Mechanism for the posture-specific plasma volume increase after a single intense exercise protocol

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Nagashima, Kei, Gary W. Mack, Andrew Haskell, Takeshi Nishiyasu, and Ethan R. Nadel. Mechanism for the posture-specific plasma volume increase after a single intense exercise protocol. J. Appl. Physiol. 86(3): 867–873, 1999.—To test the hypothesis that exercise-induced hypervolemia is a posture-dependent process, we measured plasma volume, plasma albumin content, and renal function in seven healthy subjects for 22 h after single upright (Up) or supine (Sup) intense (85% peak oxygen consumption rate) exercise. This posture was maintained for 5 h after exercise. Plasma volume decreased during exercise but returned to control levels by 5 h of recovery in both postures. By 22 h of recovery, plasma volume increased 2.4 ± 0.8 ml/kg in Up but decreased 2.1 ± 0.8 ml/kg in Sup. The plasma volume expansion in Up was accompanied by an increase in plasma albumin content (0.11 ± 0.04 g/kg; P < 0.05). Plasma albumin content was unchanged in Sup. Urine volume and sodium clearance were lower in Up than Sup (P < 0.05) by 5 h of recovery. These data suggest that increased plasma albumin content contributes to the acute phase of exercise-induced hypervolemia. More importantly, the mechanism by which exercise influences the distribution of albumin between extra- and intravascular stores after exercise is altered by posture and is unknown. We speculate that factors associated with postural changes (e.g., central venous pressure) modify the increase in plasma albumin content and the plasma volume expansion after exercise.

Exercise-induced hypervolemia; blood volume; plasma albumin

Expansion of blood volume is a well-documented response to aerobic exercise training (5, 7, 9, 11, 13, 16, 18, 23). Many factors associated with exercise training, e.g., training intensity (9, 11), frequency, duration (5), and thermal stress (7), are thought to contribute to the "signal" for exercise-induced hypervolemia. Convertino et al. (7) provided evidence that the stimuli for plasma volume expansion during training consisted of 60% exercise-related factors and 40% thermal-related factors. Davidson et al. (8) showed that plasma volume increased by 17% at 24 h after marathon running. Gillen et al. (9) reported that a 72-min single intense intermittent exercise bout induced a 10–15% expansion of plasma volume within 24 h, indicating an important role of exercise intensity as a signal for volume expansion.

The mechanism for plasma volume expansion is not clearly understood. Wyndham et al. (27) reported that total body water increased after exercise training in the heat. One explanation for the volume expansion was sodium and water retention, with expansion of the entire extracellular compartment. This would require renal adjustments, presumably through activation of the renin-angiotensin-aldosterone system or a change in renal responsiveness to this hormonal axis. An increase in extracellular fluid volume would necessarily lead to an increase in plasma volume because the plasma volume is a part of the extracellular fluid space. In support of this hypothesis, Convertino (3) reported increased water retention during exercise training, as evidenced by decreased urine volume and reduced sodium and osmotic clearance. However, neither of these studies addressed the issue of which body fluid compartment contained the retained fluid.

Plasma volume expansion after intense exercise is associated with an increase in plasma protein content and a selective expansion of the intravascular compartment (5, 7, 9, 23). The increase in plasma protein provides for a greater intravascular water retention by increasing the colloid osmotic pressure gradient. Gillen et al. (9) showed that plasma albumin content increased within 1 h of recovery from intense exercise, remained elevated for 48 h, and accounted for the increase in total plasma protein content. Thus increased plasma albumin content appears to be critical for the selective expansion of the intravascular compartment after exercise. Senay (23) postulated increased lymphatic protein return for increased plasma protein content after exercise. Recently, a decrease in transcapillary escape rate of albumin (12) and an increase in albumin synthesis (28) after intense exercise were reported; both would contribute to greater plasma protein content.

Ray et al. (18) reported that plasma volume expansion was absent during exercise training in the supine (Sup) compared with the upright posture (Up). Fluid regulatory hormone responses to exercise, such as atrial natriuretic peptide (ANP) and/or aldosterone are influenced by posture (17). Higher ANP and lower aldosterone would act to limit water retention in Sup. Moreover, increased lymph protein return due to exercise (22, 23) might be suppressed by increased outflow pressure of lymph system in Sup (25). Although Ray et al. (18) provided no direct evidence to support either of

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these hypotheses, it is clear that posture is an important factor in exercise-induced hypervolemia.

To examine the mechanism of the posture-specific plasma volume expansion after exercise, we measured changes in plasma solute contents and renal function for 22 h after intense exercise in Up and Sup. We tested the hypothesis that the ability to induce plasma volume expansion after intense exercise is dependent on an increase in plasma albumin content and that this expansion is attenuated in Sup.

METHODS

Seven healthy volunteers (5 men and 2 women) who were not engaged in an endurance training program participated in the present study. Each subject underwent a complete medical history and physical examination and gave written informed consent to a protocol that had been approved by the Yale University School of Medicine Human Investigation Committee. Their physical characteristics were 1) age, 25 ± 3 (SE) yr; 2) body weight, 70.5 ± 3.7 kg; 3) height, 172 ± 4 cm; and 4) peak oxygen consumption rate (VO2), 43.5 ± 2.2 ml·kg−1·min−1 in Up and 40.9 ± 2.6 ml·kg−1·min−1 in Sup. Posture-specific peak VO2 was determined in each subject by using a graded cycle ergometer exercise protocol 1–2 wk before any experiments.

Each subject performed two identical experiments, one in Up and the other in Sup. Each experiment consisted of 3 consecutive days, during which time water intake and diet were controlled. Data collection consisted of a 2-h posture-specific control period, 72 min of intermittent intense exercise, 5 h of posture-specific recovery, and a following 17-h recovery measurement. The order of experiments for each subject was randomly assigned. The interval between experiments was 1–2 wk in male subjects and 3–4 wk in female subjects. For the female subjects, experiments were performed within the first 10 days of their menstrual cycle. Subjects were asked to avoid vigorous exercise for 3 days before the experiments. On day 1, subjects were provided a controlled dinner diet and were asked to drink at least 15 ml of water/kg body wt between dinner and bedtime, which was smaller than the volume on previous night. Their activities within the GCRC were not restricted. On day 3 of the experiment, all day 2 procedures were repeated to the beginning of the exercise, at which time plasma volume was measured by Evans blue dye dilution.

Measurements. Blood samples were taken at control; during the final bout of intense exercise; and at 1, 2, 5, and 22 h recovery. Hematocrit (Hct, microcentrifuge) and Hb concentration (cyanmethemoglobin method; Sigma Chemical) were measured immediately in triplicate. The remaining blood was transferred into a lithium-heparin-treated tube and centrifuged at 4°C for 20 min, and the plasma was used to determine plasma osmolality (Osmol; freezing-point depression; model 3DII, Advanced Instrument), sodium ([Na+]p), potassium concentrations ([K+]p), and potassium concentrations ([K+]p) by flame photometry (IL 943 Automatic Flame Photometer, Instrumentation Laboratory), albumin and total protein concentration ([Alb]p, [TP]p), bromocresol green and biuret method, respectively; Sigma Chemical), and plasma and urine creatinine concentration (modified alkaline picrate method). An additional blood sample was taken for determination of plasma aldosterone and ANP concentrations. The blood sample for ANP was transferred to K3EDTA-aprotininetreated tube and centrifuged at 4°C. The plasma samples were stored at −70°C. Aldosterone and ANP were measured by using radioimmunoassay kits (Diagnostic Products and Instar, respectively). The intra-assay coefficient of variation for aldosterone was 0.67% at 28 pg/ml and 7.94% at 122 pg/ml, and that for ANP was 6.0% at 70.3 pg/ml.

Urine analysis. Subjects were instructed to empty their bladders completely, and urine volume was measured with a graduated cylinder. Urine electrolytes and creatinine concentration and osmolality were measured by the same methods as those used for plasma samples.

Cardiovascular variables. Heart rate (HR) was monitored throughout the experiment. Systolic (SAP) and diastolic arterial pressure (DAP) were measured every 10 min from the right arm by inflation of a cuff with a sonometric pickup (model STBP-780, Colin), and mean arterial pressure (MAP) was calculated as (SAP + 2·DAP)/3.

Statistics. Differences between variables were determined by analysis of variance for repeated measures. Significant differences at specific time points were identified by paired t-test (24). All values are presented as means ± SE, and the null hypothesis was rejected at P < 0.05.

RESULTS

Figure 1 shows HR, MAP, and pulse pressure before and after exercise in Up and Sup. At rest before exercise, HR (58 ± 4 and 55 ± 3 beats/min), MAP (79 ± 2 and 76 ± 2 mmHg), and pulse pressure (49 ± 3 and 52 ± 4 mmHg) were similar for Up and Sup, respectively. During recovery from exercise, HR was greater in Up than in Sup (P < 0.05) during the entire period except at 22 h of recovery. MAP was higher in Up than in Sup between 0.5 and 5 h of recovery (P < 0.05), whereas pulse pressure was reduced during recovery in Up (P < 0.05) but was unchanged in Sup.

Values for Hct, Hb, percent change in plasma volume (%ΔPV) from control, [Alb]p, [TP]p, [Na+]p, [K+]p, and...
Osmolp in Up and Sup are summarized in Table 1. At rest before exercise Hct and Hb were higher in Up than Sup (P < 0.05), whereas other plasma constituents were similar regardless of posture. In the two trials, [Alb]p increased during exercise (P < 0.05) and remained elevated from preexercise levels throughout the recovery except at 22 h of recovery in Up. Changes in plasma albumin content in Up and Sup were similar to those in plasma albumin content. Plasma osmotic content decreased during exercise but returned to control levels at 1 h of recovery. Plasma osmotic content increased from control by 0.60 ± 0.21 mmol/kg body wt at 22 h of recovery in Up, but it was unchanged in Sup.

Table 3 summarizes changes in renal function. Urine volume after exercise was significantly higher in Sup than in Up until 5 h of recovery. Creatinine clearance was not influenced by intense exercise. Na\(^+\) clearance was significantly (P < 0.05) lower in Up than Sup until 5 h of recovery. Osmotic clearance changed in a similar manner as sodium clearance. The ratio of sodium to potassium concentration in urine in Up was decreased from control throughout recovery, except at 22 h; it was unchanged in Sup. There were no significant differences in free-water clearance between Up and Sup. Water intake was not different between the two trials throughout each stage of experiments. Body weight decreased by 1.2 ± 0.1 and 1.6 ± 0.3% from control levels at 5 h of recovery in Up and Sup, respectively. There were no significant decreases in body weight from control at 22 h of recovery in Up (2.0 ± 0.4% of control), whereas that in Sup remained reduced (0.7 ± 0.3% of control) at 22 h of recovery.

Aldosterone was higher in Up than Sup throughout the experiment (Fig. 4). During exercise, aldosterone increased from 125 ± 25 to 480 ± 87 and 66 ± 18 to 121 ± 43 pg/ml in Up and Sup, respectively. Aldosterone remained elevated until 2 h of recovery in Up.

ANP was lower in Up than in Sup throughout the experiment. During exercise, ANP increased to 120 ± 33 and 192 ± 26 pg/ml in Up and Sup, respectively.

**DISCUSSION**

Intense upright exercise induced a 6.4% increase in plasma volume at 22 h of recovery. No increase in plasma volume occurred after intense supine exercise. Despite an increase in plasma aldosterone levels and slightly elevated sodium retention in Up, there was no excess water retention estimated by changes in body weight. An important new finding of this study is that
an increase in intravascular protein content after exercise occurred only in Up (Fig. 3). The major component of the additional protein was albumin (86 and 79% of plasma proteins at 1 and 22 h of recovery, respectively). Because of albumin’s low molecular mass (68 kDa), abundance of albumin in plasma proteins, and high colloid osmotic pressure, it has been reported that plasma albumin is important in the maintenance of blood volume (5, 9). Assuming 1 g of albumin binds 18 ml of water (21), an increase in plasma albumin content of 0.12 g/kg body wt at 22 h of recovery in Up accounts for a 2.2 ml/kg body wt of increase in plasma volume, which is 91% of the observed value.

Although the increase in plasma albumin content in Up occurred as early as 1 h of recovery, it was not accompanied by an expansion in plasma volume. This is most likely due to a reduced body water content at 1 h of recovery, with the consequent contraction of the extracellular fluid space. On the basis of the data of body weight change, the small amount of nutritional liquid (1.5 ml·h⁻¹·kg body wt⁻¹) during the 2- to 5-h recovery period was not sufficient to replace fluid loss due to intense exercise and urine output. Although a higher MAP in Up during most of the recovery period might have caused a greater shift of water from the intravascular to the interstitial space, plasma volumes between 1 and 5 h of recovery were similar in Up and Sup. The higher plasma oncotic pressure, provided by the greater albumin content, could account for maintenance of plasma volume despite the elevated filtration pressure accompanying a higher MAP. This could have contributed to the elevated plasma volume at 22 h of recovery, when MAP as well as the hydration state had returned to the control level.

The mechanism of the acute increase in plasma albumin content after exercise has not yet been defined. The increase in plasma albumin content within the first hour after intense exercise is likely due to a mobilization of interstitial albumin because it occurs too rapidly to be accounted for by the changes in albumin synthetic (28) or degradation rate or in transcapillary escape rate of albumin (12). Senay (23)
postulated that an increase in plasma albumin content after exercise in a hot environment is the consequence of a rapid shift of protein from the cutaneous interstitial to the intravascular space via the lymphatic system. Schad and Brechtelsbauer (22) reported that walking elevated lymph flow and lymph protein transport by 100 and 50% of the resting rates, respectively, with the lymph albumin-to-globulin ratio increased by 25%. Because the ratio of albumin to total protein in thoracic lymph is similar to the ratio in plasma at rest (1), the increase in intravascular protein during exercise is primarily albumin. Thus greater lymph return.

Table 3. Renal function in Up and Sup

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<td>UV, ml/min</td>
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<td>Ccr, ml/min</td>
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<td>83±9</td>
<td>112±4</td>
<td>113±3</td>
<td>110±5</td>
<td>129±10</td>
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<td>Ccr, ml/min</td>
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<td>1.0±0.1†</td>
<td>1.6±0.1</td>
<td>1.4±0.1†</td>
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<td>Ccr, ml/min</td>
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<td>−0.4±0.1†</td>
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<td>Ccr, ml/min</td>
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<td>0.2±0.0†</td>
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<td>1.0±0.2†</td>
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<td>0.4±0.1</td>
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<td>U[Na +]/[K +]</td>
<td>1.4±0.4</td>
<td>0.7±0.2†</td>
<td>0.8±0.2†</td>
<td>1.0±0.4†</td>
<td>1.7±0.5†</td>
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Values are means ± SE for 7 subjects. UV, urine volume; Ccr, creatinine clearance; Ccosm, osmotic clearance; Cch2o, free water clearance; Cna, sodium clearance; U[Na +]/[K +], ratio of sodium to potassium concentration in urine; Ex, during exercise; Rec, recovery; ON, sample collected overnight. *Significant difference between Up and Sup, P < 0.05. †Significantly different from control, P < 0.05.
appears to be a possible mechanism for the immediate increase in plasma albumin content after exercise in Up.

Szabo and Magyar (25) showed that thoracic duct lymph flow was inversely related to the outflow pressure, which is similar to right atrial pressure (RAP). Although we did not measure RAP in this study, plasma ANP is correlated with RAP (15). The higher level of ANP in Sup than in Up might then reflect a greater outflow pressure in Sup than in Up. Therefore, Sup would suppress lymph return into the intravascular space during exercise, resulting in the unchanged plasma protein content.

In Up, plasma albumin content was increased by 2 h of recovery but then became reduced from this level by 0.05 g/kg body wt at 5 h of recovery (Fig. 3). Assuming the additional albumin (0.13 g/kg body wt at 2 h of recovery) disappeared in an exponential manner during the 3-h period, the escape rate of albumin would be estimated at 11%/h, a value similar to that previously reported (21). If the albumin continued to escape from the intravascular space at the rate of 11%/h, the increase in plasma albumin content from control would have been only 0.01 g/kg body wt at 22 h of recovery instead of the observed 0.11 g/kg body wt increase. This calculation indicates that other mechanisms must also contribute to the maintenance of an increase in plasma albumin content after exercise, such as a decrease in the albumin escape rate (12) and/or an increase in albumin synthetic rate (28).

Renkin and Tucker (19) reported that ANP facilitates albumin movement from the intravascular into the interstitial space across the capillary wall. The greater increase in ANP during exercise in Sup than in Up might have promoted greater plasma albumin loss. However, higher levels of ANP were observed in Sup than in Up (Fig. 4), even at control. These differences in ANP had no effect on plasma albumin content (Fig. 3). There must be some compensation in the interstitial space that adjusts for the change in transcapillary escape rate induced by ANP. The difference in ANP between Up and Sup was similar throughout the recovery period. Therefore, it is difficult to specify a role of ANP in the plasma volume expansion process.

Changes in albumin metabolism may contribute to the maintenance of the greater plasma albumin content in Up. Carraro et al. (2) reported that exercise at 40% of maximal VO₂ for 40 min did not change albumin synthetic rate. In contrast, Yang et al. (28) reported a 16% increase in albumin synthetic rate at 3–6 h of recovery following 85% of maximal VO₂ exercise in Up. The reported values of albumin synthetic rate in steady-state range from 50 to 300 mg·kg body wt⁻¹·day⁻¹ (25). If an increase in albumin synthesis was responsible for the elevation of plasma albumin from 5 to 22 h of recovery in Up, albumin synthetic rate must have increased by 42 mg·kg body wt⁻¹·day⁻¹ (assuming a constant albumin degradation rate and no net movement of albumin between the intravascular and interstitial spaces). Although it is unknown whether the elevated albumin synthetic rate is maintained for 22 h after exercise, a change in albumin synthesis may contribute to the maintenance of a greater plasma albumin content.

Intense exercise activated the renin-angiotensin-aldosterone axis in Up but suppressed it in Sup. In Up, plasma aldosterone increased by 243 pg/ml during exercise and remained higher than control for 2 h (Fig. 4). In contrast, aldosterone in Sup increased by only 67 pg/ml and decreased from control at 1–5 h of recovery. The reduced sodium clearance and lower urine sodium/potassium concentration ratio in Up compared with Sup are consistent with the activation of the renin-angiotensin-aldosterone axis, which resulted in the smaller urine output during exercise and after 5 h of recovery in Up than in Sup. Convertino (3) reported that water was retained in the body after 10 days of training, suggesting that increased extracellular fluid volume contributed to an increase in plasma volume. The difference in urine output during the 5-h recovery period was 4.54 ml/kg body wt. However, overnight water intake and urine output after exercise were similar in the two trials. Therefore, the activation of the renin-angiotensin-aldosterone axis in Up contributed a little to the increase in plasma volume on day 3. If there were no difference in the caloric balance in the two trials, the lesser body weight loss in Up on day 3 showed that extracellular fluid volume in Up was greater than in Sup. In addition, a constant amount of plasma protein content with higher plasma protein concentration in Sup on day 3 would also indicate that the extracellular fluid volume was smaller than that of control. However, it remains unknown whether the intense exercise induced the extracellular fluid expansion with the plasma expansion in Up.

Six degrees of head-down tilt bed rest induces a decrease in plasma volume within 24–48 h (4, 6). Convertino et al. (6) reported that intense exercise 24 h before the end of 16 days of head-down tilt restored plasma volume by increased water intake and reabsorption of urine output. They proposed the importance of central venous pressure (CVP) as a signal to alter body water regulation. Prolonged dehydration during the head-down tilt reflects resetting to a lower operating point of CVP, which limits plasma volume expansion by water intake, and chronic elevation of CVP by intense exercise is effective in elevating the operating point of CVP, resulting in restoration of plasma volume with sufficient water intake (4). In the present study, CVP related to posture would be a strong acute stimulus to affect the renin-angiotensin-aldosterone axis during exercise and after recovery as long as the posture was maintained. However, there were no differences in water intake and urine output during the rest of the recovery period. Therefore, the difference in CVP during exercise and/or after 5 h of recovery had no chronic effect on renal water handling and thirst. In addition, we have no evidence that CVP has effects on albumin metabolism and/or capillary albumin permeability, which would be an important factor in maintaining greater plasma albumin content and exercise-induced hypervolemia.
In summary, plasma volume expansion after intense exercise occurs only in Up and is absent in Sup; the expansion in Up was due primarily to an increase in plasma albumin content. Although the mechanism for the posture-specific increase in plasma albumin content is still unclear, we speculate that posture modulates the response after intense exercise primarily through its impact on lymph albumin return and secondarily on albumin metabolism and/or transcapillary escape rate of albumin.

We thank Drs. Joshua Korzenik and Vahid Mohsenin for supervision of the subjects during their stay in the General Clinical Research Center at Yale University (New Haven, CT). This investigation was supported in part by National Heart, Lung, and Blood Institute Grant HL-20634, National Aeronautics and Space Administration Grant NAGW-4056, and National Institutes of Health/National Center for Research Resources/General Clinical Research Center Program Grant #00125. Address for reprint requests: G. W. Mack, The John B. Pierce Laboratory, Yale University School of Medicine, 290 Congress Ave., New Haven, CT 06519 (E-mail: gmack@jpierce.org).

Received 29 January 1998; accepted in final form 2 November 1998.

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