Plasma vasopressin and aldosterone responses to oral and intravenous saline rehydration

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1Department of Kinesiology, The University of New Hampshire, Durham, New Hampshire 03824; and Departments of 2Kinesiology, 3Physiology and Neurobiology, and 4Nutritional Sciences, University of Connecticut, Storrs, Connecticut 06269-1110

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Kenefick, Robert W., Carl M. Maresh, Lawrence E. Armstrong, John W. Castellani, Deborah Riebe, Marcos E. Echegaray, and Stavros A. Kavorous. Plasma vasopressin and aldosterone responses to oral and intravenous saline rehydration. J Appl Physiol 89: 2117–2122, 2000.—This investigation examined plasma arginine vasopressin (AVP) and aldosterone (Ald) responses to 1) oral and intravenous (IV) methods of rehydration (Rh) and 2) different IV Rh osmotic loads. We hypothesized that AVP and Ald responses would be similar between IV and oral Rh and that the greater osmolality and sodium concentration of a 0.9% IV saline treatment would stimulate a greater AVP response compared with a 0.45% IV saline treatment. On four occasions, eight men (age: 22.1 ± 0.8 yr; height: 179.6 ± 1.5 cm; weight: 73.6 ± 2.5 kg; maximum O2 consumption: 57.9 ± 1.6 ml·kg−1·min−1, body fat: 7.7 ± 0.9%) performed a dehydration (Dh) protocol (33°C) to establish a 4–5% reduction in body weight. After Dh, subjects underwent each of three randomly assigned Rh (back to −2% body wt) treatments (0.9 and 0.45% IV saline, 0.45% oral saline) and a no Rh treatment during the first 45 min of a 100-min rest period. Blood samples were obtained pre-Dh, immediately post-Dh, and at 15, 35, and 55 min post-Rh. Before Dh, plasma AVP and Ald were not different among treatments but were significantly elevated post-Dh. In general, at 15, 35, and 55 min post-Rh, AVP, Ald, osmolality, and plasma volume shifts did not differ between IV and oral fluid replacement. These results demonstrated that the manner in which plasma AVP and Ald responded to oral and IV Rh or to different sodium concentrations (0.9 vs. 0.45%) was not different given the degree of Dh (−4.5% body wt) and Rh and amount of time after Rh (55 min).

arginine vasopressin; oropharyngeal; osmotic load

PROLONGED EXERCISE HEAT STRESS without rehydration (Rh) has been shown to induce a state of hypovolemic hypovolemia (5, 11, 26, 28) and increase plasma arginine vasopressin (AVP) (3, 8) and aldosterone (Ald) (3, 10, 14) concentrations. The response of these fluid-regulating hormones has generally been shown to be lower when subjects were rehydrated, either during or after exercise (31), especially when electrolytes were also given (3, 15). However, to our knowledge, the response of AVP and Ald to various Rh methods, such as intravenous (IV) infusion and oral drinking, has not been fully investigated. Comparison of the responses of these fluid-regulating hormones to differing methods of Rh and, additionally, differing osmotic loads may help to identify which may provide a more effective means of Rh. These findings may have important applications regarding the most efficacious method for Rh for athletes, laborers, and military personnel during subsequent exercise heat stress.

Moses et al. (22, 23) used dehydration (Dh) and IV saline infusion to examine mediators of AVP release and suggested that expansion of plasma volume (PV) after infusion may serve to attenuate the osmotic stimulus for AVP secretion. Francesconi et al. (14) observed reduced Ald responses in subjects who received water or an electrolyte solution before or during exercise. However, the responses of fluid-regulating hormones to IV Rh remain unclear. We are unaware of any investigations that have specifically compared the effects of IV infusion and oral ingestion on AVP and Ald. Therefore, the primary purpose of the present study was to address the following question: After exercise-induced Dh (−4% body wt), what are the responses of plasma AVP and Ald after Rh via different routes (ingestion vs. infusion) of administration? In the present study, Rh occurred over a 45-min period, followed by 55 min of additional standing rest. Given the amount of time allowed for Rh and rest, we hypothesized that plasma AVP and Ald would be similar between these different routes of administration because PV could likely be restored to a similar degree. Use of the IV infusion methodology also permitted us to address a second question: After Dh, what are the responses of plasma AVP and Ald to Rh using different osmotic loads (0.45 vs. 0.9% IV saline)? In this regard, we hypothesized that the 0.9% IV saline treatment would lead to higher plasma AVP and Ald concentra-

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tions because of a higher plasma sodium and osmolality (Osm) compared with the 0.45% IV saline treatment.

METHODS

Subjects. Eight men, unacclimatized to heat, volunteered to participate in this investigation. Physical characteristics were as follows: age, 22.1 ± 0.8 (SE) yr; height, 179.6 ± 1.5 cm; weight, 73.6 ± 2.4 kg; maximal O2 consumption (\( \text{VO}_{2\max} \)), 57.9 ± 1.6 ml·kg\(^{-1}\)·min\(^{-1}\); percent body fat, 7.7 ± 0.9%. Each subject completed a written, informed consent document and a medical history questionnaire after being informed of the purpose of the experiment and possible risks. The Committee on the Use of Human Subjects in Research at the university approved all procedures. Subjects were given a stipend for their participation.

Preliminary measures. \( \text{VO}_{2\max} \) was determined by using a continuous treadmill running test as previously described (6). The hydrostatic weighing technique described by Katch and Katch (20) was utilized to determine body density. Body fat was calculated from the formula of Brozek et al. (4). Measurement of residual lung volume was made by using a nitrogen washout technique (32) on a pulmonary analysis system (model 1070, Medical Graphics, St. Paul, MN).

Experimental design. Testing involved four treatments, each consisting of two stages: 1) exercise-induced Dh and 2) Rh. The Rh treatment protocols were randomly assigned and separated by at least 14 days. The treatments were as follows: 0.9% IV infusion (0.9% IV); 0.45% IV infusion (0.45% IV); 0.45% saline oral ingestion (0.45% Oral); and no Rh [no fluid (NF)]. Subjects were asked to maintain similar diets and compositions of 0.45% Oral was 78.6 ± 1.1 meq Na\(^+\)/l and 145.6 ± 1.1 mosmol/kgH2O. Fluid intake was 25 ml/kg of pre-Dh body weight. This volume has been shown to be the upper range for fluids orally ingested after exercise-induced Dh (24). Immediately after Rh, subjects assumed a standing posture for 5 min post-Rh.

Physiological measures. During all Dh bouts, the subject's heart rate and T\(_{re} \) were measured every 15 min to monitor physiological strain. Heart rates that exceeded 180 beats/min or T\(_{re} \) of 39.5°C. Oxygen consumption was measured once every 30 min during the Dh protocol for a 7- to 10-min period. Expired gas samples were analyzed by using an on-line breath-by-breath metabolic system (Medical Graphics CPX-D system).

Analysis of blood samples. Blood was transferred to tubes containing EDTA, lithium heparin, or SST gel and clot activator for serum separation, depending on the specifications for each blood variable. Serum or plasma was separated from each sample and stored at −80°C for later analysis. Samples of whole blood were taken for analysis of Hb and hematocrit (Hct). After centrifugation, plasma was separated and analyzed for Osm, sodium (Na\(^+\)), and potassium (K\(^+\)).

Hct was determined in triplicate by the microcapillary technique after centrifugation for 4 min at 9,500 g. Values were not corrected for trapped plasma. Hb was determined in triplicate by the cyanomethemoglobin method (kit 525, Sigma Chemical, St. Louis, MO). Percent change in PV (%ΔPV) was calculated by using the equation of Dill and Costill (13) from appropriate Hct and Hb values. All %ΔPV values were calculated by using post-Dh as the initial time point. Plasma Osm was measured in triplicate via freezing-point depression (microosmometer model 3MO, Advanced Instruments, Needham Heights, MA). Plasma and urine Na\(^+\) and K\(^+\) concentrations were determined in duplicate by se-
Oral, 0.9% IV, and NF treatments, respectively. \( \text{P}, 0.05 \) with repeated measures. The 0.05 level of significance was an absolute change (\( D \)) variables measured after Rh, all comparisons were made as

\[ \frac{\text{Post-Dh} - \text{Pre-Dh}}{\text{Pre-Dh}} \]

ences among trials. A Newman-Keuls post hoc analysis was

\[ \text{Table 2. Selected Dh and Rh variables} \]

Table 1. Selected plasma and urine variables pre- and post-Dh

<table>
<thead>
<tr>
<th></th>
<th>Pre-Dh</th>
<th>Post-Dh</th>
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<tbody>
<tr>
<td></td>
<td>0.45% IV</td>
<td>0.45% Oral</td>
</tr>
<tr>
<td>AVP, pg/ml</td>
<td>5.5 ± 0.8</td>
<td>5.8 ± 0.6</td>
</tr>
<tr>
<td>Ald, pg/ml</td>
<td>410 ± 69</td>
<td>277 ± 51</td>
</tr>
<tr>
<td>Osm, mosmol/kgH₂O</td>
<td>284 ± 1</td>
<td>282 ± 2</td>
</tr>
<tr>
<td>Na⁺, meq/l</td>
<td>146 ± 0.4</td>
<td>145 ± 1.0</td>
</tr>
<tr>
<td>K⁺, meq/l</td>
<td>4.3 ± 0.1</td>
<td>4.2 ± 0.1</td>
</tr>
<tr>
<td>Osm, mosmol/kgH₂O</td>
<td>607 ± 108</td>
<td>665 ± 97</td>
</tr>
<tr>
<td>Na⁺, meq/l</td>
<td>61 ± 9</td>
<td>75 ± 14</td>
</tr>
<tr>
<td>K⁺, meq/l</td>
<td>83 ± 27</td>
<td>60 ± 17</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n = 8 \) subjects. Pre- and Post-Dh, pre- and postdehydration; AVP, arginine vasopressin; Ald, aldosterone; Osm, osmolality. Treatment groups are as follows: 0.9 and 0.45% intravenous saline infusion (0.9% IV and 0.45% IV, respectively), 0.45% saline oral ingestion (0.45% Oral), and no rehydration [no fluid (NF)].*Significant difference (\( P < 0.05 \)) from corresponding Post-Dh measure within

ullative ion-sensitive electrodes (model 984-S, AVL Scientific, Roswell, GA).

**Endocrine measures.** After extraction on silica columns (DiaSorin, Stillwater, MN), plasma AVP was determined in duplicate by a commercially available radioimmunoassay kit (DiaSorin). AVP values were not corrected for extraction recovery, which was 91.3%. Assay sensitivity was \( 7.042 \times 10^{-7} \) pg/ml. Serum levels of Ald were determined in duplicate by radioimmunoassay (Diagnostik Products, Los Angeles, CA). Assay sensitivity was 11.0 pg/ml. Within- and between-assay coefficients of variability for both assays were <5%. Concentrations of AVP and Ald were not corrected for %DV.

**Statistical analysis.** Analysis of variance (treatment \( \times \) time) with repeated measures was used to compare differences among trials. A Newman-Keuls post hoc analysis was employed to determine significant differences within and between conditions. For the purpose of observing changes in variables measured after Rh, all comparisons were made as an absolute change (\( \Delta \)) from the post-Dh values and analyzed by using a two-way (treatment \( \times \) time) analysis of variance with repeated measures. The 0.05 level of significance was selected. All data are presented as means ± SE.

**RESULTS**

**Pre-Dh.** Pre-Dh dietary carbohydrate, sodium, and total kilocalorie intakes were similar over the 3 days before each experimental treatment. Pre-Dh body weights were not different (\( P > 0.05 \)) and were \( 75 \pm 2, 74 \pm 3, 74 \pm 3, \) and \( 74 \pm 3 \) kg for the 0.45% IV, 0.45% Oral, 0.9% IV, and NF treatments, respectively. Pre-Dh plasma and urine Osm, Na⁺, and K⁺ were not different (\( P > 0.05 \)) among treatments (Table 1).

**Post-Dh UsG values were \( 1.018 ± 0.002, 1.017 ± 0.003, 1.018 ± 0.004, \) and \( 1.014 ± 0.004 \) for 0.45% IV, 0.45% Oral, 0.9% IV, and NF, respectively, and were not different among treatments.

**Post-Dh plasma and urine values.** Overall, post-Dh values of plasma AVP and Ald were not different (Table 1). Similarly, plasma and urine Osm and electrolytes were similar among treatments pre- and post-Dh (Table 1). In each treatment, post-Dh plasma AVP, Ald, Osm, Na⁺, and K⁺ were significantly (\( P < 0.05 \)) elevated above pre-Dh after the Dh protocol (Table 1).

**Dh and Rh.** There were no differences among treatments in exercise intensity (%\( \text{VO}_2 \max \)), exercise time, urine volume, and percent weight loss during the Dh protocol (Table 2). Also, there were no differences in the volume of fluid given during infusion or ingestion. Post-Rh percent weight loss (compared with the pre-Dh body wt) was similar among the three treatment conditions (Table 2).

**Plasma Osm.** After Rh, \( \Delta \text{Osm} \) was greater (\( P < 0.05 \)) in the infusion and ingestion treatments vs. NF, with no differences (\( P > 0.05 \)) among 0.9% IV, 0.45% IV, and 0.45% Oral treatments (Fig. 1A).

**Plasma sodium.** At 15, 35, and 55 min post-Rh, the \( \Delta \text{Na}^+ \) concentration was significantly greater (\( P < 0.05 \)) in 0.45% IV and 0.45% Oral vs. 0.9% IV and NF (Fig. 1B).

\( \Delta \text{PV}. \) %\( \Delta \text{PV} \) was different (\( P < 0.05 \)) at 15 min post-Rh between the 0.45% Oral (+4 ± 2%) and IV infusions (+16 ± 2 and +11 ± 3% for 0.9% IV and 0.45% Oral treatments, respectively.)

\[ \frac{\text{Post-Dh}}{\text{Pre-Dh}} \]

Table 2. Selected Dh and Rh variables

<table>
<thead>
<tr>
<th></th>
<th>0.45% IV</th>
<th>0.45% Oral</th>
<th>0.9% IV</th>
<th>NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dh %( \text{VO}_2 \max ), ml·kg⁻¹·min⁻¹</td>
<td>51 ± 2</td>
<td>50 ± 2</td>
<td>50 ± 3</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>Exercise time, min</td>
<td>190 ± 12</td>
<td>182 ± 8</td>
<td>179 ± 12</td>
<td>180 ± 10</td>
</tr>
<tr>
<td>Post-Dh urine volume, liter</td>
<td>0.34 ± 0.12</td>
<td>0.45 ± 0.15</td>
<td>0.44 ± 0.11</td>
<td>0.48 ± 0.09</td>
</tr>
<tr>
<td>Rh fluid volume, ml</td>
<td>1,890 ± 45</td>
<td>1,856 ± 65</td>
<td>1,889 ± 62</td>
<td>1,789 ± 100</td>
</tr>
<tr>
<td>Post-Dh weight loss, %</td>
<td>4.4 ± 0.07</td>
<td>5.1 ± 0.14</td>
<td>4.5 ± 0.07</td>
<td>4.6 ± 0.07</td>
</tr>
<tr>
<td>Post-Rh weight loss, %</td>
<td>2.1 ± 0.10</td>
<td>2.3 ± 0.07</td>
<td>2.1 ± 0.10</td>
<td>4.3 ± 0.04*</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n = 8 \) subjects. %\( \text{VO}_2 \max \), percentage of maximum \( \text{O}_2 \) consumption; Rh, rehydration.*Significant difference (\( P < 0.05 \)) from 0.9% IV, 0.45% IV and 0.45% Oral treatments.
this state of hyperosmotic hypovolemia was maintained when body fluids were not restored. Consequently, concentrations of vasopressin and Ald remained elevated throughout the NF trial. These responses are in agreement with other investigations that have shown that Dh stimulates an increase in these fluid regulatory factors (7, 10). However, it is unknown how different Rh modes (oral vs. IV) or different IV fluids (osmotic stimulus) affect circulating vasopressin or Ald concentrations after exercise-induced Dh. Our findings demonstrate that the manner in which plasma AVP and Ald respond to different Rh modes or sodium concentration (0.9 or 0.45%) was not different, given the period of time allowed for Rh.

Infusion vs. drinking. The post-Rh ΔAVP was not different between the 0.45% IV and 0.45% Oral conditions. Additionally, there was no difference observed in plasma Osm between these two treatments, which has been demonstrated to be the major stimulus for AVP release (19). PV has also been shown to be another factor influencing AVP (19). In the present study, %ΔPV was different at 15 min post-Rh between the 0.45% Oral and 0.45% IV treatments. Given the greater time required for fluid to empty the gut, it might be expected that the ΔAVP might not be as great in drinking compared with infusion. Although not statistically significant, however, ΔAVP at 15 min post-Rh fell to a greater extent in 0.45% Oral compared with infusions, despite the lower %ΔPV. One mechanism might be the residual effects of the oropharyngeal reflex, which exerts its influence on plasma AVP concentrations almost immediately (18, 27). During oral ingestion of fluid in animals and humans, the reduction in AVP release seems to be an anticipatory response to the absorption of water and the decrease in plasma Osm after water intake (2, 18, 25, 27, 29, 30). Collectively, these studies suggest that oropharyngeal receptors may initiate a more rapid inhibition of AVP before a decline in plasma Osm or PV is detectable.
humans, oropharyngeal receptors have been implicated in the rapid, transient fall in plasma AVP due to drinking (18, 27). A comparable decrease in plasma AVP may have occurred in 0.45% Oral; however, the 15-min post-Rh measure may have been too late to observe this well-documented response. The ΔAld was not different among any of the Rh treatments at 15 min post-Rh. However, ΔAld was different between the infusion and ingestion treatments and NF at 35 and 55 min post-Rh (Fig. 3). Changes in blood volume have been shown to be one of the primary influences on Ald secretion (16). Additionally, plasma Ald concentrations have been demonstrated to be affected by circadian variation and dietary sodium and potassium intake (8, 17, 21, 31). The Ald response in this study was primarily determined by factors related to the maintenance of PV for the following reasons. First, experimental testing occurred at the same time of day for each trial. Second, dietary sodium and potassium intake was similar for 3 days before each treatment, and pre-Dh measures of plasma sodium and potassium were not different (Table 1). Third, with the exception of 15 min post-Rh, %ΔPV was not different between infusion and ingestion, and the amount of fluid restored during Rh was not different among these treatments (Table 2).

We also hypothesized that PV shifts would not be different among the Rh treatments because of the consistent volume infused or orally ingested. Costill and Sparks (12) reported that Rh with a glucose-electrolyte solution resulted in a better recovery of PV than did tap water after thermal Dh. Nose et al. (24) reported a greater restoration of PV with a sodium-chloride solution compared with water after exercise-induced Dh. In the present study, both the infused and ingested solutions contained sodium chloride. Because of the similar composition of the oral and IV fluids, post-Rh %ΔPV tended not to be different. The only difference in %ΔPV found among Rh treatments was at 15 min post-Rh. At this time point, the PV recovered to a greater extent in both the 0.9% IV and 0.45% IV trials compared with the 0.45% Oral treatment. By 35 min post-Rh, however, no differences in %ΔPV existed among Rh treatments. The difference observed at 15 min post-Rh was likely due to limitations imposed by gastric emptying (9) and transit compared with IV administration. By 35 min post-Rh, the %ΔPV in 0.45% Oral was not different compared with the IV treatments, and a greater amount of fluid had emptied from the gut and entered the circulation.

0.9% IV vs. 0.45% IV. In the present study, Rh with both 0.9% and 0.45% saline concentrations equally blunted AVP and Ald responses. In previous studies in which subjects received water or an electrolyte solution before or during exercise in a warm environment, plasma AVP and Ald were also reduced (3, 14, 15). We reasoned that the 0.9% saline infusion used in this study would increase the plasma sodium concentration above that of the 0.45% saline treatment and subsequently continue to elevate plasma Osm after Rh and stimulate AVP secretion. Although the sodium concentration in the 0.9% IV treatment was significantly greater at 15, 35, and 55 min post-Rh, compared with that in 0.45% IV, plasma Osm was not different post-Rh between treatments, and ΔAVP values were not different. Plasma Osm in the present study did parallel plasma sodium at each of the recovery time points, as previously observed by Nose et al. (24). It is possible that, whereas the volume or concentration of IV saline infused was large enough to cause differences in plasma sodium in the 0.9% IV treatment, it may not have been large enough to cause differences in plasma Osm between the 0.9% IV and 0.45% IV treatments. It is also possible that the addition of 0.9% saline did, in fact, temporarily raise plasma Osm. Because osmotic forces cause water to move between intravascular and interstitial compartments (24), this temporary increase might have caused a fluid shift from the interstitium into the vasculature, thereby reducing plasma Osm and plasma AVP.

In brief, the results of the present investigation demonstrated that the manner in which fluid regulatory hormones responded to different methods of Rh (IV or oral) or sodium concentration (0.9 or 0.45%) was not different.
different. Clearly, the use of IV reinfusion offers no advantage over oral Rh and is equally effective in restoring fluid volume, given the degree of Dh (−4% body wt) and time permitted for Rh (100 min). This finding is important for individuals who exercise multiple times in 1 day, and our laboratory has shown (6) that there is no performance or thermoregulatory advantage to rehydrating by using IV infusion before the performance of subsequent exercise.

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