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Intense exercise stimulates albumin synthesis in the upright posture

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Nagashima, Kei, Gary W. Cline, Gary W. Mack, Gerald I. Shulman, and Ethan R. Nadel. Intense exercise stimulates albumin synthesis in the upright posture. *J. Appl. Physiol.* 88: 41–46, 2000.—We tested the hypothesis that an elevation in albumin synthetic rate contributes to increased plasma albumin content during exercise-induced hypervolemia. Albumin synthetic rate was measured in seven healthy subjects at 1–5 and 21–22 h after 72 min of intense (85% peak oxygen consumption rate) intermittent exercise and after 5 h recovery in either upright (Up) or supine (Sup) postures. Deuterated phenylalanine (d_5 -Phe) was administered by a primed-constant infusion method, and fractional synthetic rate (FSR) and absolute synthetic rate (ASR) of albumin were calculated from the enrichment of d_5 -Phe in plasma albumin, determined by gas chromatography-mass spectrometry. FSR of albumin in Up increased significantly ($P < 0.05$) from $4.9 \pm 0.9\%/day$ at control to $7.3 \pm 0.9\%/day$ at 22 h of recovery. ASR of albumin increased from 87.9 ± 17.0 to 141.1 ± 16.6 mg albumin · kg body wt⁻¹ · day⁻¹. In contrast, FSR and ASR of albumin were unchanged in Sup (3.9 ± 0.4 to $4.0 \pm 1.4\%/day$ and 74.2 ± 8.9 to 85.3 ± 23.9 mg albumin · kg body wt⁻¹ · day⁻¹ at control and 22 h of recovery, respectively). Increased albumin synthesis after upright intense exercise contributes to the expansion of greater albumin content and its maintenance. We conclude that stimuli related to posture are critical in modulating the drive for albumin synthesis after intense exercise.

stable isotope; exercise-induced hypervolemia

EXERCISE-INDUCED HYPERVOLEMIA is associated with an increase in plasma albumin content (4, 6, 17). Gillen et al. (6) showed that plasma albumin content increased immediately after upright intense exercise and remained elevated for 48 h. Several factors contribute to the increase in plasma albumin content, including a redistribution of albumin from the interstitial to the intravascular space (6, 17, 18, 26), a reduced transcapillary escape rate (TER) of albumin (9), and increased albumin synthesis (29). However, we recently reported that the increase in plasma albumin content was absent after intense exercise in the supine posture (17), indicating that alterations in intravascular hydrostatic

pressure have an impact on albumin dynamics after intense exercise.

The increase in plasma albumin content after intense upright exercise occurs within the first hour of recovery (6, 17). Thus a redistribution of albumin from the interstitial to the intravascular space is the most likely mechanism for this response (6, 9, 17, 26). This redistribution of albumin could be the result of increased lymph flow during and after exercise (18). In support of this hypothesis, the immediate increase in plasma albumin content is blunted after intense exercise in the supine posture (17), in which elevated central venous pressure, a major determinant of lymph outflow pressure, would act to limit thoracic duct albumin flow at the same time (17, 25). In addition, the major driving forces for increased lymph flow, skin hyperemia and muscle pumping (18, 26), should return to control levels within several hours after exercise. We have estimated that the immediate increase in plasma albumin content after exercise (~8–12 g of albumin) would eventually return to the control state within 24 h if no other compensatory mechanisms existed (17).

Haskell et al. (9) reported a reduction in TER of albumin at 24 h after upright intense exercise, which was associated with a greater plasma albumin content. A decrease in albumin TER would act to conserve plasma albumin and contribute to the retention of the redistributed albumin within the vascular compartment. In addition, Yang et al. (29) reported that albumin synthetic rate was increased between 3 and 6 h after upright intense intermittent exercise. Although an increase in albumin synthesis would contribute to the maintenance of the elevated plasma albumin content, no data exist to support the hypothesis that albumin synthetic rate is elevated for 24–48 h after exercise.

The purpose of this study was to examine the contribution of increased albumin synthetic rate on plasma albumin content after intense exercise. We tested the hypothesis that albumin synthetic rate was elevated after intense exercise and this elevation was maintained for 22 h of recovery. In addition, we evaluated the impact of posture on albumin synthesis after intense exercise, testing the hypothesis that factors associated with the supine posture would prevent the increase in albumin synthetic rate.

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METHODS

Seven healthy volunteers (five men and two women) participated in the present study. They 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 1) age, 25 ± 3 (SE) yr, 2) body weight of 70.5 ± 3.7 kg, and 3) peak oxygen consumption rate ($\dot{V}O_{2\text{peak}}$), 43.45 ± 2.17 ml·kg⁻¹·min⁻¹ in the upright posture (Up) and 40.91 ± 2.64 ml·kg⁻¹·min⁻¹ in the supine posture (Sup). Posture-specific $\dot{V}O_{2\text{peak}}$ was determined in each subject by using a graded cycle ergometer before experiments. Each subject performed two identical experiments, one in Up and the other in Sup, and the order of experiments was randomized. The interval between experiments was 1–2 wk in male subjects, and 3–4 wk in female subjects. In female subjects, experiments were performed within the first 10 days of their menstrual cycle. The protocol is summarized in Fig. 1. Subjects came to the laboratory at 7:00 AM and rested in Up or Sup position for 2 h in an environmental chamber (ambient temperature = 27°C). Then, in an adjacent chamber adjusted to 19°C, subjects performed eight bouts of cycle ergometer exercise in each posture. Each bout consisted of 4 min of intense exercise at 85% of $\dot{V}O_{2\text{peak}}$ followed by 5 min of light exercise at 20–30% of $\dot{V}O_{2\text{peak}}$. After the exercise, subjects returned to the 27°C environmental chamber and recovered in the appropriate posture for 5 h. After the recovery period, subjects were admitted overnight to the Yale University General Clinical Research Center, where their activity was not restricted. On the next day, subjects came to the laboratory again at 7:00 AM and rested for 2 h in the same posture of the previous day's protocol.

Diet and fluid intake were controlled from 6 PM on the day before the exercise day until the end of the experiment. The total caloric and protein contents of the dinner meal were 15 and 21 kcal/kg body wt and 0.35 and 0.45 g protein/kg body wt on the day before and on the exercise day, respectively. Breakfast was at 6:00 AM and consisted of 8 kcal/kg body wt and ~0.2 g protein/kg body wt. Approximately 35% of the total calories in each diet were from fat. Subjects also ingested 0.25 ml/body wt of alimentary liquid containing essential and nonessential amino acids, vitamins, and some ions (1 kcal/ml; Vivonex, Sandoz) every 10 min between 2.5 and 5 h of recovery from exercise.

Pyrogen-negative [*ring*-²H₅]phenylalanine (d₅-Phe, 98%, Cambridge Isotope Laboratories) was delivered via a catheter in a right forearm vein by the primed constant-infusion method (priming dose, 2 μmol/kg body wt for 1 min; constant-infusion rate, 0.05 μmol/kg body wt) (28). The infusion was maintained between 0 h of control (7:30 AM) and the end of the 5-h recovery period on the day of exercise, and between 19 h (7:30 AM) and 21 h of recovery (9:30 AM) on the following

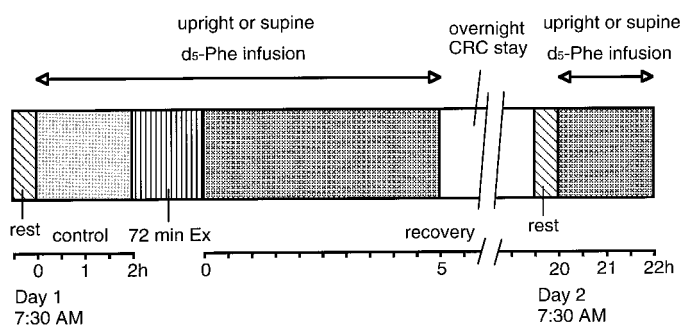


Fig. 1. Summary of experimental schedule. d₅-Phe, [*ring*-²H₅]phenylalanine; CRC, Yale University Clinical Research Center; Ex, exercise.

day (Fig. 1). The Yale University Investigational Drug Service diluted d₅-Phe to 17.5 mM with normal saline.

A 10-ml blood sample was taken at 1 and 2 h of control and at 1, 5, 21, and 22 h of recovery from exercise from a second catheter placed in a left forearm vein. The blood sample was transferred into a heparin sodium-treated tube and centrifuged at 4°C. Absolute plasma volume at the end of each experiment was determined by Evans blue dye dilution method, and plasma volumes at the rest of measuring periods were estimated by changes in hematocrit and hemoglobin. Albumin concentration was measured by the bromocresol method. Plasma albumin content was calculated as the product of plasma volume and plasma albumin concentration. The remainder of the plasma sample was stored at -70°C.

Gas chromatography-mass spectrometry (GC-MS) was used to quantify d₅-Phe enrichment in the free plasma pool and that incorporated in plasma albumin. To extract plasma free amino acids, 1 ml of plasma was deproteinized with 0.3 N ZnSO₄ and neutralized with an equal volume of 0.3 N Ba(OH)₂, and the supernatant was run through a cation-exchange resin column (dry mesh 100–200, Dowex 50WX8–200, Sigma Chemical). Amino acids were then eluted with 4 ml of 4 N NH₄OH. To extract the amino acids incorporated in plasma albumin, 150 μl of plasma were precipitated with 2.5 ml of 10% trichloroacetic acid, and the pellet was dissolved in 5 ml of 100% ethanol to isolate albumin in the residue (13). We made sure that albumin was isolated from other proteins with SDS-PAGE. The supernatant was dried under vacuum, and the residue was dissolved in 6 ml of 0.3 M NaOH. Albumin was reprecipitated by adding 1.2 ml of 40% perchloric acid and then hydrolyzed at 110°C for 24 h with constant boiling 6N HCl. All amino acid samples were evaporated to dryness overnight by vacuum centrifugation (Speedvac, Savant Instruments, Farmingdale, NY). Amino acids were esterified with 200 μl of acidified *n*-butanol-4 N HCl at 60°C for 45 min and the residual *n*-butanol was evaporated in a vacuum oven (40°C) overnight. The *n*-butyl ester was acylated with 140 μl of methylene chloride and 70 μl of trifluoroacetic anhydride (14).

GC-MS analysis was performed with a Hewlett-Packard 5890 gas chromatograph (30 m × 0.53 mm capillary column) interfaced to a Hewlett-Packard 5971A mass selective detector operating in the positive chemical ionization mode with methane as the reagent gas. The GC conditions were initial temperature, 110°C (held for 1 min), ramped at 10°C/min to 200°C, then held constant for 2 min.

The mole percent excess of d₅-Phe in the free plasma pool was determined by monitoring the mass-to-charge ratio (*m/z*) of 323/319 (*m*+5/*m*+1) ions. For low-enrichment samples derived from plasma albumin, ions with *m/z* of 323/320 (*m*+5/*m*+2) were monitored, which allowed for detection of tracer at low moles percent excess between 0.03 and 0.50% (Fig. 2). The intra-assay coefficient of variation for free plasma Phe samples was 1.9 and 1.1% for 3.8 and 7.5 mol% excess standard sample, respectively, and that for albumin-bound Phe sample was 2.1, 1.0, 1.5, and 7.1% for 0.03, 0.05, 0.1, and 0.5 mol% excess standard sample, respectively.

Fractional synthetic rate (FSR) of albumin (%/day) between times of measurement was calculated by the following equation (28)

$$\text{FSR} = \frac{E_B(t_2) - E_B(t_1)}{\int_{t_1}^{t_2} E_F(t) dt}$$

where $E_B(t)$ is defined as atoms percent excess of d₅-Phe incorporated into albumin at *time t* (h), and $E_F(t)$ is atoms

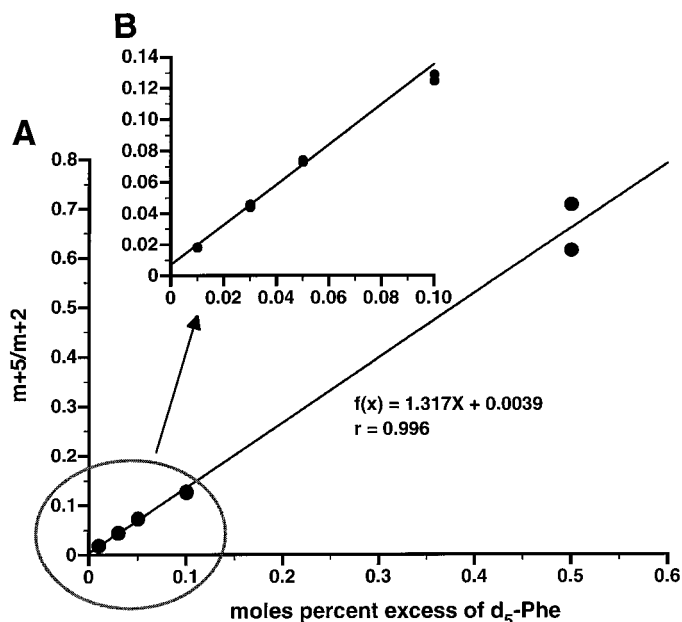


Fig. 2. Isotopic dilution standard curve for *N*-trifluoroacetyl-*n*-butyl ester derivatives of phenylalanine by gas chromatography-mass spectrometry (A). Points indicate mass-to-charge ratio (m/z) of 323/320 for standards (0.01, 0.3, 0.5, 0.1, and 0.5 mol% excess of d_5 -Phe). Each point represents the average of 3 replicates. Correlation coefficient was significant even at range between 0.01 and 0.1%. B: expansion of circled area in A.

percent excess of free d_5 -Phe in plasma at *time t*. The equations for $E_F(t)$ were determined by fitting the following nonlinear regression curves to the values for $E_F(t_1)$ and $E_F(t_2)$ because these values were not always the same level in each subject (1, 29).

If $E_F(t_2) > E_F(t_1)$

$$E_F(t) = a(1 - e^{-bt})$$

If $E_F(t_2) < E_F(t_1)$

$$E_F(t) = ae^{-bt} + c$$

FSR of albumin was measured between 1 and 2 h of control and between 1 and 5 h and 21 and 22 h of recovery.

Statistical differences were determined by using analysis of variance for repeated measures. The *t*-test was used for post hoc analysis to identify significant differences in specific pairwise comparison (27). All values are presented as means \pm SE, and the null hypothesis was rejected at $P < 0.05$. Regression analysis was performed by using the standard least-squares method.

RESULTS

The data of albumin concentration, plasma volume, and plasma albumin content were reported previously (17). Briefly, plasma albumin concentration in Up increased ($P < 0.05$) at 1 h of recovery and returned to the control level at 22 h of recovery (4.17 ± 0.06 g/dl at control, and 4.54 ± 0.06 and 4.20 ± 0.05 at 1 h and 22 h of recovery, respectively). Plasma albumin concentration at 1 h of recovery in Sup increased ($P < 0.05$) slightly from 4.08 ± 0.06 g/dl at control to 4.19 ± 0.06 at 1 h of recovery and remained increased ($P < 0.05$) throughout the rest of the recovery period. The control plasma albumin contents were similar in Up and Sup (1.84 ± 0.07 and 1.87 ± 0.07 g/kg body wt). Plasma albumin content increased ($P < 0.05$) above control at 1 h of recovery and remained elevated throughout 22 h of recovery in Up (1.96 ± 0.06 , 1.93 ± 0.06 , and 1.96 ± 0.05 g/kg body wt at 1, 5, and 22 h of recovery). Plasma albumin content was unchanged throughout the Sup protocol (1.85 ± 0.05 g/kg body wt at 22 h of recovery).

Table 1 shows atoms percent excess of d_5 -Phe in the free plasma pool (E_F) and that incorporated into albumin (E_B) in Up and Sup. The values of E_F were not different between measuring periods; 1 and 2 h of control, 1 and 5 h and 21 and 22 h of recovery.

The control values of albumin FSR were similar in Up and Sup, averaging 4.85 ± 0.92 and $3.90 \pm 0.35\%$ /day, respectively (Fig. 3). FSR of albumin in Up decreased by 30% ($P < 0.05$) without difference from that in Sup at 1–5 h of recovery, but increased by 51% ($P < 0.05$, $7.32 \pm 0.86\%$ /day) between 21 and 22 h of recovery. FSR of albumin in Sup was unchanged from control between 1 and 5 h and 21 and 22 h of recovery (2.84 ± 0.69 and $4.02 \pm 1.39\%$ /day, respectively).

Resting absolute synthetic rate (ASR) of albumin in Up was also similar to that in Sup (87.86 ± 17.1 and 74.16 ± 8.89 mg/kg body wt, respectively; Fig. 4). Changes in ASR of albumin paralleled those of FSR. In Up, ASR of albumin decreased to 58.62 ± 13.23 mg·kg body wt $^{-1}$ ·day $^{-1}$ between 1 and 5 h of recovery and then increased to 141.11 ± 16.55 mg·kg body wt $^{-1}$ ·day $^{-1}$ between 21 and 22 h of recovery.

DISCUSSION

Plasma albumin content increased within 1 h after upright intense exercise; however, albumin synthesis

Table 1. Enrichment of [*ring*- 2H_5]phenylalanine in free plasma pool and that incorporated in albumin

	Control		Recovery From Exercise			
	1 h	2 h	1 h	5 h	21 h	22 h
Up						
E_B , %	0.046 ± 0.017	0.062 ± 0.015	0.087 ± 0.011	0.121 ± 0.012	0.133 ± 0.014	0.156 ± 0.014
E_F , %	7.26 ± 0.60	8.69 ± 0.65	9.82 ± 0.51	8.57 ± 0.28	6.70 ± 0.25	8.51 ± 0.50
Sup						
E_B , %	0.064 ± 0.017	0.078 ± 0.018	0.122 ± 0.028	0.147 ± 0.028	0.186 ± 0.037	0.196 ± 0.039
E_F , %	7.58 ± 0.63	8.15 ± 0.47	8.92 ± 0.77	7.33 ± 0.75	5.89 ± 0.67	7.00 ± 0.54

Values are means \pm SE for $n = 7$ subjects. E_B , atoms percent excess of [*ring*- 2H_5]phenylalanine (d_5 -Phe) incorporated in plasma albumin; E_F , d_5 -Phe in free plasma pool; Up, upright; Sup, supine.

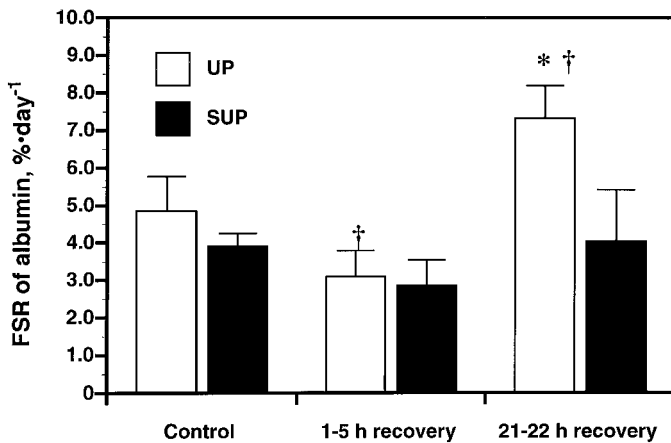


Fig. 3. Fractional synthetic rate (FSR) of albumin at control and 1–5 h and 21–22 h of recovery in upright (Up) and supine (Sup) postures. Values are means \pm SE for $n = 7$ subjects. *Significant difference between Up and Sup; $P < 0.05$. †Significantly different from control; $P < 0.05$.

was reduced at 1–5 h of recovery and then elevated only at 21–22 h of recovery. Increased albumin synthesis would have partly contributed to an increase in plasma albumin content after upright intense exercise, but it cannot explain the increase between 1 and 5 h after exercise. In addition, the supine posture blocked both the immediate increase in plasma albumin content (17) and the subsequent increase in albumin synthetic rate.

Numerous factors influence albumin synthetic rate, including hepatic interstitial albumin concentration (23); circulating levels of cortisol, thyroid hormone, glucagon, and epinephrine (7, 15, 16, 21, 24); and nutritional state (5, 10, 22). A decrease in hepatic interstitial albumin concentration during dextran infusion stimulates albumin synthesis in the rabbit (23). In the present study, plasma albumin concentration remained elevated from control between 1 and 5 h of recovery in both postures. Despite the claim that extravascular and intravascular albumin do not necessarily change in a parallel fashion (23), plasma albumin

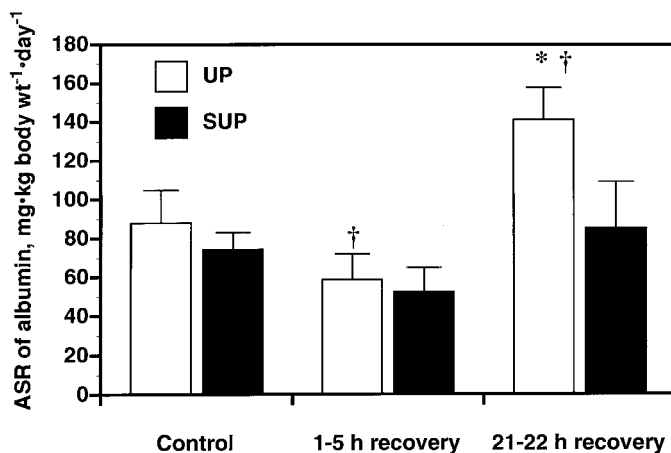


Fig. 4. Absolute synthetic rate (ASR) of albumin at control and 1–5 and 21–22 h of recovery in Up and Sup subjects. Values are means \pm SE for $n = 7$ subjects. *Significant difference between Up and Sup; $P < 0.05$. †Significantly different from control; $P < 0.05$.

should easily move into the hepatic interstitial space through the fenestrated walls of hepatic sinusoids (20). Therefore, the higher plasma albumin concentration after intense exercise would alter hepatic interstitial albumin concentration in a direction expected to attenuate albumin synthesis. The lower albumin synthetic rate in Up between 1 and 5 h of recovery may then be attributed to the higher plasma albumin concentration immediately after exercise.

Intense exercise is associated with an increased secretion of several stress hormones, e.g., catecholamines (19), cortisol (8), and glucagon (3). Rothschild et al. (24) found an increase in albumin synthesis during administration of cortisone and desiccated thyroid in rabbits. McNurlan et al. (16) reported that infusion of a cocktail of stress hormones, cortisol, epinephrine, and glucagon induced an increase in albumin FSR in humans by 1.15% 18 h after the infusion. It is unclear which of these hormones induced the elevation of albumin FSR. The elevated stress hormone levels during exercise might stimulate albumin synthesis, but effects related to posture appear to be much more important.

Nutritional condition would be a major factor to influence albumin synthesis. Rothschild et al. (22) showed that an extended fast (24–36 h) reduced albumin synthetic rate by 33% in rabbits, and refeeding immediately restored the ability of the hepatocytes to synthesize albumin. Amino acids plus glucose supplementation can help optimize anabolic activity of the liver to synthesize albumin at rest (5). Although we controlled the diet of subjects in the present study, the nutritional state at each measuring period would have been different. Yang et al. (29) reported that albumin synthetic rate after intense intermittent upright exercise was higher than in a nonexercise time control trial by 15% between 2 and 6 h of recovery. On the contrary, FSR of albumin was reduced or unchanged at 1–5 h after upright and supine exercise in the present study, without any difference between the two trials. We suppose that the difference in nutritional condition between the two trials resulted in that in albumin synthesis. Even though our subjects began to ingest an alimentary liquid at 2.5 h of recovery to maintain the plasma amino acids pool, this pool might not have reached a sufficiently high level to optimize albumin synthesis between 1 and 5 h after exercise. Yang et al. (29) showed that the phenylalanine pool reached a higher level only 2 h after the onset of Vivonex ingestion (0.24 ml·kg body wt⁻¹·10 min⁻¹ at 1–6 h after exercise; 7.2 kcal/kg body wt). In addition, the caloric content of the nutritional supplement in this study (3.5 kcal/kg body wt) was probably inadequate to counter the caloric deficit after exercise. These results may indicate that upright intense intermittent exercise is a potent stimulus for an immediate increase in albumin synthetic rate and that fasting state after exercise is a sufficient signal to downregulate albumin synthesis, despite a competing exercise stimulus.

Carraro et al. (2) reported that albumin synthetic rate was unchanged during 4 h of mild (40% maximum

oxygen consumption rate) treadmill exercise or during 4 h of recovery. Their results suggest that mild exercise is not a sufficient stimulus for increased albumin synthesis within this time frame. In the present study, intense exercise stimulated albumin synthesis in Up but not in Sup subjects. However, resting albumin synthetic rate was independent of posture. The mechanism by which posture alters albumin synthesis after intense exercise is unclear. One contributing factor might be related to a difference in stress hormone secretion during and/or after exercise between Up and Sup. Perrault et al. (19) showed that the supine posture attenuated increases in plasma catecholamines and aldosterone levels and renin activity during and after exercise. We also reported that plasma aldosterone remained higher after intense upright exercise than control through 5 h of recovery (17). Another contributing factor might be that plasma albumin concentration remained elevated above control at 22 h of recovery in Sup, resulting in a sustained suppression of albumin synthesis.

It is difficult to assess the contribution of increased albumin synthetic rate to the increase in plasma albumin content because we know little about the dynamics of albumin distribution between the intravascular and the interstitial space, especially during and immediately after exercise. Yang et al. (29) presented a model that progressive elevation of albumin synthetic rate (FSR of 4%/h) with constant albumin degradation rate (0.125%/h) and albumin escape rate of ~4%/h is necessary to maintain elevated plasma albumin content. Our data showed that FSR of albumin was elevated by only 51% of control level at 21–22 h of recovery. In addition, we recently reported that TER of albumin after the same intense intermittent exercise protocol tended to decrease from 8.4 to 6.5%/h on the next day of experiment (9). If the excess plasma albumin (0.12 ± 0.03 g/kg body wt), which occurred within the first hour of recovery in Up, escaped from the intravascular space at the rate range 4–8.4%/h, plasma albumin content at 22 h of recovery would have been elevated by 0.02–0.05 g/kg body wt (25–42% of the excess albumin). Assuming that ASR of albumin between 5 and 22 h of recovery had been constant at the level seen at 22 h of recovery, then 37.7 mg/kg body wt of additional albumin (31% of the excess albumin) would be accounted for by hepatic albumin synthesis. By this assumption, the increase in albumin synthesis may not be the only mechanism for the maintenance of the increased plasma albumin content in the present study. However, our data would have clearly showed that the increase in albumin synthesis is largely responsible for chronic increase in plasma albumin content, because net flux of albumin between the intra- and extravascular space should return to zero.

One additional factor that could contribute to the maintenance of an elevated plasma albumin content is a reduction in the rate of albumin degradation. However, albumin degradation rate after exercise has not been estimated so far, and whole body protein degradation is not changed after exercise (12). On the contrary,

protein degradation rate in active muscle has been reported to increase after exercise (11).

We gave our subjects alimentary diet in the middle of measurement of FSR of albumin to avoid affecting measurements of fluid-regulating hormones up to 2.5 h after exercise for another study (17). Although there was no significant difference in E_F at 1 and 5 h of recovery (Table 1), it may have affected the plateau of plasma amino acids. On the contrary, measurements of albumin synthetic rate at control and at 21–22 h of recovery were done after the same breakfast in our study; therefore, the nutritional state should not have limited comparisons of changes in albumin synthesis between the two time points. The study by Yang et al. (29) showed a significant increase in plasma albumin content at 5–6 h after exercise (6–7% of preexercise level) in the middle of the measurement period for albumin synthesis. The difference may have come from the fact that their subjects sat in a semirecumbent position after exercise, because the increase in plasma albumin content immediately after exercise is not seen in supine posture (17). The calculation for FSR of albumin should be done in the steady state of plasma albumin pool (28); therefore the lymph albumin return after exercise that did not contain d_5 -Phe would have disturbed precise measurement of albumin FSR. Thus the immediate measurement of albumin synthesis after exercise would be difficult without the effects of lymph albumin return and nutritional state.

In summary, we measured changes in albumin synthetic rate over 22 h after intense exercise in the upright and supine postures using a primed constant infusion of d_5 -Phe. Albumin synthesis increased at 22 h of recovery but only in the upright posture. These results indicate that increased albumin synthesis after intense upright exercise contributes to the maintenance of greater plasma albumin content during exercise-induced hypervolemia. Moreover, the impact of exercise on the control of albumin synthesis is modulated by posture.

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