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## Interactions of plasma osmolality with arterial and central venous pressures in control of sympathetic activity and heart rate in humans

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**Charkoudian, N., J. H. Eisenach, M. J. Joyner, S. K. Roberts, and D. E. Wick.** Interactions of plasma osmolality with arterial and central venous pressures in control of sympathetic activity and heart rate in humans. *Am J Physiol Heart Circ Physiol* 289: H2456–H2460, 2005. First published September 30, 2005; doi:10.1152/ajpheart.00601.2005.—Plasma osmolality alters control of sympathetic activity and heart rate in animal models; however, it is unknown whether physiological increases in plasma osmolality have such influences in humans and what effect concurrent changes in central venous and/or arterial pressures may have. We tested whether physiological increases in plasma osmolality (similar to those during exercise dehydration) alter control of muscle sympathetic nerve activity (MSNA) and heart rate (HR) in humans. We studied 17 healthy young adults (7 women, 10 men) at baseline and during arterial pressure (AP) transients induced by sequential injections of nitroprusside and phenylephrine, under three conditions: control (C), after 1 ml/kg intravenous hypertonic saline (HT1), and after 2 ml/kg hypertonic saline (HT2). We continuously measured HR, AP, central venous pressure (CVP; peripherally inserted central catheter) and MSNA (peroneal microneurography) in all conditions. Plasma osmolality increased from  $287 \pm 1$  mosmol/kg in C to  $290 \pm 1$  mosmol/kg in HT1 ( $P < 0.05$ ) but did not increase further in HT2 ( $291 \pm 1$  mosmol/kg;  $P > 0.05$  vs. C). Mean AP and CVP were similar between C and HT1, but both increased slightly in HT2. HR increased slightly but significantly during both HT1 and HT2 vs. C ( $P < 0.05$ ). Sensitivity of baroreflex control of MSNA was significantly increased vs. C in HT1 [ $-7.59 \pm 0.97$  (HT1) vs.  $-5.85 \pm 0.63$  (C) arbitrary units (au)·beat<sup>-1</sup>·mmHg<sup>-1</sup>;  $P < 0.01$ ] but was not different in HT2 ( $-6.55 \pm 0.94$  au·beat<sup>-1</sup>·mmHg<sup>-1</sup>). We conclude that physiological changes in plasma osmolality significantly alter control of MSNA and HR in humans, and that this influence can be modified by CVP and AP.

baroreflex; sympathetic nervous system; hydration; plasma volume

CHANGES IN HYDRATION ELICIT important alterations in neural mechanisms controlling arterial pressure (AP) via the baroreflex (5, 6, 17). Influences of increased plasma osmolality, which can accompany decreases in volume seen with certain types of dehydration (such as with prolonged exercise), may also interact with changes in volume to alter autonomic mechanisms that have important implications for control of blood pressure in these conditions.

Because increased plasma osmolality often accompanies dehydration, physiological responses to hyperosmolality are generally those that would tend to defend plasma volume and AP. In animal models, these have been shown to include sympathoexcitation (2, 7) and decreased urine output (20). Furthermore, hyperosmolality has been shown to alter arterial baroreflex control of both heart rate (HR) and sympathetic

activity in rats (1, 7). Such influences of osmolality on baroreflex control mechanisms may also involve osmolality-induced increases in circulating volume-regulatory hormones such as AVP, which itself can alter baroreflex control of sympathetic outflow (3, 14).

The interactions among influences of plasma osmolality, central venous pressure (CVP), and AP on baroreflex control of sympathetic activity and HR have not been studied previously in humans. We previously showed (6) that increases in CVP [that did not alter mean arterial pressure (MAP)] inhibited baroreflex control of muscle sympathetic nerve activity (MSNA) in healthy humans but did not affect baroreflex control of HR. We also showed (5) that exercise-induced dehydration, which included both decreased CVP and increased plasma osmolality, increased resting HR and decreased cardiac baroreflex sensitivity in healthy humans. Our goal in the present studies was to use hypertonic saline infusions to mimic the increase in plasma osmolality associated with mild to moderate exercise-induced dehydration in the absence of decreased CVP and other factors associated with actual exercise dehydration. We tested the hypothesis that increases in plasma osmolality would increase sensitivity of baroreflex control of MSNA in humans and decrease the sensitivity of baroreflex control of HR. We further hypothesized that this influence would be offset by concurrent increases in baseline CVP and/or MAP at higher levels of hypertonic saline infusion.

### METHODS

**Subjects.** The protocol for these studies was approved by the Institutional Review Board of the Mayo Foundation. Seventeen healthy, normotensive nonsmokers (7 women, 10 men) volunteered to participate in these studies [age  $23 \pm 1$  (SE) yr, height  $1.77 \pm 0.03$  m, weight  $74.8 \pm 2.5$  kg]. Subjects did not have any history of cardiovascular or other chronic disease and were not taking any medications including over-the-counter cold or pain medications. All subjects gave written informed consent to participate in these studies. All women were studied in the early follicular phase of the menstrual cycle or in the low-hormone phase of oral contraceptives to minimize variability in autonomic control of cardiovascular function due to reproductive hormone status (4, 19).

**Measurements.** HR was measured from a three-lead electrocardiogram. AP was measured on a beat-by-beat basis by finger photoplethysmography (Finapres) regularly verified by automated sphygmomanometry on the contralateral arm. CVP was measured in 15 subjects by placement of a peripherally inserted central catheter (PICC) in an antecubital vein and advancing to the level of the

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superior vena cava. Placement of the PICC was estimated with external measurement of the distance from the antecubital fossa to the manubrium. The PICC was connected to a pressure transducer placed at the level of the heart.

In 15 subjects, multiunit MSNA was recorded with a tungsten microelectrode in the peroneal nerve, posterior to the fibular head, as described by Sundlöf and Wallin (24). The recorded signal was amplified 80,000-fold, band-pass filtered (700–2,000 Hz), rectified, and integrated (resistance-capacitance integrator circuit, time constant 0.1 s) by a nerve traffic analyzer.

**Protocol.** All studies were performed in a General Clinical Research Center laboratory in which ambient temperature was controlled between 22 and 24°C. Subjects reported to the laboratory between 7 and 8 AM. They were instructed not to consume any food or beverage after midnight of the evening before the study and not to exercise or drink alcohol within 24 h of the study. Subjects rested supine during placement of PICC and a regular 18-gauge intravenous catheter in the contralateral arm for nitroprusside and phenylephrine boluses as well as placement of ECG electrodes, a Finapres cuff on the middle finger, and an automated sphygmomanometer cuff on the upper arm. Each experiment consisted of three baroreflex trials, as described below. Two to three minutes before the baseline period for each trial (see below), blood samples were collected from the intravenous catheter for measurement of plasma osmolality, Na<sup>+</sup>, K<sup>+</sup>, hemoglobin, hematocrit, and AVP levels (because of technical limitations at the beginning of these studies, AVP was measured in the last 8 subjects only). Total volume withdrawn at each of the three time points was 20–25 ml.

**Control baroreflex trial.** In the control baroreflex trial (C), subjects rested supine for a 5-min baseline period during which MSNA, ECG, and AP were recorded continuously. AP was verified by measuring arm cuff pressure before and after this 5-min period. This was followed by a bolus of nitroprusside (100 µg) and, 60 s later, by a bolus of phenylephrine (150 µg) (modified Oxford technique) (5, 6, 12). Data were collected for a further 2 min. Subjects then rested supine for 25–30 min before the next trial.

**Hypertonic saline trial 1 (HT1).** Approximately 15 min into the waiting period, 1 mg/kg of hypertonic (3%) NaCl was infused into an antecubital vein over 10 min (for a rate of 0.1 mg·kg<sup>-1</sup>·min<sup>-1</sup>). Five minutes after this infusion, and two to three minutes before the next recorded baseline period, blood samples were drawn as noted above. This was followed by a 5-min recorded baseline and baroreflex test as above.

**Hypertonic saline trial 2 (HT2).** Approximately 15 min after the HT1 baroreflex test, 2 mg/kg hypertonic saline was infused into the antecubital venous catheter over 10 min (for a rate of 0.2 mg·kg<sup>-1</sup>·min<sup>-1</sup>). This was followed by blood sampling, baseline measurement, and baroreflex test as for HT1.

**Data analysis.** HR, AP, CVP, and MSNA were sampled at 250 Hz with data acquisition software (Windaq; Dataq Instruments, Akron, OH) and stored on a personal computer for offline analysis. Data were analyzed with signal processing software (CODAS; Dataq Instruments).

MSNA data were analyzed using custom software as previously described (10). MSNA was quantified as total integrated activity, which was defined as the summed area under the curve of the bursts of MSNA. Each MSNA recording was normalized by assigning the largest sympathetic burst under resting conditions an amplitude of 1,000. All other bursts for a particular study were calibrated against that value. The zero nerve activity level was determined from the mean voltage during a period of neural silence between sympathetic bursts. A period in which bursts were absent for ≥6 s was found in each neurogram; the average voltage during this period was assigned a value of zero.

**Assessment of integrated baroreflex control of HR and MSNA.** We assessed the sensitivity of baroreflex control of the heart by using the relationship between HR or R-R interval (RRI) and systolic blood pressure during vasoactive drug boluses as previously described (5,

12). Values for HR and RRI from baroreflex trials were pooled over 2-mmHg ranges for analysis to minimize variability due to nonbaroreflex influences such as respiration. The slope of the linear portion of this relation was used as an index of baroreflex sensitivity. The operating point for the relation in terms of resting AP and HR was calculated as the average values over the 5-min period immediately preceding the nitroprusside bolus.

An index of baroreflex control of sympathetic outflow was provided by the relationship between MSNA and diastolic blood pressure (DBP) during the drug boluses (5, 10–13). To perform a linear regression between MSNA and pressure, values for MSNA from baroreflex trials were first signal averaged over 3-mmHg pressure ranges (“bins”) via custom software as described above. As above, this pooling procedure reduces the statistical impact of the inherent beat-by-beat variability in nerve activity due to nonbaroreflex influences. A window of nerve activity that was 1.0 s in length and synchronized by the R wave of the ECG was signal averaged. The window was time shifted to account for the latency between R waves and sympathetic bursts. The duration of the shift was varied as needed from subject to subject but averaged 1.3 s. Any cardiac cycle not followed by a burst was assigned a total integrated activity of zero. The operating point for the relation in terms of resting AP and nerve activity was assessed as the averaged values over the 5-min period immediately preceding the nitroprusside bolus. DBP was used because MSNA correlates more closely with DBP than with systolic pressure (23).

**Statistical analysis.** Data are presented as means ± SE. One-way repeated-measures ANOVA was used to compare cardiovascular variables and baseline MSNA, as well as cardiac and sympathetic baroreflex sensitivities among C, HT1, and HT2 trials. Bonferroni post hoc test was used for pairwise comparisons to identify individual differences.  $P < 0.05$  was accepted as statistically significant.

## RESULTS

**Baseline hemodynamic variables and blood values.** Figure 1 shows resting values before each trial for MAP, CVP, and HR. MAP was significantly increased above C in HT2. CVP tended to increase above C in HT2, but this increase did not reach statistical significance ( $P = 0.10$ ). Despite the increased MAP, HR was significantly increased above C in both HT1 and HT2 trials ( $P < 0.05$ ). Systolic blood pressure was  $122 \pm 3$  and  $122 \pm 2$  mmHg in C and HT1 trials, respectively ( $P > 0.05$ ) and then increased to  $126 \pm 3$  mmHg in HT2 ( $P < 0.01$  vs. C and HT1). DBP was not significantly different among trials (C  $72 \pm 2$ , HT1  $73 \pm 2$ , HT2  $74 \pm 2$  mmHg;  $P > 0.05$  for all comparisons).

Table 1 shows values for plasma osmolality and plasma concentrations of Na<sup>+</sup>, K<sup>+</sup>, hemoglobin, hematocrit, and AVP during the three trials. Plasma osmolality was significantly increased above C in both HT1 and HT2 trials but was not different between the latter two trials. AVP tended to increase in HT1 but was only statistically greater than C in HT2. Hemoglobin was significantly lower than C in both HT1 and HT2 trials; hematocrit was not different between C and HT1 trials but was significantly decreased in HT2.

**Control of sympathetic nerve activity.** Figure 2 shows representative neurograms from one individual showing MSNA during the baseline period before each of the three trials. In this individual, as in all subjects, baseline MSNA was not altered in either HT1 or HT2 trials. Overall averages for total integrated activity were  $2,252 \pm 416$  arbitrary units (au)/min in C,  $2,407 \pm 318$  au/min in HT1, and  $2,066 \pm 367$  au/min in HT2 ( $P > 0.05$ ).

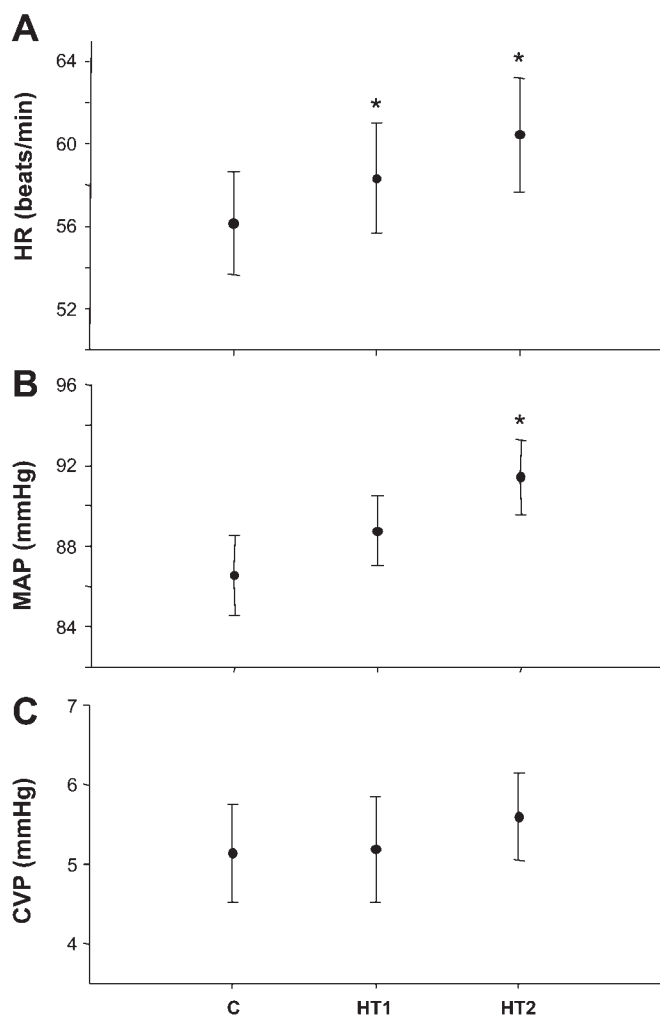


Fig. 1. A: average resting heart rate (HR) before vasoactive drug administration in each of the 3 trials. HR was slightly, but significantly, elevated above control trial (C) level in both hypertonic saline (HT)1 and HT2 trials. B: average resting mean arterial pressure (MAP) before vasoactive drug administration in each of the 3 trials. MAP tended to increase in HT1 and was significantly elevated above C in HT2. C: average resting central venous pressure (CVP) before vasoactive drug administration in each of the 3 trials. CVP tended to increase in HT2; however, this increase was not statistically significant ( $P = 0.10$ ). \* $P < 0.05$  vs. C.

Figure 3A shows a representative example of the baroreflex relationships between MSNA and DBP in an individual subject in the three trials. The slope of this relationship, representing the sensitivity of baroreflex control of MSNA, was increased in HT1, an effect that was reversed in HT2. Figure 3B shows average values for sensitivity of baroreflex control of MSNA for all subjects, showing a significant increase in sensitivity in HT1 and a reversal of this effect in HT2, such that values in HT2 were not significantly different from C.

**Sensitivity of baroreflex control of HR.** Analysis of baroreflex control of HR showed slightly decreased sensitivity in HT1 and HT2 trials when expressed in terms of RRI [C  $17.5 \pm 1.8$ , HT1  $15.1 \pm 1.8$  ( $P < 0.05$  vs. C), HT2  $15.1 \pm 1.6$  ( $P = 0.05$  vs. C) ms/mmHg]. However, no difference among trials was observed when data were expressed in terms of HR (C  $-1.01 \pm 0.08$ , HT1  $-0.89 \pm 0.08$ , HT2  $-0.97 \pm 0.08$  beats  $\cdot$  min $^{-1} \cdot$  mmHg $^{-1}$ ;  $P > 0.05$  for all comparisons). Over-

all, there were no sex differences in any measured or calculated variable, with the exception of hemoglobin and hematocrit, which are normally lower in women compared with men.

## DISCUSSION

The major new findings of the present study are twofold. First, relatively small increases in plasma osmolality resulted in increased sensitivity of baroreflex control of MSNA in humans; this increased sensitivity appeared to be counteracted by increased baseline AP, and potentially by the trend for increased CVP in HT2. Second, infusion of hypertonic saline increased resting HR, an effect that persisted despite increased AP in the HT2 trial. The increases in osmolality observed in the present study were similar in magnitude to those observed in our previous study (5) involving exercise-induced dehydration. In that study, exercise-induced dehydration resulted in an increase in plasma osmolality of  $\sim 3$  mosmol/kg. Thus the present study isolates the effect of increased plasma osmolality (at a physiologically relevant magnitude) in the absence of several of the other factors that change with exercise-induced dehydration.

Because increased osmolality often accompanies dehydration, our present findings of augmented sympathetic baroreflex sensitivity with increased plasma osmolality complement previous reports of interactions between volume regulation and baroreflex control of sympathetic activity. Reports from our laboratory (6) and others (17, 18) have indicated an inverse relationship between volume status and baroreflex control of sympathetic activity in humans. For example, we recently showed (6) that sensitivity of baroreflex control of MSNA is decreased during increases in CVP elicited by volume infusion. Conversely, Kimmerly and Shoemaker (17) demonstrated augmented sympathetic neural responses to lower body negative pressure during diuretic-induced hypovolemia. This inverse relationship may be an important mechanism by which the organism works to counteract the potential for decreased orthostatic tolerance that accompanies a decrease in blood volume. Indeed, work from Cooper and Hainsworth (8, 9) indicates that baroreflex-mediated sympathetic vasoconstrictor responses are important determinants of successful orthostasis; thus improving the sensitivity of reflex sympathetic vasoconstriction would tend to be an effective mechanism for defending orthostatic tolerance during dehydration.

In the present study, one of our goals in using smaller infusions of hypertonic saline was to minimize fluid shifts that would result in large changes in AP with these infusions. As can be seen from the blood and hemodynamic data, however, we did not avoid fluid shifts altogether. It is likely that the

Table 1. Blood data from baseline period preceding each baroreflex trial

	C	HT1	HT2
Osmolality, mosmol/kg	287 $\pm$ 1	290 $\pm$ 1*	291 $\pm$ 1*
Na <sup>+</sup> , meq/l	139 $\pm$ 1	140 $\pm$ 1*	142 $\pm$ 1*
K <sup>+</sup> , meq/l	3.9 $\pm$ 0.1	3.9 $\pm$ 0.1	3.9 $\pm$ 0.1
Hematocrit, %	41.6 $\pm$ 1.0	41.1 $\pm$ 1.0	40.6 $\pm$ 1.0*
Hemoglobin, mg/dl	14.3 $\pm$ 0.3	14.1 $\pm$ 0.4*	13.8 $\pm$ 0.4*
AVP, pg/ml	0.9 $\pm$ 0.3	1.2 $\pm$ 0.3	1.4 $\pm$ 0.3*

Values are means  $\pm$  SE. C, control baroreflex trial; HT1, hypertonic saline trial 1; HT2, hypertonic saline trial 2. \* $P < 0.05$  vs. C.

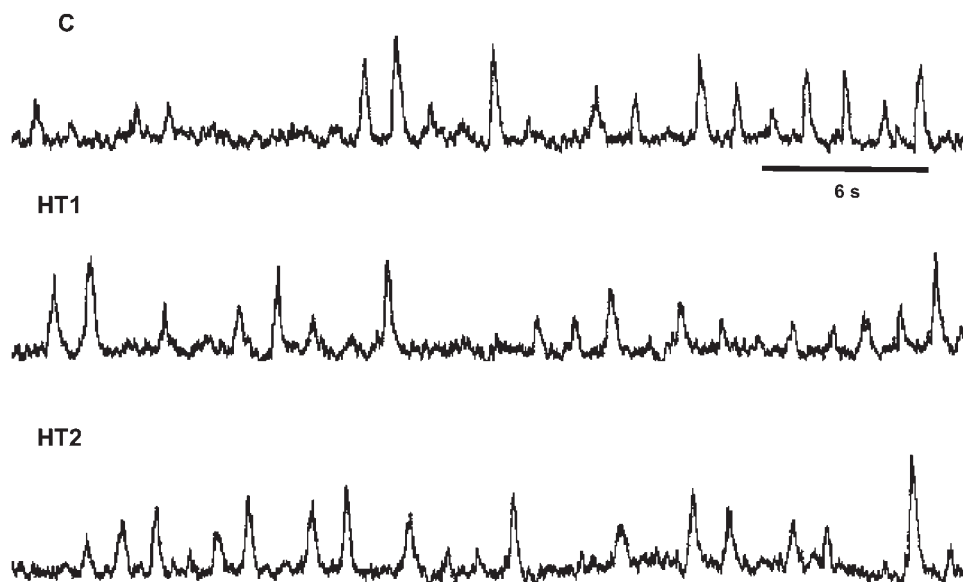


Fig. 2. Representative neurograms showing integrated muscle sympathetic nerve activity (MSNA) from an individual subject during the baseline period before each of the 3 trials, as indicated. As in this subject, there were no significant differences in resting MSNA among trials in the group as a whole.

reason that plasma osmolality did not increase further in HT2 (compared to HT1) was an accumulation of fluid in the intravascular space due to the osmotic load. This is consistent with the increased AP and decreased hematocrit and the trend for increased CVP in the HT2 trial.

Although we observed increased sensitivity of baroreflex control of MSNA with increased plasma osmolality, we did not observe changes in baseline MSNA in any trial (see Fig. 2). In previous studies in animals, the influence of increased osmolality on resting sympathetic nerve activity (SNA) has been variable, depending on the branch of SNA (2, 7) and the route of administration of hypertonic saline (2, 7, 25). In general, hyperosmolality does appear to have a sympathoexcitatory influence, at least part of which is mediated by osmosensitive neurons in the paraventricular nucleus of the hypothalamus (7, 25). Importantly, previous reports in animals have involved much larger changes in osmolality than those reported here in humans. It is therefore possible that larger changes in osmolality would elicit changes in baseline MSNA in humans that we were not able to observe in the present study.

As part of the normal volume-regulatory response, increased plasma osmolality causes release of AVP from the posterior pituitary. In the present study, we observed small increases in plasma AVP that were statistically significant in HT2. Several studies in animal models (3, 14, 15) suggest that circulating AVP has central sympathoinhibitory influences, involving interactions at circumventricular organs such as the area postrema (15). These influences include a decrease in gain of baroreflex control of SNA (3). Such an influence of AVP in the present study could have contributed (in the HT2 trial) to the reversal of the osmolality-induced increase in sympathetic baroreflex sensitivity we observed in HT1. However, those previous reports involved pressor doses of AVP at much higher concentrations than those observed in the present study. Furthermore, because we only included one measurement of AVP per trial, it is possible that we missed the peak AVP responses to the hypertonic saline infusion. Clearly, further investigations in humans of the role of AVP in interactions between volume regulation and autonomic/baroreflex control mechanisms are important areas for future work.

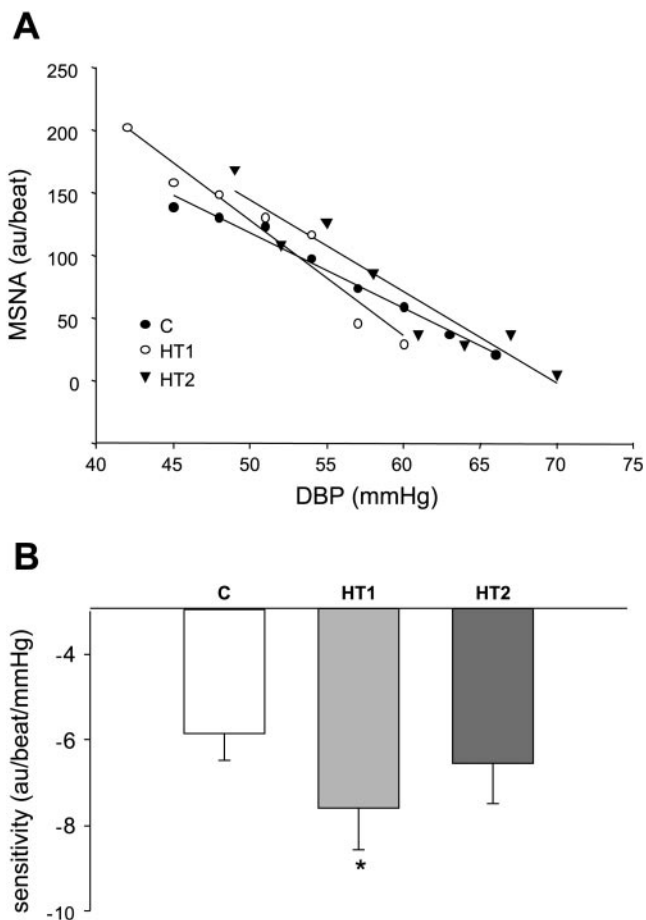


Fig. 3. A: individual example of relationship between MSNA and diastolic blood pressure (DBP) during vasoactive drug boluses in a representative subject. As can be seen from the slopes of the regression lines, the sensitivity of the MSNA response was increased in HT1, and this increase tended to be reversed in HT2. B: average values for sensitivity of baroreflex control of MSNA in all subjects for whom MSNA was measured ( $n = 15$ ). Sensitivity was significantly increased in HT1 ( $*P < 0.01$  vs. C), an effect that tended to be reversed in HT2, such that values in HT2 were not different from C ( $P > 0.05$ ). au, Arbitrary units.

In the present study, we observed small increases in baseline HR with increased plasma osmolality. HR increased 2 beats/min in HT1 and 4 beats/min in HT2, both significantly increased compared with C. Although this tachycardia may also represent a blood pressure-defending response to increased plasma osmolality, its cause is unclear. Because the increased HR occurred despite increased MAP, the slight tachycardia may have represented reset baroreflex control of HR or movement of the operating point on the baroreflex to higher HR values.

Previously, Bealer (1) demonstrated that increased osmolality decreased the sensitivity of baroreflex control of HR in rats. As noted above, the increase in osmolality in the present study ( $\sim 3$  mosmol/kg) was smaller than that in the studies by Bealer ( $\sim 13$  mosmol/kg). In the present study, we observed a small decrease in cardiac baroreflex sensitivity when expressed in terms of RRI and no significant difference when expressed in terms of HR. Because of the reciprocal ( $1/x$ ) relationship between HR and RRI, an increase in baseline HR (such as we observed) results in a shift in position on the relationship between the two variables, such that a given  $\Delta$ HR results in a  $\Delta$ RRI that is smaller than a similar  $\Delta$  would have been at the original baseline HR. This can have the mathematical effect of decreasing RRI sensitivity without affecting sensitivity as calculated with HR [see O'Leary (21) for in-depth discussion of this point]. Thus, in the present study, the discrepancy between modes of expression, in combination with the small magnitude of the effect on RRI sensitivity, makes it less likely that the osmolality per se had a physiologically significant effect on cardiac baroreflex sensitivity.

Although our results point to significant influences of acute increases in plasma osmolality on baroreflex control mechanisms in humans, they do not specifically address the role of long-term changes in osmolality on blood pressure control mechanisms. For example, a high-salt diet in humans can cause increases in plasma osmolality similar to those seen in the present study, but on a longer-term basis (16). The influences of such a chronic increase on autonomic control mechanisms are unknown in humans, although chronic changes in osmolality have been shown to have important roles in control of sympathetic activity and blood pressure in the rat (22).

In summary, we report here that physiological increases in plasma osmolality, similar to those seen with mild to moderate exercise-induced dehydration, result in increased sensitivity of baroreflex control of MSNA in humans, an effect that appeared to be counteracted by small increases in baseline MAP and may have been influenced by CVP as well. Increased plasma osmolality did not affect resting MSNA but did significantly increase resting HR. We conclude that small, physiological increases in plasma osmolality in humans have influences on sympathetic and cardiac control mechanisms that are consistent with blood pressure-defending responses that are protective to the organism in conditions of dehydration.

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