Increased renal tubular sodium reabsorption during exercise-induced hypervolemia in humans

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Nagashima, Kei, Jauchia Wu, Stavros A. Kavouras, and Gary W. Mack. Increased renal tubular sodium reabsorption during exercise-induced hypervolemia in humans. J Appl Physiol 91: 1229–1236, 2001.—We tested the hypothesis that renal tubular Na+ reabsorption increased during the first 24 h of exercise-induced plasma volume expansion. Renal function was assessed 1 day after no-exercise control (C) or intermittent cycle ergometer exercise (Ex, 85% of peak O2 uptake) for 2 h before and 3 h after saline loading (12.5 ml/kg over 30 min) in seven subjects. Ex reduced renal blood flow (p-aminohippurate clearance) compared with C (0.83 ± 0.12 vs. 1.49 ± 0.24 l/min, P < 0.05) but did not influence glomerular filtration rates (97 ± 10 ml/min, inulin clearance). Fractional tubular reabsorption of Na+ in the proximal tubules was higher in Ex than in C (P < 0.05). Saline loading decreased fractional tubular reabsorption of Na+ from 99.1 ± 0.1 to 98.7 ± 0.1% (P < 0.05) in C but not in Ex (99.3 ± 0.1 to 99.4 ± 0.1%). Saline loading reduced plasma renin activity and plasma arginine vasopressin levels in C and Ex, although the magnitude of decrease was greater in C (P < 0.05). These results indicate that, during the acute phase of exercise-induced plasma volume expansion, increased tubular Na+ reabsorption is directed primarily to the proximal tubules and is associated with a decrease in renal blood flow. In addition, saline infusion caused a smaller reduction in fluid-regulating hormones in Ex. The attenuated volume-regulatory response acts to preserve distal tubular Na+ reabsorption during saline infusion 24 h after exercise.

The body fluid adjustments associated with exercise-induced hypervolemia can be characterized by an acute response to the exercise stimulus, usually described as a selective expansion of plasma volume (PV) within the first 24–48 h after the exercise (9, 22), and a chronic adaptation, identified as a general expansion of the extracellular fluid compartment (20). One mechanism contributing to the selective expansion of PV immediately after exercise is an increase in plasma albumin content (9, 11, 22, 23, 31). Plasma albumin retains water in the vascular space through its colloid osmotic properties. A redistribution of extracellular albumin between the intra- and extravascular space (9, 11, 23) and an increase in albumin synthesis (22, 31) contribute to the increase in plasma albumin content over the first 24–48 h. Increased Na+ and water retention by the kidney is thought to contribute to plasma expansion after acute exercise; however, evidence supporting this hypothesis is surprisingly lacking. Increased plasma aldosterone and plasma renin activity (PRA) during exercise mediate an increase in renal Na+ retention within the first few hours after exercise, but these hormones return to the control levels within 3–6 h along with Na+ excretion (25). One might expect that the renal response to the elevated aldosterone after exercise would enhance distal tubular Na+ reabsorption. However, significant increases in Na+ and/or water retention by the kidney have not been consistently detected between 4 and 24 h after exercise (9, 11, 23). Nagashima et al. (23) observed smaller urine output and a slight reduction in Na+ clearance during a 5-h recovery period after intense exercise. However, Na+ clearance returned to the control level by 17 h after exercise. The reason for the inability of earlier research to consistently identify adaptations in renal function in euhydrated individuals is unclear. One possibility is that the adjustments in renal Na+ handling are small and difficult to detect, especially if the experimental design is not optimized for evaluating renal function. This is likely the case in several earlier studies (9, 11, 23) where evaluation of renal function was considered a secondary measurement.

We propose that increased water and Na+ retention by the kidney is important in the process of exercise-induced hypervolemia and the rapid expansion of PV 24 h after exercise. Specifically, we examined the hypothesis that Na+ retention in the distal tubules is enhanced 24 h after exercise. To test this hypothesis, we compared renal function, hemodynamics, and fluid-regulating hormones 1 day after a single intense exercise protocol with a no-exercise control. To fully evaluate adaptations in renal function after the exercise stimulus, we examined water and Na+ retention in euhydrated conditions and after a water and salt load. Finally, to identify the renal mechanisms responsible for increased Na+ retention, we used an...
METHODS

Protocol. Seven healthy volunteers (3 men and 4 women) gave written informed consent for the protocol, which had been approved by the Yale University School of Medicine Human Investigation Committee. Their physical characteristics were as follows: 25 ± 1 (SE) yr of age, 68.5 ± 3.5 kg body wt, and 35.5 ± 0.9 ml-kg body wt⁻¹·min⁻¹ peak O₂ uptake (V\textsubscript{O₂ peak}). A graded cycle ergometer was used to determine V\textsubscript{O₂ peak} ≥ 1 wk before participation in the experimental trials. Each subject performed two identical trials to assess renal functions with and without a prior exercise bout. The order of trials was randomized, and the interval between the trials was 1–2 wk in male subjects and 3–4 wk in female subjects. Trials for female subjects were performed within the first 7 days of their menstrual cycle. Subjects were instructed not to engage in vigorous exercise and/or an exercise protocol during this experiment. The protocol is summarized in Fig. 1.

Each trial involved 2 days of testing. Subjects ate and drank only the food and beverage we provided starting 16 h before day 1 (dinner: 5.9 MJ, 35 g fat, 225 g carbohydrate, 48 g protein, 1,820 mg sodium; breakfast: 1.6 MJ, 2 g fat, 87 g carbohydrate, 7 g protein, 200 mg sodium), which included 1 liter of water to drink on the night before each testing day, with additional water intake at home allowed ad libitum. On day 1, the subjects arrived at the laboratory at 7:30 AM and ingested 10 ml/kg body wt of water over a 30-min period. The subject then emptied his/her bladder and moved into an environmental chamber and rested in the upright, seated position at 27°C. From this point, subjects drank 1.5 ml/kg body wt of water every 30 min. At the end of the 60-min baseline period, a 10-ml blood sample was collected as well as a urine sample (completely voiding the bladder). On the exercise trial day (Ex), subjects moved into another environmental chamber adjusted to 19°C to exercise. Exercise consisted of eight bouts of high-intensity exercise (85% V\textsubscript{O₂ peak}), each lasting 4 min and followed by 5 min of recovery at 20–30% V\textsubscript{O₂ peak}. This exercise protocol has consistently produced significant expansion of PV in previous experiments (9–11, 18, 22, 23, 31). On the control trial day (C), subjects did not perform exercise after the baseline period. All subjects were sent home with food and beverage and were asked to ingest a 300-mg lithium carbonate tablet at 10 PM for Li\textsuperscript{+} clearance measurements on the next day.

On day 2, subjects came to the laboratory at the same time of day 1 and performed an identical baseline period. Teflon catheters were placed in large superficial veins of the left and right forearm for blood sampling and infusion of an inulin/p-aminohippurate (PAH) cocktail used for estimating glomerular filtration rate (GFR, inulin clearance) and effective renal plasma flow (PAH clearance). Heart rate was monitored from an electrocardiogram, and cardiac stroke volume was measured by impedance cardiography. Cardiac output was determined as heart rate times stroke volume. Blood pressure was measured noninvasively from the brachial artery by a sonometric pickup, and mean arterial pressure was calculated as one-third systolic pressure plus two-thirds diastolic pressure.

Stable plasma levels of inulin and PAH for the determination of renal clearances were established with a primed-constant infusion technique. A priming dose of 35 and 6 mg/kg body wt of inulin and PAH, respectively, was given over a 2-min period followed immediately by a constant infusion of 15 and 6 mg/kg body wt of inulin and PAH, respectively. The infusion was started at the beginning of the baseline period and maintained throughout the entire experiment. To maintain adequate urine flow, subjects drank 1.5 ml/kg body wt of water every 30 min during the entire experimental protocol. At the end of the baseline period (1 h after the onset of the infusion), we measured heart rate, blood pressure, and stroke volume and collected a blood sample while subjects rested in the seated position. Subjects then walked to the bathroom to provide a urine sample (~3 min) and returned to the upright seated position in the chamber. At this point, we began a series of nine 30-min periods of data collection consisting of drinking 1.5 ml/kg body wt of water and resting seated for 30 min, with heart rate, blood pressure, and stroke volume measured during the last 5 min of each period, collection of a blood sample in the seated position, and collection of a urine sample. Subjects repeated this protocol for four consecutive euhydrated periods (EH1, EH2, EH3, EH4). The kidney was then challenged.
with an infusion of 12.5 ml/kg body wt of 0.9% saline over a 90-min period. After saline infusion, subjects repeated the protocol for four consecutive overhydrated periods (OH1, OH2, OH3, OH4). After OH4, subjects rested for an additional 60 min (OH5), during which absolute plasma was determined by Evans blue dye dilution. Additional blood samples were collected at EH2, OH1, and OH2 for determination of plasma levels of fluid-regulating hormones: PRA, aldosterone, arginine vasopressin (AVP), and atrial natriuretic peptide (ANP).

Renal functions. The period between consecutive urine samples was accurately timed while subjects were instructed to empty their bladders completely. Total urine volume was measured using a graduated cylinder, and a 5-ml sample was stored for analysis. The renal clearances of inulin (C_{inulin}), PAH (C_{PAH}), and Li^+ (C_{Li}) were calculated by standard methods, where C_{inulin} is GFR and C_{PAH} is effective renal plasma flow. C_{Li} allows us to estimate proximal renal tubular handling of Na^+, because filtered Li^+ is reabsorbed almost exclusively by the proximal tubules in the same proportion as Na^+ and water (29, 30). The urinary excretion of Na^+ was calculated as the product of urine volume and Na^+ concentration (V_{Na}). The following equations were used to describe renal function: filtered load of Na^+ (FL_{Na}) = plasma Na^+ concentration-1.05 (Donnan factor)-GFR, fractional tubular reabsorption of Na^+ (FR_{Na}) = (FL_{Na} - V_{Na}/P_{Na})/FL_{Na}; fractional reabsorption of Na^+ in proximal tubules (PFR_{Na}) = 1 - C_{Li}/C_{inulin}; fractional reabsorption of Na^+ in distal tubules (DFR_{Na}) = 1 - C_{Na}/C_{Li}; fractional reabsorption of water in proximal tubules (PFR_{H2O}) = 1 - C_{Li}/C_{inulin}; fractional reabsorption of water in distal tubules (DFR_{H2O}) = 1 - urine flow rate/C_{Li}; and effective renal blood flow (ERBF) = 0.90 × C_{PAH}/(1 - Hct × 0.96), where correction factors for trapped plasma (0.96) and F cell ratio (0.90) were applied to the hematocrit (Hct) data.

Blood analysis. Hct (microcentrifuge) and hemoglobin (Hb) concentration (cyanmethemoglobin method) were measured in triplicate. The remaining blood was centrifuged at 4°C for 20 min. The plasma was used to determine osmolarity (freezing-point depression; model 3DII, Advanced Instrument), Na^+ concentration (flame photometry; model IL943 Automatic Flame Photometer, Instrumentation Laboratory), and albumin concentration (bromcresol method; Sigma). Colloid osmotic pressure was measured using a small sample colloid osmometer with pore restriction of 30 kDa. For the determination of plasma inulin and Li^+ concentrations, 1,250 μl of plasma were deproteinized by addition of equal amounts of 0.3 M ZnSO_4 and 0.3 M Ba(OH)_2. The supernatant (1.5 ml) was dried with a vacuum centrifuge (Speed Vac, Savant) and resuspended with 90 μl of a 140:5:0 mmol/l Na^+-K^+-Li^+ solution. Li^+ concentration of the reconstituted solution was measured by flame photometry, and the plasma concentration was determined from a standard curve that was prepared for each experiment using the subject’s plasma taken on the 1st day of the experiment and spiked with graded concentrations of LiCl. The intra- and interassay coefficients of variation for plasma standard at 0.1 mmol/l were 1.1 and 2.4%, respectively. For the determination of plasma inulin concentration, 1 ml of 70% H_2SO_4 was added to 200 μl of supernatant. After addition of 1 ml of anthrone reagent (2 g anthrone/70% H_2SO_4), the sample was incubated for 9 min at 70°C, and the absorbance at 540 nm was measured on a spectrophotometer. For the determination of plasma PAH concentration, 500 μl of distilled water were added to a 125-μl plasma sample. Then, 750 μl of sodium nitrate, 400 μl of ammonium sulfamate, and 400 μl of N-(1-naphthyl)ethylenediamine dihydrochloride were added to the sample in sequence, and the absorbance was measured at 560 nm.

Blood samples for aldosterone and AVP were transferred into K_3-EDTA tubes, and those for ANP and PRA were transferred into K_3-EDTA aprotinin-treated and lithium heparin tubes, respectively. The plasma samples were stored at −70°C until radioimmunoassay (Diagnostic Products and Incstar). The intra-assay coefficient of variation for aldosterone was 0.7% at 28 pg/ml and 7.9% at 122 pg/ml, and that for ANP was 6.0% at 70.3 pg/ml. The intra-assay coefficients of variation for PRA and AVP were 2.6% at 5.4 ng angiotensin I·ml⁻¹·h⁻¹ and 17.1% at 2.0 pg/ml, respectively.

Urine analysis. Urine Na^+ concentration and osmolality were measured by a method similar to that described for measurement of plasma samples. Samples for Li^+ concentration were determined in the same manner as plasma samples without deproteinization. The intra- and interassay coefficients of variation were 5.7% at 0.25 mmol/l and 3.1% at 1.00 mmol/l, respectively. The urine sample for the determination of inulin concentration was diluted 1:90–1:400 with distilled water, and that for PAH was diluted 1:40. The urine concentrations of inulin and PAH were measured using the same assay used for the blood samples.

Calculations. PV at any time point (t) during the experiment was expressed as a percentage of the final time period (OH5) on the basis of Hb and Hct values as follows

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\text{PV} = 100 \times \left( \frac{\text{Hb}_{\text{OH5}}}{\text{Hb}} \right) \times \left[ 1 - \frac{\text{Hct}_{\text{OH5}}}{\text{Hct}} \times \left( \frac{1 - (\text{Hct}_{\text{OH5}}/10^{-2})}{1 - (\text{Hct}_{\text{OH5}}/10^{-2})} \right) \right]
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The absolute value for PV at OH5 was directly determined by Evans blue dye dilution. Absolute values of PV at each time point before OH5 were converted by multiplying the percent PV by the absolute value made with Evan’s blue dye. Plasma albumin and Na^+ content were calculated as the product of PV and plasma albumin and Na^+ concentrations.

Statistics. Differences between variables were determined by ANOVA for repeated measures. Significant differences at specific time points were identified by paired t-test. Values are means ± SE, and the null hypothesis was rejected at P < 0.05.

RESULTS

Urine flow rate was similar for C and Ex throughout the experimental protocol (i.e., 4.3 ± 0.7 and 4.0 ± 0.4 ml/min at EH2 and 3.3 ± 0.6 and 2.7 ± 0.5 ml/min at OH3 in C and Ex, respectively). Renal Na^+ excretion was reduced in Ex (P < 0.05) in EH3–EH4 and OH1–OH2, i.e., 0.08 ± 0.01 vs. 0.13 ± 0.02 mmol/min at EH3 and 0.08 ± 0.01 vs. 0.16 ± 0.02 mmol/min at OH2 (Ex vs. C). Plasma albumin was smaller in C and Ex and stable during each trial, averaging 285 ± 1 and 284 ± 1 mmol/kgH_2O at EH2 and 284 ± 1 and 284 ± 1 mmol/kgH_2O at OH3, respectively.

PV in the euvhedral state (EH2) was larger in Ex than in C (39.69 ± 1.69 vs. 37.46 ± 0.94 ml/kg body wt, P < 0.05), and this difference was maintained after saline infusion (42.75 ± 1.78 and 40.25 ± 1.12 ml/kg body wt at OH5, respectively). Plasma Na^+ content was increased in proportion to the increase in PV (5.10 ± 0.14 and 5.45 ± 0.24 mmol/kg body wt at EH2 to 5.49 ± 0.16 and 5.88 ± 0.24 mmol/kg body wt at OH3 in C and Ex, respectively). Plasma albumin content was larger in Ex than in C at all measurement points (1.75 ± 0.04
and 1.85 ± 0.07 g/kg body wt at EH2 and 1.82 ± 0.04 and 1.93 ± 0.07 g/kg body wt at OH5 in C and Ex, respectively, P < 0.05).

Figure 2 shows the impact of intense exercise on cardiovascular function and ERBF at rest and after saline infusion. Resting heart rate, cardiac output, and mean arterial pressure were similar for C and Ex. Heart rate and mean arterial pressure were not altered by the saline infusion. In contrast, cardiac output increased in response to the saline infusion to a similar degree in C and Ex (P < 0.05). ERBF was markedly lower in Ex than in C (829 ± 118 and 1,485 ± 1,271 ml/min in Ex and C at EH2, respectively, P < 0.05) but was unchanged by saline infusion.

GFR and the filtered load of Na\(^+\) were maintained at similar levels for C and Ex and unaltered by saline infusion (Fig. 3). Fractional tubular reabsorption of Na\(^+\) was increased in Ex compared with C (P < 0.05), with significant differences at EH3, EH4, saline infusion period (INF), and OH3–OH4 (Fig. 3). Fractional tubular reabsorption of Na\(^+\) decreased after saline infusion in C and remained low through OH1–OH5 (P < 0.05). The decrease in fractional tubular reabsorption of Na\(^+\) occurred faster in C (INF, OH1) than in Ex (OH3, P < 0.05). Free water clearance was higher in C than in Ex (P < 0.05), with specific differences at EH3, OH1, and OH3.

Figure 4 compares the fractional reabsorption of Na\(^+\) and H\(_2\)O in the proximal and distal tubules. Fractional reabsorption of Na\(^+\) in the proximal tubules was always higher in Ex than in C (P < 0.05). Fractional reabsorption of Na\(^+\) in the proximal tubules decreased in response to saline infusion in C and remained low throughout OH1–OH5 (P < 0.05). In contrast, fractional reabsorption of Na\(^+\) in the proximal tubules was similar for C and Ex. After saline infusion, fractional Na\(^+\) reabsorption in the distal tubules was immediately reduced in C (OH3 and OH2, P < 0.05) but recovered to euhydrated levels by OH3. Fractional Na\(^+\) reabsorption in the distal tubules was

Fig. 2. Changes in heart rate (HR; A), mean arterial pressure (MAP; B), cardiac output (Qc; C), and effective renal blood flow (ERBF; D) during euhydrated and overhydrated periods in control (C) conditions and 24 h after exercise (Ex). Values are means ± SE of 7 subjects. *P < 0.05, C vs. Ex. †P < 0.05 vs. EH4.

Fig. 3. Changes in renal functions in euhydrated and overhydrated periods in control conditions and 24 h after exercise. GFR, glomerular filtration rate (A); FLNa\(^+\), filtered load of Na\(^+\) (B); TFR Na\(^+\), total fractional reabsorption of sodium (C); CH\(_2\)O, free water clearance (D). Values are means ± SE of 7 subjects. *P < 0.05, C vs. Ex. †P < 0.05 vs. EH4.
also reduced after saline infusion in Ex; however, this reduction was significantly delayed (until OH 5) compared with C (P < 0.05). Fractional water reabsorption in the distal tubules was similar for both trials throughout the experiments and was not affected by saline infusion.

At baseline euhydrated conditions, PRA, ANP, and AVP were similar in C and Ex trials (Fig. 5). However, baseline plasma aldosterone was slightly elevated in Ex compared with C (172.5 ± 29.8 vs. 137.2 ± 25.5 pg/ml, P < 0.05) at EH 2. Volume loading with saline reduced PRA, aldosterone, and AVP in C and Ex. The decrease in PRA was greater in C than in Ex (P < 0.05), while the reduction in aldosterone was similar for C and Ex. The decrease in AVP after volume loading occurred by OH 1 in C but was delayed until OH 3 in Ex. ANP levels were not influenced by previous exercise or saline infusion.

Colloid osmotic pressure was elevated in Ex compared with C (Fig. 6; P < 0.05). Saline infusion produced a similar decrease in colloid osmotic pressure in C and Ex (P < 0.05).

DISCUSSION

Data from the present study support the hypothesis that increased Na⁺ retention by the kidney occurs during the rapid expansion of PV 1 day after intense exercise that induced hypervolemia. Several significant new findings characterizing the mechanism by which exercise impacts net tubular Na⁺ reabsorption were identified: 1) in the euhydrated condition, increased proximal tubular Na⁺ reabsorption contributed to the net tubular Na⁺ reabsorption, 2) augmented proximal tubular Na⁺ reabsorption is associated with a 50% reduction in ERBF, 3) reflex reductions in fluid regulatory hormones (PRA and AVP) after saline infusion were significantly delayed and attenuated after exercise, and 4) the attenuated volume-regulatory reflex contributed to a better maintenance of distal tubular Na⁺ reabsorption after saline loading. Overall, net tubular Na⁺ reabsorption after a

Fig. 5. Changes in fluid-regulating hormones in euhydrated and overhydrated periods in control conditions and 24 h after exercise. PRA, plasma renin activity (A); Aldo, plasma aldosterone (B); ANP, plasma atrial natriuretic peptide (C); AVP, plasma arginine vasopressin (D). Values are means ± SE of 7 subjects. *P < 0.05, C vs. Ex. †P < 0.05 vs. EH 4.
saline load is enhanced 1 day after intense exercise as a result of increased proximal tubular Na\(^+\) reabsorption and the maintenance of distal tubular Na\(^+\) reabsorption.

Before the bolus saline infusion, the fractional reabsorption of Na\(^+\) by renal tubules was higher in Ex than in C (Fig. 3C). Fractional tubular Na\(^+\) reabsorption decreased immediately after the saline infusion in C. In contrast, the reduction in fractional tubular Na\(^+\) reabsorption was delayed until the end of the overhydrated period (OH3 and OH4) in Ex. GFR and the filtered load of Na\(^+\) were similar for Ex and C (Fig. 3, A and B). However, free water clearance tended to be higher in C than in Ex before (EH3, Fig. 3D) and after saline infusion (OH2 and OH3). These findings indicate that, under our experimental conditions (constant water intake), suppression of net tubular Na\(^+\) and water reabsorption after a bolus saline infusion is attenuated 1 day after intense exercise. In support of this concept, Na\(^+\) excretion rate in urine was smaller in Ex than in C during the euhydrated periods (EH3–EH4) and after saline loading (OH1–OH2). The difference in net Na\(^+\) excretion for these periods was 34 mmol or 9.1% of the plasma Na\(^+\) content. Contributing to the attenuated Na\(^+\) secretion at baseline would be the elevation in aldosterone in Ex compared with C. After saline infusion, the reduction in AVP was delayed in Ex (Fig. 5, B and D) and may have attenuated the reduction in free water clearance during the overhydrated periods in Ex.

Regional differences in tubular reabsorption of Na\(^+\) and water were estimated using an Li\(^+\) clearance technique (30). It is widely accepted that most Li\(^+\) reabsorption takes place in the proximal tubules and is proportional to Na\(^+\) and water reabsorption (29). In the proximal tubules of superficial nephrons, changes in Na\(^+\) reabsorption due to changes in volume status are paralleled by changes in proximal Li\(^+\) reabsorption (2). However, fractional excretion of Li\(^+\) does not purely represent changes in proximal Na\(^+\) reabsorption, because Li\(^+\) can also be handled beyond the proximal tubules (15). Li\(^+\) handling can occur in the loop of Henle and late distal and collecting tubules in rats and dogs. The activity of this Li\(^+\)-handling system appears to be much lower in humans than in rats or dogs (15). Na\(^+\) restriction has been shown to enhance Li\(^+\) transport in the loop of Henle. It has been estimated that Li\(^+\) reabsorption in the loop of Henle can range from 0 to 15% of the filtered load of Li\(^+\) (15). However, our experimental conditions (i.e., adequate Na\(^+\) balance) work to minimize the possibility of Li\(^+\) reabsorption in the loop of Henle. In addition, the changes in body fluid status were small and did not involve excessive changes in fluid-regulating hormones (a slight elevation in aldosterone). Thus we expect the relative changes in proximal Na\(^+\) and water handling to be closely reflected by the Li\(^+\) clearance data. Reabsorption of Na\(^+\) and water in the proximal tubules in the euhydrated state was greater in Ex than in C at all measurement points, while Na\(^+\) reabsorption in the distal tubules was similar for both groups (Fig. 4, A and B). In addition, saline infusion attenuated Na\(^+\) and water reabsorption in the proximal tubules in C, but this response was abolished in Ex. Thus, on the basis of our interpretation of Li\(^+\) clearance data, we conclude that a major impact of the intense exercise on the kidney appears to be at the level of the proximal tubules.

One possible mechanism for enhanced Na\(^+\) reabsorption in the proximal tubules would be increased filtration fraction, i.e., unchanged GFR with reduced RBF (Figs. 2D and 3A). Brenner et al. (3) showed that a reduction in RBF caused an increase in oncotic pressure and a decrease in hydrostatic pressure in the peritubular capillaries. This change in Starling forces in the peritubular capillaries results in an increase in renal tubular reabsorption of Na\(^+\). The peritubular circulation of proximal tubules is derived from renal medullary blood flow. Changes in RBF affect renal medullary blood flow in a linear fashion (19). Thus, despite similar levels of filtered Na\(^+\) load, net Na\(^+\) reabsorption is augmented by increased Na\(^+\) reabsorption in the proximal tubules. In contrast, RBF was unchanged after saline infusion, yet Na\(^+\) reabsorption in the proximal tubules was decreased in C. Increase in peritubular capillary pressure after saline infusion could contribute to the observed reduction in tubular Na\(^+\) reabsorption in C (19). Moreover, the inability of saline infusion to reduce Na\(^+\) reabsorption in the proximal tubules in Ex may reflect the inability of the volume load to raise the peritubular capillary hydrostatic pressure.

Exercise had no impact on resting cardiac output or mean arterial blood pressure but induced a selective reduction in RBF (Fig. 2, B–D). In addition, RBF was unaltered by volume loading. The most likely interpretation of the decrease in RBF without a change in GFR would be a selective increase in the renal sympathetic nerve activity (RSNA) directed toward the efferent arterioles. A higher baseline level of aldosterone provides limited support for this interpretation (Fig. 5, A and B); however, corresponding changes in PRA were
not observed. Saline infusion induced a volume expansion that reduced PRA in C and Ex, but the magnitude of the reduction in PRA was smaller in Ex than in C. These data support our proposed hypothesis that a postexercise attenuation of baroreflex function participates in the induction of PV expansion by intense exercise (10). It is unclear whether this attenuated baroreflex function contributes to the proposed changes in RSNA and eventual modulation of Na\(^+\) reabsorption. Increased RSNA facilitates tubular Na\(^+\) reabsorption by directly affecting the tubular cell membrane (4). This effect occurs with small changes in RSNA that do not affect RBF (27). Thus increased RSNA is one mechanism involved in greater Na\(^+\) absorption in the proximal and distal tubules 1 day after intense exercise. However, support for this hypothesis is limited. The sympathetic nerve response after exercise has been examined with respect to postexercise hypotension. These studies have focused their attention on the first few hours after exercise and have generally used hypertensive subjects or animals (7, 16). In general, postexercise hypotension is associated with sympathoinhibition and vasodilation in hypertensive individuals. Postexercise sympathoinhibition is not generally seen in normotensive humans after intense exercise (6). In contrast to studies using hypertensive animals, RSNA is increased 2 h after exercise in normotensive rabbits (13). Persistent elevation in RSNA would contribute to a reduction in RBF 1 day after exercise. Alternatively, increased angiotensin II or endothelin or decreased nitric oxide levels would also cause a reduction of RBF (1, 12, 28).

The expected reduction in PRA and AVP immediately after saline infusion was attenuated in Ex compared with C (Fig. 5, A and D). Because blood pressure (Fig. 2B) and plasma osmolality were similar between C and Ex, the differences in hormone levels probably reflect in large part the contribution of atrial reflex controls, i.e., cardiac-renal-neural reflex and/or Henry-Gauer reflex (8, 21). One possible mechanism for the attenuated response in Ex may be a smaller change in atrial pressure, despite infusion of identical amounts of saline. A greater vascular capacitance after intense exercise could account for this response. Another possibility is that intense exercise causes a change in the sensitivity or operating point for the reflex that regulates the reductions in PRA and AVP after the elevation of atrial pressure with saline infusion.

Plasma albumin content and PV were increased 1 day after the intense exercise; however, plasma colloid osmotic pressure was lower in Ex than in C at each measurement point (Fig. 6). The reduction in transcapillary hydrostatic pressure gradient acts to reduce outward fluid flux. Another possibility is that venous tone is reduced after exercise. This would contribute to a decrease in postcapillary venous pressure and aid in the retention of water in the vascular compartment.

We used a water (10 ml/kg body wt initial volume followed by 1.5 ml/kg body wt water every 30 min) and salt load to evaluate changes in renal Na\(^+\) handling in response to intense exercise. This model has been successfully used to evaluate renal function in response to a variety of environmental stressors (i.e., microgravity, head-down tilt) (5, 24) or disease states (17). The constant water intake allowed for a high urinary flow rate prerequisite for accurate assessment of GFR and RBF by clearance methods. The combination of these factors provided a high Na\(^+\) output by the kidney, permitting us to identify small changes in renal Na\(^+\) handling that might occur in response to the intense exercise protocol. These experimental conditions exaggerate the effect of exercise on renal Na\(^+\) handling. However, even small changes in the renal handling of Na\(^+\) over an extended period of time can cause major alterations in body fluid balance. Our experimental design increased renal Na\(^+\) excretion, in part by inducing some medullary washout, and possibly altered the hormonal response to saline loading. The frequent drinking and infusion of a large saline load would act to suppress AVP to barely detectable levels. The lowered AVP levels could remove inhibition of PRA release (14, 26), potentially contributing to local effects on the kidney tubular function. However, the similarity in PRA in C and Ex trials provides little support for this mechanism.

In summary, a single bout of intense exercise that produced PV expansion reduced Na\(^+\) and water excretion by the kidney 1 day after intense exercise. Exercise increased Na\(^+\) reabsorption in the proximal tubules, a response most likely mediated by the reduction in RBF. Moreover, the baroreflex-mediated reduction in fluid-regulating hormones after saline infusion was delayed and attenuated. These data support the hypothesis that renal and hormonal adaptations after intense exercise participate in the initial (first 24–48 h) process of PV expansion. From a quantitative perspective, the importance of these renal mechanisms to the overall increase in PV within the first 24–48 h is undefined. However, the acute renal response to exercise clearly compliments the role of albumin in the expansion of PV immediately after exercise. The role of this renal adaptation in response to an acute bout of intense exercise to extracellular fluid volume expansion associated with chronic exercise training remains to be identified.

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