Human Llamas

ADAPTATION TO ALTITUDE IN SUBJECTS WITH HIGH HEMOGLOBIN OXYGEN AFFINITY

ROBERT P. HEBBEL, JOHN W. EATON, RICHARD S. KRONENBERG, ESMAIL D. ZANJANI, LORNA G. MOORE, and ELAINE M. BERGER, *Divisions of Hematology and Pulmonary Medicine, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota 55455, and Department of Anthropology, University of Colorado, Denver, Colorado 80202*

ABSTRACT To assess the adaptive value of the right-shift of the oxyhemoglobin dissociation curve (decreased affinity for oxygen) observed in humans upon altitude exposure, the short-term physiologic responses to altitude-induced hypoxia were evaluated in two subjects with a high oxygen affinity hemoglobin (Hb Andrew-Minneapolis) and in two of their normal siblings. In striking contrast to normal subjects, at moderately high altitude (3,100 m) the high affinity subjects manifested: (*a*) lesser increments in resting heart rate; (*b*) minimal increases in plasma and urinary erythropoietin; (*c*) no decrement in maximal oxygen consumption; and (*d*) no thrombocytopenia. There was no difference between subject pairs in 2,3-diphosphoglycerate response to altitude exposure. These results tend to contradict the belief that a decrease in hemoglobin oxygen affinity is of adaptive value to humans at moderate altitudes. Rather, they support the hypothesis that, despite disadvantages at low altitude, a left-shifted oxyhemoglobin dissociation curve may confer a degree of preadaptation to altitude.

INTRODUCTION

Both newcomers and permanent residents at high altitude have decreased hemoglobin oxygen affinity (a right-shift of the oxyhemoglobin dissociation curve [ODC][1]). For many years, physiologists believed that this altitude-induced right-shift of the ODC is of adaptive significance because it facilitates oxygen unloading at the tissue level (1–4). However, in evaluating the efficacy of physiologic responses to various challenges, it is imperative to remember that the hemostatic adjustments of living organisms generally reflect, and are appropriate for, the environmental stresses they most frequently encounter. Because hominids evolved at low altitudes, exposure to hypoxia has most frequently been due to a decrement in oxygen-carrying capacity (anemia) rather than a limitation in the availability of oxygen (hypoxic hypoxia). In the former circumstance, a right-shift of the ODC is unquestionably advantageous; it facilitates oxygen unloading without compromising uptake from the oxygen-rich environment. In contrast, water breathing animals are most often made hypoxic through environmental oxygen deprivation (e.g., due to temperature-dependent changes in the solubility of oxygen in water). In this situation, a left-shift of the ODC is appropriate because it facilitates oxygen loading in the gill. Those species of fish and eel studied thus far do, in fact, increase their hemoglobin oxygen affinity (left-shift their ODC) in response to decreases in ambient oxygen tensions (5, 6). In terms of the logistics of oxygen loading and unloading, the human at altitude is more like the fish in an oxygen-poor environment than like the sea-level human with anemia. Despite this, the human response to both types of hypoxia is the same: a right-shift of the ODC (7). Thus, humans may respond inappropriately to altitude exposure. Indeed, it is unreasonable to as-

This paper was presented, in part, at the 1978 Intersociety Plenary Session of the American Society for Clinical Investigation, the American Federation for Clinical Research, and the Association of American Physicians, held in San Francisco, Calif. on 30 April 1978.

Dr. Kronenberg and Dr. Eaton are the recipients of National Institutes of Health Research Career Development Awards. Dr. Hebbel is the recipient of a National Institutes of Health Young Investigator Research Award.

Received for publication 25 January 1978 and in revised form 22 May 1978.

[1] *Abbreviations used in this paper*: 2,3-DPG, 2,3-diphosphoglycerate; Ep, erythropoietin; Hb, hemoglobin; ODC, oxyhemoglobin dissociation curve; $\dot{V}O_{2\,max}$, maximal oxygen consumption.

sume that an organism which lacks evolutionary exposure to an oxygen-poor environment should necessarily respond appropriately to altitude-induced hypoxia.

We previously tested the hypothesis that a left-shift of the ODC might improve oxygen uptake at very high altitudes while still allowing adequate delivery. In these studies, a carbamylation-induced increase of hemoglobin oxygen affinity was found to protect rats from death due to extreme altitude (9,200 m) exposure, suggesting that a level-shift of the ODC might be of similar advantage to humans at altitude (8, 9). Although these observations clearly demonstrate the advantage of high oxygen affinity at extreme altitude, they are not directly relevant to the altitudes more commonly encountered by man (3,000–5,000 m). Furthermore, information derived from these small rodents with their higher basal metabolic rates may not be applicable to humans (10).

Consequently, we have taken advantage of a unique opportunity afforded by the availability of a family with a rare high oxygen affinity mutant hemoglobin to study the short-term responses to altitude exposure in humans with left-shifted ODCs. It was the purpose of this investigation to determine whether abnormally high hemoglobin oxygen affinity would confer some degree of preadaptation to altitude. The "high" altitude chosen for this study was that of Leadville, Colorado (3,100 m); it is moderate enough to allow permanent human residence, yet great enough to elicit a variety of hematologic and physiologic responses in normal humans. The parameters chosen for evaluation in this noninvasive study were those known to undergo some alteration in response to environmental oxygen deprivation.

METHODS

Subjects. Four healthy adolescents were studied from a family with Hb Andrew-Minneapolis, a stable beta-chain mutant ($\beta^{144Lys\rightarrow Asn}$) with high oxygen affinity (whole blood $P_{50} \cong 17$ mm Hg) (11). Two of the subjects, a 12-yr-old male and an 18-yr-old female, were heterozygous for the mutant hemoglobin and had low P_{50}s and elevated hemoglobin concentrations. Their normal siblings, a 14-yr-old male and a 16-yr-old female, served as controls (Table I). None of the subjects was iron or vitamin deficient. Signed, informed consent was obtained from both the subjects and their parents.

Protocol. Due to the youth of the participants, this investigation was as noninvasive as possible. Subjects were studied at low altitude (Minneapolis, 245 m) during the month preceding exposure to moderately high altitude (Leadville, 3,100 m). Subjects resided at altitude for 10 days after traveling by air to Denver, Colorado, with immediate ground transportation to Leadville. The first evaluations were done within a few hours of initial exposure. Sampling intervals depended upon the parameter being evaluated and are indicated below as the number of days of altitude exposure. With the exception of the day of arrival (day 0), all measurements were done in midmorning.

Acid-base status. Previous studies on these subjects indicated that altitude-induced hyperventilation would be identical in all four (12). During the current investigation, their acid-base status was monitored indirectly. The pH of arterialized capillary blood, obtained by finger stick (after 5 min of forearm immersion in warm water), was measured with an IL213 micro pH electrode (Instrumentation Laboratory, Inc., Lexington, Mass.). Aliquots of fresh urine and plasma were stored frozen, under mineral oil in glass tubes, for subsequent bicarbonate determination in our institution's clinical laboratory. Resting minute ventilation and resting end-tidal P_{CO_2} were determined by means of a dry gas flow meter (Parkinson Cowan Measurement, Manchester, England) connected to a Lloyd valve modified to allow syringe sampling of end-tidal gas tensions (IL213 blood gas analyzer). The above parameters were measured on days 0–2, 4, 6, and 10 of altitude exposure.

Hematologic parameters. Duplicate microhematocrits were done in the standard manner. Duplicate cyanomethemoglobin concentrations were determined spectrophotometrically on whole blood stored frozen until return to low altitude. No attempt was made to monitor changes in plasma volume. Reticulocyte counts were done by counting 500 cells on single smears stained in the field. Duplicate extracts (10% trichloroacetic acid) were made on fresh blood and stored frozen in glass tubes for subsequent 2,3-diphosphoglycerate (2,3-DPG) determination by an enzymatic method (13). Quadruplicate platelet counts were done using Rees–Ecker diluting fluid. These parameters were determined on days 0–4, 6, 8, and 10 (2,3-DPG, hemoglobin [Hb], hematocrit, retic count) and days 1, 2, 4, 6, and 10 (platelets). The volume of blood taken for these measurements was 3 ml unless plasma for erythropoietin was obtained, in which case 22 ml were drawn. The estimated total blood volume for all subjects was at least 3,500 ml, and phlebotomy-induced blood loss over the 10-day study period amounted to <4% of this.

Erythropoietin (Ep). Urinary excretion and plasma concentration of Ep were assayed by the technique of ^{59}Fe incorporation in polycythemic (exhypoxic) mice (14). The amount of Ep in each sample was determined by observing its effect on 10–15 mice. Base line (low altitude) urinary excretion was established by determining the Ep content of six consecutive 8-h collections 3 wk before altitude exposure. In Leadville, 250-ml aliquots of 24-h collections were frozen in sterile plastic containers for subsequent analysis. To verify adequacy of 24-h collections, total volumes were recorded, and aliquots were frozen for subsequent creatinine determination; all collections were felt to have been complete. Heparinized plasma was frozen for Ep determination on days 0–2, 4, 6, and 10; base line plasma Ep values were obtained 2 and 3 wk before exposure.

Heart rate. Resting (sitting) heart rates were measured three times daily. In addition, heart rate was monitored throughout each exercise period.

Oxygen consumption ($\dot{V}O_2$). Maximal oxygen consumption ($\dot{V}O_{2\ max}$) was determined on each subject three times at low altitude and four times at high altitude (days 0, 1, 2, 4). The method chosen was to exercise subjects (at progressively greater work loads) to voluntary fatigue on a bicycle ergometer to ensure an elapsed time of ≅10 min, a plateau of $\dot{V}O_2$, and a redistribution of cardiac output (15, 16). Thus, work loads were individualized, and the attainment of valid comparative exercise tolerance data was sacrificed for the sake of obtaining a valid $\dot{V}O_{2\ max}$. Subjects began exercising (50 rpm) at a work load of 10% of their own predicted maximal tolerated load. Load was increased by an additional 10% every 90 s. At the higher altitude, load at each stage was reduced to 90% of the comparable low altitude load. During exercise, subjects breathed through a low-resistance Lloyd respiratory valve modified to allow syringe sampling of end-tidal gases, which

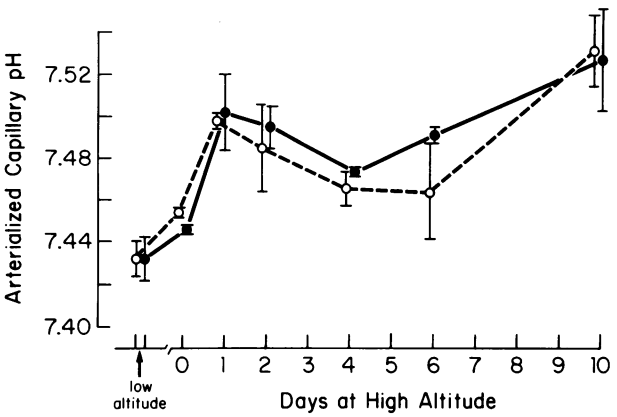

FIGURE 1 Effect of altitude exposure on arterialized capillary pH. Normal (●) and high affinity (○) subjects manifested no difference in pH consequent to altitude exposure. Points represent mean ±1 SEM.

were analyzed as above. At each stage of exercise, a 1-min collection of expired gas was obtained after passage through a dry gas flow meter into a 100-liter Douglas bag (Warren E. Collins, Inc., Braintree, Mass.). Before this investigation, the dry gas flow meter was calibrated at various flow volumes and rates against a Tissot spirometer (Warren E. Collins, Inc.) and was found to be accurate within 1%. Barometric pressure, temperature, and ambient P_{O_2} were recorded for each exercise period; the corrected results are expressed as milliliters per minute per kilogram (standard temperature and pressure, dry).

Statistical methods. In those cases where enough independent replicates were obtained so that statistical analysis could be performed, Student's unpaired (two-tailed) *t* test was used.

RESULTS

Acid-base status. The pH of arterilized capillary blood increased upon altitude exposure, but there was no difference in this parameter between normal and high affinity subjects (Fig. 1). Serial determinations of resting end-tidal P_{CO_2} and ventilation, urine bicarbonate, and plasma bicarbonate also showed no difference between subjects (data not shown).

2,3-DPG. Steady state, low altitude levels of 2,3-DPG were lower in high affinity subjects than in their normal siblings (Table I). During altitude exposure, high affinity and normal subjects reached mean peak 2,3-DPG increases of 1.49 and 1.79 μM/g Hb, respectively. Inclusion of serial 2,3-DPG levels obtained on the four (normal) investigators did not confer statistical significance upon this small difference between normal and high affinity subjects in peak levels. Similarly, averaging the levels measured on all days after the initial 48-h burst of 2,3-DPG synthesis revealed no difference between subject pairs (increases of 0.95 and 0.92 μM/g Hb for normal and high affinity subjects, respectively).

Erythropoiesis. The increases of hemoglobin concentration and hematocrit consequent to altitude exposure (means of 1.1 g/dl and 3.0%, respectively) were the same for both pairs. However, no measurements of plasma volume or erythrocyte mass were made. Serial determinations of reticulocyte counts (Fig. 2A) revealed a mean peak reticulocytosis of 4.0% in high affinity subjects and 5.0% in normal subjects; the small number of replicates precludes statistical analysis.

Ep. All four subjects manifested some increase in Ep excretion at altitude (Table II). However, the normal subjects showed greater peak increases (171% for N1 and 113% for N2) than did the high affinity subjects (37% for H1 and 50% for H2) (Fig. 2B). Determinations of plasma Ep concentrations (Table II) confirmed this difference. Normal subjects showed measurable and significant increases in plasma Ep at altitude (peaks of 0.25 and 0.15 U/ml), while on only 1 day did the plasma Ep of high affinity subjects rise to the very lower end of the detectable range for this laboratory (0.05 U/ml) (Fig. 2C). The difference in 24-h Ep excretion and plasma Ep concentration between low and high altitudes was statistically significant for normal subjects only ($P < 0.001$ and $P < 0.01$, respectively).

TABLE I

Low Altitude (245 m) Parameters of Subjects from a Family with Hb Andrew-Minneapolis

Oxygen affinity	Subject	Age	Sex	Height and weight	P_{50}	Hb	Hct	Retic count	2,3-DPG	Platelet count	Resting heart rate
		yr		*cm/kg*	*mm Hg*	*g/dl*	*%*	*%*	*μM/g Hb*	*10^3/mm^3*	*beats/min*
Normal	N1	14	M	154.0/47.8	26.9	14.1	41.1	1.1	15.79	291	67
	N2	16	F	152.0/62.2	27.0	13.5	39.0	1.1	15.00	243	67
High	H1	12	M	153.0/42.8	17.0	16.8	48.1	0.8	11.76	217	100
	H2	18	F	152.5/63.8	17.2	17.3	50.2	1.3	13.48	170	88

P_{50}, whole blood P_{50} at pH 7.4 and 37°C; Hb, whole blood hemoglobin concentration (mean of four determinations); Hct, microhematocrit (mean of four determinations); retic count = mean of four determinations; 2,3-DPG, erythrocyte 2,3-DPG (mean of four determinations); platelet count = mean of four determinations; and resting heart rate = mean of nine determinations.

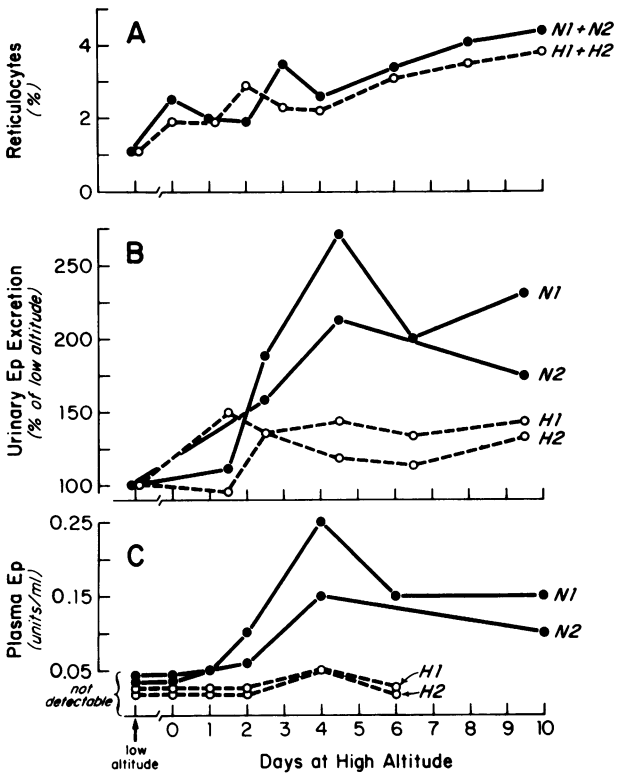

FIGURE 2 Effect of altitude exposure on erythropoiesis. Normal subjects are indicated by ● and high affinity subjects by ○. (A) On most days, mean reticulocyte counts were lower in high affinity subjects. (B) Urinary Ep excretion, expressed as percent of baseline (low altitude) levels, increased significantly only for normal subjects at altitude ($P < 0.001$). (C) Plasma Ep concentrations rose significantly ($P < 0.01$) above the normal (undetectable) range for normal subjects, whereas high affinity subjects generally maintained undetectable levels.

Platelets. Although high affinity subjects showed no decrement in platelet count during altitude exposure, thrombocytopenia developed in normal subjects, a mean decrement of 131,000/mm^3 being observed on day 4 (Fig. 3). This difference between subject pairs was statistically significant on days 4, 6, and 10 ($P < 0.02$). High altitude platelet counts differed from low altitude counts significantly in normal subjects on days 4, 6, and 10 ($P < 0.05$) but not on days 1 and 2. Peripheral blood smears did not reveal any change in platelet size during altitude exposure.

Heart rate. The increase in resting heart rate at altitude was consistently greater for normal subjects (Fig. 4) and differed significantly from that of high affinity subjects ($P < 0.02$ on day 1 and $P < 0.01$ on days 3–10). Although high affinity subjects achieved slightly lesser maximal heart rates at low altitude than did the normal subjects, at the higher altitude normal subjects manifested a small decrement in maximal heart rate, whereas high affinity subjects maintained their low altitude maximal rates (Table III).

Maximal oxygen consumption ($\dot{V}O_{2\,max}$). At low altitude, high affinity subjects achieved a lesser $\dot{V}O_{2\,max}$ than their sex-matched normal sibling (mean $\dot{V}O_{2\,max}$ of 43.0 and 34.9 ml/min per kg for normal and high affinity subjects, respectively) (Table III). These results represent the average of three low altitude determinations on each subject. At the higher altitude, four determinations were attempted on each subject. Although their inclusion in this analysis widens the differences between normal and high affinity subjects, the data obtained during the first two test periods were felt to be suspect due to a combination of factors: fatigue from travel (day 0), technical difficulties (day 1), and failures of $\dot{V}O_2$ to plateau (both days). Hence, the data reported herein represent the average of two determinations (days 2 and 4) on each subject, the only values of $\dot{V}O_{2\,max}$ felt to be valid. At altitude, normal subjects showed the expected decrement in $\dot{V}O_{2\,max}$ (23.2%), whereas high affinity subjects showed no decrement (Table III). These differences are statistically significant: normal subjects at high versus low altitude, $P < 0.01$; normal versus high affinity subjects at high altitude, $P < 0.01$.

TABLE II
*Erythropoietin Response to Altitude Exposure**

Subject	Sex	Urinary Ep excretion‡ (U/24 h±SEM)						Plasma Ep concentration§ (U/ml)						
		Low altitude	Days at high altitude					Low altitude	Days at high altitude					
			1–2	2–3	4–5	6–7	9–10		0	1	2	4	6	10
N1	M	3.4±0.3	3.8±0.5	6.4±0.4	9.2±0.3	6.8±0.5	7.9±0.3	ND	ND	0.05	0.10	0.25	0.15	0.15
N2	F	2.4±0.2	T	3.8±0.1	5.1±0.3	T	4.2±0.2	ND	ND	0.05	0.06	0.15	T	0.10
H1	M	4.3±0.2	4.1±0.3	5.9±0.2	5.1±0.3	4.9±0.2	5.7±0.3	ND	ND	ND	ND	0.05	ND	T
H2	F	3.2±0.3	4.8±0.5	4.3±0.3	4.6±0.4	4.3±0.5	4.6±0.4	ND	ND	ND	ND	0.05	ND	T

* ND, not detectable; T, toxic to mice.
‡ Base line (low altitude) urinary Ep excretion was determined on six consecutive 8-h collections. Normal 24-h excretion is 2.8±0.3 U for females and 3.5±0.3 U for males. 1–2 represents urine collection from 8 a.m. on day 1 through 8 a.m. on day 2.
§ Base line (low altitude) plasma Ep was determined on two separate days; normal = ND.

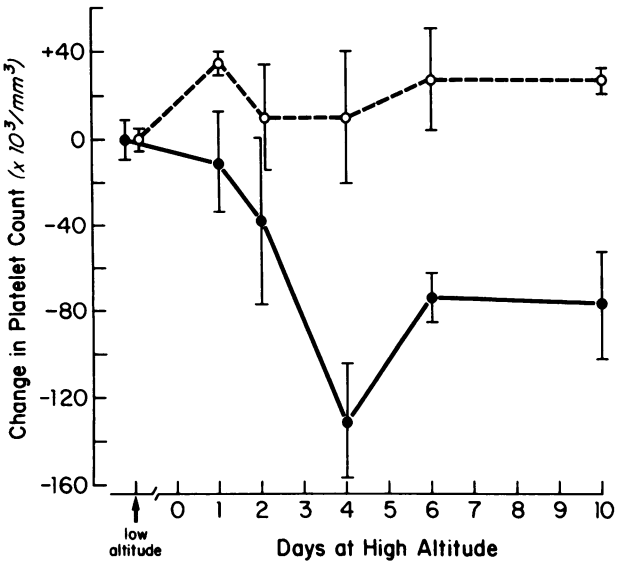

FIGURE 3 Effect of altitude exposure on platelet count. Normal subjects (●) developed thrombocytopenia at altitude (mean decrement of 131,000/mm³ on day 4), whereas high affinity subjects (○) did not. This decrement was statistically significant: normals at high versus low altitude ($P < 0.05$); normals versus high affinity subjects at high altitude ($P < 0.02$). Points represent mean increment or decrement ±1 SEM.

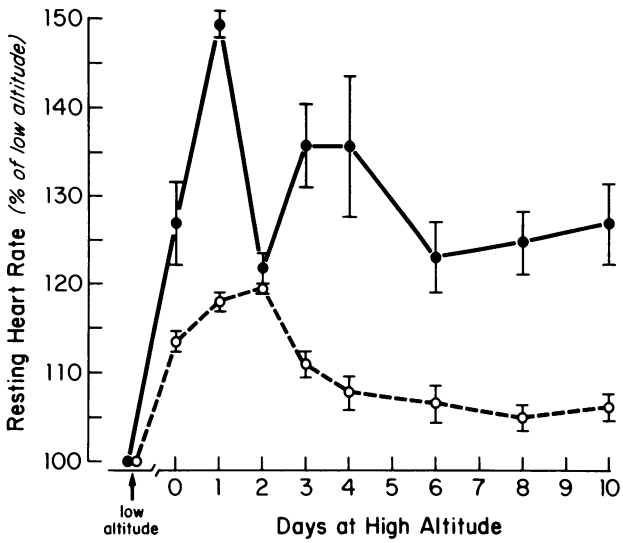

FIGURE 4 Resting heart rate at altitude. High affinity subjects (○) showed significantly lesser increments in resting heart rate at altitude than did normal subjects (●). Heart rate is expressed as percent of low altitude resting rate; points represent mean ±1 SEM.

DISCUSSION

To our knowledge, the investigations reported here represent the first direct attempt to test the hypothesis that a left-shifted ODC might be of adaptive benefit to humans at moderately high altitudes. The P_{50}s of our subjects (Table I) and the ambient P_{O_2} at Leadville (101 mm Hg) are such that the high affinity subjects manifested a calculated altitude-induced decrement in arterial oxygen saturation of < 1%, whereas the normal subjects desaturated to <90% (12). Because the physiologic impact of altitude-induced hypoxia lies in the arterial desaturation consequent to low ambient oxygen tensions, we anticipated that these high affinity subjects would show few of the normal physiologic responses to the stress of altitude exposure. In general, the results reported here tend to support this hypothesis.

We cannot, of course, totally exclude the possibility that our subjects with high oxygen affinity are preadapted to altitude by virtue of being slightly hypoxic even at sea level. The presence of a high oxygen affinity Hb confers a significant deficit in oxygen unloading, for which compensation must occur (17). Because the erythrocytosis of our high affinity subjects is

TABLE III
Maximal Oxygen Consumption ($\dot{V}O_{2_{max}}$) and Maximal Heart Rate at Low and High Altitudes

	Maximal oxygen consumption (ml/min/kg±1 SEM)		Maximal heart rate§ (beats/min)	
Subject	Low altitude*	High altitude‡	Low altitude	High altitude
N1	51.7±5.3	37.4±3.9	196	190
	43.0±4.6	32.6±3.3	194.5	188.5
N2	34.2±0.6	27.8±1.9	193	187
H1	44.1±2.9	44.7±3.1	189	190
	34.9±4.3	39.5±3.2	187	187.5
H2	25.7±1.3	34.4±0.7	185	185

* Mean of three determinations.
‡ Mean of two determinations.
§ Highest observed during exercise to fatigue.

not fully compensatory (12), the possibility of other, tissue-level adaptations (18) exists. There is, however, no reason to suspect that their erythrocytosis would provide a buffer against additional, altitude-induced hypoxia, because it is not fully compensatory even at low altitude (*vide infra*). Quite the contrary, there is reason to believe that individuals with high oxygen affinity are exquisitely sensitive to additional hypoxic stress, such as that induced by phlebotomy (19). It is, therefore, unlikely that the physiological adjustments made to compensate for chronic low altitude hypoxia in these individuals would be of any adaptive value upon exposure to the added hypoxic stress of high altitude.

Erythropoiesis and Ep. There was no difference between normal and high affinity subjects in increment of Hb concentration, hematocrit, or reticulocyte count at altitude. However, we consider these parameters to be poor indicators of erythropoietic activity stimulated by altitude exposure per se. We did not monitor changes in erythrocyte mass or plasma volume, and the latter may be markedly but variably influenced by an altitude-induced diuresis (20). Furthermore, the subjects were repeatedly bled during their stay at altitude.

Nevertheless, the increase in urinary Ep excretion at altitude was significantly greater for the normal subjects (Table II, Fig. 2B). Confirming this, in high affinity subjects plasma Ep rose above the (normal) undetectable range on only one day, and even then, the levels were only at the borderline of detection. In contrast, normal subjects manifested large increases in plasma Ep at altitude (Fig. 2C). The combined Ep data indicate that the Ep-producing tissues of high affinity subjects were not exposed to the same decrement in oxygen delivery at altitude as were those of the normal subjects.

Platelets. The marked decrements in platelet count observed in our normal subjects during altitude exposure (Fig. 3) were similar to those previously demonstrated in experimental animals exposed to simulated altitude. Although the precise mechanism thereof remains unclear, it is clearly one manifestation of altitude-induced hypoxia (21–24). Thrombocytopenia developed only in the normal subjects, it was unaccompanied by increased platelet size, and the nadir of platelet count was coincident with (i.e., did not follow) peak Ep response. This suggests that altitude-induced thrombocytopenia in humans is a direct consequence of deficient oxygen delivery to megakaryocytes and further supports the hypothesis that high affinity subjects suffered little decrement in oxygen delivery at altitude.

Heart rate. Altitude-induced resting tachycardia may derive in part from transient increases of sympathetic nervous activity and does not simply represent compensation for deficient oxygen delivery (4, 18). Nevertheless, the marked difference in this parameter between normal and high affinity subjects (Fig. 4) is yet another indication that the latter were less affected by altitude-induced hypoxia. Although seemingly insignificant, the small differences in maximal heart rate were consistently observed. Because maximal heart rate is directly proportional to maximal cardiac output at $\dot{V}O_{2\,max}$ (25, 26), this slight difference between subject pairs is consistent with the $\dot{V}O_{2\,max}$ data.

$\dot{V}O_{2\,max}$. $\dot{V}O_{2\,max}$ is regarded as a direct, reliable, and noninvasive measurement of overall oxygen delivery, reflecting both tissue oxygen utilization and ability to deliver oxygen (15, 16). Classically and most simply, it represents the product of the maximal cardiac output and the maximal A-V extraction of oxygen (16). The pathophysiology of the well-known decrement in $\dot{V}O_{2\,max}$ at altitude is not fully understood (4, 25, 27). It has been demonstrated that breathing oxygen at altitude does not fully restore either $\dot{V}O_{2\,max}$ or maximal cardiac output to sea-level values in altitude-acclimated humans (25, 28) and that the factors limiting $\dot{V}O_{2\,max}$ at low and high altitudes may be somewhat different (29). Because hyperventilation appears to be the major human adaptive response to altitude (18, 30), oxygen loading may be a crucial determinant of $\dot{V}O_{2\,max}$ at altitude. Compared with the numerous and potent homeostatic mechanisms available to facilitate oxygen unloading (increased Hb concentration and 2,3-DPG, Bohr and temperature effects, lowering of end-capillary P_{O_2}), pulmonary function is, in a sense, rather inflexible because it is so highly efficient to begin with. Under conditions of $\dot{V}O_{2\,max}$ at altitude, where the vast majority of total blood flow is diverted to tissues with high extraction requirements (16) and where oxygen loading is limited by low ambient oxygen tensions, the presence of a left-shifted ODC may become quite advantageous. This concept is expanded upon in Fig. 5.

To a great extent, the absolute values of $\dot{V}O_{2\,max}$ in our subjects (Table III) represent age, sex and training differences (16). Nevertheless, the $\dot{V}O_{2\,max}$ determinations seem to indicate a deficiency for high affinity subjects at low altitude, which is unlikely to have been due to hyperviscosity (31, 32). Rather, this low altitude $\dot{V}O_{2\,max}$ deficit appears to be a consequence of their diminished ability to unload oxygen at the tissue level (perhaps thereby limiting the maximal cardiac output, either through A-V node hypoxia or generally diminished myocardial oxygenation [26, 33]).

The failure of the high affinity subjects to manifest the "normal" decrement in $\dot{V}O_{2\,max}$ at altitude (Table III) appears to have been a direct benefit of the left-shifted ODC, which was probably protective insofar as it prevented the oxygen-loading deficit manifested by normal subjects at altitude and served to main-

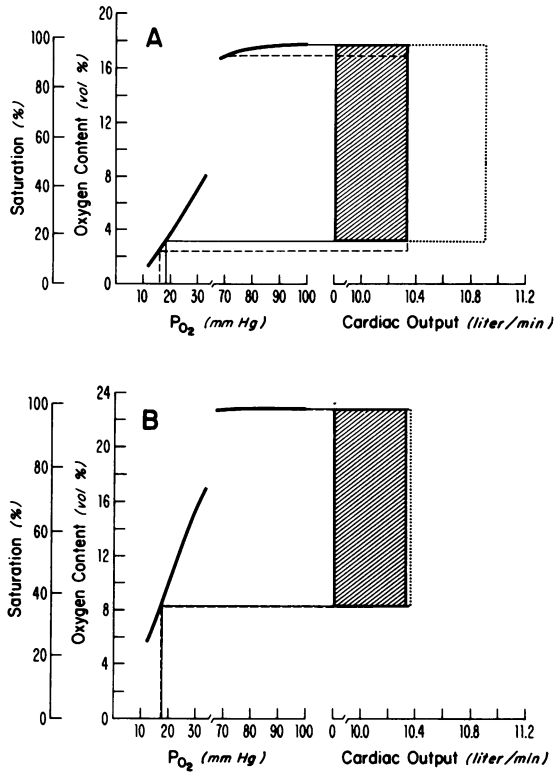

FIGURE 5 Ability to deliver oxygen as a function of altitude and oxygen affinity. The depicted ODCs were derived mathematically for hypothetical subjects similar to our subjects N2 and H2. Normal subject (A) with Hb 13.5 g/dl and P_{50} = 27.0 mm Hg; high affinity subject (B) with Hb 17.3 g/dl and P_{50} = 17.2 mm Hg. The curves attempt to illustrate the physiologic situation at $\dot{V}O_{2\,max}$ in a high extraction tissue bed and make the following assumptions: (*a*) normal Bohr effect with arterial pH 7.40 and end-capillary pH 7.10 (34); (*b*) an arterial-venous oxygen extraction of 14.5 vol.% (16, 33); (*c*) end-capillary P_{O_2} in the range of 16–18 mm Hg (33); (*d*) a required oxygen delivery of 1,500 ml/min, as indicated by the hatched box (which represents the product of 14.5 vol.% extraction (vertical dimension) and the cardiac output (horizontal dimension) required to yield the required 1,500 ml/min delivery). At low altitude (——) with Pa_{O_2} assumed to be 100 mm Hg, the normal subject (A) obtains the required oxygen delivery with an end-capillary P_{O_2} of 18.1 mm Hg and a cardiac output of 10.34 liters/min. In contrast, the high affinity subject (B) must function with an end-capillary P_{O_2} of 17.4 mm Hg to achieve the same delivery at the same cardiac output. At high altitude (– – –) with Pa_{O_2} assumed to be 70 mm Hg, the normal subject (A) must decrease end-capillary P_{O_2} to 16.1 mm Hg to obtain the required oxygen delivery at his low altitude cardiac output (10.34 liters/min); or he must increase cardiac output to 10.90 liters/min (extension of hatched box indicated by . . . .) to obtain the required delivery at his low altitude end-capillary P_{O_2} (18.1 mm Hg). In contrast, the high affinity subject (B) at altitude (– – –) must lower end-capillary P_{O_2} <0.1 mm Hg or increase cardiac output <0.1 liter/min to satisfy the same oxygen delivery requirements. Thus, although he is at a disadvantage at low altitude, the high affinity subject is at an apparent advantage at high altitude.

tain a greater functional oxygen-carrying capacity (Fig. 5).

The evidence presented suggests that subjects with high oxygen affinity hemoglobins are, in a sense, preadapted to altitude. By certain parameters (e.g., $\dot{V}O_{2\,max}$) the high affinity subjects are at a disadvantage at low altitude but fail to show the "normal" decrements at high altitude. Other parameters (Ep response, resting heart rate, and lack of altitude-induced thrombocytopenia) clearly support the advantage of high oxygen affinity at altitude. Thus, under conditions of hypoxic hypoxia, the maintenance of oxygen loading is of greater physiologic importance than the facilitation of unloading. Although our results do not directly address the relative advantage or disadvantage of small (i.e., 3–4 mm Hg) shifts in P_{50} at altitude, they do seem to indicate that a major left-shift of the ODC confers upon humans a larger degree of protection against the adverse effects of altitude exposure than does the normal small right-shift. We suggest that the normal human response to altitude (slightly decreased Hb oxygen affinity) is possibly maladaptive, reflecting man's lack of evolutionary experience in this oxygen-poor environment.

ACKNOWLEDGMENTS

We gratefully acknowledge the participation of the "G" family, without whose cooperation, patience, and steadfast good humor, this work could not have been done. We were aided by discussions with Dr. J. A. Faulkner and Dr. J. Haldane and by assistance from S. Sanders. We thank the staff of St. Vincent's Hospital in Leadville for allowing us to use their facilities.

This research was supported in major part by a grant from the University of Minnesota Graduate School; by National Institutes of Health grants HL 16833, IT32-HL07062, HL 70356, and HL 07009; National Cancer Institute grants CA 23021 and CA 18755; and the Veteran's Administration Research Fund.

REFERENCES

1. Aste-Salazar, H., and A. Hurtado. 1944. The affinity of hemoglobin for oxygen at sea level and at high altitudes. *Am. J. Physiol.* **142**: 733–743.
2. Lenfant, C., J. Torrance, E. English, C. A. Finch, C. Reynafarje, J. Ramos, and J. Faura. 1968. Effect of altitude on oxygen binding by hemoglobin and on organic phosphate levels. *J. Clin. Invest.* **47**: 2652–2656.
3. Eaton, J. W., G. J. Brewer, and R. F. Grover. 1969. The role of red cell 2,3-diphosphoglycerate in the adaptation of humans to altitude. *J. Lab. Clin. Med.* **73**: 603–609.
4. Frisancho, A. R. 1975. Functional adaptation to high altitude hypoxia. *Science (Wash. D. C.).* **187**: 313–319.
5. Wood, S. C., and K. Johansen. 1972. Adaptation to hypoxia by increased Hb02 affinity and decreased red cell ATP concentration. *Nat. New Biol.* **237**: 278–279.
6. Wood, S. C., K. Johansen, and R. E. Weber. 1975. Effects of ambient P_{02} on hemoglobin-oxygen affinity and red cell ATP concentrations in a benthic fish, Pleuronectes Platessa. *Respir. Physiol.* **25**: 259–267.

7. Finch, C. A., and C. Lenfant. 1972. Oxygen transport in man. *N. Engl. J. Med.* **286:** 407–415.
8. Eaton, J. W., T. D. Skelton, and E. Berger. 1974. Survival at extreme altitude: protective effect of increased hemoglobin oxygen affinity. *Science (Wash. D. C.).* **183:** 743–744.
9. Eaton, J. W. 1974. Oxygen affinity and environmental adaptation. *Ann. N. Y. Acad. Sci.* **241:** 491–497.
10. Turek, Z., F. Kreuzer, and L. J. C. Hoofd. 1973. Advantage or disadvantage of a decrease of blood oxygen affinity for tissue oxygen supply at hypoxia: a theoretical study comparing man and rat. *Pflügers Arch. Eur. J. Physiol.* **342:** 185–197.
11. Zak, S. J., B. Brimhall, R. T. Jones, and M. E. Kaplan. 1974. Hemoglobin Andrew-Minneapolis $\alpha_2^A\beta_2^{144\ lys\rightarrow asn}$: a new high-oxygen-affinity mutant human hemoglobin. *Blood.* **44:** 543–549.
12. Hebbel, R. P., R. S. Kronenberg, and J. W. Eaton. 1977. Hypoxic ventilatory response in subjects with normal and high oxygen affinity hemoglobins. *J. Clin. Invest.* **60:** 1211–1215.
13. Keitt, A. S. 1971. Reduced nicotinamide adenine dinucleotide linked analysis of 2,3-diphosphoglyceric acid: spectrophotometric and fluorometric procedures. *J. Lab. Clin. Med.* **77:** 470–475.
14. Zanjani, E. D., J. D. Lutton, R. Hoffman, and L. R. Wasserman. 1977. Erythroid colony formation by polycythemia vera bone marrow in vitro. *J. Clin. Invest.* **59:** 841–848.
15. Faulkner, J. A., G. J. Brewer, and J. W. Eaton. 1970. Adaptation of the red blood cell to muscular exercise. *In* Red Cell Metabolism and Function. G. J. Brewer, editor. Plenum Publishing Corp., New York. 213–227.
16. Rowell, L. B. 1974. Human cardiovascular adjustments to exercise and thermal stress. *Physiol. Rev.* **54:**75–159.
17. Adamson, J. W., and C. A. Finch. 1975. Hemoglobin function, oxygen affinity, and erythropoietin. *Annu. Rev. Physiol.* **37:** 351–369.
18. Lenfant, C., and K. Sullivan. 1971. Adaptation to high altitude. *N. Engl. J. Med.* **284:** 1298–1309.
19. Adamson, J. W., J. T. Parer, and G. Stamatoyannopoulos. 1969. Erythrocytosis associated with Hemoglobin Ranier: oxygen equilibria and marrow regulation. *J. Clin. Invest.* **48:** 1376–1386.
20. Heath, D., and D. R. Williams. 1977. Man at High Altitude: the Pathophysiology of Acclimatization and Adaptation. Churchill Livingstone, London.
21. Birks, J. W., L. W. Klassen, and C. W. Gurney. 1975. Hypoxia-induced thrombocytopenia in mice. *J. Lab. Clin. Med.* **86:** 230–238.
22. Gray, G. W., A. C. Bryan, M. H. Freedman, C. S. Houston, W. F. Lewis, D. M. McFadden, and G. Newell. 1975. Effect of altitude exposure on platelets. *J. Appl. Physiol.* **39:** 648–651.
23. Cooper, G. W., and B. Cooper. 1977. Relationships between blood platelet and erythrocyte function. *Life Sci.* **20:** 1571–1580.
24. Langdon, J. R., and T. P. McDonald. 1977. Effects of chronic hypoxia on platelet production in mice. *Exp. Hematol. (Oak Ridge).* **5:** 191–198.
25. Cerretelli, P. 1976. Limiting factors to oxygen transport on Mount Everest. *J. Appl. Physiol.* **40:** 658–667.
26. Pugh, L. G. C. E. 1964. Cardiac output in muscular exercise at 5800m (19,000 ft.). *J. Appl. Physiol.* **19:** 441–447.
27. Grover, R. F., J. T. Reeves, E. B. Grover, and J. E. Leathers. 1967. Muscular exercise in young men native to 3100 m altitude. *J. Appl. Physiol.* **22:** 555–564.
28. Pugh, L. G. C. E., M. B. Gill, S. Lahiri, J. S. Milledge, M. P. Ward, and J. B. West. 1964. Muscular exercise at great altitudes. *J. Appl. Physiol.* **19:** 431–440.
29. Clark, B. J., and R. F. Coburn. 1975. Mean myoglobin oxygen tension during exercise of maximal oxygen uptake. *J. Appl. Physiol.* **39:** 135–144.
30. Torrance, J. D., C. Lenfant, J. Cruz, and E. Marticorena. 1970/71. Oxygen transport mechanisms in residents at high altitude. *Respir. Physiol.* **11:** 1–15.
31. Ekblom, B., A. N. Goldbarg, and B. Gullbring. 1972. Response to exercise after blood loss and reinfusion. *J. Appl. Physiol.* **33:** 175–180.
32. Thorling, E. B., and A. J. Erslev. 1968. The "tissue" tension of oxygen and its relation to hematocrit and erythropoiesis. *Blood.* **31:** 332–343.
33. Grover, R. F., and J. K. Alexander. 1971/72. Cardiac performance and the coronary circulation of man in chronic hypoxia. *Cardiology.* **56:** 197–206.
34. Hermansen, L., and J-B. Osnes. 1972. Blood and muscle pH after maximal exercise in man. *J. Appl. Physiol.* **32:** 304–308.