Enhanced synthesis of albumin and fibrinogen at high altitude

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1Department of Internal Medicine, University of Berne, and 4Institute for Chemical Pathology, Inselspital, CH-3010 Berne; and 2Kantonsspital, CH-8401 Winterthur, Switzerland; 3Department of Surgery, State University of New York at Stony Brook, Stony Brook, New York 11794-8191; and 5Department of Sports Medicine, University of Heidelberg, D-69115 Heidelberg, Germany

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Imoberdorf, Reinhard, Peter J. Garlick, Margaret A. McNurlan, George A. Casella, Edgar Peheim, Meral Turgay, Peter Bartsch, and Peter E. Ballmer. Enhanced synthesis of albumin and fibrinogen at high altitude. J Appl Physiol 90: 528–537, 2001.—The acute effects of active and passive ascent to high altitude on plasma volume (PV) and rates of synthesis of albumin and fibrinogen have been examined. Measurements were made in two groups of healthy volunteers, initially at low altitude (550 m) and again on the day after ascent to high altitude (4,559 m). One group ascended by helicopter (air group, n = 5), whereas the other group climbed (foot group, n = 9), so that the separate contribution of physical exertion to the response could be delineated. PV was measured by dilution of 125I-labeled albumin, whereas synthesis rates of albumin and fibrinogen were determined from the incorporation of isotope into protein after injection of [ring-2H5]phenylalanine. In the air group, there was no change in PV at high altitude, whereas, in the foot group, there was a 10% increase in PV (P < 0.01). Albumin synthesis (mg·kg−1·day−1) increased by 13% in the air group (P = 0.058) and by 32% in the foot group (P < 0.001). Fibrinogen synthesis (mg·kg−1·day−1) increased by 40% in the air group (P = 0.068) and by 100% in the foot group (P < 0.001). Hypoxia and alkalosis at high altitude did not differ between the groups. Plasma interleukin-6 was increased modestly in both groups but C-reactive protein was not changed in either group. It is concluded that increases in PV and plasma protein synthesis at high altitude result mainly from the physical exercise associated with climbing. However, a small stimulation of albumin and fibrinogen synthesis may be attributable to hypobaric hypoxia alone. AL

THE PATHOLOGICAL CONSEQUENCES of ascent to high altitude are well recognized, ultimately leading to acute mountain sickness (AMS) and pulmonary edema, but the associated physiological and metabolic changes are less clear. Earlier reports have indicated a loss of body weight and lean body mass (22, 35) as well as a variety of circulatory changes. Increases in plasma concentra-

ions of total protein, thyroxine binding globulin, and coeruloplasmin and a depression in prealbumin have been detected during the first 2 wk at high altitude (57). A decrease in plasma volume (PV), determined by Evans blue or radiolabeled albumin, has been demonstrated in humans exposed to high altitude if the measurements were made 3 days or later after ascent (23, 28, 32, 34, 46, 51, 55, 58). However, inconsistent PV changes have been reported after 24 h of high-altitude exposure, depending on the method of measuring PV (29, 43, 52, 62). The major factor regulating PV is the plasma oncotic pressure, which in turn is strongly dependent on the serum albumin concentration. Albumin degradation has been measured previously at high altitude, with inconsistent results (57, 61), but there have been no studies of albumin synthesis. The main purpose of the present study was therefore to investigate the effects of ascent to high altitude on albumin synthesis and PV in healthy volunteers.

Albumin synthesis rates have been shown to depend on a variety of factors. In healthy humans, nutritional stimulation of albumin synthesis has been demonstrated both acutely, after consumption of a meal (33), and chronically, in response to high dietary protein (24). Moreover, albumin synthesis was increased after intense intermittent exercise (63) but only in upright and not in supine posture (40). Downregulation of albumin synthesis has been demonstrated in patients with diminished liver function (8, 9) and in volunteers during experimental acidosis (6). In animals, a decrease in albumin synthesis has been shown to result from inflammation induced by injection of turpentine or interleukin-1 (3, 4). An inflammatory response after ascent to high altitude has been induced by an increase in plasma concentration of tumor necrosis factor (37). Albumin synthesis rates in the present study have therefore been compared with fibrinogen synthesis, which is known to be enhanced by inflammation (45, 50).

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An additional determining factor at high altitude may be the physical exercise associated with climbing at low oxygen tension. Several authors have demonstrated an expansion of PV after acute, severe exercise (14, 25, 31, 54). However, the mechanisms leading to volume expansion are not well understood. Moreover, exercise has previously been shown to stimulate the synthesis of acute phase proteins, such as fibrinogen (18). We have therefore investigated the acute effects of hypobaric hypoxia and physical exercise on albumin and fibrinogen synthesis and PV in relation to blood gases, plasma electrolytes, and water balance in healthy subjects exposed to high altitude. Measurements were initially made in volunteers at low altitude and then again after they either walked or were flown to the summit of an alpine peak, at an altitude of 4,559 m (~15,000 ft).

METHODS

Subjects and study design. Healthy mountaineers with former exposure to high altitude (~3,000 m), but without history of relevant symptoms of AMS or high-altitude pulmonary edema (HAPE), were prospectively investigated. Exclusion criteria were age under 18 and above 55 yr; pregnancy; heart, lung, or thyroid disease; arterial hypertension; diabetest mellitus; neoplasms; and protein-losing nephropathies.

Subjects on regular medication, which may influence PV and protein synthesis, were also excluded. All participants gave written, informed consent to the study, which was approved by the Ethical Committee of the Medical Faculty of the University of Berne.

The subjects were initially investigated at the metabolic unit of the University Hospital of Berne [low altitude, 550 m, Berne, time point 1 (tp 1)] and 4–5 wk later at the Capanna Regina Margherita (4,559 m, Monte Rosa Massiv, Swiss-Italian Alps). Seventeen healthy subjects (mean age = 35.4 ± 9 yr and range of 24–53 yr, 6 women and 11 men) were randomly assigned to one of two groups. The subjects in the “foot group” (n = 9) traveled to Alagna (1,191 m), went up to 3,220 m by cable car, then walked up to 3,611 m (Capanna Gnifetti) in ~1.5 h. After an overnight stay, they ascended to 4,559 m (Capanna Margherita) in a 4-h walk on the next morning, where they stayed for 3 days. The subjects in the “air group” (n = 8) traveled to Zermatt (1,608 m) and were flown to 3,480 m (Testa Grigia) by helicopter. After an overnight stay, they flew up to 4,559 m (Capanna Margherita) on the second day.

The rate of ascent was coordinated to get equal time periods of high-altitude exposure in the two groups before the measurements. The air group arrived at 3,480 m by 14:00, and the foot group arrived at 3,611 m by 17:00. This time point was designated as the beginning of high-altitude exposure. After an overnight stay, the foot group climbed and the air group was flown up to 4,559 m [time point 2 (tp 2)]. Measurements of PV and albumin synthesis were made at 4,559 m (tp 3), i.e., 40–44 h after arrival at 3,480 m in the air group and 38–42 h after arrival at 3,611 m in the foot group.

Clinical examinations were carried out after a 30-min rest in a supine position at low altitude (550 m, tp 1), and three times at high altitude: immediately after arrival at 4,559 m (between 11:00 and 14:00, tp 2, i.e., 21–24 h after arrival at 3,480 m in the air group and 18–21 h after arrival at 3,611 m in the foot group), at tp 3, and tp 4, i.e., 64–67 h after high-altitude exposure in the air group and 62–65 h after high-altitude exposure in the foot group. Venous and arterial blood samples were drawn during these clinical examinations. Fibrinogen synthesis was determined at tp 1 and 3. Food intake was assessed by daily dietary records. Calorie and protein intake were calculated using a computer-assisted program.

Measurements of albumin/fibrinogen synthesis rates and PV. Albumin and fibrinogen synthesis rates were measured by the flooding method with [ring-2H5]phenylalanine as described previously (7, 8, 10). In brief, [ring-2H5]phenylalanine (Tracer Technologies, Sommerville, MA) at 0.043 g/kg body wt with an isotopic enrichment of 10 mol% in the first measurement and 20 mol% in the second measurement was intravenously injected over 10 min. The [ring-2H5]phenylalanine was mixed with unlabeled l-phenylalanine (Merck, Darmstadt, Germany) in 0.45% NaCl, and the solution was filtered sterilly by the hospital pharmacy. Blood samples were drawn from the opposite cubital vein at 10-min intervals up to 90 min. Plasma samples were stored at ~20°C. After thawing, albumin was isolated by ethanol extraction from trichloroacetic acid-precipitated plasma proteins as described previously (7, 9). In every subject, the purity of the albumin isolates was checked by sodium dodecyl sulfate gel electrophoresis and compared with a human albumin standard (Sigma, Poole, Dorset, UK). All isolates presented as a single band corresponding to human albumin. After repeat washes with 2% perchloric acid, the albumin was hydrolyzed in 6 M HCl for 24 h at 105°C. The hydrolysates were purified by washing with distilled water and then dried in a stream of N2.

Fibrinogen was isolated from plasma according to the method of Takeda (60). In brief, 5 ml of citrated plasma were diluted with the same volume of 0.09 mol/l sodium citrate and repeatedly precipitated with 4 mol/l ammonium sulfate, resuspended in 0.005 mol/l sodium citrate, and finally precipitated with 1 mol/l ammonium sulfate. The purity of fibrinogen was checked against a human fibrinogen standard (Chromogenix, Mölndal, Sweden) in every patient by a 10% polyclonal anti-fibrinogen antibody. After reprecipitation in 0.005 mol/l sodium citrate, the fibrinogen was washed with 0.5 ml of 2 mol/l HClO4 and hydrolyzed in 6 mol/l HCl. The hydrolysates were washed and dried as described above for albumin.

Phenylalanine from protein hydrolysates was converted to β-phenethylamine by enzymatic conversion with tyrosine decarboxylase (Sigma). The enrichment of β-phenethylamine was measured on a Fisons MD 800 quadrupole mass spectrometer as described previously (7, 17, 38). The enrichment of plasma-free phenylalanine, reflecting the precursor pool for albumin/fibrinogen synthesis, was determined by gas chromatography-mass spectrometry on the Fisons MD 800 mass spectrometer, using the tertiary butyldimethylsilyl derivative (17, 38).

Albumin and fibrinogen synthesis rates were calculated as both fractional synthesis rates (FSR) and absolute synthesis rates (ASR; as described previously in Refs. 4 and 6–10). The FSR, i.e., the percentage of the intravascular albumin/fibrinogen mass synthesized per day, equals the increase in [ring-2H5]phenylalanine enrichment in albumin/fibrinogen between 50 and 90 min divided by the corresponding area under the curve of the plasma-free phenylalanine enrichment times 100, expressed as percent per day. The intravascular albumin/fibrinogen mass is the product of the PV times the plasma albumin/fibrinogen concentration. By multiplying the FSR by the intravascular albumin/fibrinogen mass, ASR of albumin/fibrinogen was calculated and expressed as milligrams per kilogram body weight per day.
PV was measured by the dilution method as previously described (9, 10). In brief, all subjects received 60 mg of potassium iodide orally before injection of 125I-labeled albumin and thereafter daily for 14 days to block 125I uptake by the thyroid gland. After baseline plasma samples, 5 μCi of 125I-albumin (Sorin Biomedica, Saluggia, Italy) was injected intravenously, and blood samples were drawn at 10-min intervals up to 60 min from the opposite cubital vein. Radioactivity was counted in duplicate in 2-ml samples in a gamma counter (1,260 Multigamma II, LKB, Wallac). PV was calculated as the ratio of the injected radioactivity and the counts in plasma at tp 0 obtained by extrapolation of the counts-time curve to the y-axis.

Fluid balance measurements. Blood was collected from a cannulated cubital vein and cooled immediately in crushed ice before centrifugation at 3,000 g for 15 min at 4°C. Plasma was frozen and stored initially in liquid N2 and then kept at ice before centrifugation at 3,000 g. Blood samples were drawn at 10-min intervals up to 60 min from the opposite cubital vein. Radioactivity was counted in duplicate in 2-ml samples in a gamma counter (1,260 Multigamma II, LKB, Wallac). PV was calculated as the ratio of the injected radioactivity and the counts in plasma at tp 0 obtained by extrapolation of the counts-time curve to the y-axis.

Other determinations. Total plasma protein concentration was determined with a biuret method, plasma albumin with bromcresol purple (20), and plasma fibrinogen according to the method of Clauss (19). C-reactive protein was determined by turbidimetry using a Hitachi 717 autoanalyzer (Wako, Pure Chemical Industries, Osaka, Japan) and interleukin-6 (IL-6) plasma concentrations with a commercial enzyme immunoassay (Quantikine, Research and Diagnostics Systems, Minneapolis, MN). Plasma aldosterone (Serono Diagnostika, Freiburg, Germany) and vasopressin concentrations were measured by radioimmunoassays.

Measurement of plasma protein synthesis rates. The plasma specific rates of albumin and fibrinogen synthesis were determined using the ASR method (17). After baseline plasma samples, 5 Ci of 125I-albumin (Sorin Biomedica, Saluggia, Italy) was injected intravenously, and blood samples were drawn at 10-min intervals up to 60 min from the opposite cubital vein. Radioactivity was counted in duplicate in 2-ml samples in a gamma counter (1,260 Multigamma II, LKB, Wallac). PV was calculated as the ratio of the injected radioactivity and the counts in plasma at tp 0 obtained by extrapolation of the counts-time curve to the y-axis.

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RESULTS

Clinical characteristics of the subjects are shown in Table 1. There were no significant differences in baseline values between the air and foot groups. In both groups, no significant weight changes occurred during the sojourn at high altitude.

In the air group, PV was 43.6 ± 6.9 ml/kg body wt at tp 1 compared with 42.1 ± 4.8 ml/kg at tp 3 (P = 0.3, Fig. 1). In contrast, PV increased significantly in the foot group from 43.8 ± 7 to 48.3 ± 6.6 ml/kg body wt (P < 0.01, Fig. 1). At the time points in which protein synthesis rates and PV were measured (tp 1 and 3), total plasma protein concentrations, plasma albumin concentrations, and COP showed no significant differences between the groups (Fig. 2). Over time, however, there was a significant increase in each of these variables at tp 2 in both groups (Fig. 2). Plasma fibrinogen concentrations (Fig. 2) showed a slight increase within the normal range over time but without any difference between the groups (P = 0.028 for time, P = 0.49 between the groups, by ANOVA). Compared with tp 1, plasma osmolality and plasma sodium concentrations did not change significantly at high altitude at tp 3 in either group (Table 2). Figures 3 and 4 illustrate the FSR, ASR, and intravascular mass of albumin and fibrinogen. For both proteins, the FSR increased significantly at tp 3 compared with tp 1 in both groups. However, the ASR is a better reflection of the rate of secretion of newly synthesized protein into the circulation. The ASR of albumin and fibrinogen showed small increases in the air group, which approached statistical significance.

Table 1. Clinical characteristics of the subjects in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Air Group</th>
<th>Foot Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>5/3</td>
<td>6/3</td>
</tr>
<tr>
<td>Age, yr</td>
<td>32.6 ± 9.1</td>
<td>37.8 ± 8.9</td>
</tr>
<tr>
<td>Range</td>
<td>24–53</td>
<td>28–52</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>69.9 ± 10.3</td>
<td>74.1 ± 18.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3 ± 2.1</td>
<td>23.6 ± 4.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. See text for explanation of groups.

Fig. 1. Plasma volume (PV) at low (time point 1 (tp 1)) and high altitude (tp 3) in the air group (●) and the foot group (○). *P < 0.01 for difference between tp 1 and tp 3 in the foot group. †P < 0.01 for difference of changes between groups. See text for explanation of groups.
cance in both cases ($P = 0.057$ and $0.068$, respectively). However, much larger increases in ASR of albumin and fibrinogen were apparent after active ascent. The mean increase of albumin ASR between tp 1 and tp 3 was 14.7 ± 18.4 mg·kg⁻¹·day⁻¹ in the air group compared with 34.8 ± 16.4 mg·kg⁻¹·day⁻¹ in the foot group ($P = 0.03$ between groups, by unpaired $t$-test). The increase of fibrinogen ASR was 4.2 ± 5.5 mg·kg⁻¹·day⁻¹ in the air group and 10.2 ± 5.1 mg·kg⁻¹·day⁻¹ in the foot group ($P = 0.03$ between groups). In the air group, caloric intake decreased from 42 ± 1.4 (tp 1) to 38 ± 1.2 (tp 2), 35 ± 0.5 (tp 3), and 33 ± 1.2 kcal·kg⁻¹·day⁻¹ (tp 4). The foot group consumed 38 ± 1.2 (tp 1), 34 ± 1.2 (tp 2), 42 ± 1.6 (tp 3), and 24 ± 1.2 (tp 4) kcal·kg⁻¹·day⁻¹ ($P < 0.01$ for time, $P = 0.6$ between the groups). Protein intake in the air group was 1.3 ± 0.4 (tp 1), 1.1 ± 0.5 (tp 2), 1.0 ± 0.6 (tp 3), and 1.0 ± 0.6 (tp 4) g·kg⁻¹·day⁻¹. In the foot group, the values were 1.1 ± 0.4 (tp 1), 1.1 ± 0.5 (tp 2), 1.2 ± 0.4 (tp 3), and 0.8 ± 0.4 (tp 4) g·kg⁻¹·day⁻¹ ($P = 0.02$ for time, $P = 0.6$ between the groups).

In the air group, urine output did not change after ascent, whereas, in the foot group, urine output decreased significantly ($P < 0.001$) on the first day of ascent (tp 2) from 1,484 ± 384 to 888 ± 156 ml/day (Fig. 5). Figure 5 also illustrates the relation between fluid intake and urinary output. In the foot group, the difference between fluid input vs. output was significantly higher on tp 3 compared with the air group (foot group: 27 ± 5.8 ml/kg, air group: 10 ± 6.9 ml/kg; $P < 0.01$). Plasma concentrations of aldosterone and ADH (Table 2) showed no substantial response, basically confirming the findings reported previously (13, 16, 39, 47, 59).

Figure 6 illustrates arterial blood gas analyses. The arterial pressure of oxygen decreased significantly over time after ascent compared with low-land values ($P < 0.0001$ for time) but without significant differences

### Table 2. Plasma chemistry at time points 1–4 in the air and foot groups

<table>
<thead>
<tr>
<th></th>
<th>Osmolality, mosmol/kgH₂O</th>
<th>Na, mmol/l</th>
<th>Creatinine, μmol/l</th>
<th>Aldosterone, pg/ml</th>
<th>ADH, pg/ml</th>
<th>CRP, mg/ml</th>
<th>IL-6, pg/ml</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>281–297</td>
<td>132–142</td>
<td>&lt;116</td>
<td>12–150</td>
<td>0.3–4.2</td>
<td>&lt;10</td>
<td>2–6</td>
</tr>
<tr>
<td>Air Group tp 1</td>
<td>285 ± 6</td>
<td>139 ± 2</td>
<td>90 ± 10</td>
<td>129 ± 76</td>
<td>1.2 ± 2.1</td>
<td>2 ± 2</td>
<td>2 ± 6</td>
</tr>
<tr>
<td>tp 2</td>
<td>288 ± 4</td>
<td>140 ± 2</td>
<td>91 ± 9</td>
<td>125 ± 175</td>
<td>1.3 ± 1.3</td>
<td>2 ± 1</td>
<td>0 ± 4</td>
</tr>
<tr>
<td>tp 3</td>
<td>286 ± 5</td>
<td>138 ± 1</td>
<td>90 ± 7</td>
<td>56 ± 32</td>
<td>1.4 ± 1.0</td>
<td>2 ± 1</td>
<td>4 ± 11</td>
</tr>
<tr>
<td>tp 4</td>
<td>287 ± 3</td>
<td>139 ± 1</td>
<td>93 ± 10</td>
<td>52 ± 22</td>
<td>1.0 ± 1.0</td>
<td>2 ± 1</td>
<td>12 ± 17</td>
</tr>
<tr>
<td>Foot Group tp 1</td>
<td>284 ± 5</td>
<td>138 ± 2</td>
<td>94 ± 11</td>
<td>221 ± 253</td>
<td>0.5 ± 0.4</td>
<td>2 ± 1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>tp 2</td>
<td>291 ± 6</td>
<td>140 ± 2</td>
<td>96 ± 14</td>
<td>83 ± 59</td>
<td>0.8 ± 0.5</td>
<td>3 ± 3</td>
<td>1 ± 2</td>
</tr>
<tr>
<td>tp 3</td>
<td>287 ± 5</td>
<td>139 ± 2</td>
<td>94 ± 12</td>
<td>63 ± 37</td>
<td>1.2 ± 0.5</td>
<td>3 ± 2</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>tp 4</td>
<td>288 ± 6</td>
<td>140 ± 2</td>
<td>98 ± 10</td>
<td>86 ± 47</td>
<td>1.5 ± 1.2</td>
<td>4 ± 3</td>
<td>6 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SD. tp, Time point; ADH, antidiuretic hormone; CRP, C-reactive protein; IL-6, interleukin-6.
between the groups \((P = 0.92\) between groups, by ANOVA\). Also, carbon dioxide tension decreased significantly after ascent \((P < 0.0001\) for time, by ANOVA\). The degree of respiratory alkalosis, however, was not statistically different between the groups \((P = 0.84\) between groups, by ANOVA\). C-reactive protein values did not change with time and showed no significant differences between the groups (Table 2). At tp 1, IL-6 was detectable in one subject from the air group and in no subjects from the foot group. At high altitude, IL-6 levels tended to rise modestly but progressively until tp 4 \((P = 0.003\) for time, \(P = 0.32\) between the groups, Table 2\).

Two of eight subjects suffered from AMS in the air group and three of nine in the foot group. Chest X-rays were normal in all participants, without indication of HAPE.

**DISCUSSION**

In the present study, we investigated the acute effects of high-altitude exposure and physical exercise on body fluid compartments and various aspects of protein metabolism in healthy subjects. Exercise induced a significant increase in PV, which was unaffected by high-altitude exposure. In contrast, high-altitude exposure caused an increase in ASR of albumin and fibrinogen in both groups, but the increase in ASR in the foot group at high altitude was much greater than in the air group, suggesting that both altitude and physical exercise influenced the synthesis of these proteins.

Previously reported changes in PV after exposure to high altitude have been inconsistent, possibly related to the degree of AMS, duration at high altitude, and the altitude gained. Acute exposure to high altitude was shown to induce peripheral edema and an increase in PV and body weight, possibly as a result of water and salt retention \((11, 42, 48)\). In the present study, 5 of 17 subjects suffered from AMS, 2 in the air group and 3 in the foot group. The low incidence of AMS of 29% may be due to the preselection of healthy mountaineers with former exposure to high altitude but without history of AMS. The similar average AMS
scores in the two groups and the lack of a significant correlation between the degree of AMS and changes in both ASR of albumin and PV argue against an effect of AMS on PV. PV, determined by radiolabeled albumin or by Evans blue, has been shown to be reduced consistently 3–12 days after arrival at high altitude (23, 28, 32, 34, 46, 51, 55, 58). In contrast, no differences in PV, assessed by the same methods, could be found in subjects investigated after 24 h (29, 43). However, PV measurements obtained using a carbon monoxide rebreathing method (43) or by use of radiolabeled erythrocyte methodology (52) showed a decrease on the first day of arrival (10–14 h postarrival). Similarly, Wolfel et al. (62) reported an early reduction of PV, estimated from changes in hematocrit, on ascent to 4,300 m, which was even more pronounced 3 wk later. The mechanism responsible for the discrepancy between the methods remains unknown (43). Obviously, apart from the method used, the time scale also plays an important role. Because our measurements were obtained between 38 and 44 h after arrival at high altitude (tp 3), the results in the air group are in line with those of Hansen et al. (29), in which no changes in PV, also assessed by labeled albumin, could be detected 24 h after passive ascent to 4,350 m. Furthermore, the PV at tp 3 was unchanged in the air group but significantly increased in the foot group, suggesting an exercise rather than a high-altitude effect.

The interrelation between physical exercise and expansion of PV has been reported previously. PV expansion by ~12% occurred 8 h after severe exercise (14). Also, Schmidt et al. (54) demonstrated in 15 male athletes that PV increased 16% on the second day after a marathon. During exercise, however, acute hemococoncentration, i.e., PV reduction, is a common feature (21, 25). The magnitude of the subsequent hypervolemia is related to the degree of PV reduction with exercise (26), suggesting an osmotic effect. We therefore measured plasma osmolality, which surprisingly remained unchanged (tp 3 vs. tp 1) in the foot group despite the significant increase in PV. Also, COP, the reflection of the forces induced by plasma proteins maintaining fluid in the intravascular space, showed no changes. Finally, the lack of a substantial hormonal response (ADH, Table 2) confirms the findings reported previously (13, 16, 39, 47, 59) and might suggest an impairment of osmoregulatory mechanisms after exercise at high altitude.

The fact that an iso-osmotic volume expansion occurred in the foot group suggests a corresponding increase in the total intravascular solute content, i.e., plasma electrolytes and proteins. In fact, the intravascular protein mass increased from 219 to 238 g in the foot group at high altitude. This increase in protein content of 19 g should result in an increase in PV of 266–285 ml, since 1 g of protein binds 14–15 ml of H2O (53). This is perfectly in line with the measured increase in PV of ~250 ml. An increase in intravascular protein mass has been reported previously after endurance exercise (21), but the mechanisms of this increase were not clear. Lymphatic return of plasma protein into the vascular space was suggested, since exercise can increase lymphatic flow by 20-fold (27). Gillen et al. (25) showed an early increase in plasma albumin content 1 h after recovery from a single, intense exercise, presumably causing the observed PV expansion. Furthermore, Nagashima et al. (41) demonstrated an increase in albumin content after intense exercise in upright position but not in supine posture. The present results offer an additional possible mechanism for the increased intravascular protein mass. Albumin accounted for ~70% of the increase of total plasma protein content. Thus increased de novo synthesis of plasma proteins, in particular the synthesis of an extra 2.5 g/day of albumin, is an additional factor resulting in the observed increase of the protein mass. However, the major reason for the increase in intravascular protein must be a redistribution between the intra- and extravascular spaces. Haskell et al. (31) hypothesized that a decrease in transcapillary escape rate (TER) was associated with PV expansion 24 h after exercise, which would contribute to a larger albumin mass in plasma. However, there was not a strong association because some subjects displayed PV expansion without a change in TER. Furthermore, we have previously shown that short-term exposure to high altitude does
not alter systemic capillary permeability, as shown by an unchanged TER (36).

Although the foot group exhibited a significant increase in the ASR of albumin, a much smaller change occurred in the air group (Fig. 3). Moreover, the mean difference of ASR between tp 1 and tp 3 was significantly higher in the foot group compared with the air group, indicating a larger increase in ASR of albumin in the foot group. This is consistent with the observed increase in PV in the foot group but not in the air group and confirms the view that the main effects observed were related to exercise rather than high altitude. In the air group, however, the increases in ASR of albumin and fibrinogen, although small, almost attained statistical significance (P = 0.057 and 0.068, respectively), suggesting that high altitude in itself, independent of exercise, might have some stimulatory effect on the synthesis of these proteins.

There have been few previous studies of albumin and fibrinogen turnover at high altitude. Surks (57) studied albumin turnover in five men at the summit of Pikes Peak, Colorado (4,300 m), by means of $^{131}$I-labeled albumin and reported an increased degradation rate, a finding that could not be confirmed by Westergaard et al. (61). Moreover, the separate effects of exercise on plasma protein dynamics have not been clearly delineated. Rocker et al. (49) showed a lower plasma protein concentration but a higher intravascular protein mass in endurance athletes compared with sedentary subjects. They concluded that endurance exercise may stimulate albumin and globulin synthesis. However, Carraro et al. (18) were not able to detect a change in albumin synthesis when investigating plasma protein synthesis in exercise and recovery in human subjects by constant infusion of $^{13}$C-leucine. In contrast, Yang et al. (63) found an increase of albumin synthesis 3–6 h after intense intermittent exercise. Nagashima et al. confirmed these results and were able to demonstrate that the elevation of albumin synthesis rate was maintained for 22 h, but only in upright posture, possibly mediated by a difference in stress hormone secretion between upright and supine exercise (40). In line with these findings, the present results clearly show an increase in ASR of both albumin and fibrinogen, which is mostly attributable to exercise. The increase due to high altitude alone, although smaller, is surprising in view of the much-depressed oxygen tension and hemoglobin saturation seen in both groups. Hypoxia has previously been shown to inhibit liver protein synthesis in animals (44), possibly due in part to ATP depletion (1). Moreover, in rats with respiratory depression resulting from opiate administration, liver protein syn-
thesis correlated very strongly with arterial pH (30). Hyoxia at high altitude results in alkalosis (Fig. 6). Moreover, it has been shown in perfused heart and cultured hepatocytes that alkalosis stimulates protein synthesis (15, 56). It is therefore possible that the small stimulation in albumin and fibrinogen synthesis seen in the air group results from respiratory alkalosis, which more than compensates for any negative effect of hyoxia.

It is notable that synthesis of the two plasma proteins responds similarly. It therefore seems unlikely that the observed changes result from inflammation, which has been shown to cause an increase in fibrinogen synthesis (8, 45, 50) but a decrease in albumin synthesis (2, 4). In line with previous work (36), high-altitude exposure caused no inflammatory response, as C-reactive protein was not altered in this study. Similarly, nutritional factors (5, 33) are unlikely to have caused the observed changes, since calorie and protein intake were not different between the groups and no significant weight changes occurred in both groups during the sojourn at high altitude.

Interestingly, urinary output was not different in the two groups at tp 3, although the foot group showed a significant decrease in urinary output at tp 2, i.e., on the day of ascent. In contrast, at tp 3, the difference between urinary output and fluid intake was significantly higher in the foot group (Fig. 5). This suggests that the subjects in the foot group had additional fluid losses by sweating and breathing during ascent, and the kidney preserved body fluids by decreasing urinary volume. On the following day, however, the subjects obviously had a fluid deficiency, which they tried to compensate for by increased fluid intake. In line with these findings, COP and plasma albumin concentration significantly increased at tp 2 but had returned toward normal at tp 3 (Fig. 2).


REFERENCES


