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Research Article

Once ventilatory acclimatization begins in sea level residents sojourning at high altitude, abrupt restoration of normal oxygen tensions will not restore ventilation to normal. We have investigated the role of cerebrospinal fluid (CSF) [H^+] in this sustained hyperventilation by measuring CSF acid-base status in seven men (lumbar) and five ponies (cisternal) in normoxia, first at sea level and then periodically over 13-24 h of "deacclimatization" after 3-5 d in hypoxia (P_B = 440 mm Hg). After 1 h deacclimatization, hyperventilation continued at a level only slightly less than that obtained in chronic hypoxia (+1–2 mm Hg Pa_{CO_2}), whereas CSF pH was either equal (in man) or alkaline (in pony, +0.02, $P < 0.01$) to sea level values. Between 1 and 12-13 h deacclimatization in all humans and ponies Va fell progressively (Pa_{CO_2} increased 4-7 mm Hg) and CSF pH became increasingly more acid (–0.02 to –0.05, $P < 0.01$). Between 12 and 24 h of normoxic deacclimatization in ponies, Pa_{CO_2} rose further toward normal, coincident with an increasing acidity in CSF (–0.02 pH). Similar negative correlations were found between changes in arterial pH and Va throughout normoxic deacclimatization. We conclude that [H^+] in the lumbar or cisternal CSF is not the mediator of the continued hyperventilation and its gradual dissipation with time during normoxic deacclimatization from chronic hypoxia. These negative […]

Role of Cerebrospinal Fluid [H^+] in Ventilatory Deacclimatization from Chronic Hypoxia

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ABSTRACT Once ventilatory acclimatization begins in sea level residents sojourning at high altitude, abrupt restoration of normal oxygen tensions will not restore ventilation to normal. We have investigated the role of cerebrospinal fluid (CSF) [H^+] in this sustained hyperventilation by measuring CSF acid-base status in seven men (lumbar) and five ponies (cisternal) in normoxia, first at sea level and then periodically over 13–24 h of "deacclimatization" after 3–5 d in hypoxia (P_B = 440 mm Hg). After 1 h deacclimatization, hyperventilation continued at a level only slightly less than that obtained in chronic hypoxia (+1–2 mm Hg $P_{A_{CO_2}}$), whereas CSF pH was either equal (in man) or alkaline (in pony, +0.02, $P < 0.01$) to sea level values. Between 1 and 12–13 h deacclimatization in all humans and ponies $\dot{V}_A$ fell progressively ($P_{A_{CO_2}}$ increased 4–7 mm Hg) and CSF pH became increasingly more acid (−0.02 to −0.05, $P < 0.01$). Between 12 and 24 h of normoxic deacclimatization in ponies, $P_{A_{CO_2}}$ rose further toward normal, coincident with an increasing acidity in CSF (−0.02 pH). Similar negative correlations were found between changes in arterial pH and $\dot{V}_A$ throughout normoxic deacclimatization. We conclude that [H^+] in the lumbar or cisternal CSF is not the mediator of the continued hyperventilation and its gradual dissipation with time during normoxic deacclimatization from chronic hypoxia. These negative relationships of $\dot{V}_A$ to CSF [H^+] in normoxia are analogous to those previously shown during acclimatization to hypoxia.

INTRODUCTION

Upon acute exposure to hypoxia, ventilation increases abruptly and then, with continued hypoxic exposure, gradually increases further over 1–2 wk. With acute exposure to normoxia in the acclimatized sojourner at high altitudes, hyperventilation persists and is only slowly reduced to normal with further time in normoxia (1). The mediation of these time-dependent processes of ventilatory acclimatization to and deacclimatization from chronic hypoxia remain controversial. Crawford et al. (2, 3) claim they are both accounted for by the usual measurable chemical stimuli in arterial blood and cerebrospinal fluid (CSF).[1] Specifically, they attribute the ventilatory changes to small changes in CSF pH acting at the level of the intracranial chemoreceptors—such that CSF pH decreases as ventilation rises with time in hypoxia and moves to the acid side of normal as hyperventilation persists with acute normoxia in the acclimatized sojourner. Our own data obtained during acclimatization points to a completely different conclusion. We found that an increasing ventilation with time at high altitudes was not positively correlated with accompanying changes in CSF or plasma acid-base status or P_{O_2} (4–8).

This study tests the proposed role for CSF pH as a mediator of the continued hyperventilation that occurs when the hypoxic stimulus is removed from the acclimatized sojourner at high altitude. This hypothesis was examined in humans and ponies acclimatized to high altitude by asking two specific questions: (*a*) Does an acid CSF pH accompany the hyperventilation that continues during the 1st h of acute normoxia? and (*b*) Are ventilation and CSF [H^+] positively correlated as ventilation slowly decreases over the time-course of deacclimatization in normoxia?

METHODS

This study was designed for measurements during three conditions: (*a*) at sea level under normal oxygen conditions

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[1] *Abbreviation used in this paper*: CSF, cerebrospinal fluid.

(chronic normoxia); (*b*) during 3–5 d of chronic exposure to a hypoxic environment (altitude sojourn); and (*c*) during the initial 24 h of normal oxygen conditions after altitude sojourn (acute normoxia). The same seven humans and five ponies were studied during all three conditions. Arterial blood and CSF gas tensions, acid-base status, and electrolyte concentrations, pulmonary ventilation, and metabolic rate were the major variables measured.

Studies on humans. The seven humans were all sea level adult males in excellent health and familiar with the required procedures of the study, but only two were aware of the study's objective. Measurements during chronic normoxia were made in Madison, Wis. (P_B = 740 mm Hg) either before or 2 mo after sojourn at altitude. Altitude sojourn consisted of 3–5 d stay at 4,300 m altitude (Mt. Evans, Colo., P_B = 440 mm Hg). On the final day at 4,300 m altitude, acute normoxia was initiated by appropriate flow of 100% O_2 through a nasal delivery system. Subjects were then transported for 0.5 h to more suitable laboratory conditions located at 3,200 m altitude (Echo Lake, Colo.). Acute normoxia was sustained uninterrupted for the subsequent 24.5 h.

Blood was sampled from an indwelling brachial artery catheter: (*a*) three to six times over the final 2 h of altitude sojourn; (*b*) at 15–20-min intervals over the 1st h of acute normoxia; and (*c*) hourly over the subsequent 10–12 h of normoxia. This procedure permitted precise adjustment of nasal O_2 flow to maintain Pa_{O_2} near normal sea level values (95–105 mm Hg). During chronic normoxia (at 250 m) blood was sampled once from the brachial artery via needle puncture. All other blood sampling was from an indwelling catheter in a dorsal hand vein heated to 41°C. The close agreement of arterialized with brachial arterial blood acid-base status has been reported (9).

Expired ventilation ($\dot{V}_E$), O_2 consumption ($\dot{V}_{O_2}$), and CO_2 production ($\dot{V}_{CO_2}$) were measured at 250 m ($P_IO_2 \cong 150$ mm Hg), during the final 2 h at 4,3000 m ($P_IO_2 \cong 85$ mm Hg) and after 1, 6, and 12 h acute normoxia ($P_IO_2 \cong 150$ mm Hg). Subjects were attached to a noseclip and breathing valve, timed expired ventilation was collected in neoprene bags and their volume measured with a calibrated volume meter and expired gas contents were analyzed chromatographically (QuinTron Instrument Co., Milwaukee, Wis.).

Procedures for obtaining simultaneous anaerobic samples of arterial blood and lumbar CSF during a relative steady state for ventilation and arterial acid-base status have been described in detail (4). Lumbar CSF was sampled during chronic normoxia and after 1 and 13 h of acute normoxia.

Studies on ponies. Five healthy female ponies, of mixed breed, were purchased from farms in the vicinity of Madison, Wis. The ponies were studied on 2–4 d during chronic normoxia before altitude sojourn. They were then placed in a hypo/hyperbaric chamber (Ft. Collins, Colo.) for a total of 85 h exposure to P_B = 740 or 440 mm Hg, in the following sequence: (*a*) 36 h at 440 mm Hg; (*b*) 1 h at 740 mm Hg; (*c*) 24 h at 440 mm Hg; and (*d*) 24 h at 740 mm Hg. This protocol permitted repeated study in the hypoxic acclimatized state, twice after 1 h of acute normoxia, and then repeatedly over 25 h of acute normoxia.

The specifics of procedures on ponies have been published in detail (7, 8, 10). At least 24 h before each study, a Teflon aortic catheter was placed percutaneously in the descending aorta for arterial blood sampling using local anesthesia (lidocaine HCl) and aseptic technique (10). These catheters were in place throughout the 85 h in the pressure chamber. CSF was sampled from the cisterna magna after local anesthesia (lidocaine HCl) of the skin and subcutaneous tissue over the cisterna magna. Sampling was through a 7.5-cm 20-gauge needle inserted into the cistern. For measurement of ventilation and metabolic rate, a muzzle mask and breathing valve (dead space = 150–250 ml) were taped securely in place over the nose and mouth of the pony. $\dot{V}_E$ was measured using a 120-liter respirometer (Warren E. Collins, Inc., Braintree, Mass.) and mixed expired O_2 and CO_2 were analyzed chromatographically.

On each of 4 d during chronic normoxia, after 36 h of hypoxia, and after 1, 6, 12, and 24 h of acute normoxia, measurements were made in the following sequence: (*a*) 2–4 blood samples to establish steady-state conditions; (*b*) simultaneous sampling of blood and CSF; and (*c*) simultaneous sampling of blood and collection of expired air. Arterial blood was also sampled after 60 h of hypoxia, at 15-min intervals during the 1st h of acute normoxia and hourly over the subsequent 13 h of normoxia.

Analyses and calculations. Details of our analysis techniques have been published (4). Plasma and CSF gas tensions and pH were measured with the Radiometer system (The London Co., Cleveland, Ohio). P_{O_2} and P_{CO_2} microelectrodes were calibrated with humidified gases of known P_{O_2} and P_{CO_2}, and the appropriate fluid (human or pony blood or mock CSF) tonometered with the known gas mixtures. The pH electrode was calibrated with standard buffers and with mock CSF of known P_{CO_2} (by tonometry), known $[HCO_3^-]$ (by manometric analysis of C_{CO_2}) and thus known pH. Analysis of CSF was completed within 5 min of withdrawal and blood analysis was completed within 30 min of withdrawal. Human lumbar CSF samples were also analyzed manometrically for C_{CO_2}. Hence, all values for CSF P_{CO_2}, and pH and $[HCO_3^-]$ represent average values obtained from the manometric and electrode measurements (with appropriate calculations). No systematic difference and random variation of ±3% were found between these methods of determining CSF acid-base status. Plasma and CSF $[Cl^-]$ were analyzed with an automatic chloride titrator, and $[Na^+]$ and $[K^+]$ were determined by flame photometry. Lactic acid in plasma and CSF was measured by a modified Barker and Summerson (11) method.

Plasma and CSF $[HCO_3^-]$, $\dot{V}_A$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and R were calculated using appropriate formulas and constants for each species. Ventilatory and metabolic variables of ponies were expressed as units per square meter of body surface area (body surface area in m^2 = 10.5 × weight in grams, 0.67/10,000) (12). Statistical differences between means were determined by combining analysis of variance over all conditions and the Student's *t* test for paired comparisons.

RESULTS

Chronic normoxia and altitude sojourn. Values obtained during these two conditions are shown in Table I and Fig. 1. These data are consistent with previous findings on both species (4, 6–8). Ventilatory acclimatization of ponies to this degree of hypoxia is fully achieved within 12–18 h; hence, their 10–13 mm Hg reduction of $P_{A_{CO_2}}$ observed after 36 h was maintained at 60 h of hypoxia. It is important to note that CSF pH was, relative to chronic normoxia, 0.04 alkaline in pony after 36 h hypoxia. Ventilatory acclimatization of man to 4,300 m altitude is more gradual over the first 2 wk of sojourn. In this study, $P_{A_{CO_2}}$ fell with time to 31 mm Hg after 4 d at 4,300 m and this was accompanied by a significantly alkaline shift in pH_a (Fig. 1). Judging from present and past data (6),

TABLE I

Mean and SEM of Blood and Cerebrospinal Fluid Parameters in Man (n = 7)

Conditions	Blood								Cerebrospinal fluid						
	P_{O_2}	P_{CO_2}	pH	HCO_3^-	Lactate	K^+	Na^+	Cl^-	P_{CO_2}	pH	HCO_3^-	Lactate	K^+	Na^+	Cl^-
	mm Hg				*mM/liter*				*mm Hg*			*mM/liter*			
Chronic normoxia	95.0	39.4	7.417	25.1	1.4	4.0	143.2	104.9	50.8	7.317	24.8	2.0	3.3	145.0	123.2
(CN)	1.4	0.4	.001	0.2	0.1	0.2	1.0	1.6	0.7	.004	0.2	0.1	0.1	1.0	0.9
1 H acute normoxia	98.0	32.0	7.435	21.3	1.8	4.5	140.7	109.2	41.4	7.319	20.2	2.2	3.4	138.0	120.9
(1 h AN)	1.7	0.7	.005	0.3	0.1	0.1	1.7	1.2	0.9	.006	0.4	0.2	0.2	4.0	3.6
12–13 h acute normoxia	99.0	35.5	7.413	22.5		4.3	140.3	107.5	46.5	7.292	21.3	2.0	3.9	143.5	127.3
(13 h AN)	2.2	0.5	.006	0.2		0.1	2.0	1.5	0.5	.004	0.3	0.2	0.2	1.2	0.8

P values for differences between means: CN vs. 1 h AN: PA_{CO_2}, CSF P_{CO_2} and $[HCO_3^-] = P < 0.001$; $pH_a = P < 0.02$; CN vs. 13 h AN: PA_{CO_2}, $[HCO_3^-]_a$, CSF $[HCO_3^-] = P < 0.001$; CSF P_{CO_2} and pH = $P < 0.01$: 1 h AN vs. 13 h AN: PA_{CO_2}, CSF P_{CO_2} and pH = $P < 0.001$; pH_a, $[HCO_3^-]_a$ and CSF $[HCO_3^-]_a = P < 0.01$.

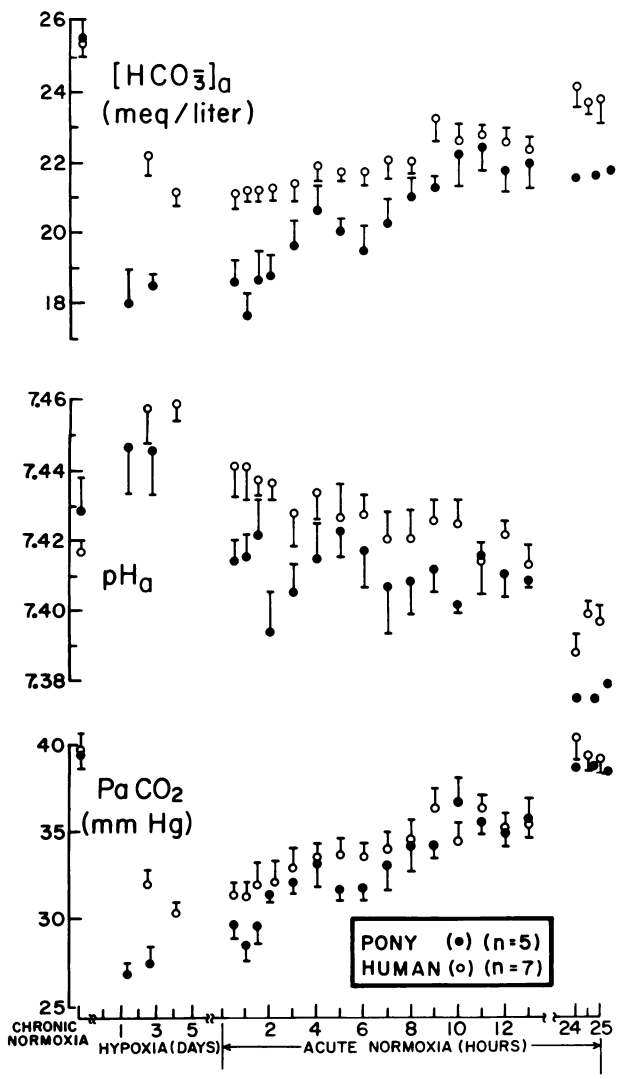

FIGURE 1 Arterial acid-base status (mean±SEM) in man and pony during normal sea level conditions (chronic normoxia), during 3–5 d at 4,300 m altitude (hypoxia), and during the initial 25 h after hypoxia (acute normoxia).

we estimate acclimatization in man was 40–50% complete before initiation of acute normoxia.

Ventilatory deacclimatization from altitude sojourn. Changes in PA_{CO_2} are used to characterize the temporal pattern of ventilatory deacclimatization over the first 24 h in normoxia after acclimatization to 4,300 m (Fig. 1). Over the first 13 h of normoxia in both species, there appear to be three periods in which PA_{CO_2} is increasing toward normal, interspersed by periods of relative stability. By the 30th min, PA_{CO_2} had increased 2.1 mm Hg in ponies and 1.3 mm Hg in man. After relative stability between 0.5 and 1.5 h, PA_{CO_2} increased gradually until between the 11th and 13th h in both species. The total change of PA_{CO_2} over the first 13 h of acute normoxia was 7.6 mm Hg in pony and 4.9 mm Hg in man. After 24 h of acute normoxia, PA_{CO_2} had returned to normal in man, but in the three ponies studied at 24 h, PA_{CO_2} was 3 mm Hg above normal in 1 and 3 mm Hg below normal in the other two.

Less frequent measurements of $\dot{V}E$, $\dot{V}CO_2$, and $\dot{V}O_2$ showed that changes in $\dot{V}A/\dot{V}CO_2$ followed those in PA_{CO_2} in a predictable fashion. These mean changes are detailed in Table II for ponies. In humans, resting $\dot{V}CO_2$ and $\dot{V}O_2$ remained unchanged during acclimatization and deacclimatization. Mean $\dot{V}A$ was 5.25±0.3 liter/min at 250 m normoxia and showed significant increases after 3 d in hypoxia (+29%) and after 1 h (+25%) and 12 h (+14%) of deacclimatization in normoxia.

These data characterize ventilatory deacclimatization from chronic hypoxia as follows: (*a*) gradual and substantial in both species over the first 13 h; (*b*) greater in pony than in man over the first 13 h; and (*c*) complete restoration of PA_{CO_2} in man by the 24th h.

Arterial acid-base and electrolytes during deacclimatization. Arterial pH and $[HCO_3^-]$ differed considerably between the two species during deacclimatization (Fig. 1). In man, pH_a was significantly alkaline relative to chronic normoxia during the first 10 h of deacclimatization, and then between 10 and 24 h it was either the same or acid relative to chronic normoxia.

TABLE II

Mean and SEM of Ventilatory and Metabolic Parameters in Pony (n = 5)

Conditions	$\dot{V}_E$	$\dot{V}_A$	f	$\dot{V}_T$	$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	R	$\dot{V}_A/\dot{V}_{CO_2}$
	liter/m²				*liter/m²*			
Chronic normoxia	8.39	3.16	18.7	0.458	0.169	0.144	0.84	22.2
(CN)	0.9	0.2	2.8	0.051	0.008	0.010	0.03	0.7
36 h hypoxia	11.49	5.49	17.3	0.690	0.163	0.147	0.93	37.4
(H)	0.67	0.36	1.8	0.037	0.02	0.007	0.06	1.2
Acute normoxia	8.50	4.88	11.6	0.755	0.160	0.146	0.92	33.6
(AN) 1 h	0.4	0.8	1.0	0.035	0.04	0.009	0.02	0.7
Acute normoxia	7.22	4.23	10.8	0.674	0.142	0.142	1.0	29.8
(AN) 6 h	0.3	0.8	0.6	0.048	0.07	0.04	0.20	1.0
Acute normoxia	8.19	4.96	10.6	0.755	0.177	0.177	1.0	28.0
(AN) 12–13 h	0.6	0.5	0.6	0.037	0.009	0.01	0.01	1.1
Acute normoxia	7.13	3.99	8.3	0.843	0.155	0.152	0.98	25.9
(AN) 24–25 h								

P values for differences between means: CN vs. 36 h H: $\dot{V}_E$, $\dot{V}_A$, $\dot{V}_T$, $\dot{V}_A/\dot{V}_{CO_2} = P < 0.01$; 36 h H vs. AN, 1 h: $\dot{V}_E$, $f = P < 0.005$; AN, 1 h vs. AN, 6 h: $\dot{V}_A$, $\dot{V}_{O_2}$, R, $\dot{V}_A/\dot{V}_{CO_2} = P < 0.01$; AN, 1 h vs. AN, 12 h: R and $\dot{V}_A/\dot{V}_{CO_2} - P < 0.005$; CN vs. AN, 12 h: $\dot{V}_{O_2}$ and $\dot{V}_{CO_2} = P < 0.01$.

In pony, pH_a was acidic throughout most of the period of deacclimatization. pH_a also tended to fluctuate more in pony than in man, which reflected differences in the temporal pattern of $[HCO_3^-]$ change. In man $[HCO_3^-]_a$ increased in a rather gradual fashion, 3 meq/liter over the 24 h, whereas in pony nearly the same total change was characterized by greater hour-to-hour variability. At 24 h of deacclimatization, arterial $[HCO_3^-]$ remained 1 (man) to 3 (pony) meq/liter below chronic normoxia. In both species, plasma lactate concentration and serum $[Na^+]$, $[Cl^-]$, and $[K^+]$ were the same over all conditions that measurements were made (Tables I and III).

CSF acid-base and electrolytes during deacclimatization. After 1 h of acute normoxia, lumbar CSF pH in man did not differ from chronic normoxia, whereas in pony cisternal CSF pH was significantly alkaline relative to chronic normoxia (Fig. 2; Tables I and III). In both species, CSF pH decreased as deacclimatization proceeded. Lumbar CSF pH decreased in all human subjects (−0.02 to −0.05) and, on the average, fell from a normal value at 1 h acute normoxia to a significant

TABLE III

Mean and SEM of Blood and Cerebrospinal Fluid Parameters in Pony (n = 5)

Conditions	Blood									Cerebrospinal fluid						
	P_{O_2}	P_{CO_2}	pH	HCO_3^-	Lactate	K^+	Na^+	Cl^-	Hc't	P_{CO_2}	pH	HCO_3^-	Lactate	K^+	Na^+	Cl^-
	mm Hg			*mM/liter*						*mm Hg*		*mM/liter*				
Chronic normoxia	88.1	39.4	7.429	25.5	2.0	—	—	—	24.7	46.6	7.331	23.2	2.8	—	—	—
(CN)	1.6	1.1	.010	0.5	0.2	—	—	—	2.1	1.0	.004	0.4	0.2	—	—	—
36 h hypoxia	48.8	26.9	7.447	18.0	2.9	4.1	135.6	101.6	29.4	35.0	7.370	19.1	3.5	3.4	137.4	117.0
(H)	2.0	0.9	.013	1.0	0.9	0.2	0.9	0.9	2.1	0.3	.002	0.2	0.4	0.3	4.1	4.0
60 h hypoxia	47.3	27.6	7.447	18.6	—	—	—	—	—	—	—	—	—	—	—	—
(H)	1.2	0.9	.01	0.2	—	—	—	—	—	—	—	—	—	—	—	—
Acute normoxia	101.0	27.7	7.432	18.0	2.5	4.3	135.0	102.1	—	36.4	7.341	18.5	3.2	4.4	135.5	116.0
(AN) 1 h (*a*)*	2.3	1.2	.012	0.9	0.3	0.3	1.3	0.8	—	0.9	.006	0.6	0.3	1.1	10.4	10.0
Acute normoxia	98.3	28.2	7.411	17.4	2.8	4.1	135.3	100.2	30.0	37.4	7.350	19.5	3.0	—	—	—
(AN) 1 h (*b*)*	6.0	0.9	.014	0.9	0.4	0.3	0.8	1.4	0.9	1.1	.007	0.5	0.2	—	—	—
Acute normoxia	97.7	31.7	7.418	20.1	2.1	4.2	133.0	99.2	27.3	40.6	7.344	20.9	3.0	3.4	134.9	114.0
(AN) 6 h	2.6	1.0	.011	0.7	0.3	0.2	1.1	1.1	1.1	0.6	.007	0.5	0.2	0.2	6.5	6.0
Acute normoxia	95.9	35.1	7.411	21.9	2.0	4.5	134.1	99.6	—	42.6	7.322	20.8	3.0	3.1	142.9	121.3
(AN) 12 h	0.7	0.8	.007	1.0	0.2	0.1	1.5	1.2	—	0.6	.007	0.4	0.7	0.2	2.4	3.0

*Ponies were studied after 1 h of acute normoxia after 36 h [AN − 1 h (*a*)] and again after 60 h [AN − 1 h (*b*)] of hypoxia at 4,300 m.

P values for differences between means: CN vs. 36 h H: Blood P_{O_2}, P_{CO_2}, $HCO_3^- = P < 0.004$; CSF P_{CO_2}, pH, $HCO_3^- = P < 0.002$; 36 h H and 60 h H vs. AN, 1 h (*a*): CSF pH $= P < 0.01$; CN vs. AN, 1 h: Blood P_{O_2}, P_{CO_2} and $HCO_3^- = P < 0.004$; CSF P_{CO_2}, pH, $HCO_3^- = P < 0.04$; AN, 1 h (*b*) vs. 6 h AN: blood and CSF $HCO_3^- = P < 0.004$ and < 0.03; AN, 1 h (*b*) vs. AN, 12 h: blood P_{CO_2} and $HCO_3^- = P < 0.001$ and < 0.02; CSF P_{CO_2}, pH and $HCO_3^- = P < 0.01$; AN, 6 h vs. AN, 12 h: $PA_{CO_2} = P < 0.003$; CSF P_{CO_2} and pH $= P < 0.04$ and < 0.001.

0.027 acidosis at 13 h of normoxia ($P < 0.01$). In pony, cisternal CSF pH decreased from the alkalinity observed at 1 and 6 h to normal control levels at 13 h normoxia. In both species, CSF [HCO_3^-] increased ≅1 meq/liter between 1 and 13 h, but it remained 2–3.5 meq/liter below chronic normoxia at 13 h of deacclimatization. Lactate concentration in CSF did not differ from chronic normoxia in either species during deacclimatization (Tables I and III). In pony, [K^+], [Na^+], and [Cl^-] in CSF were the same after 36 h of sojourn and over each measurement period during deacclimatization (Table III). In man, CSF electrolytes did not differ from chronic normoxia after 1 and 13 h deacclimatization (Table I).

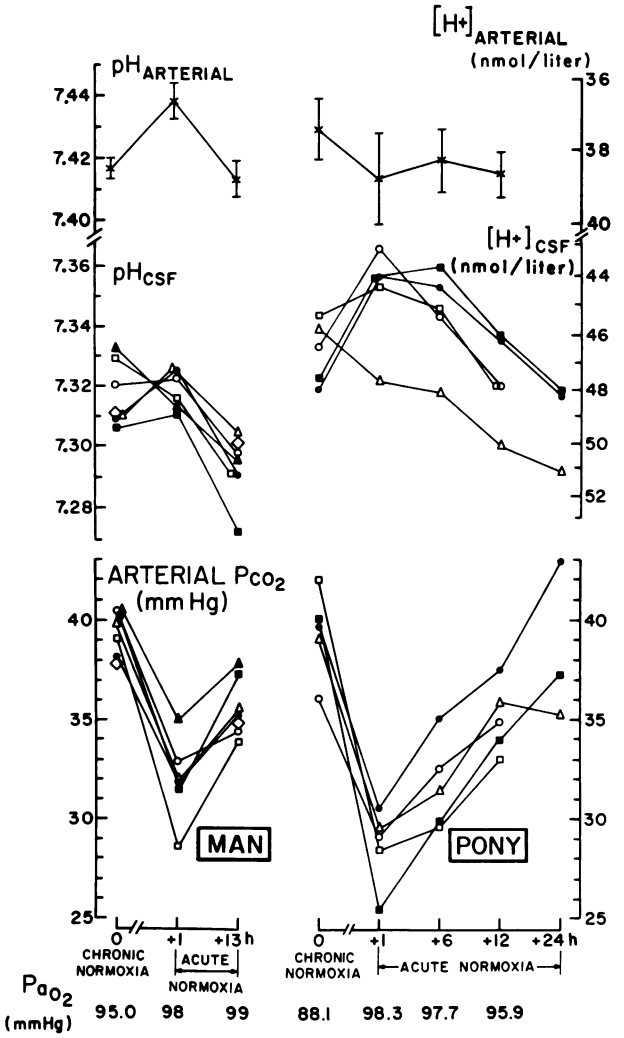

FIGURE 2 Status of arterial and CSF chemical stimuli to ventilation during normal sea level conditions (chronic normoxia) and at various times during the initial 24 h of normal oxygen conditions (acute normoxia) after 3–5 d sojourn at 4,300 m altitude. The individual man and pony data are plotted for $P_{A_{CO_2}}$ and CSF pH. The means (±SEM) are plotted for pH_a and mean values are listed for P_{aO_2}.

DISCUSSION

To our knowledge, this study provides unique information on the temporal pattern of ventilatory changes during the first 24 h of normoxia after sojourn at high altitude. In both man and pony, the slight decrease in ventilation and 1–2 mm Hg rise in $P_{A_{CO_2}}$ observed from ambient hypoxia to the initial 30–60 min of normoxia (Fig. 1) are consistent with findings by many previous investigators (1–3, 13, 14). As normoxia was continued, ventilation gradually fell further in both species, until at +13 h posthypoxia, $P_{A_{CO_2}}$ had risen (+5 to 8 mm Hg) to within ≅4 mm Hg of normal and at 24 h had returned to normal control values in humans and was within 2–3 mm Hg of normal in ponies. Although these data suggest that ventilatory deacclimatization from chronic hypoxia in humans may be complete within 1 d, we emphasize that our subjects spent only 3–5 d at 4,300 m and experienced a level of ventilatory acclimatization that was <50% complete by this time. When acclimatization is completed in humans after longer sojourns at high altitudes, there is ample evidence to indicate that the process of ventilatory deacclimatization is more gradual and is not completed for at least 3 and as much as 7 d of continuous normoxia (15–19). Our finding (Fig. 1) that compensatory increases in plasma [HCO_3^-] were still not complete in either species, suggests that all aspects of the deacclimatization process are not completed within 24 h normoxia, after even a relatively brief sojourn at high altitude.

This study assessed the role of measurable chemical stimuli in the arterial blood and CSF as mediators of ventilatory deacclimatization from chronic hypoxia. Two types of findings suggest that this deacclimatization process is not mediated by changes in CSF [H^+].

First, after 1 h of acute normoxia we found that lumbar CSF pH was not different from sea level control values in six humans who continued to hyperventilate (Fig. 2). Individually, two subjects showed measurable acid shifts in CSF pH, two showed alkaline shifts, and two showed no change at this 1 h period. These data are similar to those of Crawford and Severinghaus (2) obtained in four humans after 45 min of acute normoxia at 3,810 m. In ponies after 1 h of acute normoxia, four of five showed an alkaline shift in cisternal CSF pH relative to chronic sea level values (Fig. 2). This alkalinity in cisternal CSF pH agrees with that reported in humans by Weiskopf et al. (14) who estimated, from measured changes in jugular venous P_{CO_2}, that 20 min of acute hyperoxia after 5 d at 4,300 m would leave "intracranial" CSF pH alkaline to sea level control values. Finally, our data are also consistent with the lack of positive correlation reported between CSF pH

and the spontaneous hyperventilation that persisted after 26 h of voluntary hyperventilation in normoxia and hypoxia (20).

Second, our data obtained over the remaining 13 (humans) to 24 (ponies) h of deacclimatization in normoxia showed that alveolar ventilation was gradually declining coincident with either an unchanging or increasing acidity in CSF pH (Fig. 2). Between 1 and 13 h of acute normoxia all human subjects showed a measurable reduction in CSF pH (−0.02 to −0.05 U), whereas $\dot{V}_A$ gradually fell and $P_{A_{CO_2}}$ rose. In pony, $P_{A_{CO_2}}$ also rose gradually over the 24-h measurement period of deacclimatization as cisternal CSF pH showed either no systematic change between 1 and 6 h or a consistent fall in all ponies studied between 6 and 12 h and 12–24 h of normoxia. We are not aware of other studies that have investigated changes in CSF [H^+] over the time-course of ventilatory deacclimatization from chronic hypoxia. However, these data are analogous to those obtained in nonhuman species (such as dog, pony, goat, and cat) who show a decline in ventilation and rising $P_{A_{CO_2}}$—while still hypoxic—after a few days to weeks of sojourn at high altitude (8, 21–23). In this condition of continued hypoxia, as in the acute normoxia studies reported here, the gradually declining ventilation in pony and dog coincides with rising acidity in CSF and plasma (8, 21).

In summary, our present data and that previously outlined by ourselves and others are consistent in showing no positive correlation and most often even a negative correlation of changes in CSF [H^+] with those in alveolar ventilation during deacclimatization from high altitude. This conclusion holds whether awake humans or ponies were studied, whether lumbar or cisternal CSF was sampled, or whether the measured CSF [H^+] was unchanging, rising, or falling during the deacclimatization period. Similar negative correlations are also available during acclimatization to hypoxia, in which the time-dependent increase in alveolar ventilation is accompanied by significant increases in alkalinity in lumbar and especially cisternal CSF (4, 8, 21).

It is relevant to note that changes in P_{O_2} and(or) pH in arterial blood also do not correlate positively with ventilation during deacclimatization from chronic hypoxia. Both P_{aO_2} and pH_a in ponies and pH_a in humans decreased as ventilation decreased during deacclimatization (Fig. 2). Conversely, during acclimatization from acute to chronic hypoxia, pH_a and especially P_{aO_2} increase as ventilation increases (2, 4, 6–8). If the view is taken that the combination of measurable chemical stimuli in blood and(or) CSF must mediate these ventilatory changes (2), then CSF pH must change significantly and in the opposite direction to that most often observed in order to offset the opposing inhibition or augmentation to breathe presented by the changing arterial P_{O_2} or pH. We propose that all three potential chemical stimuli—in arterial blood and CSF—appear as functions rather than determinants of the accompanying ventilatory acclimatization in hypoxia or deacclimatization in normoxia.

Our findings that measurable pH changes are not mediators of ventilatory acclimatization or deacclimatization do not preclude a role for pH acting at some cerebral site other than that measurable in the large cavity CSF (24, 25). Recent findings in short- and long-term hypoxia show that brain intracellular pH in dogs (26) and interstitial fluid pH in goats (27) are acid to sea level control (primarily because of an increased brain tissue lactic acid production) at a time when bulk CSF pH is alkaline. Hence, a potential [H^+] stimulus to increased ventilation is available, at least at a single time-point in hypoxia. It remains to be shown if changes in cerebral fluid [H^+] are positively correlated with ventilatory changes throughout the time-course of acclimatization to hypoxia. Further, it is difficult, theoretically, to apply these data to this study of deacclimatization, because a return to normoxic conditions should remove the source of brain tissue lactic acid production. Hence, our observed increase in acidity in bulk CSF secondary to a gradually rising P_{CO_2} during normoxic deacclimatization (+1 to +13 h [human] or +6 to +12 to +24 h [pony]; Fig. 2) should also be reflected at least to some extent in other cerebral fluids.

In summary, we propose that the accumulated negative evidence points clearly to the need for detailed examination of potential mediators of ventilatory acclimatization and deacclimatization beyond the usual "measurable" chemical stimuli. To date, some promising alternatives include pH changes in cerebral fluids other than large cavity CSF (26, 27) and hypoxic-induced alterations in suprapontine influences on medullary respiratory neurons (7, 23, 28–30).

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