

## Urine Acid–Base Compensation at Simulated Moderate Altitude

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### ABSTRACT

Ge, Ri-Li, Tony G. Babb, Mark Sivieri, Geir K. Resaland, Trine Karlsen, Jim-Stray-Gundersen, and Benjamin D. Levine. Urine acid–base compensation at simulated moderate altitude. *High Alt. Med. & Biol.* 7:64–71, 2006.—Acute exposure to high altitude elicits respiratory alkalosis, and this is partially corrected by renal compensation. To determine the time course and magnitude of renal compensation during short-term moderate altitude exposure, we measured urine gas tensions and acid–base status in 48 healthy men and women at four levels of simulated altitude exposures. Each subject was exposed in pseudorandom order to simulated altitudes of 1780, 2085, 2455, and 2800 m in a decompression chamber for 24 h, separated by 1 week at sea level. Fresh urine was collected anaerobically at sea level and after 6 and 24 h of each altitude exposure. Urine pH increased significantly ( $p < 0.01$ ) after 6 h at all altitudes and returned to baseline values by 24 h at the lowest altitudes. In contrast, urine pH remained elevated at the highest altitudes. The mean value of urine  $\text{HCO}_3^-$  at sea level was  $1.67 \pm 0.25$  mmol/L, increased significantly after 6 h at all altitudes, and then returned to near baseline after 24 h at three lower altitudes (1780, 2085, and 2455 m). However, it remained elevated at 2800 m.  $\text{P}_{\text{CO}_2}$  in urine was significantly increased after 6 h and returned to baseline after 24 h at all altitudes. These results suggest that (1) short-term low to moderate altitude exposure results in a marked  $\text{HCO}_3^-$  diuresis, which may be caused by inhibition of the secretion of renal tubular  $\text{H}^+$ , and (2) renal  $\text{HCO}_3^-$  compensation was completed by 24 h at low to moderate altitude, but still incomplete at higher altitude.

**Key Words:** renal  $\text{HCO}_3^-$ ; high altitude;  $\text{SaO}_2$ ; acclimatization; decompression chamber

### INTRODUCTION

**A**CCLIMATIZATION TO HIGH ALTITUDE takes place through a variety of compensatory mechanisms. The initial response to hypobaric hypoxia primarily involves the cardiovascular

and respiratory systems due to stimulation of peripheral chemoreceptors, leading to hyperventilation and sympathetic activation (Wagner et al., 1987; Wolfel et al., 1994). Second, renal regulation of acid–base balance and body fluid distribution (Hannon et al., 1969; Frayser

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et al., 1975; Hackett et al., 1982) is particularly important in the subsequent short-term acclimatization response and seems to play a significant role in the development of acute mountain sickness, as well as high altitude pulmonary and cerebral edema (Hackett, 1999).

Acute respiratory alkalosis during high altitude exposure elicits two responses with opposing effects on acid–base status. In the short term, the decrease in  $P_{aCO_2}$  alkalinizes extracellular fluid to the extent calculated by the Henderson–Hasselbalch equation. In the longer term, however, this hypocapnia is moderated by renal compensation, which reduces plasma  $HCO_3^-$  and acidifies extracellular fluid. This renal response is generally considered to be a very slowly adapting mechanism, taking several days to exert a significant influence on the plasma bicarbonate ion. Studies of the renal response to acute hypocapnia in experimental animals indicate that acute hypoxic exposure can induce an increase in  $HCO_3^-$  excretion, and this response is diminished when  $CO_2$  is added to the hypoxic gas mixture (Walker, 1982; Olsen et al., 1998). Also, the effects of acute and chronic respiratory alkalosis on renal regulation of acid–base status have been studied in normal subjects at sea level (Krapf et al., 1991; Olsen et al., 1998). However, such studies provide only limited information on the renal response to moderate high altitude exposure. In particular, there are limited data on the time course and degree of renal pH compensation and its relationship to ventilatory acclimatization, especially at low to moderate altitude where the majority of occupational and recreational exposures occur (Moore, 1987).

The current study tested the hypothesis that the time course and magnitude of renal acid–base compensation depend on the severity of hypobaric hypoxia. To test this hypothesis, we investigated urinary gas tensions, acid–base status, and  $SaO_2$  in 48 healthy men and women at sea level and at four different simulated altitude exposures, encompassing a broad range of low (1,500–2,000 m), moderate (2,000–2,500 m), and high (>2,500 m) altitudes (Levine and Stray-Gundersen, 1996; Hultgren, 1997).

## METHODS

### *Subjects*

Forty-eight healthy individuals (32 men, 16 women), mean age,  $21 \pm 2.5$  yr; weight,  $61.3 \pm 10.4$  kg; and height,  $170 \pm 12$  cm, volunteered to take part in this study. All subjects received both a written and verbal explanation of the experiment before giving consent. The Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas approved this study.

### *Study protocol*

Each week at sea level for a total of 4 weeks the subjects spent 24 h in a decompression chamber at simulated altitudes of 1780, 2085, 2455, and 2800 m in pseudorandom order (last altitude fixed at 1780 m to minimize the effect on subsequent field exposures). The temperature ( $25 \pm 0.5^\circ C$ ), humidity ( $28 \pm 1\%$ ), and concentration of  $CO_2$  ( $0.07 \pm 0.02\%$ ) of the chamber were carefully controlled.

Urine samples were collected anaerobically at sea level and after 6 and 24 h at each simulated altitude using the following procedure: (1) void to empty bladder; (2) following the first void, each subject drank 500 mL to 1000 mL of a hypotonic sports drink (Gatorade); (3) subjects then voided through an external catheter to a vinyl bag about 30 min after drinking the Gatorade, avoiding exposure to air. For men, this was achieved with a standard condom-style catheter (C.R. Bard, Murray Hill, NJ). For women, an external collection device developed for use in space was employed (Medpoint Corporation, Chicago, IL, USA). This procedure produced a urine flow rate of 5 to 10 mL/min; (4) immediately after collection the urine samples were drawn into a 2-mL syringe and placed immediately on ice. The urine pH,  $P_{CO_2}$ , and  $HCO_3^-$  were analyzed using a blood gas analyzer (Instrumentation Laboratory, Lexington, MA).

Arterial oxygen saturation ( $SaO_2$ ) was measured by pulse oximetry (Ohmeda 3700, Madison, WI) at sea level and at 6 and 24 h at each simulated altitude.

## STATISTICAL ANALYSIS

Data are expressed as means  $\pm$  SE. Sea-level values (baseline) were taken from the mean values of four measurements, which were made immediately prior to each simulated altitude exposure. The urine gas values and  $\text{SaO}_2$  data at different altitudes and times were analyzed by means of a two-way analysis of variance (ANOVA) with repeated measures. The Newman-Keuls post hoc test was used for multiple comparison between variables. Linear regression analysis and correlation coefficients were used to assess the relationships between variables. Comparison and correlation were considered significant when  $p < 0.05$ .

## RESULTS

### Urine acid-base status

The mean value of urine pH was  $5.95 \pm 0.05$  at sea level. After hypoxic exposure for 6 h, it increased significantly by 0.489 to 0.52 unit at 1780, 2085, and 2455 m and 0.721 unit at 2800

m. After 24 h, urine pH returned to sea-level values at 1780 and 2085 m, but remained higher at 2445 and 2800 m (Fig. 1). Urine  $\text{HCO}_3^-$  varied widely both at sea level and at each altitude (Table 1). Urine  $\text{HCO}_3^-$  increased significantly after 6 h from a mean sea-level value of 1.67 to 6.58 mmol/L at 1780 m, 6.21 mmol/L at 2085 m, 5.73 mmol/L at 2455 m, and 10.99 mmol/L at 2800 m. It declined to baseline by 24 h at 1780, 2085, and 2455 m, but remained elevated at 2800 m (Fig. 2).

### Urine $\text{P}_{\text{CO}_2}$

The values of urine  $\text{P}_{\text{CO}_2}$  varied widely in all experiments. The mean urine  $\text{P}_{\text{CO}_2}$  at sea level was 44.4 mmHg (range from 35 to 55 mmHg) and increased significantly after 6 h at all simulated altitudes (range from 40 to 122 mmHg). After 24 h, it returned to baseline value (Fig. 3).

### Arterial oxygen saturation

$\text{SaO}_2$  at sea level was  $98.1 \pm 0.4\%$ , decreased slightly by 6 h at 1780 and 2085 m (1.1% and 1.6%, respectively), and significantly decreased

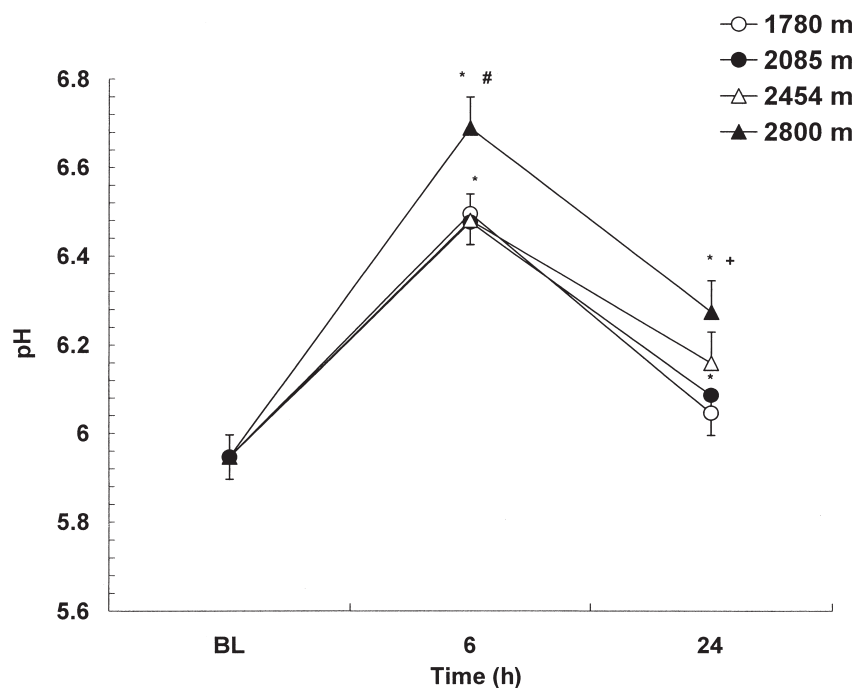


FIG. 1. Urine pH at sea level (baseline, BL) and after 6 h and 24 h of simulated altitudes of 1780, 2085, 2455, and 2800 m in 48 young subjects. Values are means  $\pm$  SEM. Significantly different from baseline ( $*p < 0.01$ ). Significantly different from 1780, 2085, 2455 at 6 h ( $\#p < 0.01$ ). Significantly different from 1780 and 2085 m at 24 h ( $+p < 0.01$ ).

TABLE 1. MEAN CHANGES OF ACID-BASE IN URINE, BLOOD AND SPINAL FLUID AT DIFFERENT ALTITUDES AND DURATION

	pH	$P_{\text{CO}_2}$ (mmHg)	$\text{HCO}_3^-$ (mEq/L)	References
Spinal fluid				Forster et al. (2)
250 m	7.342	50.2	24.9	
4300 m (5 days)	7.360	36.8	19.9	
4300 m (10 days)	7.366	35.6	19.5	
Arterial blood				Forster et al. (2)
250 m	7.396	40.0	24.4	
4300 m (5 days)	7.458	28.5	20.1	
4300 m (10 days)	7.449	25.2	17.9	
Arterial blood ( $P_{\text{I}_2} = 100$ mmHg)				Gledhill et al. (7)
2 h	7.480	31.4	21.3	
12 h	7.442	32.5	22.0	
24 h	7.430	31.3	21.0	
Urine ( $P_{\text{I}_2} = 100$ mmHg)				Gledhill et al. (7)
2 h	6.470	—	1.9	
12 h	6.000	71.9	9.1	
24 h	5.640	60.6	9.7	
Urine				This study
Sea level	5.967	42.7	1.50	
1780 m				
6 h	6.494	61.56	5.58	
24 h	6.045	45.2	1.82	
2085 m				
6 h	6.475	63.1	5.35	
24 h	6.054	39.5	1.90	
2455 m				
6 h	6.474	50.2	5.02	
24 h	6.159	43.1	2.21	
2800 m				
6 h	6.689	58.1	9.04	
24 h	6.274	45.3	3.58	

at 2455 and 2800 m (4.8% and 5.4%, respectively). It returned to baseline value by 24 h at 1780 and 2085 m, but remained significantly reduced at 2455 and 2800 m (Fig. 4). These data for  $\text{O}_2$  saturation, as well as more detail regarding renal oxygenation and erythropoietin release, are presented in more detail in a previously published manuscript (Ge et al., 2002).

## DISCUSSION

The main finding of the current study was that the time course and the magnitude of renal  $\text{HCO}_3^-$  compensation to acute hypoxic exposure depend on the degree of hypoxic stimulus. Short-term altitude exposure caused a marked  $\text{HCO}_3^-$  diuresis, even at altitudes that would be considered low or moderate, that is, <2000 or 2500 m, respectively. This renal com-

pensation was complete by 24 h at 1780, 2085, and 2455 m, but was incomplete at 2800 m.

### Methodological considerations

Several aspects of our experimental protocol and method must be considered. Measurements of urinary gas values, unlike arterial blood gases, are complicated not only by technical problems with urine collection, urine volume and flow; but also by sodium and water intake and other antidiuretic factors. Therefore, we collected urine samples carefully avoiding exposure to air or the formation of air bubbles. The urinary samples were collected anaerobically at high flow rates (>4 mL/min) in each experimental session; this was produced by drinking a 500- to 1000-mL hypotonic sports drink (Gatorade) after emptying the bladder. All subjects were fed a comparable diet pre-

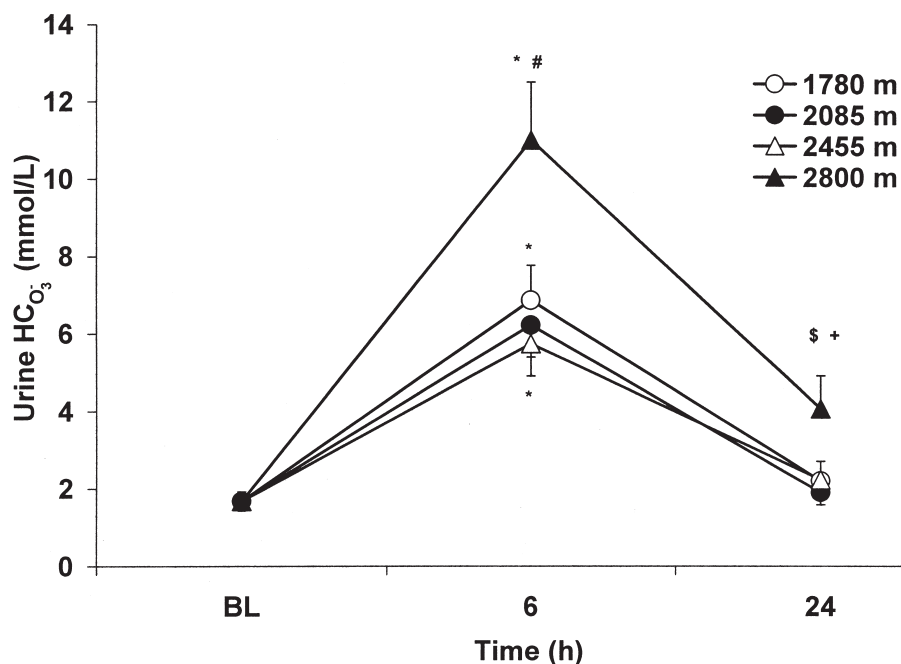


FIG. 2. Urine bicarbonate ion ( $\text{HCO}_3^-$ ) at sea level (baseline, BL) and after 6 and 24 h of simulated altitudes of 1780, 2085, 2455, and 2800 m in 48 young subjects. Values are means  $\pm$  SEM. Significantly different from baseline ( $*p < 0.01$ ). Significantly different from 1780, 2085, and 2455 m at 6 h ( $\#p < 0.01$ ). Significantly different from 1780, 2085, and 2455 m at 24 h ( $+p < 0.01$ ).

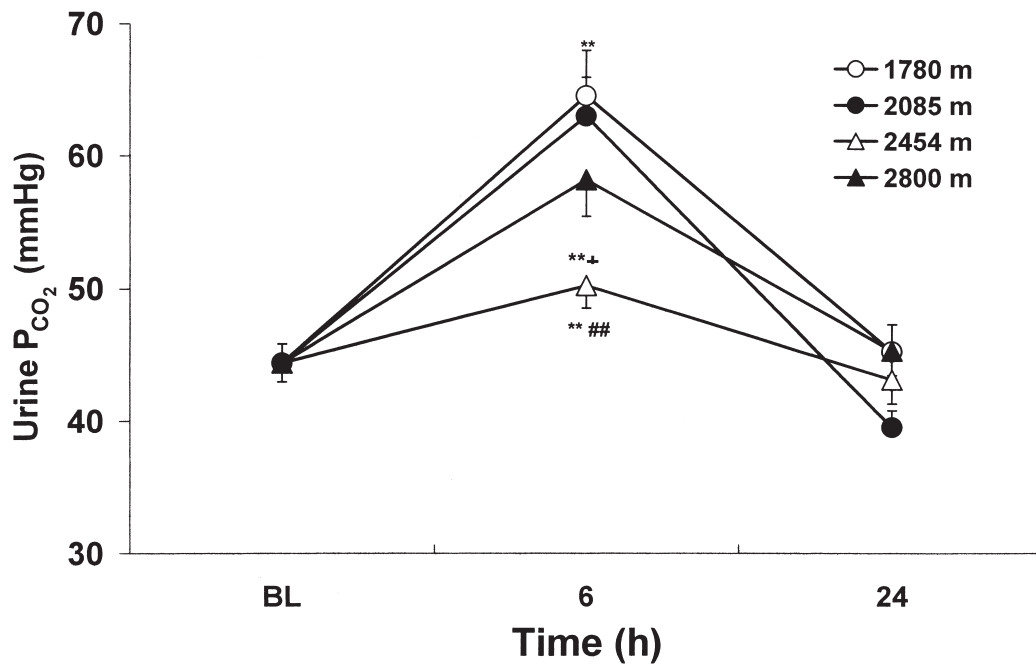
pared by our research staffers during each simulated high altitude. The blood gas analyzer was calibrated daily by using standard electrodes and buffers, which were provided by Instrumentation Laboratories. In view of the foregoing, we consider it unlikely that there was any major methodological error in the measurement of urine gas values. Moreover, using the same procedures for each collection ensured that the comparison among altitudes was valid.

#### Changes in urine acid–base balance

Studies in both humans and animals indicate that hypocapnia with or without hypoxemia causes increases in urine pH and bicarbonate excretion (Gledhill et al., 1975; Eiam-ong et al., 1994; Hultgren, 1997), which is associated with a decrease in tubular bicarbonate reabsorption. These responses may involve multiple factors, including increases in renal sympathetic nerve activity and changes in the regulation of hormonal activation (Sundstroem, 1919; Hildebrandt et al., 1995). In the present study, the mean values of urine pH and  $\text{HCO}_3^-$  at sea level

were 5.95 and 1.67 mmol/L, respectively, which are similar to the results of other studies at sea level in experimental animals. Surprisingly, there was a significant increase both in pH and  $\text{HCO}_3^-$  after 6 h at simulated altitudes despite only mild hypoxia at the lowest altitudes. This renal response of hypoxic  $\text{HCO}_3^-$  diuresis is likely the result of reduced renal tubular  $\text{HCO}_3^-$  reabsorption caused by acute respiratory alkalosis, which in turn may have resulted from the acute ventilatory response to hypoxic stimulation.

It is known that  $\text{HCO}_3^-$  reabsorption in the renal tubules depends not only on the filtered load of  $\text{HCO}_3^-$ , but also on the rate of  $\text{H}^+$  secretion by the distal tubular cells. The rate of  $\text{H}^+$  secretion and the rate of  $\text{HCO}_3^-$  reabsorption, therefore, are proportionate to the  $\text{Pco}_2$ . With a fall in the  $\text{PaCO}_2$  due to acute respiratory alkalosis, renal tubular  $\text{H}^+$  secretion is hindered, and the renal  $\text{HCO}_3^-$  excretion is increased, thus further reducing the already low plasma  $\text{HCO}_3^-$  and reducing the pH toward normal. In general, at much higher altitudes than studied in this experiment ( $>4000$  m), re-



**FIG. 3.** Partial pressure of urine CO<sub>2</sub> (P<sub>CO<sub>2</sub></sub>) at sea level (baseline, BL) and after 6 and 24 h of simulated altitudes of 1780, 2085, 2455, and 2800 m in 48 young subjects. Values are means  $\pm$  SEM. Significantly different from baseline (\*\* $p < 0.01$ ). Significantly different from 1780 and 2085 m at 6 h ( $\#\#p < 0.01$ ). Significantly different from 2800 m at 6 h ( $^+p < 0.05$ ).

nal compensation for respiratory alkalosis takes several days or even longer. For example, Forster et al. (1975) reported that pH in both blood and cerebrospinal fluid (CSF) rose significantly after a 5-day exposure to 4300 m and remained essentially unchanged during an 11-day sojourn. In Tibet (Ge et al., 1994a, 1994b) the mean arterial pH in Han Chinese newcomers, who immigrated from sea level to 4700 m 3 yr earlier, was  $7.47 \pm 0.01$ , while it was  $7.46 \pm 0.01$  in Tibetan natives who permanently inhabited the area. This suggests that hypocapnia in Han newcomers persisted even after they had lived at high altitude (>4000 m) for 3 yr. In contrast, Tibetan natives living at very high altitude have a normal sea-level value of blood pH, which may be attributed to a blunted hypoxic ventilatory response (Ge et al., 1994a, 1994b).

In contrast to previous findings at these very high altitudes, the urine pH in the present study, after significantly increasing in the first 6 h, returned to baseline after 24 h at 1780, 2085, 2455 m, but remained above baseline at 2800 m. Similarly, after a 24-h exposure to high altitude, the urine HCO<sub>3</sub><sup>-</sup> returned to baseline at low to moderate altitude (1780 to 2455 m) but,

was still elevated at high altitude (2800 m). These findings suggest that the renal contribution to acid-base compensation at low to moderate altitude is more rapid and complete than previously reported. Furthermore, the magnitude of the renal correction of alkalosis is different at low to moderate altitude when compared to high altitude. For example, below 2500 m, the renal HCO<sub>3</sub><sup>-</sup> compensation appears to be completed rapidly, but it is comparatively slow above approximately 3000 m.

The key question in the present study is the relationship between urine HCO<sub>3</sub><sup>-</sup> excretion and ventilatory acclimatization. Early investigators believed that renal excretion of HCO<sub>3</sub><sup>-</sup> induces metabolic acidosis, which in turn stimulates breathing (Swenson et al., 1995). Therefore, it was presumed that the progressive increase in breathing during ventilatory acclimatization would contribute to the renal lowering of plasma bicarbonate, compensating for the respiratory alkalosis. This theory, however, has been questioned by the evidence that arterial pH after ascent to high altitude always becomes higher than at sea-level values and continues to rise over several weeks. Thus, ven-

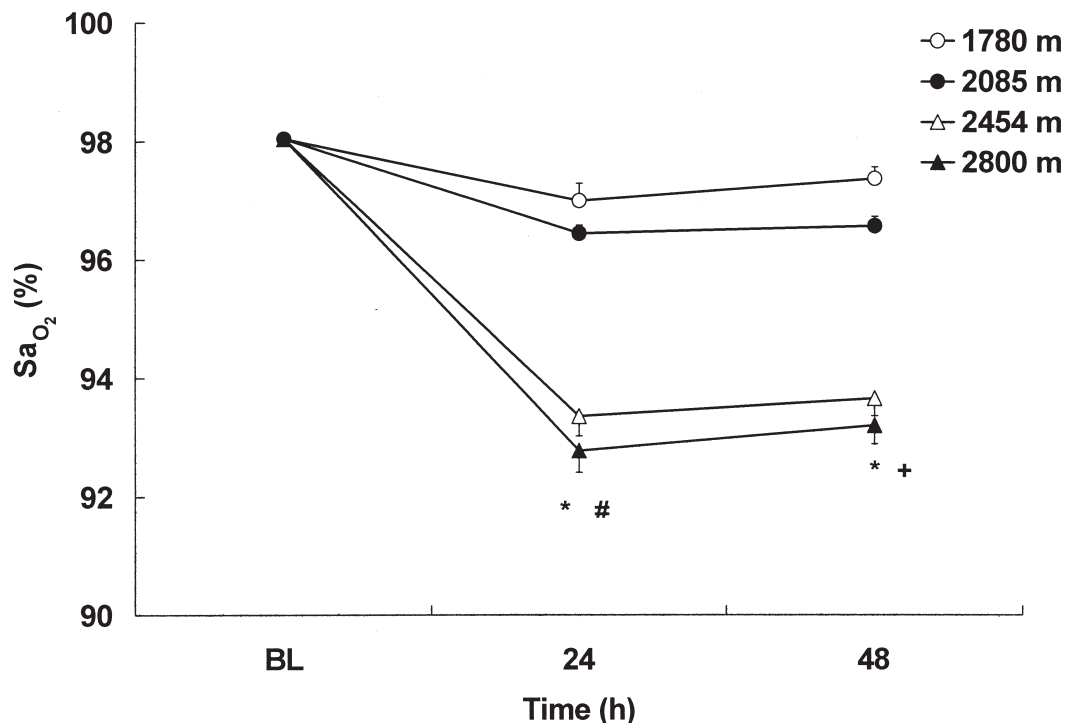


FIG. 4. Oxyhemoglobin saturation ( $Sa_{O_2}$ ) at baseline and after 6 and 24 h of simulated altitude. Significantly different from baseline ( $*p < 0.01$ ). Significantly different from 1780 and 2085 m at 6 h ( $\#p < 0.05$ ). Significantly different from 1780 and 2085 m at 24 h ( $+p < 0.05$ ).

tilatory acclimatization cannot be explained simply by renal compensation of arterial pH. Forster et al. (1975) demonstrated that persistent alkalosis during acclimatization to high altitude could be caused by the gradually increasing sensitivity of the peripheral chemoreceptors. Our data indicate that the urine  $HCO_3^-$  returned to baseline by 24 h at low to moderate altitude and remained above baseline at high altitude. This suggests that the renal metabolic compensation process was essentially complete at low to moderate altitudes, with little evidence seen of ongoing alterations in chemosensitivity. In contrast, at high altitudes acclimatization may require a more continuous process, including changes in chemosensitivity. We speculate that this may occur once the  $Pa_{O_2}$  decreases to the steep portion of the Hb dissociation curve, where  $O_2$  content is very sensitive to small changes in ventilation and  $Pa_{O_2}$ .

#### Changes in urine $P_{CO_2}$

Urine  $P_{CO_2}$  values varied widely at both sea level and simulated altitude, ranging from 35

to 112 mmHg. Previously, Gledhill et al. (1975) reported that the mean value for urine  $P_{CO_2}$  at sea level was 42.5 mmHg and increased to 65.6 mmHg by 7 h at a simulated altitude of 3100 m, which is consistent with the present results: the mean urine  $P_{CO_2}$  rose significantly by 6 h, and the magnitude of the increase, except at 2080 m, was similar at both moderate and high altitude. In contrast to Gledhill findings, the urine  $P_{CO_2}$  in this study returned to sea-level value by 24 h at all altitudes, which likely indicated that the respiratory alkalosis was corrected rapidly by renal compensation.

$Sa_{O_2}$  was returned to baseline after 24 h at moderate altitudes and also, though low, at the highest altitudes (Fig. 4). Although we did not measure the ventilation or end-tidal  $CO_2$ , we speculate that ventilatory acclimatization in our young subjects was achieved quickly, leading to a more effective acceleration in renal bicarbonate compensation, particularly at low to moderate altitude.

In summary, we measured urine pH,  $P_{CO_2}$ , and  $HCO_3^-$  concentration in the 48 young men and women at sea level and for 24 h at four lev-

els of simulated altitudes. The results suggest that short-term low to moderate altitude exposure causes a marked  $\text{HCO}_3^-$  diuresis and that renal  $\text{HCO}_3^-$  compensation was completed by 24 h at low to moderate altitude, but was still incomplete at higher altitude.

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