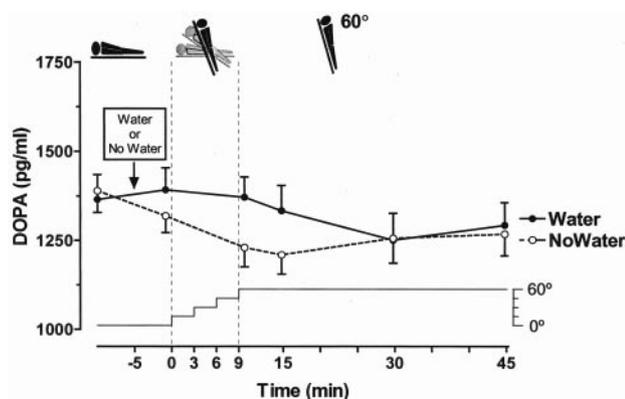


Figure 5. Changes in plasma concentration of plasma dopa comparing tilt with water vs tilt without water. Water ingestion attenuated decrease in dopa at 15 minutes after tilt. $P < 0.05$.

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.²⁶ They found a biphasic change in plasma volume. Initially, there was early hemoconcentration, 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 norepinephrine¹⁰ or increased muscle sympathetic activity²⁷ 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, ≈ 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.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.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.¹⁰ Thus, the caloric fluids and food usually available at blood donation centers might paradoxically be less prophylactic against syncope in such circumstances 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.

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References

- Chen LY, Gersh BJ, Hodge DO, et al. Prevalence and clinical outcomes of patients with multiple potential causes of syncope. *Mayo Clin Proc.* 2003;78:414–420.
- Stewart JM. Orthostatic intolerance in pediatrics. *J Pediatr.* 2002;140:404–411.
- Robertson RM, Medina E, Shah N, et al. Neurally-mediated syncope: pathophysiology and implications for treatment. *Am J Med Sci.* 1999;317:102–109.
- Kapoor WN. Syncope. *N Engl J Med.* 2000;343:1856–1862.
- Trouern-Trend JJ, Cable RG, Badon SJ, et al. A case-controlled multi-center study of vasovagal reactions in blood donors: influence of sex, age, donation status, weight, blood pressure and pulse. *Transfusion.* 1999;39:316–320.
- Sheldon R. Pacing to prevent vasovagal syncope. *Cardiol Clin.* 2000;18:81–93.
- Raj SR, Sheldon RS. Permanent cardiac pacing to prevent vasovagal syncope. *Curr Opin Cardiol.* 2002;17:90–95.
- Kapoor WN, Smith MA, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med.* 1994;97:78–88.
- Jordan J, Shannon JR, Grogan E, et al. A potent pressor response elicited by drinking water. *Lancet.* 1999;353:723.
- Jordan J, Shannon JR, Black BK, et al. The pressor response to water drinking in humans: a sympathetic reflex? *Circulation.* 2000;101:504–509.
- Grubb BP, Kimmel S. Head-upright tilt table testing: a safe and easy way to assess neurocardiogenic syncope. *Postgrad Med.* 1998;103:133–138, 140.
- Grubb BP, Olshansky B, eds. *Syncope: Mechanisms and Management.* New York, NY: Futura; 1998:1–416.
- Jacob G, Ertl AC, Shannon JR, et al. The effect of standing on neuro-humoral responses and plasma volume in healthy subjects. *J Appl Physiol.* 1998;84:914–921.
- Allen TH, Peng MT, Chen KP, et al. Prediction of blood volume and adiposity in man from body weight and cube of height. *Metabolism.* 1975;5:328–345.
- Lundvall J, Bjerkhoel P. Pronounced and rapid plasma-volume reduction upon quiet standing as revealed by a novel approach to the determination of the intravascular volume change. *Acta Physiol Scand.* 1995;154:131–142.
- Elashoff J. *nQuery Advisor Version 3.0 Users's Guide.* Los Angeles, Calif: 1999.
- Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc (A).* 1972;135:185–206.
- Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika.* 1982;69:239–241.
- Cox DR. Regression models and lifetables. *J R Stat Soc (B).* 1972;34:187–220.
- SPSS [computer program]. Version 11.0. Chicago, Ill: SPSS Inc; 2001.
- Shannon JR, Diedrich A, Biaggioni I, et al. Water drinking as a treatment for orthostatic syndromes. *Am J Med.* 2002;112:355–360.
- Mosqueda-Garcia R, Furlan R, Fernandez-Violante R, et al. Sympathetic and baroreceptor reflex function in neurally mediated syncope evoked by tilt. *J Clin Invest.* 1997;99:2736–2744.
- Morillo CA, Eckberg DL, Ellenbogen KA, et al. Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. *Circulation.* 1997;96:2509–2513.
- Jardine DL, Ikram H, Crozier IG. Autonomic control of asystolic vasovagal syncope. *Heart.* 1996;75:528–530.
- Furlan R, Piazza S, Dell'Orto S, et al. Cardiac autonomic patterns preceding occasional vasovagal reactions in healthy humans. *Circulation.* 1998;98:1756–1761.
- Endo Y, Torii R, Yamazaki F, et al. Water drinking causes a biphasic change in blood composition in humans. *Pflugers Arch.* 2001;442:362–368.
- Scott EM, Greenwood JP, Gilbey SG, et al. Water ingestion increases sympathetic vasoconstrictor discharge in normal human subjects. *Clin Sci (Colch).* 2001;100:335–342.
- Goldstein DS. *Stress, Catecholamines and Cardiovascular Disease.* New York: Oxford; 1995:1–539.
- Schroeder C, Bush VE, Norcliffe LJ, et al. Water drinking acutely improved orthostatic intolerance in healthy subjects. *Circulation.* 2002;106:2806–2811.