Women at altitude: carbohydrate utilization during exercise at 4,300 m

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EXPOSURE TO HYPOBARIC hypoxia at high altitudes alters substrate utilization at rest and during exercise (6, 7, 21, 29–31, 40). Brooks (5) and Hochachka (20) proposed that a change in the regulation of metabolic pathways to favor greater dependence on glucose, rather than fatty acids, would aid in maintaining homeostasis by optimizing the energy yield per unit O2. Experimental evidence tends to support this theory; results from studies on rat hindlimbs exposed to hypoxic buffer (11), hypoxic dogs (42), high-altitude natives (21), and lowlanders exposed to high altitude (7, 30, 31) show a shift toward increased glucose utilization relative to normoxic conditions. Women at altitude: carbohydrate utilization during exercise at 4,300 m. J. Appl. Physiol. 88: 246–256, 2000.—To evaluate the hypothesis that exposure to high altitude would reduce blood glucose and total carbohydrate utilization relative to sea level (SL), 16 young women were studied over four 12-day periods: at 50% of peak O2 consumption in different menstrual cycle phases (SL-50), at 65% of peak O2 consumption at SL (SL-65), and at 4,300 m (HA). After 10 days in each condition, blood glucose rate of disappearance (Rd) and respiratory exchange ratio were measured at rest and during 45 min of exercise. Glucose Rd during exercise at HA (4.71 ± 0.30 mg·kg⁻¹·min⁻¹) was not different from SL exercise at the same absolute intensity (SL-50 = 5.03 mg·kg⁻¹·min⁻¹) but was lower at the same relative intensity (SL-65 = 6.22 mg·kg⁻¹·min⁻¹, P < 0.01). There were no differences, however, when glucose Rd was corrected for energy expended (kcal/min) during exercise. Respiratory exchange ratios followed the same pattern, except carbohydrate oxidation remained lower (−23.2%, P < 0.01) at HA than at SL when corrected for energy expended. In women, unlike in men, carbohydrate utilization decreased at HA. Relative abundance of estrogen and progesterone in women may partially explain the sex differences in fuel utilization at HA, but subtle differences between menstrual cycle phases at SL had no physiologically relevant effects.

stable isotope; hypobaric hypoxia; substrate utilization; glucose flux; gender differences; ovarian hormones; menstrual cycle

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with sea-level exercise at the same relative intensity. Finally, we anticipated that making comparisons between elevations in the same phase of the menstrual cycle would be important, because carbohydrate utilization would be greater in the follicular than in the luteal phase of the cycle.

METHODS

Study Design

As part of a larger study of how women acclimatize to high altitude, we measured blood glucose utilization and total carbohydrate oxidation during rest and submaximal exercise three times at sea level and again after 10 days of exposure to 4,300-m elevation. The potential confounding effects of weight loss were limited by feeding subjects a controlled diet (see Dietary Control) to maintain energy balance and body weight. The first two sea-level study periods were identical (subjects exercised at exactly the same workload), except they were conducted in opposite phases of the menstrual cycle (order was randomized), so that the single high-altitude study period could be directly compared with the matching cycle phase at sea level. The third sea-level study period included exercise at a higher intensity and was designed to allow comparison between sea level and high altitude at the same absolute and relative exercise intensities.

Subjects

Eighteen women, 21–34 yr old, completed the sea-level portion of the study. Because of illness not related to participation in the study, two women did not perform the test at high altitude, and one test was canceled because of a prolonged power outage (final n = 15). All the women were sea-level residents (<1,500-m elevation), although one woman spent several days at >1,500 m shortly before the high-altitude phase; the subjects were nonsmokers and had regular menstrual cycles (see Menstrual Cycle Phase Determinations). All subjects were in moderately to very physically active and underwent a standard blood glucose concentrations. All subjects were in good overall health on the basis of a routine physical examination and were in the clinically normal range for standard blood and urine chemistry panels, including Hb and serum ferritin. They had normal fasting and 2-h postprandial blood glucose concentrations. All subjects reported being moderately to very physically active and underwent a standard graded exercise test to peak \( \dot{V}O_2 \) (\( \dot{V}O_2 \text{peak} \)) on a cycle ergometer. Subject characteristics are summarized in Table 1. The protocol was approved by institutional review boards at Stanford University, the US Army Research Institute of Environmental Medicine, and the University of Colorado.

Before admission, subjects were briefed on all aspects of the studies and gave written consent to participate.

Sea-Level and High-Altitude Conditions

At sea level (Palo Alto, CA, 15-m elevation, atmospheric pressure 748–762 Torr), subjects participated in the study for 12 days on each of three occasions, usually 6 wk apart. The women were admitted as patients to the metabolic ward at the Palo Alto Veterans Affairs Health Care System and were housed there on nights 6–11 of each study period. One to 3 mo after the sea-level studies, subjects were flown to Colorado Springs, CO (1,850 m), and immediately driven by car to Pikes Peak, CO, arriving at the summit (4,300 m, atmospheric pressure 458–464 Torr) 2 h later. On Pikes Peak, women were housed in the laboratory facility, managed by the US Army Research Institute of Environmental Medicine, for the entire 12-day study.

Protocol

At sea level, \( \dot{V}O_2 \text{peak} \) was determined on day 5 by graded cycle ergometry at a cadence of 60 rpm, starting at 50 W (3 min) and increasing the work by 25 W/min until voluntary exhaustion with standard criteria [attainment of \( \dot{V}O_2 \text{peak} \)] employed to validate the test. Because \( \dot{V}O_2 \text{peak} \) does not change during at least several weeks of acclimatization to high altitude (5–7, 27), the value recorded on day 5 was assumed to be applicable on day 10. Subjects fasted after 9 PM on day 9. On the next morning, subjects consumed a standardized breakfast meal (energy content = 2,063 kJ = 493 kcal) composed of 70% carbohydrate, 10% protein, and 20% fat. After completion of the meal, a catheter was inserted into the radial artery for blood sampling and a second catheter was placed in the antecubital vein of the contralateral arm for infusion of isotope. Subjects rested semisupine for the duration of the resting measurements. Two to 3 h after the meal was completed, arterial blood samples were collected for determination of background isotopic enrichment, and the \( \dot{V}O_2 \) and \( \dot{CO}_2 \) concentrations in expired air were analyzed by indirect calorimetry with a metabolic cart (model 2900, SensorMedics, Anaheim, CA). A priming bolus of 200 mg of [6,6-\( ^2 \)H]glucose (Cambridge Isotope Lab, Andover, MA) in 0.9% sterile saline (125 times the resting minute infusion rate) was rapidly injected into the venous catheter. A continuous infusion of [6,6-\( ^2 \)H]glucose in 0.9% sterile saline was started at a rate of 1.67 mg/min. Arterial blood samples were collected (for analysis of glucose isotopic enrichment and concentrations of glucose, lactate, and glucoregulatory hormones), and gas exchange was measured 75 and 90 min after the start of the infusion. Immediately after the last resting measurement, subjects moved to an electrically braked cycle ergometer (SensorMedics) and began pedaling at 60 rpm. The infusion rate of [6,6-\( ^2 \)H]glucose was increased to 5.00 mg/min to maintain a steady isotopic enrichment of blood glucose. Subjects were allowed to drink water ad libitum and were cooled with a fan. During sea-level trial 1, the workload was adjusted during the first 15 min until \( \dot{V}O_2 \) was steady at ~50% of sea-level \( \dot{V}O_2 \text{peak} \) (SL-50). After the appropriate \( \dot{V}O_2 \) was obtained, the workload was kept constant from minutes 15 to 45. Blood and breath samples were collected at 15, 30, and 45 min of exercise, as described above. In trial 2 (alternate menstrual phase, see below), the workload was manipulated to exactly simulate the pattern from

<table>
<thead>
<tr>
<th>Table 1. Subject characteristics</th>
<th>Sea Level</th>
<th>4,300 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>21.7 ± 0.7</td>
<td>21.7 ± 0.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167.4 ± 1.3</td>
<td>167.4 ± 1.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.2 ± 1.2</td>
<td>62.6 ± 1.2</td>
</tr>
<tr>
<td>( \dot{V}O_2 \text{peak}, \text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>42.0 ± 1.7</td>
<td>31.9 ± 1.3*</td>
</tr>
<tr>
<td>Estrogen, pg/ml</td>
<td>51 ± 19</td>
<td>80 ± 17†</td>
</tr>
<tr>
<td>E</td>
<td>96 ± 11†</td>
<td>83 ± 12</td>
</tr>
<tr>
<td>Progesterone, pg/ml</td>
<td>0.43 ± 0.10</td>
<td>0.81 ± 0.15*</td>
</tr>
<tr>
<td>E</td>
<td>7.66 ± 1.35†</td>
<td>5.72 ± 1.96†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Serum estrogen and progesterone concentrations were measured the day of metabolic tests, usually day 10 of cycle phase. E, estrogen-only phase ("follicular"); E + P, estrogen + progesterone phase ("luteal"); \( \dot{V}O_2 \text{peak} \), peak \( \dot{V}O_2 \) consumption. *Significantly different between elevations. †Significantly different across cycle phases.
trial 1. In sea-level trial 3, the workload was adjusted in the first 15 min to achieve a VO2 of 65% sea-level VO2peak (SL-65).

At 4,300 m, the workload was adjusted to exactly mimic sea-level trials 1 and 2, so that comparisons between elevations could be made at the same VO2 (same absolute exercise intensity). Because VO2peak at 4,300 m is reduced by ~25% compared with sea level, the exercise workload at 4,300 m was expected to elicit 65% high-altitude VO2peak, allowing comparison with sea-level trial 3 at the same percent VO2peak (same relative intensity).

Relative and Absolute Exercise Intensities

The actual exercise intensities, exercise workloads, and VO2 values are shown in Table 4. At sea level, work output (140 vs. 102 W), VO2, percent sea-level VO2peak (64.8 vs. 52.0%), and energy expenditure were significantly higher during SL-65 than during SL-50. Work output, VO2, percent sea-level VO2peak (52.0 vs. 51.1%), and energy expenditure were similar between SL-50 and 4,300 m. At 4,300 m, VO2peak declined by 23.4%, so that exercise at 102 W required 66.0% of altitude-specific VO2peak, which was very similar in relative intensity to SL-65 (64.8%).

Dietary Control

To minimize the effects of changes in energy balance, body weight, and carbohydrate intake on substrate utilization, subjects consumed the same standardized diet every day of each 12-day study period. The diet was composed of whole, readily available foods along with a liquid supplement (Ensure, Ross Laboratories, Columbus, OH). Approximately 64% of energy came from carbohydrate, 12% from protein, and 24% from fat at sea level and 4,300 m. Energy intake was adjusted daily to compensate for any changes in body weight. There was no significant change in body weight during days 1–12 at sea level (62.33 ± 2.09 to 62.20 ± 1.98 kg) or 4,300 m (63.07 ± 2.28 to 62.61 ± 2.28 kg). Individual diet components and the effects of high altitude on energy and nitrogen balance in these subjects are described in detail elsewhere.

Menstrual Cycle Phase Determinations

To ensure that testing occurred in the appropriate phase at the appropriate time, each subject kept a menstrual cycle diary in which she noted the date of her menses, the date of a hormone surge (indicated by a competitive binding with Coat-A-Count RIA kits and double-antibody RIA kits (Diagnostic Products, Los Angeles, CA), respectively. To measure glucose isotopic enrichment, plasma was neutralized by backtitration with 2 N KOH, passed through anion- and cation-exchange resins (Bio-Rad Life Sciences, Hercules, CA), lyophilized, reconstituted with acetic anhydride-pyridine (2:1), dried under a stream of nitrogen, and reconstituted in 100 µl of ethyl acetate. The sample was injected, and pentaacetate derivatives were separated on a model 5890 gas chromatograph, with spectra recorded on a model 5989A mass spectrometer (both Hewlett-Packard Analytical, Wilmington, DE). Selected ion monitoring was used to compare the abundance of the unlabeled fragment (mass-to-charge ratio = 331) with that of the dideuterated isotopomer (mass-to-charge ratio = 333). After correction for background enrichment (~0.06%) the abundance of [6,6-H]Glucose was expressed as a percentage of total glucose species.

Calculations

Glucose rates of appearance (Rap) and disappearance (Rdp) were calculated using equations originally designed by Steele

### Table 2. Overview of hormonal conditions in which subjects were tested at sea level and 4,300 m

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Trial 4</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL-50</td>
<td>E</td>
<td>E + P</td>
<td>E</td>
<td>E</td>
<td>5</td>
</tr>
<tr>
<td>E + P</td>
<td>E</td>
<td>E</td>
<td>E + P</td>
<td>E + P</td>
<td>4</td>
</tr>
<tr>
<td>E</td>
<td>E + P</td>
<td>E + P</td>
<td>E + P</td>
<td>E + P</td>
<td>3</td>
</tr>
<tr>
<td>E + P</td>
<td>E</td>
<td>E + P</td>
<td>E + P</td>
<td>E + P</td>
<td>2</td>
</tr>
<tr>
<td>E + P</td>
<td>E</td>
<td>E</td>
<td>E + P</td>
<td>E</td>
<td>1</td>
</tr>
</tbody>
</table>

Tests used for comparisons between sea level and 4,300 m are shown in boldface.
and later modified for use with stable isotopes (40).

\[
\text{glucose } R_d (\text{mg/min}) = \frac{F - V[(C_1 + C_2)/2][(I - E_2 - I - E_1)/(t_2 - t_1)]}{(I - E_2 + I - E_1)/2}
\]

where \( F \) represents the isotopic infusion rate, \( I - E_1 \) and \( I - E_2 \) are the isotopic enrichments of plasma glucose with [6,6-\(^2\)H]glucose at times \( t_1 \) and \( t_2 \), respectively, \( C_1 \) and \( C_2 \) are the concentrations of plasma glucose at \( t_1 \) and \( t_2 \), respectively, and \( V \) is the estimated volume of distribution for glucose of 180 ml/kg. At rest, glucose \( R_d \) was calculated using the isotopic enrichment at 75 and 90 min after the infusion was started. During exercise, glucose \( R_d \) was calculated from the isotopic enrichment at 30 and 45 min after exercise was started. To account for the higher rate of energy expenditure during SL-65, glucose \( R_d \) per unit energy expenditure (mg glucose·kcal\(^{-1}\)·min\(^{-1}\)) was calculated. Carbohydrate oxidation (mg carbohydrate/l O\(_2\)) was calculated from RER by using standard values (23) and multiplied by V\(_\text{O}_2\) (l/min) to obtain carbohydrate oxidation rates in milligrams of carbohydrate per minute. Again, to account for differences in energy expenditure, carbohydrate oxidation rates per unit energy (mg·kcal\(^{-1}\)·min\(^{-1}\)) were calculated.

Statistical Analysis

Values are means ± SE. Statistical comparisons between menstrual cycle phases at sea level and high altitude and between elevations within the same menstrual cycle phase were made with a two-way ANOVA with repeated measures (by group, over time, and group × time interaction). Tukey’s Studentized range test was used to compare individual time points when significant (\( P < 0.05 \)) F ratios were obtained. Correlations between ovarian hormone concentrations and carbohydrate utilization were evaluated by Pearson product-moment analysis.

RESULTS

Comparison Across Menstrual Cycle Phase

As shown in Table 2, 15 subjects were studied at sea level in the follicular (E) and luteal (E + P) phases of the cycle. Exercise workload and V\(_\text{O}_2\) were the same between E and E + P (Table 3). Because V\(_\text{O}_2\)\(_\text{peak}\) was not different, relative exercise intensity (\%V\(_\text{O}_2\)\(_\text{peak}\)) was also the same. Glucose \( R_d \) and \( R_p \) were not different between E and E + P at rest or during exercise. RER was also similar between cycle phases at rest. RER was significantly greater at 30 min of exercise for E (\( P < 0.05 \)), but the magnitude of the difference (−0.014 unit) was very small (87.5 vs. 82.8% of energy attributable to carbohydrate oxidation). Concentrations of blood glucose, lactate, insulin, and cortisol were generally similar between menstrual cycle phases at sea level with a couple of exceptions (Table 3): insulin concentration was higher in E at 15 min of exercise (\( P < 0.01 \)), and plasma lactate values tended to be lower in E + P at 30 min of exercise (0.05 < \( P < 0.10 \)).

Comparison Across Elevations

Glucose kinetics. As shown in Fig. 1, isotopic enrichment of plasma glucose with the [6,6-\(^2\)H]glucose isotope reached a stable plateau during the last sampling points at rest and during exercise in all three conditions. Glucose \( R_d \) and \( R_p \) at rest (Fig. 2) were significantly lower (mean decline −18%) after 10 days at high altitude (4,300 m) than in sea-level conditions. During exercise, glucose \( R_d \) was significantly higher at SL-65 (6.22 ± 0.26 mg·kg\(^{-1}\)·min\(^{-1}\)) than at SL-50 (5.03 ± 0.22 mg·kg\(^{-1}\)·min\(^{-1}\)) or 4,300 m (4.71 ± 0.24 mg·kg\(^{-1}\)·min\(^{-1}\)). When compared at the same absolute exercise intensity (102 ± 3 W at SL-50 and 4,300 m), glucose \( R_d \) was not different between elevations: 4,300 m was lower by 9.4%. At the same relative intensity, however (140 ± 5 W at SL-65 vs. 102 ± 3 W at 4,300 m), glucose \( R_d \) was 24.3% lower at 4,300 m. When glucose utilization rates were scaled to rates of exercise energy expenditure (Table 4), the glucose \( R_d \) per unit energy expenditure was almost identical (differences <2.5%) among all three conditions (Fig. 3). Gas exchange. As shown in Fig. 4, resting RER was significantly lower at both sampling times at high...
Glucose and lactate concentrations. Figure 6A shows the plasma glucose concentration at each time point. At rest, plasma glucose concentration was significantly lower after 10 days at 4,300 m than in either sea-level condition. At sea level, plasma glucose concentrations declined significantly in the transition from rest to exercise and remained lower throughout the exercise bout, with values lower at SL-65 than at SL-50. A different pattern was observed during exercise at 4,300 m: glucose concentrations did not fall in the rest-to-exercise transition and were greater than at SL-50 or SL-65. Plasma lactate concentrations were virtually the same at rest in all three conditions (Fig. 6B). During exercise, plasma lactate concentration rose at sea level and 4,300 m. Plasma lactate concentrations were considerably higher during exercise at SL-50 than at 4,300 m. Relative to SL-65, however, plasma lactate levels at 4,300 m were not different.

Glucoregulatory hormones. Mean plasma concentrations of epinephrine and norepinephrine between 30 and 45 min of exercise are shown in Fig. 7. Epinephrine was the same at SL-65 and 4,300 m and was significantly higher than at SL-50. Norepinephrine was significantly elevated during moderate-intensity (SL-65) compared with low-intensity (SL-50) exercise at sea level and was even higher at 4,300 m. The plasma concentration of cortisol (Fig. 8A) was not different at rest in all three conditions. Cortisol concentrations rose throughout the exercise period and were significantly higher than at rest at 30 and 45 min of exercise. Cortisol concentrations were significantly higher at SL-65 than at SL-50 and were elevated even further at 4,300 m relative to SL-65. As shown in Fig. 8B, plasma insulin concentrations were variable at rest and did not differ

**Fig. 1.** Isotopic enrichment of plasma glucose with [6,6-2H]glucose in all 3 conditions. Pre, before isotope infusion; Rest, during 90 min of infusion with subjects resting semi-supine; Exercise, during 45 min of steady-state cycle ergometry. Mean values are shown without error bars to indicate how isotopic enrichment changed over time and reached a steady state at relevant sampling times. SL, sea level; \( V_{\text{O2peak}} \), peak \( O_2 \) consumption.
among conditions. During exercise, plasma insulin concentrations fell to lower values than at rest. Insulin levels at SL-50 remained elevated above those observed in the other two conditions, but this difference was significant only at 45 min of exercise. Insulin response at 4,300 m was virtually identical to that at sea level.

Gas exchange during daily measurements of basal metabolic rate. The RER values measured during daily assessments of basal metabolic rate at sea level and over the 12 days at 4,300 m are shown in Fig. 9. RER values were significantly lower on days 2–7 and 10 at 4,300 m than at sea level.

Correlations between ovarian hormones and glucose utilization. Glucose Rd or RER values were not significantly correlated with estrogen or progesterone concentrations alone, estrogen plus progesterone, or the estrogen-to-progesterone ratio (data not shown).

**DISCUSSION**

The main findings in this study were that blood glucose utilization rates in young women after 10 days of exposure to 4,300-m elevation were lower at rest and not different during submaximal exercise from those observed at sea level. Whole body carbohydrate utilization, as determined by RER, was lower at rest and during exercise at the same relative intensity at 4,300 m than at sea level. Blood glucose utilization was not different, and carbohydrate oxidation was only marginally altered (lower at 30 min of exercise in E + P than in E) across phases of the menstrual cycle. Neither measure was correlated with circulating levels of estrogen and/or progesterone.

**Effects of Energy Balance**

Our main findings could be confounded by negative energy balance, resulting in weight loss, which reduces carbohydrate utilization (13). At high altitude, a reduction in energy intake coupled with increased basal

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**Table 4. Comparison of selected physiological parameters and catecholamine concentrations during exercise trials at the same absolute and relative exercise intensity**

<table>
<thead>
<tr>
<th>Condition</th>
<th>SL-50</th>
<th>4,300 m</th>
<th>SL-65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workload, W</td>
<td>102 ± 3</td>
<td>102 ± 3</td>
<td>140 ± 5*</td>
</tr>
<tr>
<td>O2 consumption, l/min</td>
<td>1.40 ± 0.05</td>
<td>1.37 ± 0.06</td>
<td>1.75 ± 0.06*</td>
</tr>
<tr>
<td>Energy expenditure, kcal/min</td>
<td>6.99 ± 0.22</td>
<td>6.80 ± 0.21</td>
<td>8.76 ± 0.28*</td>
</tr>
<tr>
<td>V̇O2peak, l/min</td>
<td>2.70 ± 0.10</td>
<td>2.08 ± 0.11*</td>
<td>2.70 ± 0.10</td>
</tr>
<tr>
<td>%Sea-level V̇O2peak</td>
<td>52.0 ± 0.3</td>
<td>51.1 ± 0.4</td>
<td>64.8 ± 1.1*</td>
</tr>
<tr>
<td>%High-altitude V̇O2peak</td>
<td>66.0 ± 0.9</td>
<td></td>
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</tr>
</tbody>
</table>

Values are means ± SE. *Significantly different from other conditions.
energy demands commonly results in weight loss (10). For example, men who spent 18 days at 4,300 m and lost several kilograms of body weight used less muscle glycogen and had lower RER values during exercise than at sea level or with acute altitude exposure (41). In contrast, when men were kept at 4,300 m for 21 days in a weight-stable condition, blood glucose utilization during rest and exercise was higher (7, 30) and muscle glycogen use was unchanged (17) relative to that at sea level. In the present study, energy balance was maintained and body weights were unchanged after a slight loss during the initial 4 days of altitude exposure. Therefore, it is likely that the reduction in whole body carbohydrate oxidation we observed is attributable to altitude exposure and not a consequence of negative energy balance.

Time Course of Changes

Because we made a single measurement after 10 days at 4,300 m, we cannot address how substrate utilization might change over time during high-altitude acclimatization in women. Roberts et al. (31) found that blood glucose $R_d$ and glucose uptake by the working leg muscles declined in men after 21 days at 4,300 m relative to acute exposure (although both parameters remained modestly elevated over sea-level values). In contrast, Larsen et al. (24) reported no change in resting glucose $R_d$ and a rise in insulin-stimulated glucose uptake in men after 7 days, compared with 2 days, at 4,550 m. The only data available on women were provided by Hannon et al. (19). All ($n = 8$) women showed a decrease in fasting plasma glucose concentrations and an increase in plasma free fatty acid concentrations during 14 days of exposure to 4,300 m. Those changes were transient: free fatty acid levels returned to sea-level values after 7 days, and glucose concentrations approached baseline after 14 days. Although the authors interpreted those data to suggest that fat utilization was not enhanced at high altitude, without directly measuring substrate utilization, that conclusion remains speculative. In the present study, basal $V_{O_2}$ and $CO_2$ production were measured on three mornings at sea level and every morning at 4,300 m. The RER (Fig. 8) was consistently lower at 4,300 m throughout the altitude exposure than at sea level. These data independently confirm the reduction in rest and exercise RER we observed on day 10 and imply that this effect was likely to have been present throughout the stay at altitude. One pitfall related to use of gas exchange measurements at altitude is the increase in ventilation that occurs. During acclimatization, a non-steady-state relationship between alveolar and arterial gases could limit the accuracy of the RER. In the present study, however, ventilatory acclimatization, as...
measured by resting ventilation and end-tidal CO₂ values, was complete with reestablishment of steady-state conditions by day 5 at 4,300 m (S. R. Muza, personal communication). Therefore, it is unlikely that hyperventilation was a confounding variable during the metabolic studies on day 10.

Relative vs. Absolute Exercise Intensity

Although comparing data between sea level and high altitude is straightforward at rest, making similar comparisons during submaximal exercise is complicated by altitude-induced changes in the relative exercise intensity. In the present study, VO₂peak was reduced by 23.4% at 4,300 m compared with sea level. As a consequence, an exercise workload of 102 W elicited 51.1% of sea-level VO₂peak but represented 66.0% of high-altitude VO₂peak. For this reason, our sea-level studies were done at 102 W (producing the same absolute exercise intensity as at 4,300 m to match energy flux) and 140 W (producing the same relative exercise intensity as at 4,300 m to match percentage of maximal capacity). The choice of comparison has a profound impact on the interpretation of the metabolic data. At the same absolute exercise intensity, blood glucose utilization was approximately the same and whole body carbohydrate oxidation tended to be lower (P = 0.07) at 4,300 m than at sea level. At the same relative exercise intensity, blood glucose utilization and total carbohydrate oxidation were markedly reduced at 4,300 m.

Several lines of evidence suggest that comparison across elevations at the same relative exercise intensity is more appropriate. Substrate utilization during exercise at sea level is directly related to the relative exercise intensity (8, 32). Plasma epinephrine and norepinephrine concentrations during exercise at 4,300 m (Fig. 7) are much more closely matched with sea-level exercise at the same relative intensity. Furthermore, plasma concentrations of the glucoregulatory hormones cortisol (Fig. 8A) and insulin (Fig. 8B) during exercise at 4,300 m more closely resemble the pattern observed during sea-level exercise at the same relative intensity. Lactate concentrations (Fig. 6B) follow a similar pattern, but there appears to be a slightly greater response early in exercise (15 min) during SL-65. Although there is no significant difference between the pattern of change at SL-65 and 4,300 m, higher lactate levels and lower blood pH may result in greater production of nonmetabolic CO₂, potentially inflating gas exchange values and leading to an overestimate of carbohydrate utilization. The absolute difference between SL-65 and 4,300 m (maximum difference...
is 1.08 mM at 15 min) is fairly minor, however, and the potential contribution to CO2 production is unlikely to be quantitatively important.

A major pitfall with making the comparison between sea level and high altitude at the same relative exercise intensity, however, is the higher rate of energy expenditure (−23.4%) at sea level (Table 2). To correct for this, a reasonable approach is to scale blood glucose utilization and carbohydrate oxidation to the rate of energy expenditure. Blood glucose Rd per unit energy expenditure (Fig. 3) is almost identical across all three conditions. Expressed in this way, there is clearly no change in the contribution of blood glucose to energy production at 4,300 m compared with sea level. If it is assumed that 70–100% of blood glucose Rd is oxidized (14, 29), the contribution of blood glucose to total energy expenditure ranges from 12.4 to 17.7% (SL-50), from 12.0 to 17.1% (4,300 m), and from 12.2 to 17.5% (SL-65). These data are in excellent agreement with results reported recently by McClelland et al. (29) in female rats acclimated to high altitude. Female rats exercising at high altitude utilized less blood glucose, in absolute terms, than rats exercising at the same relative intensity at sea level. When the difference in energy expenditure was accounted for, the blood glucose Ra was the same between elevations. In the present study, however, the rate of total carbohydrate oxidation scaled to the rate of energy expenditure (Fig. 5) was still significantly lower at 4,300 m than at sea level. Taken together, these data suggest that, relative to sea level, the contribution of intramuscular carbohydrate sources (glycogen) to total energy expenditure may be diminished after high-altitude exposure in these young women. This result is consistent with observations made in men losing body weight (41) but not with observations made in weight-stable men (7, 17, 31).

Comparison With Men

Compared with studies done under similar experimental conditions in men, the present results show some striking differences. Using isotopic tracer techniques (whole body substrate use) and arteriovenous differences across the leg (muscle substrate use) in young men, Brooks and colleagues (7, 31) consistently demonstrated that glucose uptake and oxidation were markedly increased after 2 h and still significantly higher after 21 days at 4,300 m than at sea level. Although there were two notable differences (women in this study were more physically trained, and the period of acclimatization was 10, rather than 21, days), several key parameters were nearly identical in those studies and the present one: the same elevation (4,300 m), strict maintenance of energy balance, the same exercise protocol (45 min at ~50% of sea level VO2peak), and almost identical absolute workload (100 W for men and 102 W for women). Blood glucose, lactate, and insulin concentrations in these women do not differ from values reported in men. These similarities serve to highlight the disparate results: unlike men, blood glucose uptake at high altitude in women does not increase, and total carbohydrate oxidation is lower than at sea level.

The difference in acclimatization time between studies on men and women is not likely to have a big impact on the comparison; glucose utilization in men decreased between the acute and acclimatized studies at 4,300 m, and a shorter exposure might have exaggerated, rather than diminished, the differences from our study in men. The effects of training state on the results are potentially important, however. Longitudinal studies of exercise training in women showed that glucose flux and carbohydrate oxidation were decreased in both sexes at the same absolute exercise intensity (but unchanged at the same relative intensity), and women showed a decrease in RER at the same relative exercise intensity (14). It is possible that a predisposition to conserve carbohydrate, especially intramuscular glycogen (as evidenced by a lower RER with no change in blood glucose Rd), in trained subjects explains at least part of the “sex difference” in carbohydrate utilization at altitude. Further studies using untrained women and/or trained men are necessary to separate the effects of training status from the effects of biological sex.

There is a wealth of evidence, from several independent lines of research, that women utilize less muscle glycogen and/or total carbohydrate under conditions in which catecholamine concentrations are elevated (1, 9, 12, 14, 15, 22, 33, 34, 36–39). At the same relative intensity, women tend to use more fatty acids and less glycogen to fuel exercise than men (14, 22, 34, 36–38). In response to induced hypoglycemia, women switch to fatty acid utilization more readily than men (1, 12). Men and women increase sympathoadrenal activity in response to altitude, resulting in higher concentrations of the catecholamines epinephrine (increase on acute exposure, then return to sea level after ~7 days) and norepinephrine (steadily increasing over the course of 2–3 wk) (27, 28). Catecholamines upregulate the rate of lipolysis as well as muscle glycogenolysis (27, 30, 31) and also stimulate hepatic glucose production. Although epinephrine concentrations were similar at the same relative exercise intensity (4,300 m vs. SL-65), norepinephrine was higher at 4,300 m than at SL-65. The same increase at 4,300 m was observed in plasma cortisol concentrations (Fig. 8A), which could further stimulate lipolysis and reduce the uptake of blood glucose. Larsen et al. (24) observed a sharp rise in plasma cortisol levels at 4,550 m in association with lower blood glucose uptake. In the present study, plasma glucose Rd exceeded Rd and glucose concentration declined in the early stages of exercise at sea level, indicating that glucose uptake by cells exceeded hepatic glucose production (Fig. 6A). At 4,300 m, however, blood glucose did not decrease in the rest-to-exercise transition and remained higher than sea-level values throughout exercise. Taken together, the data suggest that, in women, physiological stresses that stimulate the production of catecholamines and cortisol, such as exposure to high altitude, provoke a shift away from
carbohydrate utilization and toward greater reliance on fatty acids.

Effects of Ovarian Hormones

Substrate use at high altitude may be altered by the presence of the ovarian hormones estrogen and progesterone, both of which have direct and indirect effects on carbohydrate and lipid metabolism (9, 16, 25, 33, 34, 36–39). Administration of estrogen to women with amenorrhea causes blood glucose utilization to diverge from that seen in men (35). Differences from men may be especially pronounced if women are studied during the midluteal phase of the menstrual cycle, when the concentrations of estrogen and progesterone are highest (2, 9, 16, 18, 33, 34). Rates of carbohydrate oxidation during exercise in the follicular phase of the cycle are often, but not always, lower than in the luteal phase of the cycle (2, 9, 34, 36–39). We showed that glucose tolerance was significantly reduced in the E + P compared with the E only phase of the cycle in this same group of women (3).

Glucose utilization was not different in the E and E + P phases of the menstrual cycle (Table 3). When the absolute or relative concentrations of estrogen and/or progesterone were regressed against blood glucose uptake or RER, there were no significant correlations. The finding that there were no (glucose Ra and Rd) or minor (RER and possibly lactate) changes in response to fluctuations in ovarian hormone levels may be due to the subject population chosen. Differences in the relative concentrations of estrogen and progesterone across cycle phases (Table 1) in this group of physically fit, lean women tended to be small. Similar studies in less-trained women with larger variations in estrogen and progesterone across the menstrual cycle might result in more obvious cycle phase differences and a stronger relationship between the ovarian hormones and carbohydrate use. Our results do not exclude the ovarian hormones as mediators of sex differences in substrate utilization at high altitude. The changes in ovarian hormone levels between cycle phases are always subtle in comparison with differences between the sexes. In addition, the presence or relative absence of testosterone is likely to be important. Also, interactions with other hormones, receptor and postreceptor metabolism, and the physiological characteristics of the organism modulate the magnitude and direction of any metabolic perturbation.

“Oxygen-Efficiency” Theory

Brooks (5) and Hochachka (20) independently proposed hypotheses to explain a shift toward greater utilization of carbohydrate at high altitude. Because the caloric equivalent of 1 liter of consumed O2 is higher when pure carbohydrate is oxidized (5.05 kcal/l) vs. pure fat (4.68 kcal/l), it follows that any increase in the percentage of energy derived from carbohydrate sources will result in a more economical use of O2 resources. Data obtained in the present study in women do not support the theory, however, and suggest that increased carbohydrate utilization at high altitude may occur only in men.

Recently, a new perspective was introduced by McClelland et al. (29) challenging the “oxygen-efficiency” theory. These investigators identified the relative exercise intensity as the primary determinant of substrate utilization in female rats acclimated to high altitude. Furthermore, they speculated that the energetic advantages of increased dependence on glucose may be balanced by the need to conserve limited glycogen stores. Our data are consistent with this perspective and suggest that, in women, conservation of carbohydrate stores may not only balance but may override a shift toward increased glucose utilization in response to hypoxia. Whatever the mechanism, the net effect of femaleness appears to be a constraint on carbohydrate utilization at high altitude.

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