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Time course and magnitude of ventilatory and renal acid-base acclimatization following rapid ascent to and residence at 3,800 m over nine days

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Abstract

Rapid ascent to high altitude imposes an acute hypoxic and acid-base challenge, with ventilatory and renal acclimatization countering these perturbations. Specifically, ventilatory

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AUTHOR CONTRIBUTIONS

J.D.B., P.O., T.A.D., R.J.A.W., and N.G.J. conceived and designed research; J.D.B., S.F.T., A.L.S., P.O., T.A.D., G.E.F., C.A.R., B.A.P., and B.R.M.B. performed experiments; J.D.B., T.A.D., and G.E.F. analyzed data; J.D.B., S.A.H., C.D.S., D.B., T.A.D., J.K.L., R.J.A.W., and K.D.O. interpreted results of experiments; J.D.B. and T.A.D. prepared figures; J.D.B. and T.A.D. drafted manuscript; J.D.B., S.F.T., A.L.S., S.A.H., C.D.S., D.B., P.O., T.A.D., J.K.L., G.E.F., C.A.R., R.J.A.W., K.D.O., N.G.J., B.A.P., and B.R.M.B. edited and revised manuscript; J.D.B., S.F.T., A.L.S., S.A.H., C.D.S., D.B., P.O., T.A.D., J.K.L., G.E.F., C.A.R., R.J.A.W., K.D.O., N.G.J., B.A.P., and B.R.M.B. approved final version of manuscript.

DISCLOSURES

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acclimatization improves oxygenation, but with concomitant hypocapnia and respiratory alkalosis. A compensatory, renally mediated relative metabolic acidosis follows via bicarbonate elimination, normalizing arterial pH(a). The time course and magnitude of these integrated acclimatization processes are highly variable between individuals. Using a previously developed metric of renal reactivity (RR), indexing the change in arterial bicarbonate concentration ($\Delta[HCO_3^-]a$; renal response) over the change in arterial pressure of CO_2 (ΔPa_{CO_2}; renal stimulus), we aimed to characterize changes in RR magnitude following rapid ascent and residence at altitude. Resident lowlanders ($n = 16$) were tested at 1,045 m (*day* [*D*]*0*) prior to ascent, on *D2* within 24 h of arrival, and *D9* during residence at 3,800 m. Radial artery blood draws were obtained to measure acid-base variables: Pa_{CO_2}, $[HCO_3^-]a$, and pHa. Compared with *D0*, Pa_{CO_2} and $[HCO_3^-]a$ were lower on *D2* ($P < 0.01$) and *D9* ($P < 0.01$), whereas significant changes in pHa ($P = 0.072$) and RR ($P = 0.056$) were not detected. As pHa appeared fully compensated on *D2* and RR did not increase significantly from *D2* to *D9*, these data demonstrate renal acid-base compensation within 24 h at moderate steady-state altitude. Moreover, RR was strongly and inversely correlated with ΔpHa on *D2* and *D9* ($r \leq -0.95$; $P < 0.0001$), suggesting that a high-gain renal response better protects pHa. Our study highlights the differential time course, magnitude, and variability of integrated ventilatory and renal acid-base acclimatization following rapid ascent and residence at high altitude.

NEW & NOTEWORTHY We assessed the time course, magnitude, and variability of integrated ventilatory and renal acid-base acclimatization with rapid ascent and residence at 3,800 m. Despite reductions in Pa_{CO_2} upon ascent, pHa was normalized within 24 h of arrival at 3,800 m through renal compensation (i.e., bicarbonate elimination). Renal reactivity (RR) was unchanged between *days 2* and *9*, suggesting a lack of plasticity at moderate steady-state altitude. RR was strongly correlated with ΔpHa, suggesting that a high-gain renal response better protects pHa.

Keywords

acid-base; high altitude; hypoxia; renal compensation; ventilatory acclimatization

INTRODUCTION

Sojourners to high altitude (≥2,500 m) are exposed to reductions in atmospheric pressure, leading to hypobaric hypoxia and resultant hypoxemia. Initial high altitude exposure reduces arterial partial pressure of oxygen (Pa_{O_2}), arterial blood oxygen saturation (Sa_{O_2}), and arterial oxygen content (Ca_{O_2}), triggering a cascade of integrated physiological responses. Acute responses include the hypoxic ventilatory response (HVR), whereby increases in alveolar ventilation increases the amount of oxygen carried in the blood (1) but with concomitant respiratory alkalosis (2, 3). With chronic hypoxic exposure to high altitude, acclimatization processes are mounted in respiratory, hematological, and renal systems, improving oxygenation and countering hyperventilation-induced acid-base imbalances (1, 4–6).

Peripheral chemoreceptors (i.e., carotid bodies) initially detect hypoxemia and elicit the HVR (7, 8). The HVR increases resting ventilation in attempt to partially restore Pa_{O_2}

while simultaneously decreasing the arterial partial pressure of carbon dioxide (Pa_{CO_2}) causing hypocapnia and respiratory alkalosis. The resultant hypocapnia dampens both central and peripheral respiratory chemoreceptor activation, blunting ventilatory drive (e.g., 9–11). Thus, for the HVR to successfully increase oxygenation, the inhibitory effects of concomitant hypocapnia must be countered. This is accomplished by ventilatory acclimatization to chronic hypoxia (VAH; 5, 12), which increases sensitivity of the HVR through carotid body type I glomus cell hyperplasia within the first 3 days of sustained hypoxia (13), and subsequent increases in carotid body sensitivity to hypoxia (14). Further, plasticity is observed within the central nervous system, through integration of afferent signaling from the carotid bodies (15). The net result is an increase in ventilatory motor output for a given hypoxic stimulus (5, 6, 15, 16). VAH progressively increases ventilation and Pa_{O_2}, which partially restores oxygenation but concurrently amplifies the initial hypocapnia and respiratory alkalosis (7, 17).

Previously, we developed a metric of steady-state chemoreflex drive (SS-CD) in contexts of acute hypoxia in a laboratory setting (18) and during incremental ascent to high altitude (16, 19). The SS-CD metric takes into account the integrated steady-state ventilatory response to prevailing respiratory chemostimuli at rest and likely captures integrated ventilatory acclimatization through the contributions of both central and peripheral chemoreceptors (16, 19). However, this SS-CD metric has yet to be characterized during rapid ascent to and residence at a single altitude over time.

With sustained exposure to hypoxia, the HVR-induced hypocapnia and respiratory alkalosis causes an acute acid-base dysregulation (e.g., 2). Two renal compensatory mechanisms arise to counteract this dysregulation: *1*) minimizing renal acid ($[H^+]$) excretion (by reducing secretion) and *2*) increasing bicarbonate (HCO_3^-) excretion into the urine (by reducing reabsorption; 2, 20–25). These two interrelated renal tubular cellular mechanisms return arterial blood pH (pHa) to homeostatic values (pHa ~7.4) through compensatory relative metabolic acidosis (3, 25). However, this bicarbonate diuresis increases central chemoreceptor sensitivity to a given change in Pa_{CO_2} (e.g., breath hold) by reducing buffering capacity within the respiratory control centers where the central chemoreceptors reside (5, 20, 26). In addition, the relative metabolic acidosis sensitizes central respiratory chemoreceptors and unbrakes peripheral chemoreceptor blunting resulting from hypocapnia and respiratory alkalosis, likely contributing to ventilatory acclimatization in addition to carotid body plasticity.

To describe the gain of the renal response, we previously introduced renal reactivity (RR), an index of the relative change in arterial bicarbonate concentration ($D[HCO_3^-]a$; i.e., renal response) over the relative change in arterial pressure of CO_2 (ΔPa_{CO_2}; i.e., renal stimulus), during incremental ascent to high altitude (3). We showed that RR increased with incremental ascent from 3,440 m to 3,820 m from *days 3* to *5* and plateaued with further ascent (4,240 m on *day 7* and 5,160 m on *day 10*). We also showed that at all altitudes, RR was significantly and inversely correlated with relative changes in pH (ΔpHa), with an increase in correlative magnitude (i.e., larger *r* value) with time spent at and further ascent

to altitude, suggesting those with greater renal responses to sustained hypocapnia and acute respiratory alkalosis were better able to protect pHa.

The time course and magnitude of the integrated respiratory and renal acclimatization phenotypes are variable between individuals, particularly following rapid ascent. We aimed to assess the integration between respiratory and renal acclimatization during rapid ascent and residence at high altitude (3,800 m) over 9 days. We hypothesized that *1*) steady-state chemoreflex drive would increase following ascent with ventilatory acclimatization, *2*) with subsequent renal compensation, RR magnitude would increase with duration at altitude, and *3*) RR would be inversely correlated with relative changes in pH (ΔpHa), improving with time spent at a single altitude.

MATERIAL AND METHODS

Ethics and Participant Recruitment

This study abided by the Canadian Government Tri-Council policy on research ethics with human participants (TCPS2), and it adhered to the standards set by the latest revision of the *Declaration of Helsinki*, except for registration in a database. Ethical approval was received in advance through University of Calgary Conjoint Human Research Ethics Board (Protocol REB18-0374) and Mount Royal University Human Research Ethics Board (Protocol 101879), with subsequent harmonization with the University of British Columbia Clinical Research Ethics Board Protocol (Protocol H19-01734), the North Texas Regional Institutional Research Ethics Board (Protocol 2019-110), and the University of Alberta Research Ethics Board (Protocol Pro00109336).

Healthy participants were recruited on a voluntary basis to undergo cardiorespiratory and arterial blood gas measurements during a research expedition to the Barcroft Research Station (3,800 m) in the Sierra Nevada mountains in California in August 2019. Participants were recruited via verbal communication and provided voluntary, informed, verbal, and written consent before participation in the study.

All members of the expedition consulted with their family physicians for a medical check before participating in this expedition. We prescreened and recruited 16 healthy participants for inclusion in the present study, with no self-reported medical history of cardiopulmonary, neurological, or metabolic disease. Participants were excluded if they had a body mass index >35 kg/m^2, had a history of smoking, or were taking prescription medication other than hormonal birth control. Inclusion criteria included adult participants between the ages of 18–60 years who planned to stay at the research station for the entire 10-day period. Each participant completed a prescreening questionnaire and consent form for documentation.

The participant recruitment, specific study design, research questions, and data collection were planned a priori. All participants were native lowlanders who had not been exposed to high altitude (>3,000 m) for at least 1 yr before the study. No participants included in the study took carbonic anhydrase inhibitors (e.g., acetazolamide) or any corticosteroids for AMS prevention or treatment at any point during this study.

Study Protocol and Ascent Profile

Baseline measurements were conducted at 1,045 m (Calgary, Canada; *day 0*; *D0*) over a week. Participants were then flown to, and spent one night (less than 12 h) at 610 m (Las Vegas, Nevada) before driving up to 3,800 m (Barcroft Research Station, California) the following day over 5–6 h for a study on acute ascent and sustained altitude exposure. Participants resided at 3,800 m for 10 days and nights to study acclimatization to altitude. Early exposure and late exposure arterial blood gas measurements were obtained on *days 2* (*D2*; within 24 h of arrival), and *day 9* (*D9*), respectively.

Measurements

Daily ancillary cardiorespiratory measures.—Every morning at high altitude and once at low altitude between 06:00–09:00 local time, fasted cardiorespiratory measures were taken to characterize steady-state physiological responses. Participants self-reported their acute mountain sickness (AMS) scores using the standard Lake Louise Questionnaire (27). Hemoglobin concentration [Hb] was obtained via finger capillary blood sample using sterile lancets (AccuChek, Softclix) with standard practice and universal precautions, measured via hemoglobinometer (Hemocue Hemoglobin System, Hb201+ with microcuvettes; ängelholm, Sweden). All cardiorespiratory measures were obtained at rest in the supine position with eyes closed and white noise played through headphones to limit external distraction. Three brachial blood pressure measurements were obtained via an automated blood pressure monitor (model BP786n; Omron, San Ramon, CA) then averaged. A peripheral pulse oximeter (Masimo SET Rad-5, Danderyd, Sweden) was placed on the participant's left middle finger for measurement of peripheral oxygen saturation (SpO_2; %) and heart rate (HR; beats/min). Respiratory measures were obtained using a personal mouthpiece, bacteriological filter, and nose clip. We instrumented participants with a portable capnograph (EMMA, Masimo, Danderyd, Sweden) for measurement of end-tidal PCO_2 (PET_{CO_2}; mmHg) and breathing frequency (f_B; breaths/min), and a respirometer (nSpire Haoscale, Colorado) for ventilation ($\dot{V}_E$; L/min). Once instrumentation was complete, the participants laid down with their eyes closed and after approximately 3 min, we recorded and archived their values. Steady-state chemoreflex drive (SS-CD) was calculated as previously described (16, 18, 19). First, we calculated a steady-state stimulus index (SI; PET_{CO_2}/SpO_2; mmHg/%), which represents the prevailing central and peripheral chemoreceptor stimulus. We then divided $\dot{V}_E$ by the SI to calculate SS-CD each day to characterize ventilatory acclimatization over time at 3,800 m.

Arterial blood gas and electrolytes.—Arterial blood samples were obtained in Calgary (1,045 m) and on *days 2* and *9* of the expedition at 3,800 m during the day (08:00–15:00). Arterial blood samples were acquired percutaneously from the radial artery using a preheparinized, self-filling arterial blood syringe (PICO50, Radiometer) while the participants were resting in the supine position. Standard procedures involved topical sterilization and local anesthesia (i.e., Emla topical cream; 2.5% lidocaine/2.5% prilocaine cream) with universal precautions, including a modified Allen's test to ensure redundant circulation of the hand. Samples were then immediately analyzed using a cartridge-based system for measurement/calculation of Pa_{O_2} (mmHg), Sa_{O_2} (%), Pa_{CO_2} (mmHg), [HCO_3^-]a

(mM), pHa, hematocrit (%), hemoglobin concentration (g/L), and [creatinine] (μM), using a portable analyzer and cartridges (Abbottt iSTAT, CG4+ and CHEM8+ cartridges; Abbott, Mississauga, Ontario, Canada). All samples were subject to thermal correction and atmospheric pressure calibration.

Data analysis.—Atmospheric pressure for each altitude was calculated from https://baillielab.net/critical_care/air_pressure/, and partial pressure of inspired oxygen (Pl_{O_2}) was calculated as:

$$PI_{O_2} = (P_{ATM} - 47\text{mmHg}) \times 0.21 \quad (1)$$

where 47 mmHg is water vapor pressure at normal body temperature (37°C) and 0.21 is the fraction of inspired oxygen.

Strong ion difference (SID; mEq/L) was calculated according to the traditional Stewart approach (28).

$$\text{SID} = \left(\left[Na^+\right] + \left[K^+\right] + 2\left[Ca^{2+}\right]\right) - \left(\left[Cl^-\right] + [\text{Lactate}]\right) \quad (2)$$

Serum osmolality (mOsmol/kgH_2O) was calculated from the recommended formula in (29).

$$\text{Osmolality} = 1.86\left(\left[Na^+\right] + \left[K^+\right]\right) + 1.15\left(\frac{[\text{Glucose}]}{18}\right) + \left(\frac{[\text{Urea}]}{6}\right) + 14 \quad (3)$$

Arterial oxygen content (Ca_{O_2}) was calculated as:

$$Ca_{O_2} = \left(1.36 \times [\text{Hb}] \times \frac{Sa_{O_2}}{100}\right) + (0.003 \times Pa_{O_2}) \quad (4)$$

where [Hb] = hemoglobin (g/dL); Sa_{O_2} = arterial oxygen saturation (%; or SpO_2); and Pa_{O_2} = partial pressure of arterial oxygen (mmHg). 1.36 is the binding capacity of oxygen to hemoglobin, and 0.003 is the fraction of free oxygen dissolved in blood (at 37°C). In cases where we did not have Pa_{O_2} (Table 1), Ca_{O_2} was estimated without it (using only [Hb] and SpO_2), given the negligible contribution of Pa_{O_2} when [Hb] is normal or high.

Relative delta values were calculated with respect to baseline (1,045 m) using the following equation:

$$\Delta x = x_{altitude} - x_{baseline} \quad (5)$$

where x represents any variable.

RR was calculated for both nights at altitude (*D2* and *D9*) following the formula reported in (3):

$$\mathrm{RR} = \frac{\Delta[\mathrm{HCO_3^-}]_a}{\Delta \mathrm{Pa_{CO_2}}} \quad (6)$$

where $[\mathrm{HCO_3^-}]_a$ is arterial bicarbonate (mM; i.e., renal response) and $\mathrm{Pa_{CO_2}}$ (mmHg; i.e., renal stimulus) is partial pressure of arterial carbon dioxide.

Statistical analysis.—All continuous data are represented as mean ± SD in table format unless otherwise stated. Data were assessed for normality and variance using the Shapiro–Wilk and the Brown–Forsythe test. One-factor repeated measures ANOVAs were used to assess changes in daily ancillary cardiorespiratory and hematological variables, and arterial blood oxygenation, acid-base and electrolyte metrics. Where significant *F*-ratios were detected, Student–Newman–Keuls post hoc tests were used for multiple pair-wise comparisons between testing days. Student's two-tailed *t* tests were used to evaluate the difference between delta changes from baseline on *days 2* and *9* for RR and delta pHa. A Pearson product moment correlation was used to assess RR against the change in pHa from baseline. A Cohen's *d* statistic was used to calculate effect size for the *t* test comparing RR between *D2* and *D9*. In all cases, statistical significance was assumed at $P < 0.05$ (SigmaPlot v10, Systat Software, Inc., San Jose, CA).

RESULTS

In the final analysis, we included 16 participants where we had repeated measures on all metrics (5 female, 11 male, BMI = 26.0 ± 3.8 kg/m^2; Age = 31.3 ± 11.7 yr).

Daily cardiorespiratory measures and AMS scores from *D0* to *D9* are presented in Table 1. In addition, comprehensive arterial blood gas and electrolyte values from *D0*, *D2*, and *D9* are presented in Table 2.

Figure 1 illustrates metrics of oxygenation with rapid ascent (*D2*) and residence (*D9*) at altitude. $\mathrm{Pa_{O_2}}$ and $\mathrm{Sa_{O_2}}$ were lower on *D2* and *D9* compared with *D0* ($P < 0.01$; Fig. 1, A and B) but were higher on *D9* than *D2* ($P < 0.01$; Fig. 1B). [Hb] was greater on *D9* compared with *D0* and *D2* ($P < 0.01$; Fig. 1C). $\mathrm{Ca_{O_2}}$ decreased from *D0* to *D2* ($P < 0.01$) but then was partially corrected from *D2* to *D9* ($P < 0.01$) such that *D0* and *D9* were not different (Fig. 1D).

Figure 2 illustrates metrics of acid-base homeostasis with rapid ascent (*D2*) and residence (*D9*) at altitude. Pa_{CO_2} and $[HCO_3^-]a$ were lower on *D2* compared with *D0* ($P < 0.01$), and lower still on *D9* ($P < 0.01$; Fig. 2, A and B). pHa was not different on *D2* or *D9* from *D0* ($P = 0.072$; Fig. 2C).

Figure 3 illustrates renal reactivity (RR) and the change (Δ) in pHa on *D2* and *D9*. RR was not significantly increased from *D2* to *D9* ($P = 0.056$; effect size 0.61; Fig. 3A). ΔpHa was also unchanged between *D2* and *D9* ($P = 0.4$; Fig. 3B). The magnitude of RR was negatively correlated with ΔpHa on *D2* ($r = -0.95$, $P < 0.0001$; Fig. 3C) and *D9* ($r = -0.98$, $P < 0.0001$; Fig. 3D).

Figure 4 illustrates Davenport diagrams on *D0*, *D2*, and *D9* (Fig. 4, A–C). Although these plots are qualitative, they illustrate the integrated changes in Pa_{CO_2} (right hand *y*-axis), pHa (*x*-axis), and $[HCO_3^-]a$ (left hand *y*-axis; same data as Fig. 2). Qualitatively, it is evident that Pa_{CO_2} and $[HCO_3^-]a$ values are incrementally lower with time at altitude (*D2* and *D9*) compared with *D0*, and that pHa was relatively well-maintained throughout, despite what appears to be an initial alkalinization within 24 h of arrival on *D2*. Mean data in Fig. 4D illustrate the integrated disturbances and compensation over time.

DISCUSSION

We aimed to characterize the time course and magnitude of integrated ventilatory and renal acclimatization following rapid ascent to and residence at 3,800 m for nine days. The principal findings were *1*) compared with low altitude (*D0*), Pa_{CO_2} and $[HCO_3^-]a$ were lower on *D2* and *D9*, *2*) pHa was unchanged at *D2* or *D9* due to renal compensation, *3*) RR did not increase significantly from *D2* to *D9* ($P = 0.056$), suggesting that renal acclimatization was in full effect within 24 h of rapid ascent, and *4*) there was a strong, negative correlation between RR and ΔpHa from baseline on both *D2* and *D9*. Our findings highlight the differential time course, magnitude, and variability of integrated ventilatory and renal acclimatization following rapid ascent to and residence at high altitude.

Ventilatory Acclimatization

Previous studies have assessed ventilatory acclimatization using transient peak HVR tests before and after ascent (e.g., 8, 30). However, we argue these methods are confounded due in part to the lack of equivalency between the HVR response at sea level with the HVR at altitude, given *1*) Pa_{CO_2} is lower at high altitude, resulting from the hypoxic ventilatory response in the steady state, *2*) Pa_{CO_2} continues to be reduced over time resulting from ventilatory acclimatization, and *3*) renally mediated bicarbonate elimination and relative metabolic acidosis sensitizes both central chemoreceptors and unbrakes the hypocapnia-mediated blunting of peripheral chemoreceptors, given the stimulus interaction between O_2 and $CO_2/[H^+]$ at the carotid body (10, 31). In addition, a transient peak response test may not capture the steady-state ventilatory strategy given the prevailing chemostimuli acting on both chemoreceptor compartments. Thus, we recently developed an index of steady-state chemoreflex drive (18), which we suggest captures ventilatory acclimatization in the steady-state during ascent (16, 19). Specifically, we showed that SS-CD increased with incremental

ascent to high altitude (16, 19), and thus captured ventilatory acclimatization during rest with ascent to (16, 19) and descent from 5,160 m (16). In the present study, we assessed SS-CD during rapid ascent to and residence at 3,800 m for 9 days. We showed that both $\dot{V}_E$ and SS-CD increased upon immediate ascent to 3,800 m, and both further increased by 9 days of residence at this altitude. These data suggest that an immediate HVR was elicited with rapid ascent and that ventilatory acclimatization was responsible for further hypocapnia over time at 3,800 m (Tables 1 and 2, Fig. 2). These data further validate the utility of the SS-CD metric in high altitude fieldwork contexts in assessing an integrated central and peripheral chemoreflex for resting steady state while residing at altitude. In addition, they illustrate respiratory-induced alkalosis with hypoxic exposure, which is a stimulus for renal compensation.

Renal Acclimatization and Acid-Base Regulation

Previous studies that assessed longitudinal acid-base regulation at altitude investigated Pa_{CO_2}, $[HCO_3^-]a$, and pHa following rapid ascent to and residence at ~4,300 m over 7 days (32) and 10 of 11 days (20). These investigators found that pHa compensation was incomplete, due in part to disproportionate reductions in both Pa_{CO_2} and $[HCO_3^-]a$. Participants were still alkalotic at *day 7* (pH = 7.45; 32) and *day 10* of *11* (pH = 7.449; 20). Although Forster et al. (20) tested a limited sample size ($n = 5$), the consistency of the reported acid-base variables for these two studies suggests that pHa remained alkalotic following 10 of 11 days of high altitude exposure. In contrast, Zouboules et al. (3) found during incremental ascent to high altitude that although there was alkalosis at 3,440 m following 3 days of ascent, pHa was normalized to baseline values at 3,820 m on *day 5* and 4,240 m on *day 7*. However, with further ascent, a larger prevailing hypocapnic stimulus relative to bicarbonate compensation was observed, as participants were alkalotic again at 5,160 m on *day 10*. Similar relative alkalosis when ascending from 3,647 m to 4,554 m has been demonstrated in a small cohort ($n = 5$; 33). Conversely, pHa was normalized within 24 h upon arrival at 3,800 m in the present study, suggesting that pH maintenance is largely driven by the capacity of the renal system to detect and respond to dynamic changes in Pa_{CO_2} during incremental and/or sustained residence-style ascent profiles.

Studies of chronic hypercapnia suggest that the severity of the hypercapnic stimulus determines whether the kidneys are able to facilitate a full compensatory metabolic alkalosis. Under conditions of mild chronic hypercapnia (1.5% inspired), renal compensatory mechanisms fully corrected pHa (34), whereas more severe chronic hypercapnia (3% and 6% inspired) elicited only a partial renal compensation (35–37). In fact, in a severe hypercapnic environment (6% CO_2 inspired), pHa was not fully compensated, even after 30 days of exposure (35). Further, when inspiring 3% CO_2, urine bicarbonate excretion was nonexistent until 6 of 7 days after returning to breathing room air, suggesting maximal bicarbonate retention was employed to combat the respiratory acidosis (37). When viewed together, these data suggest that there is a threshold for the efficacy of renal responses to mitigate Pa_{CO_2} challenges. Similarly, in the context of high-altitude hypoxia and hypocapnia, there may be a threshold of hypocapnic stimulus below which full renal compensation cannot be achieved, likely at an altitude between 3,800 m and 4,300 m.

Time Course, Magnitude, and Variability in Renal Responses

Our data suggest that there was an immediate HVR with ascent, which reduced Pa_{CO_2}, as expected (Tables 1 and 2 and Fig. 3A). However, we did not expect to find that pHa was fully compensated for within ~24 h upon arrival (*day 2* of exposure; see Fig. 3C), due to bicarbonate excretion (Fig. 3B). This highlights a remarkably rapid renal compensation within our sample population. This may not be surprising however, as rapid compensatory metabolic alkalosis (36) and acidosis (21) have been previously shown to begin to occur within 24 h of exposure to respiratory perturbations. In any case, as evidenced by our scatter plots on *day 2* (Fig. 3), there appears to be distinct ventilatory and renal phenotypes along a continuum within our group of participants, based on the differential and integrated ventilatory and renal responses within the first 24 h of exposure to high altitude. In one group, there was minimal HVR, and thus no renal hypocapnic stimulus, and pH remained unchanged. In yet another group, there was a robust HVR and concomitant hypocapnia, with no early renal compensation. Lastly, in another group, there was a robust HVR and concomitant hypocapnia, with early renal compensation. On balance, early HVR, hypocapnia and subsequent early renal compensation dominated the statistical analysis in our study of 16 participants, bringing mean group pHa statistically back to baseline values within 24 h of arrival to high altitude. Unfortunately, with only three time points (i.e., low altitude, *day 2* and *day 9* at 3,800 m) and 16 participants, our resolution is low to confirm the existence of three distinct phenotypes that participants move through with variable time courses and magnitudes with time spent at altitude. Future studies should aim to explore these potentially distinct 24-h postascent phenotypes more systematically to determine if they play a role in both short and longer term acclimatization. In addition, the fact that *1*) we were unable to maintain strict water and electrolyte ingestion in this field study (e.g., 38, 39) and *2*) there was heterogeneity in BMI, age, and ovarian hormone status (e.g., 40, 41) in our participant pool, these factors that may introduce additional variability, and should be better controlled for in future studies to address phenotypical variability in renal acid-base regulation at altitude.

The Davenport diagrams (Fig. 4) represent a graphical demonstration of the Henderson–Hasselbalch relationships. They depict primary acid-base disturbances and their corresponding secondary compensations, including Pa_{CO_2} isopleths (stimuli), pHa (as the controlled variable), $[HCO_3^-]a$ (response), and the non-$[HCO_3^-]a$ buffer slope (42). Here, we plotted Davenport diagrams on *D0* (1,045 m), *D2* within 24 h of arrival at 3,800 m, and *D9* at 3,800 m. As expected, we observed that on *D2*, both Pa_{CO_2} and $[HCO_3^-]a$ are reduced, with pHa slightly, but not statistically elevated. On *D9*, both Pa_{CO_2} and $[HCO_3^-]a$ are reduced further and pHa appears to be fully corrected to baseline values. The superimposed mean data in Fig. 4D shows the trajectory of disturbance-compensation relationship from *D0*, to *D2*, to *D9*. To our knowledge, this is the first time Davenport diagrams have been used to demonstrate acid-base variables with rapid ascent and residence to high altitude. This further expands our understanding of acid-base disturbances and their respective renal compensations during ascent, particularly the extent of variability between a large group of participants.

Considerations and Reconciliation with Previous Reports

In a previous study from our group, Zouboules et al. (3) developed and characterized a novel index of renal reactivity (RR) during incremental ascent to high altitude (5,160 m) whereby the change in [bicarbonate] (i.e., renal response) was indexed against the change in Pa_{CO_2} (i.e., renal stimulus). We demonstrated plasticity in renal responses with incremental ascent, where RR increased with increasing altitude from 3,440 m (*day 3*) to 3,820 m (*day 5*) but plateaued thereafter. This plasticity may have been a consequence of incremental increases in altitude, which increased the HVR-mediated hypocapnic stimuli to the renal tubules and stimulated larger renal responses over time, until the full response was realized. In the current study, we employed a rapid ascent and steady-state model, where participants ascended from 610 m to 3,800 m over 5–6 h and resided at this altitude for 10 days before descending. Thus, the present study differed from (3) in two important ways. First, we did not increase the magnitude of the hypoxic stimulus over the approximately same time course. In fact, as evidenced by the increase in Pa_{O_2}, SpO_2, [Hb], and Ca_{O_2} between *days 2* and *9* in our study, our ascent and steady-state residence model eliminated the confounder of progressive, incremental hypoxic stimulation with further ascent that occurred in (3). Second, given the VAH observed between *days 2* and *9*, as evidenced by the increased SS-CD and continued decreases in PET_{CO_2} and Pa_{CO_2}, the hypocapnic stimulus progressively increased over the duration of our study (from ~33 to 30 mmHg). However, RR did not increase significantly from *day 2* (0.46 ± 0.28) to *day 9* (0.59 ± 0.14; $P = 0.056$), suggesting that there were concomitant, proportionate decreases in both Pa_{CO_2} and $[HCO_3^-]a$, without affecting RR. In comparison, Forster et al. (20) had participants reside at 4,300 m for 10 days. A calculation from their mean data suggests similar RR values, from ~0.45 on *day 2* to ~0.6 on *day 10*, similar to the present study. This is further corroborated by Limmer et al. (33) during incremental ascent where a calculated mean RR of ~0.64 on *day 3* (3,425 m) increased to ~0.71 on *day 7* (4,554 m). These values from Limmer et al. appear to be slightly higher than other studies highlighted for two reasons. First, RR was calculated on *day 3* of ascent, allowing time for more relative bicarbonate excretion to occur. Second, baseline measurements were obtained at 100 m, thereby giving comparatively larger baseline bicarbonate values (~25.4 mM) and thus a potentially larger bicarbonate excretion capacity. These results contrast with the findings of Steele et al. (32) where an increase in RR from *day 1* (0.098) to *day 7* (0.54) was demonstrated. These considerations illustrate the biphasic nature of RR as ventilatory and renal compensations differ temporally. The low RR on *day 1* for Steele et al. can be attributed to a predominance of Phenotype B (HVR-mediated hypocapnia, but with no appreciable renal response) when the measures were taken only 12 h after ascent. As the acute HVR precedes the renal acclimatization process, there will be a point in time (e.g., <12 h postascent) where there will be relatively minor changes in bicarbonate but concurrently large changes in Pa_{CO_2} elicited by the HVR. Under these conditions, the numerator remains small (i.e., no change in bicarbonate), whereas the denominator will increase dramatically (i.e., large change in Pa_{CO_2}), resulting in a very low RR. Thus, RR should be interpreted taking into context the temporal differences between both HVR-mediated changes in Pa_{CO_2} and the subsequent renal compensation. By contrast, in (33), a larger RR was observed by *day 3* as the full renal response is realized, and

participants moved toward Phenotype C, where a HVR-mediated hypocapnia had elicited a renal compensation.

An alternative explanation for the plasticity noted in (3) may have been due to progressive exposure to superimposed hypoxia and hypocapnia. Interestingly, in the present study, the increase in hypocapnic stimulus was larger (Fig. 2) and oxygenation was improved (Fig. 1) compared with the period RR plasticity was observed in (3). There, Pa_{CO_2} was not decreased from *day 3* (30.7 mmHg) to *day 5* (30.3 mmHg), and participants were hypoxic, which suggests that a dose-dependent interaction may exist between sustained hypoxia and hypocapnia in driving renal plasticity. There is some evidence to support the hypothesis that sustained hypoxia interacts with hypocapnia to enhance renal compensation. In (22), participants voluntarily hyperventilated for 26 h in either room air or in a hypobaric hypoxia chamber simulating 3,100 m with roughly equivalent Pa_{CO_2} between the two trials over time. The hypoxic-hypocapnic trial ($n = 8$) appeared to show more complete pHa compensation over time compared with the normoxic-hypocapnic trial, although the authors report that these observed differences in pHa were not significant. However, a calculation from their mean data between groups at the 9-h time point suggests that RR was higher by ~45% in the hypoxic-hypocapnic trial compared with the hypocapnic trial alone (0.29 vs. 0.20, respectively). This potential difference between renal responses to sustained hypocapnia between hypoxia and normoxia in the same individuals hints that the comparable, iso-hypoxic stimulus between *day 2* and *9* in the present study may have attenuated the magnitude of RR compared with the incremental ascent model (3). There, Pa_{O_2} and Sa_{O_2} were maintained at ~50 mmHg and 85%, respectively, between *days 3* and *5*, and RR appeared to show plasticity, whereas in the present study, the continual rise in Pa_{O_2}, Sa_{O_2}, [Hb], and Ca_{O_2} (Tables 1 and 2; Fig. 1) over 7 days may have attenuated plasticity in RR, despite sustained hypocapnic stimulus due to VAH (Fig. 3).

With respect to the effects of systemic hypoxia on the renal system, a previous report suggests that the HVR magnitude was related to diuresis and natriuresis in response to sustained (6 h) of steady-state hypoxia (43). Indeed, anatomical substrates are already known to exist whereby both extrinsic and intrinsic systems may account for the effects of hypoxia on the renal tubules. First, renal sympathetic nerves innervate not only the renal vasculature but also the renal tubular network (44), and hypoxia enhances sympathetic outflow (45–47), likely through carotid body activation (48). Second, there is a known peritubular capillary system involved in oxygen sensing and hematological acclimatization through local hypoxia-inducible factor-1α (HIF-1α) expression and subsequent erythropoietin release (e.g., 49, 50). Thus, the intriguing possibility exists that hypoxia interacts with hypocapnia to augment renal acid-base acclimatization through bicarbonate elimination and acid retention, potentially through upregulation of membrane transporters in intercalated cells (23, 51–54). This hypothesis remains to be fully elucidated and requires further experimental attention in both animal and human models.

Conclusions

We characterized the time course, magnitude, and variability of integrated ventilatory and renal acclimatization following rapid ascent to and residence at 3,800 m for 9 days. We

found that compared with *D0* (i.e., baseline), Pa_{CO_2} and $[HCO_3^-]a$ were lower on *D2* and *D9*, and that pHa was unchanged at *D2* or *D9* due to renal compensation, suggesting a rapid time course of renal compensation (within 24 h). We also found that RR did not increase from *D2* to *D9*. This indicates a short time course of renal acclimatization followed by maintenance of pHa with progressive hypocapnia following rapid ascent and a subsequent 9-day residence at steady-state altitude (3,800 m). Similar to a previous study during incremental ascent, there was a strong negative correlation between RR and ΔpHa from baseline on both *D2* and *D9*, which suggests that carbon dioxide and bicarbonate are the dominant buffer system for acid-base homeostasis at high altitude, and those with larger renal compensation better protect pHa in the context of sustained progressive hypocapnia. Our findings highlight the differential time course, magnitude, and variability of ventilatory and renal acclimatization following rapid ascent to and residence at high altitude and suggest future work investigating the capacity for renal acclimatization and the role of renal-specific hypoxia on acid-base homeostasis.

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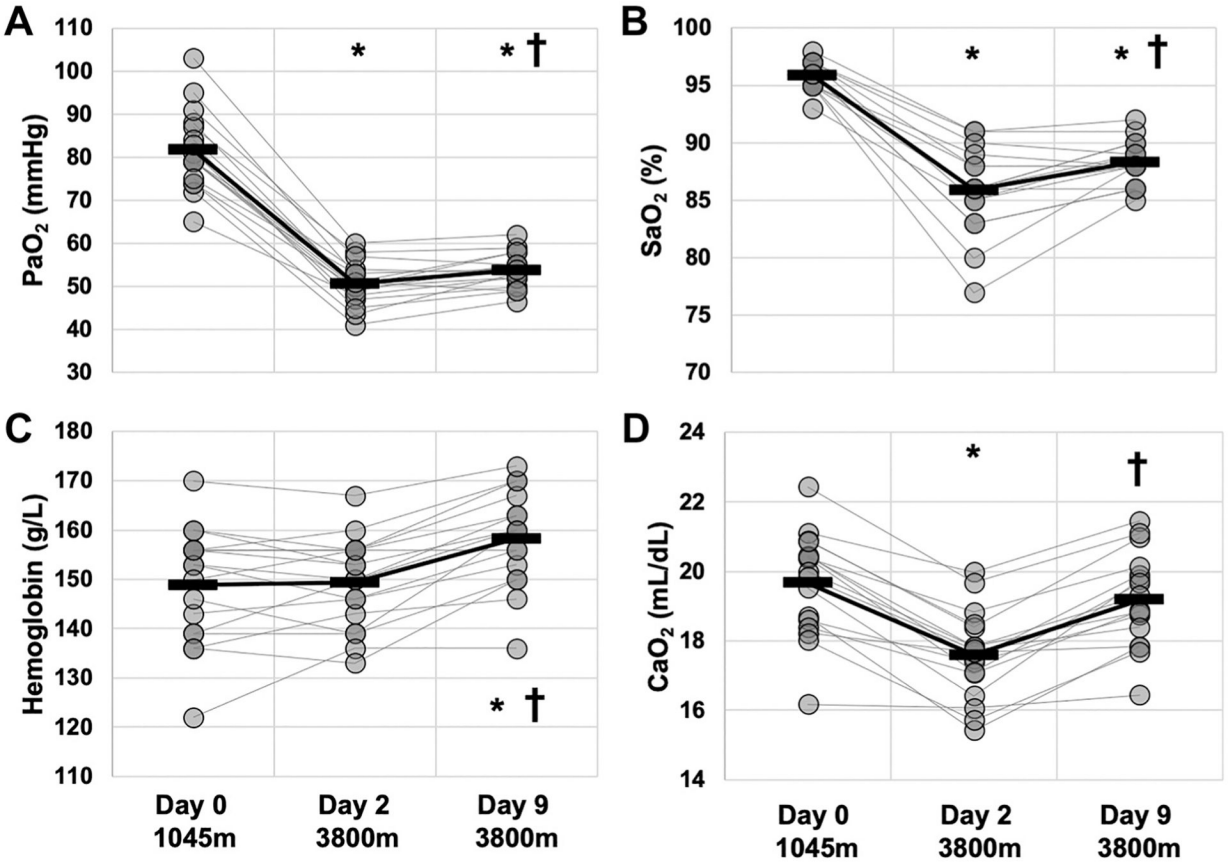

Figure 1.

Oxygenation during rapid ascent and residence at 3,800 m. Data were obtained via arterial blood gas/electrolyte measures at 1,045 m (*day 0*), prior to ascent, and at 3,800 m on *days 2* (within 24 h of arrival by rapid ascent) and *9*. *A*: Pa_{O_2}, pressure of arterial oxygen. B: Sa_2, arterial oxygen saturation. *C*: [Hb], hemoglobin concentration D: Ca_2, arterial oxygen content. *Different than *day 0*. †Different than previous day. Presented as means ± SD. n = 16.

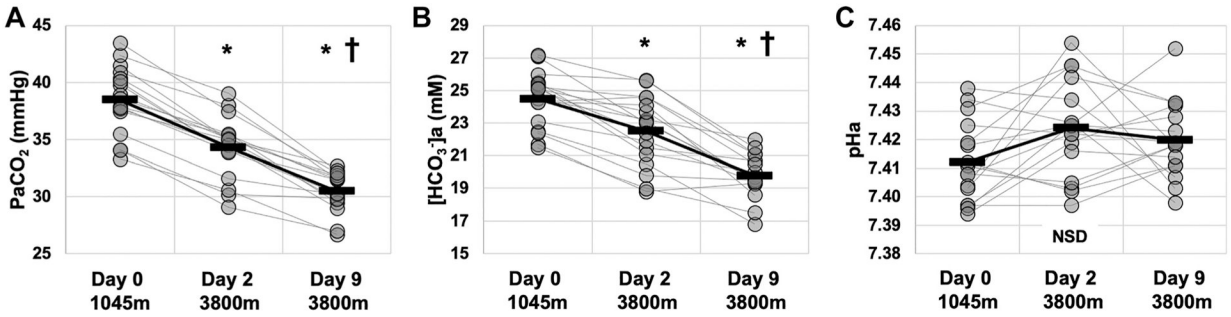

Figure 2.

Carbon dioxide and acid-base variables during rapid ascent to and residence at 3,800 m. Data were obtained via arterial blood gas/electrolyte measures at 1,045 m (*day 0*), prior to ascent, and at 3,800 m on *days 2* (within 24 h of arrival by rapid ascent) and *9*. *A*: Pa_{CO_2} partial pressure of arterial carbon dioxide. *B*: $[HCO_3^-]a$, arterial bicarbonate concentration. *C*: pHa, arterial pH. *Different than *day 0*. †Different than previous day. Presented as means ± SD. $n = 16$. NSD, nonsignificant difference.

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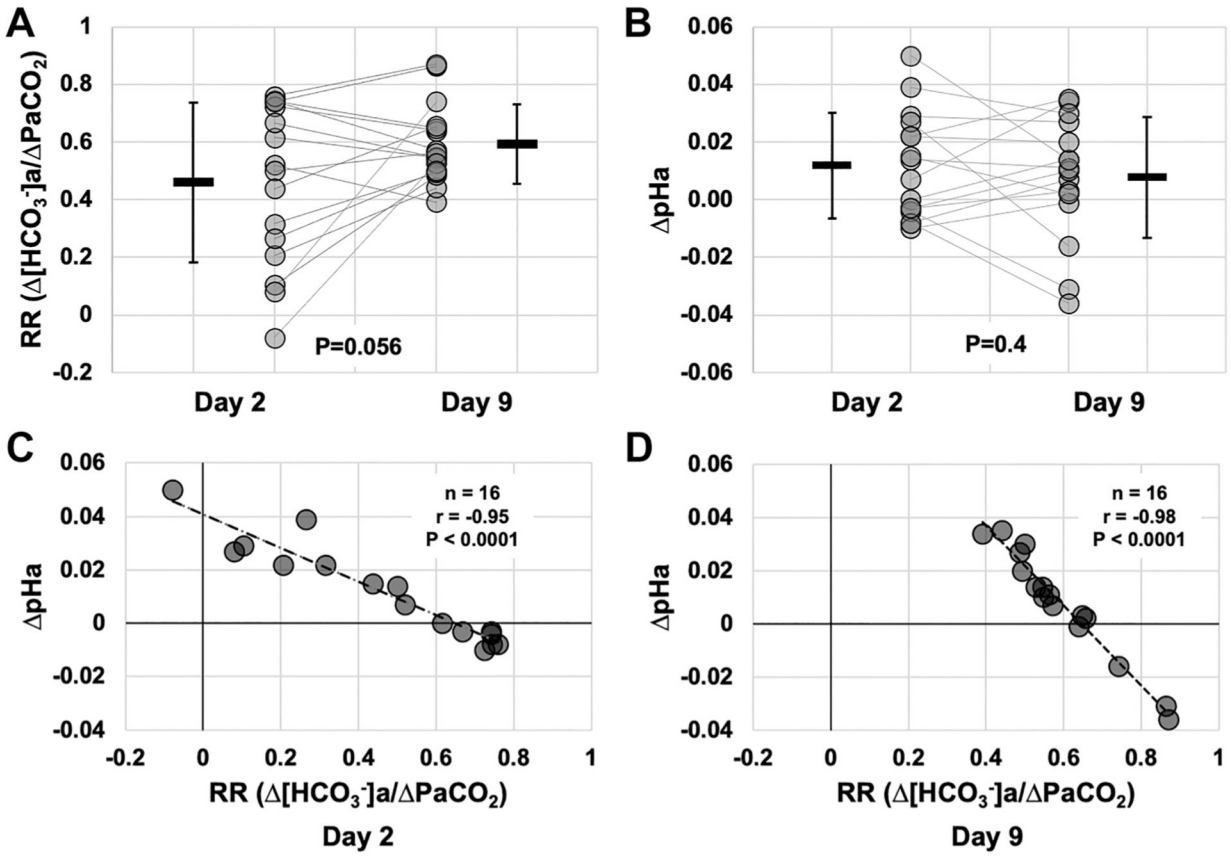

Figure 3.

Renal reactivity and changes in pHa during rapid ascent and residence at 3,800 m. Data were calculated from Pa_{CO_2}, $[HCO_3^-]a$, and pHa variables reported in Fig. 2. *A*: renal reactivity (RR) calculated on *days 2* (within 24 h of arrival by rapid ascent) and *9* at 3,800 m, compared with *D0* (1,045 m; $P = 0.056$). *B*: delta pHa calculated on *days 2* and *9* at 3,800 m, compared with *D0* (1,045 m; $P = 0.4$). *C*: correlation between RR vs. pHa at *day 2* at 3,800 m. *D*: correlation between RR vs. pHa at *day 9* at 3,800 m. For correlations (*C* and *D*), *r*, *P*, and *n* values are presented on each graph. $n = 16$. $[HCO_3^-]a$,, arterial bicarbonate concentration; Pa_{CO_2}, partial pressure of arterial carbon dioxide; pHa, arterial pH.

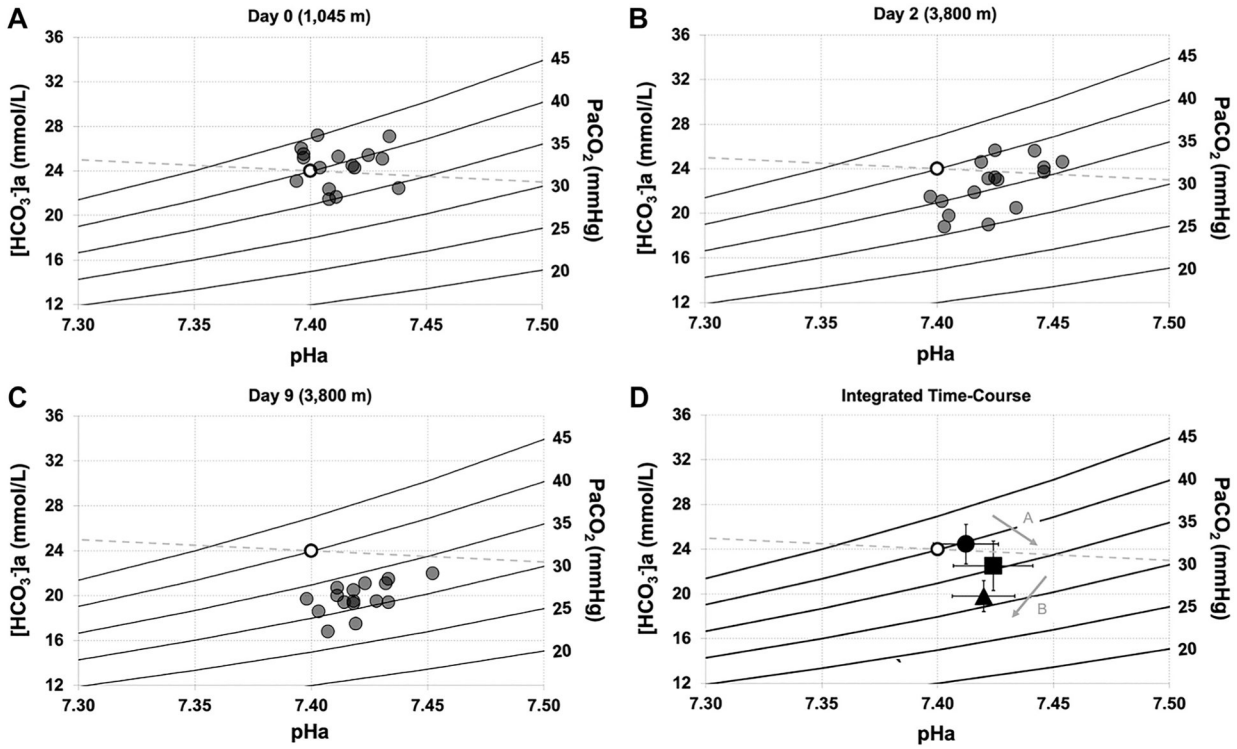

Figure 4.

Davenport diagrams during rapid ascent to and residence at 3,800 m. Individual data demonstrating relationships between Pa_{CO_2}, $[HCO_3^-]a$, and pHa at 1,045 m on day 0 (*A*), 3,800 m on *day 2* (*B*; within 24 h of arrival by rapid ascent), and 3,800 m on day 9 (*C*). *D*: mean data demonstrating dynamic relationship of stimulus-response relationships between acid-base variables and time at 3,800 m. Open circle represents reference value. For *A*, *B*, and *C*, filled circles represent individual data. For *D*, filled circle represents 1,045 m (*day 0*), filled square represents 3,800 m (*day 2*), filled triangle represents 3,800 m (*day 9*), and arrows denote the group directional changes over time. Error bars represent standard deviation. $n = 16$. $[HCO_3^-]a$, arterial bicarbonate concentration; Pa_{CO_2}, partial pressure of arterial carbon dioxide; pHa, arterial pH.

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Table 1.

Daily ancillary measures of cardiorespiratory and hematological variables before and during rapid ascent to and residence: days (D)0 (1,045 m) and D1–D9 (at 3,800 m)

Variable	Calgary	Barcroft Lab							
	(*D0*)	(*D2*)	(*D3*)	(*D4*)	(*D5*)	(*D6*)	(*D7*)	(*D8*)	(*D9*)
Altitude, m	1,045	3,800							
P_{ATM}, mmHg	665	487							
Pl_{O_2}, mmHg	130	92							
	Cardiorespiratory Variables								
HR, min^{-1}	65.5 ± 12.4	75.5 ± 9.5 *	69.1 ± 11.0	72.3 ± 12.0	72.3 ± 12.9	69.5 ± 11.1	70.3 ± 9.0	69.1 ± 11.7	70.9 ± 9.2
MAP, mmHg	90.3 ± 11.9	89.7 ± 12.8	87.5 ± 11.5	84.2 ± 11.5 *	86.3 ± 11.2	86.3 ± 9.8	84.4 ± 8.9 *	84.5 ± 9.4 *	87.0 ± 11.0
$\dot{V}_E$, L/min	8.6 ± 2.8	11.0 ± 3.8	10.4 ± 1.9	10.0 ± 2.4	9.5 ± 1.4	9.6 ± 1.9	10.0 ± 1.6	9.9 ± 2.8	10.1 ± 1.9
PET_{CO_2}, mmHg	36.9 ± 3.1	30.8 ± 4.1 *	30.3 ± 2.9 *	29.3 ± 3.6 *	28.9 ± 1.6 *	28.3 ± 2.7 *	28.8 ± 2.7 *	26.3 ± 3.0 *≠	28.2 ± 2.5 *≠
Sp_{O2}, %	97.5 ± 1.6	87.5 ± 4.2 *	88.9 ± 3.0 *	88.3 ± 2.2 *	87.9 ± 2.9 *	89.6 ± 2.3 *	89.2 ± 2.7 *	89.4 ± 2.2 *	90.6 ± 2.9 *
SS-CD, a.u.	22.8 ± 7.2	31.9 ± 11.9 *	30.5 ± 5.7 *	30.4 ± 8.2 *	28.8 ± 4.2 *	30.8 ± 8.6 *	31.3 ± 5.3 *	34.3 ± 11.9 *	32.8 ± 7.7 *
[Hb], g/L	149.9 ± 12.2	153.0 ± 11.7	151.2 ± 10.5 *a*	154.1 ± 15.4	162.2 ± 12.6 *	168.5 ± 15.8 *	166.5 ± 13.7 *	166.4 ± 10.3 *	162.7 ± 14.8 *
Ca_{O_2}, mg/dL	19.9 ± 1.5	18.2 ± 1.4 *	18.3 ± 1.4 *a*	18.5 ± 2.0 *	19.4 ± 1.7 ≠	20.5 ± 1.9	20.2 ± 1.7	20.2 ± 1.2	20.0 ± 1.6
AMS (Median, [Range])	0 [0,0]	1 [0,8] *	1 [0,4] *a*	0 [0,2] ≠*a*	0 [0,1]	0 [0,2]	0 [0,2]	0 [0,2]	0 [0,2] *b*

AMS, acute mountain sickness scores; Ca_{O_2}, arterial oxygen content (calculated using SpO_2 and without Pa_{O_2});[Hb], concentration of hemoglobin; HR, heart rate; MAP, mean arterial pressure; Pa_{O_2}, partial pressure of arterial oxygen; P_{ATM}, atmospheric pressure; PET_{CO_2}, partial pressure of end-tidal carbon dioxide; Pl_{O_2}, partial pressure of inspired oxygen; SpO_2, peripheral oxygen saturation; SS-CD, steady-state chemoreflex drive; $\dot{V}_E$, expiratory ventilation.

*Significant difference from baseline (1,045 m), $P < 0.05$.

≠Significant difference from previous day, $P < 0.05$. Unless otherwise stated, $n = 15$.

a $n = 14$.

b $n = 13$.

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Table 2.

Arterial blood gas and electrolyte data during rapid ascent to and residence at 3,800 m on days (D)0, (D)2, and (D)9

Variable, Means ± SD	Calgary (*D0*)	Barcroft Lab (*D2*)	Barcroft Lab (*D9*)
Altitude, m	1,045	3,800	
P_{ATM}, mmHg	665	487	
PI_{O_2}, mmHg	130	92	
Oxygenation and Acid-Base/Electrolyte Variables			
Pa_{O_2}, mmHg	80.8 ± 8.8	50.5 ± 5.2 *	53.8 ± 4.1 *‡
Sa_{O_2}, %	95.8 ± 1.2	85.8 ± 3.8 *	88.3 ± 1.9 *‡
[Hb], g/L	148.4 ± 12.0	149.1 ± 9.4	158.3 ± 9.8 *‡
Hct, %	43.7 ± 3.5	43.9 ± 2.8	46.6 ± 2.9 *‡
Ca_{O_2}, mL/dL	19.6 ± 1.5	17.5 ± 1.3 *	19.2 ± 1.4 ‡
Pa_{CO_2}, mmHg	38.4 ± 3.0	34.3 ± 2.8 *	30.5 ± 1.8 *‡
$[HCO_3^-]a$, mM	24.4 ± 1.8	22.5 ± 2.2 *	19.8 ± 1.4 *‡
pHa	7.412 ± 0.014	7.424 ± 0.017	7.420 ± 0.013
RR, $\Delta[HCO_3^-]a/\Delta Pa_{CO_2}$		0.46 ± 0.28	0.59 ± 0.14
SID, mEq/L	41.0 ± 2.2 [a]	39.4 ± 1.7 *	37.5 ± 1.5 *‡
Base Excess, mM	−0.13 ± 1.8	−1.8 ±2.5 *	−4.7 ± 1.5 *‡
Anion Gap, mM	15.8 ± 1.8	16.3 ± 1.3	16.5 ± 1.1
Osmolality, mOsmol/kgH_2O	283.2 ± 3.2	283.8 ± 1.8	282.3 ± 2.5
Lactate, mM	0.97 ± 0.5 [a]	0.98 ± 0.5	0.74 ± 0.3
Creatinine, μM	73.3 ± 12.4	77.3 ± 12.4	81.6 ± 14.3 *

Ca_{O_2}, arterial oxygen content; [Hb], concentration of hemoglobin; $[HCO_3^-]a$, concentration of arterial bicarbonate; Hct, hematocrit; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Pa_{O_2}, partial pressure of arterial oxygen; P_{ATM}, atmospheric pressure; pHa, arterial pH; PI_{O_2}, partial pressure of inspired oxygen; RR, renal reactivity; Sa_{O_2}, arterial oxygen saturation; SID, strong ion difference.

*Significant difference from baseline (1,045 m), $P < 0.05$.

‡Significant difference from previous day, $P < 0.05$. Unless otherwise stated, $n = 16$.

[a] $n = 15$.