Physiology International, Volume 103 (3), pp. 377–391 (2016)
DOI: 10.1556/2060.103.2016.3.1

V_ESTPD as a measure of ventilatory acclimatization to hypobaric hypoxia

JA Loeppky[1], AC Sheard[2], RM Salgado[3], CM Mermier[4]

[1]Research Section: VA Medical Center, Albuquerque, NM, USA (retired) and Adjunct Faculty: Department of Health, Exercise and Sports Sciences, The University of New Mexico, Albuquerque, NM, USA
[2]School of Kinesiology and Nutritional Science, California State University, Los Angeles, CA, USA
[3]Thermal and Mountain Medicine Division, United States Army Research Institute of Environmental Medicine, Natick, MA, USA
[4]Department of Health, Exercise and Sports Sciences, The University of New Mexico, Albuquerque, NM, USA

Received: March 1, 2016
Accepted: July 15, 2016

This study compared the ventilation response to an incremental ergometer exercise at two altitudes: 633 mmHg (resident altitude = 1,600 m) and following acute decompression to 455 mmHg (≈4,350 m altitude) in eight male cyclists and runners. At 455 mmHg, the V_ESTPD at RER <1.0 was significantly lower and the V_EBTPS was higher because of higher breathing frequency; at VO_2max, both V_ESTPD and V_EBTPS were not significantly different. As percent of VO_2max, the V_EBTPS was nearly identical and V_ESTPD was 30% lower throughout the exercise at 455 mmHg. The lower V_ESTPD at lower pressure differs from two classical studies of acclimatized subjects (Silver Hut and OEII), where V_ESTPD at submaximal workloads was maintained or increased above that at sea level. The lower V_ESTPD at 455 mmHg in unacclimatized subjects at submaximal workloads results from acute respiratory alkalosis due to the initial fall in HbO_2 (≈0.17 pHa units), reduction in $PACO_2$ (≈5 mmHg) and higher PAO_2 throughout the exercise, which are partially pre-established during acclimatization. Regression equations from these studies predict V_ESTPD from VO_2 and P_B in unacclimatized and acclimatized subjects. The attainment of ventilatory acclimatization to altitude can be estimated from the measured vs. predicted difference in V_ESTPD at low workloads after arrival at altitude.

Keywords: acclimatization, acid–base balance, breathing frequency, Haldane effect, hypobaric hypoxia, hypocapnia, hyperventilation, tidal volume

Introduction

Measurements of ventilation (V_E) at high altitudes in acclimatized males have been reported on Mount Everest at rest (25) and exercise (26), during the "Silver Hut" studies (27) and during the "Operation Everest II" (OEII) experiments by Sutton et al. (32). These latter studies and an earlier one (4) indicate that V_ESTPD at the same submaximal workloads is similar to that measured before at low altitude, but near VO_2max it exceeds that at low altitude. Reeves et al. (30) have pointed out the near constancy of the V_ESTPD/VO_2 ratio at rest and submaximal exercise in acclimatized individuals, and that it increases near maximal effort.

Detailed comparisons of V_E during exercise in the same individuals following acute (minutes to hours) exposure to different altitudes or hypobaric hypoxia are limited. It is well

Corresponding author: Jack Loeppky, PhD
Home address: 2725, 7th Street South, Cranbrook, BC V1C4R8, Canada
Phone: +1 250 489 4597; Fax: +1 250 426 4440; E-mail: Loeppkyj@telus.net

known that V_EBTPS during submaximal workloads increases at lower P_B during the acclimatization process (6). Observations after acute exposures have been reported by Stenberg et al. (31) and Elliott et al. (10); their data show that in spite of the early increase of V_EBTPS at 462 and 406 mmHg, respectively, the V_ESTPD/VO_2 ratio was lower than at sea level during steady-state submaximal workloads and at VO_2max by ≈20%. Other reports contain serial measurements after 1–3 days and later after acclimatization (9, 14, 22, 29). Lower resting V_ESTPD during the first day at altitude compared with pre-ascent and subsequent measurements 3–4 days later have also been reported, suggesting early transient hypoxic ventilatory depression and progressive hypocapnia (16). A detailed study of the ventilatory acclimatization process at altitude from resting measurements has been well described by Rahn and Otis (28), but measurements of V_ESTPD during exercise immediately after acute exposure to hypobaric hypoxia are lacking. Therefore, no quantitative comparison of V_ESTPD between acclimatized and unacclimatized individuals has been made.

In this study, where V_E measurements during incremental exercise were made at 1,600 and 4,350 m in subjects acutely exposed to higher altitude without prior acclimatization (38), it was noted that V_ESTPD was lower at submaximal workloads at 4,350 m than at 1,600 m. This led us to explore and quantify this different response from that noted in earlier studies in acclimatized subjects where ventilatory acclimatization (36) had taken place. The purpose of this report was to determine whether this difference in V_ESTPD during exercise might be useful to estimate the magnitude and temporal progression of hypoxic ventilatory acclimatization. If so, this may serve to evaluate the relative effectiveness of acclimatization aids or the "completeness" of acclimatization of an individual or group.

Materials and Methods

Eight males were recruited from the university and local community to investigate the effects of heat acclimation on VO_2max under ambient conditions (633 mmHg/1,600 m/5,250 ft) and after acute exposure to reduced pressure in an altitude chamber at 455 mmHg, equivalent to 4,350 m/14,271 ft according to the equation of West (35).

The subjects, cyclists and runners, were consistently performing an average of 6 h/week of moderate and 2–3 h/week of vigorous exercise during the year prior to the study. Mean ± SD for VO_2max, age, height, and weight were 55 ± 5 mL/min/kg, 28 ± 6 year, 1.78 ± 0.07 m, and 75.4 ± 8.4 kg, respectively. All subjects resided between 1,500 and 1,600 m during the 6 months preceding the study, maintaining their exercise routines during the study. Written informed consent was obtained for the study, as approved by the Human Research Review Committee at the University of New Mexico.

Experimental design

Subjects were tested at the same time of the day at 633 and 455 mmHg and refrained from strenuous exercise, caffeine, and alcohol for 24 h prior to testing. The exercise tests were performed in a decompression chamber at the University of New Mexico, Albuquerque, NM, USA. Subjects first completed a VO_2max test at 633 mmHg with chamber doors open, and 6–9 days later performed the same test at 455 mmHg. Between 22 and 28 days later, these tests were repeated at 455 mmHg, and 4 and 6 days later at 633 mmHg. During the 25-day interval, the subjects underwent a 10-day heat acclimation protocol (38).

All testing was performed on an electronically braked cycle ergometer (Velotron DynaFit Pro, RacerMate, Seattle, WA). The average ambient temperature for all tests was 22 ± 2 °C. Cycling began at 70 W for 1 min, with the workload then increasing 35 W every minute until volitional fatigue or inability to maintain the workload. Subjects pedaled at their preferred rate. The day-to-day error in VO_2max determination by this incremental exercise test is ≈3–4% (2, 37). Gas exchange data were continuously measured breath-by-breath by metabolic cart (ParvoMedics TrueOne 2400, Sandy, UT). Maximal aerobic capacity was the highest VO_2 value averaged over 15 s. Before exercise, the metabolic cart was calibrated with room air (20.94% O_2 and 0.03% CO_2) and a gas of known concentrations (16% O_2 and 4% CO_2). A 3-L syringe was used to calibrate the flow.

Oxygen saturation (SpO_2) measured from an index finger (GO_2 Pulse Oximeter, Philips Respironics, Andover, MA) was averaged each minute. Venous blood was drawn from an antecubital vein for the determination of hemoglobin (Hb) by established procedures (Beckman Coulter, LH750). This was averaged from samples obtained after the first and before the second VO_2max tests at 455 mmHg.

For tests at 455 mmHg, the "ascent" rate was 20 mmHg/min with subjects then resting prior to initiating exercise for approximately 30 min. The average exercise time to reach VO_2max was 9.8 ± 1.2 min at 633 mmHg and 8.4 ± 1.1 min at 455 mmHg. Resting measurements were not made because these are more affected by apprehension, voluntary control of breathing, and discomfort of measuring devices than exercise measurements (14).

Statistics and calculations

Data are reported as mean ± SD. Paired *t*-tests were used to determine the significant differences in V_E at specific equidistant VO_2 values between 633 and 455 mmHg, following a repeated-measures analysis of variance (ANOVA) test for the multiple points. The level of significance was assumed at $p \leq 0.05$. Predicted values of V_EBTPS and V_ESTPD were obtained for each subject from linear regressions of $\ln(V_E)$ (*Y*-axis) vs. VO_2 (*X*-axis). Output values, averaged at 15-s intervals, between the VO_2 of 1.0 L/min and VO_2max were included in the regressions (Fig. 1A). On average, this included 34 values (range: 23–47). For each subject, the two tests at the same P_B were averaged because there was no significant difference between the slopes and intercepts for the eight subjects by paired *t*-test. The slopes of the regression lines (Fig. 1B) were significantly higher for the runs at 455 mmHg than at 633 mmHg, and the intercepts for V_ESTPD were lower. The predicted V_E values obtained from the regression equations for each subject (Fig. 1C) were plotted and averaged at the specifically chosen VO_2 values.

Figure 1 shows how $\ln(V_E)$ values linearize the V_E–VO_2 relationship. Panel A shows the V_EBTPS output values for one subject for both tests at 633 mmHg. Each point is a 15-s average obtained by the software. Panel B shows the corresponding $\ln(V_E)$ values vs. VO_2 and panel C shows the V_EBTPS values predicted from the mean regression equation shown in panel B (curve superimposed in panel A). Similar analyses were performed for V_ESTPD vs. VO_2.

Output values for ventilatory frequency (f_R) and tidal volume (V_T), calculated from V_EBTPS, were plotted vs. VO_2 as shown in Fig. 1A for all 16 tests at each pressure. Various curve-fitting models were evaluated and selected based on the lowest r^2 for the residuals of predicted vs. actual *Y*-values. Based on this, an exponential growth model was chosen for f_R and a Gaussian model for V_T. The resulting equations are shown in Fig. 2 for the same subject as shown in Fig. 1A.

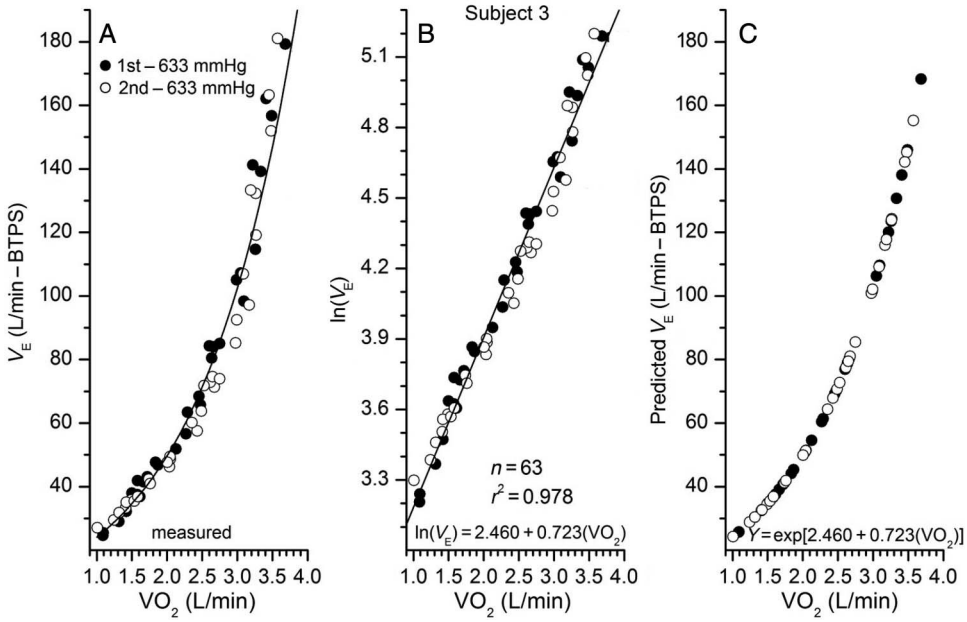

Fig. 1. Example of how predicted V_E vs. VO_2 was obtained for a single subject. Panel A: example of recorded V_EBTPS at 15-s intervals, beginning at 1.0 L/min VO_2 for the two tests at 633 mmHg for subject 3. Panel B: linear regression of ln(V_E) vs. VO_2. There was no significant difference in slope and intercept between the first and second runs for the eight subjects for these plots; therefore, values from both runs were combined from one linear regression equation for each subject at each pressure. Panel C: the predicted V_E from this regression at specific VO_2 values (as shown in Fig. 3). Similar procedures were used to obtain V_ESTPD and also V_EBTPS and V_ESTPD vs. percent of VO_2max

The accuracy of the curve fitting is indicated by the mean r^2 values for the eight tests at 633 mmHg and the eight tests at 455 mmHg in Table I (mean $r^2 = 0.92$). The predicted values of V_E, f_R, and V_T at 0.5 L/min intervals of VO_2 were then averaged at 1.0, 1.5, 2.0, 2.5, 3.0 and VO_2max values from the equations obtained for each subject.

Results

There was no significant difference between the VO_2max values measured at two different occasions at 633 mmHg (4,195 vs. 4,145 mL/min, $p = 0.57$) and 455 mmHg (3,487 vs. 3,562 mL/min, $p = 0.41$), so they were averaged for each pressure ($n = 8$). The average value at 455 mmHg (3,525 ± 333 mL/min) was significantly ($p < 0.001$) lower than at 633 mmHg (4,170 ± 484 mL/min), a percentage reduction of 15.5%. The V_EBTPS values were also not significantly different on the two different occasions at each pressure (difference < 2.5%, $p = 0.48$).

Figure 3A shows the average V_ESTPD and V_EBTPS values at both pressures. The V_EBTPS at 455 mmHg was significantly higher (by repeated-measures ANOVA) between 1.0 and 3.0 L/min of VO_2 than at 633 mmHg by an average of 15.2 L/min (24%), but not significantly higher at VO_2max ($p = 0.10$). Conversely, the mean V_ESTPD was significantly lower at 455 mmHg at VO_2 between 1.0 and 2.5 L/min by 4.1 L/min (14%) and

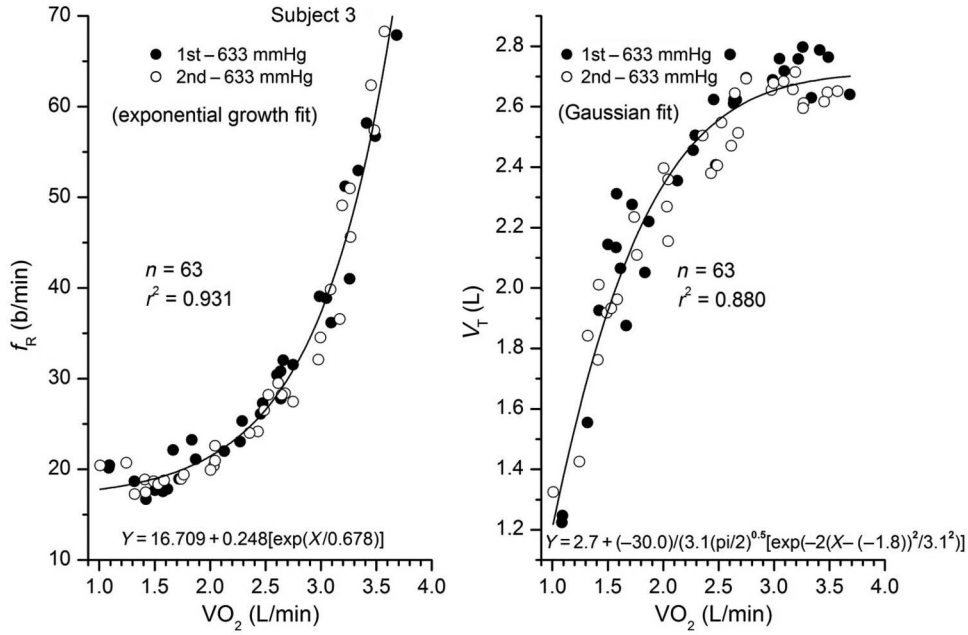

Fig. 2. Example of exponential growth fit to ventilatory frequency (f_R) values, and a Gaussian fit to tidal volume (V_T) for two tests at 633 mmHg for subject 3. V_T calculated as V_EBTPS/f_R. Predicted values from these curves for each subject at specific VO_2 values were averaged for the eight subjects to obtain the average f_R and V_T values (as shown in Fig. 4)

Table I. The r^2 values for curve fitting 16 recorded vs. predicted values

Curve	Mean	SD	Range
ln(V_E) vs. VO_2 (linear)	0.988	0.007	0.970–0.996
ln(V_E) vs. percent of VO_2max (linear)	0.988	0.007	0.970–0.996
f_R vs. VO_2 (exp. growth)	0.901	0.052	0.749–0.966
f_R vs. percent of VO_2max (exp. growth)	0.906	0.073	0.660–0.964
V_T vs. VO_2 (Gaussian)	0.869	0.051	0.738–0.957
V_T vs. percent of VO_2max (Gaussian)	0.864	0.062	0.723–0.958

V_E: ventilation (L/min-BTPS or STPD); VO_2 (L/min); f_R: breathing frequency; V_T: tidal volume. Data points (mean $n = 68$) were 15-s averages combined from both tests by each subject at the same pressure

significantly lower at VO_2max by 28 L/min. The same values are shown as percent of VO_2max in Fig. 3B, indicating that V_EBTPS was quite similar at both pressures, but V_ESTPD remained significantly lower at 455 mmHg by approximately 30% throughout the test.

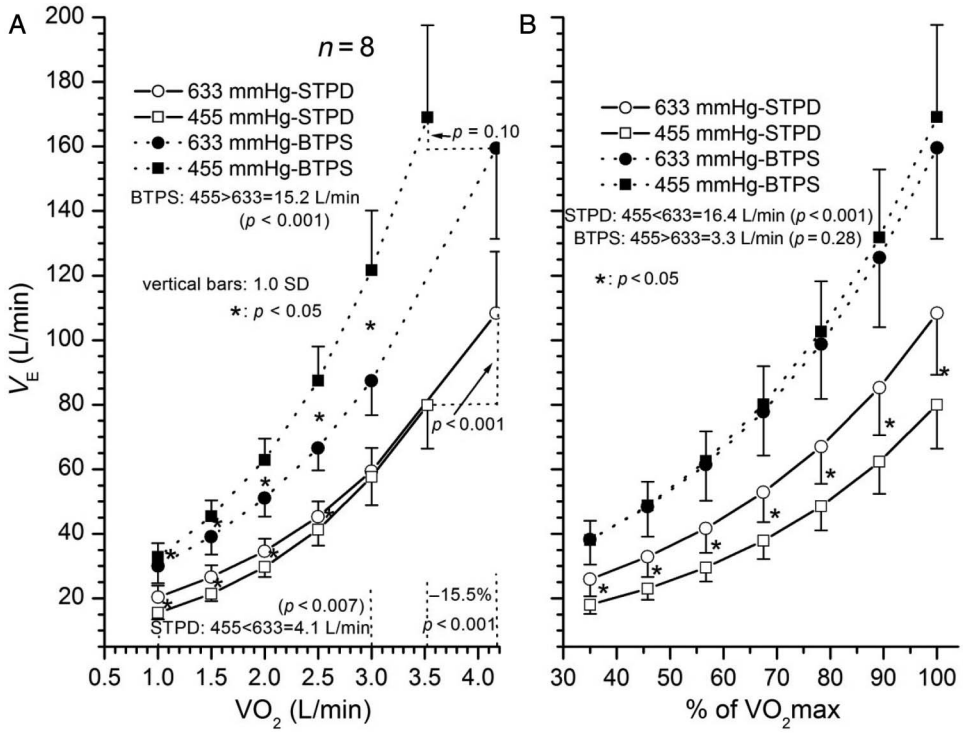

Fig. 3. Mean values for predicted V_ESTPD and V_EBTPS at specific VO_2 values at 633 and 455 mmHg (panel A) and as the average of percent of VO_2max for each subject (panel B). Averages were obtained as shown in Fig. 1. *X*-axis values were chosen equidistant from 1.0 L/min to mean VO_2max. In panel A, the V_ESTPD is significantly lower at 455 mmHg by an average of 4.1 L/min (14%) for the five values between 1.0 and 3.0 L/min and V_EBTPS is higher by an average of 15.2 L/min (24%). In panel B, V_ESTPD is significantly lower throughout at 455 mmHg, but at 633 mmHg it is similar to V_EBTPS. *p*-Values: from repeated-measures ANOVA; *: from paired *t*-test

The increase in V_EBTPS at a given VO_2 at 455 mmHg resulted almost exclusively from the significant increase in f_R with little difference in V_T (Fig. 4A). As percent of VO_2max, the consistently higher f_R at 455 mmHg was almost significant ($p = 0.059$), as shown in Fig. 4B and the V_T was significantly lower.

Comparison of V_E with other studies during exercise in hypobaric hypoxia

In Fig. 5, the measurements from this study (panel A) are presented for comparison with data combined from two other studies following acute altitude exposures (panel B) that reported data as group averages (12, 34). The exercises in the latter studies did not continue to VO_2max. At each pressure, the reported average V_EBTPS values were converted to ln(V_E) values and the exponents plotted from the linear regression vs. reported VO_2 values (as shown in Fig. 1). In each of those two studies, eight subjects residing near sea level, of similar age to those in this study, were exposed acutely to simulated altitude (632, 523, and 429 mmHg) and exercised sequentially with steady-state cycling at increasing intensity to near VO_2max. The similarity of Fig. 5A and B is apparent, the V_ESTPD being lower at

submaximal workloads at the lower pressures, but approaching sea level values as exercise intensity increased.

The reduction of submaximal V_ESTPD at higher altitude shown in Fig. 5A and B differs from studies of acclimatized subjects on mountains, as noted by Pugh et al. in the "Silver Hut" studies (27) and similar observations in the "Operation Everest II" experiments by Sutton et al. (32) and Cymerman et al. (5). Mean data from these two studies are presented in Fig. 5C and D. In these subjects, acclimatized to various altitudes, it is apparent that V_ESTPD is not diminished at low workloads at higher altitudes, but tends to progressively increase as exercise intensity increases and VO_2max is reduced at greater altitude. The V_ESTPD exceeds the values at sea level when VO_2 is above ≈60% of VO_2max. This is emphasized in Fig. 6, which shows the V_ESTPD/VO_2 ratios plotted vs. percent of VO_2max at three pressures from the measurements shown in Fig. 5C and D, along with the values from this study. The ratios at 455 mmHg in this study are clearly separated from those at 633 mmHg and those of the acclimatized subjects. The ratios increase when exercise VO_2 exceeds ≈60% of VO_2max.

The general impression from Fig. 5A, C, and D is that V_EBTPS may be the limiting factor for exercise at altitude when it reaches ≈160–200 L/min, as suggested by Reeves et al. (30) when considering data from the OEII study. The other observation from the 10 end-point values in Fig. 5C and D is that VO_2max is highly correlated with V_ESTPD ($r^2 = 0.971$), and P_B ($r^2 = 0.919$), even though subjects varied in age and aerobic fitness.

Discussion

Numerous studies have indicated that VO_2max cannot be significantly increased with altitude acclimatization [e.g., (14, 33)]. However, submaximal exercise endurance is clearly increased (22), as is the sense of well being and reduction of altitude illness. A recent meta-analysis of 80 studies, where altitude exposure was limited to 24 h, demonstrated that the decline in VO_2max with altitude was greater for subjects with higher aerobic capacity (21). Their model predicts a 25% reduction from 1,600 to 4,350 m for subjects in this study, well above 15.5%. Reports based on a few subjects have noted that VO_2max was higher upon acute (30 min) altitude exposure when compared with several days of acclimatization in spite of higher V_E during exercise in the latter (8, 9). Perhaps, a longer exposure (e.g., to 24 h) to 455 mmHg prior to exercise in this study would have reduced VO_2max toward the predicted value.

The similarity of V_EBTPS as percent of VO_2max (Fig. 3B) during incremental treadmill exercise at different pressures has been reported for residents at 1,000 ft (734 mmHg) taken acutely (40 h) to 10,200 ft (530 mmHg) and for residents at 10,200 ft taken acutely to 1,000 ft (13, 29). It was suggested that V_EBTPS "... is regulated by some mechanism which senses a given effort in terms of exercise capacity."

Why is V_ESTPD at submaximal workloads reduced in acute hypobaric hypoxia?

The lower V_ESTPD (and lower rise of V_EBTPS) upon acute exposure to lower pressure in this study is undoubtedly related to respiratory alkalosis resulting from three processes occurring simultaneously during the approximately 50 min of "ascent" and rest before and during the exercise: (a) the increase in pHa resulting from the 15 to 20% reduction in SaO_2 when exposed to the lower P_IO_2 (Haldane effect), (b) the increase in V_EBTPS from the hypoxic chemoreceptor drive in response to the relatively sudden reduction in PIO_2 (from 123 to 85 mmHg). This lowers $PaCO_2$ and further raises pHa and PaO_2, thereby reducing

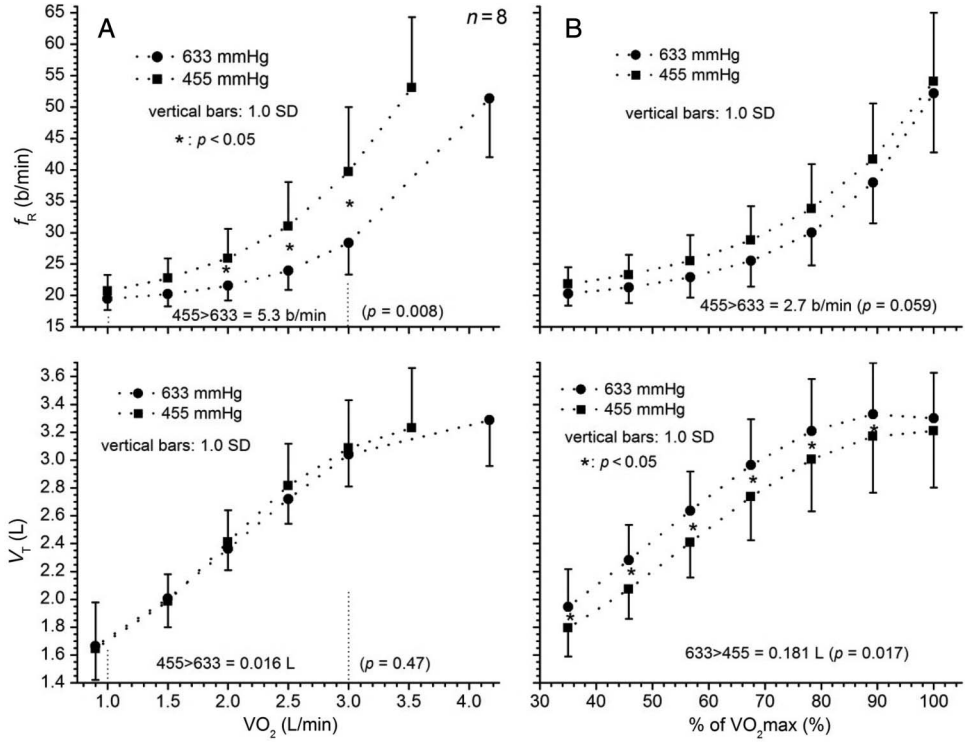

Fig. 4. Mean f_R and V_T values for the eight subjects at submaximal VO_2 and VO_2max (panel A) and as percent of VO_2max (panel B) at 633 and 455 mmHg. The f_R is significantly higher at mid-range VO_2 and V_T is similar. As percent of VO_2max, the f_R tends to be higher at 455 mmHg and V_T is significantly lower. *p*-Values: from repeated-measures ANOVA, *: from paired *t*-test

hypoxic chemoreceptor and central ventilatory drive which initiated the hypocapnia, and (c) any asymptotic decline in blood and lungs O_2 stores as PIO_2 stabilizes at the lower P_B. In chronic hypoxia, these processes have been completed during the acclimatization process prior to exercise measurements. The two main reasons for the recovery of V_ESTPD (and greater V_EBTPS) during subsequent acclimatization are the gradual elimination of HCO_3^- to lower the pHa back to near that at sea level and the increase in hypoxic chemoreceptor sensitivity (7) to compensate for the further reduction in $PaCO_2$. This results in pHa being relatively lower than in acute hypoxia in spite of $PaCO_2$ being reduced.

Measured and estimated differences between acute and chronic hypoxia in ventilation and blood gas values during exercise are summarized in Table II, showing values from this and two other studies for comparison.

For this study, alveolar pressures ($PACO_2$ and PAO_2) were approximated from measurements of mixed expired O_2 and CO_2. These were converted to alveolar values using the anatomical dead space/V_EBTPS ratio calculated for subjects of similar age and weight during exercise obtained from values of $PaCO_2$, VCO_2, and V_EBTPS reported by Wagner et al. (34). Their average ratio of 0.200 ± 0.020 for 11 measurements during exercise at 752, 523, and 429 mmHg was not significantly correlated with their VO_2 or P_B variations. The $PACO_2$ and PAO_2 values are shown in Table II at workloads of 105 W and VO_2max.

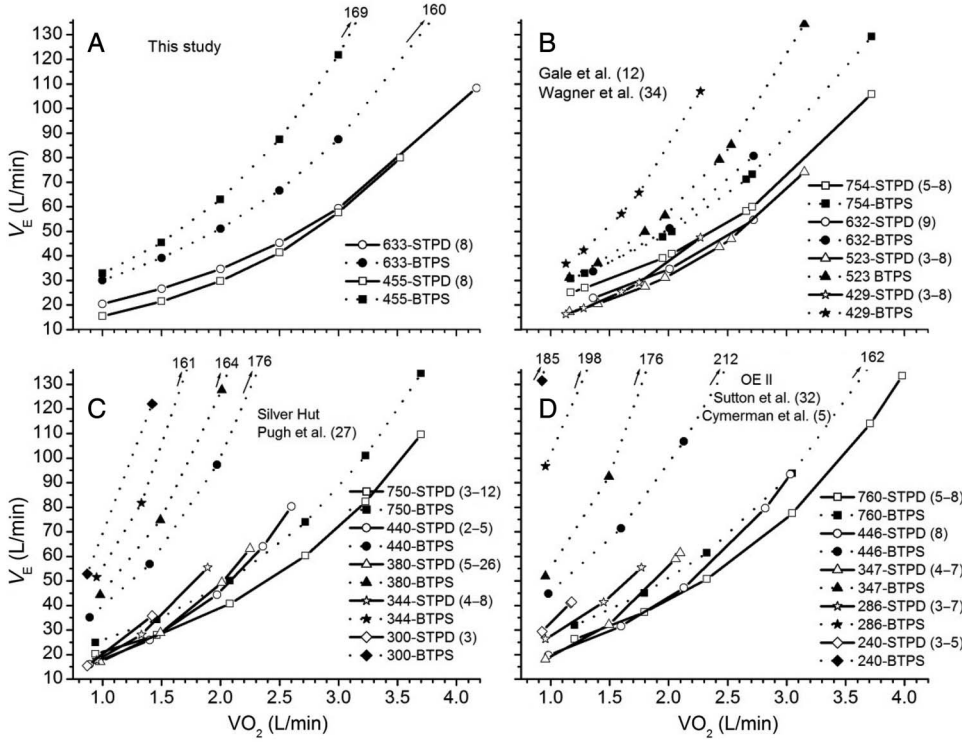

Fig. 5. Mean values for V_ESTPD and V_EBTPS after acute exposure to lower P_B in this study (A) and reported study (B), and after days and weeks of acclimatization from reported studies in the field (C), and a hypobaric study (D). Values in parentheses indicate the number of subjects included in each data point at that pressure

With the assumption of equality between $PaCO_2$ and $PACO_2$, and other measurements and assumptions noted below, the pHa at 633 and 455 mmHg was estimated. The increase in pHa with HbO_2 reduction at rest was found to be 0.008 pH units by Rahn and Otis (28) following acute exposure from sea level to 12,000 ft (3,658 m), a PAO_2 reduction of about 55 mmHg, and 10% HbO_2. In this study, SpO_2 was 15% lower at 455 mmHg than at 633 mmHg at 105 W and VO_2max. With a Haldane factor of 0.28, the steeper O_2 dissociation curve at 455 mmHg results in a greater immediate pHa increase of approximately 0.011 pH units at 105 W and 0.20 units at VO_2max (17).

Circulating Hb concentration rises with incremental exercise; therefore, resting Hb values were corrected from data published by Luft et al. (20) from a study on 10 subjects comparable to the present one (shown in column 3), where the rise was 0.76 g/dL per 1.0 L/min increase in VO_2. This increment was added to the mean resting Hb measured in the eight subjects (15.7 g/dL). The HCO_3^- was obtained from an equation derived with data from two studies. In one study, VO_2max was measured at sea level and on the first day at altitude (406 mmHg) in 10 subjects (19). Another study included an incremental exercise study in 10 subjects breathing 12% O_2, where VO_2, arterial lactate (LA), and HCO_3^- were serially obtained (10). The rise in LA as percent of VO_2max was similar in both studies. The close inverse relationship between LA rise and HCO_3^- as percent of VO_2max when PIO_2 is acutely reduced has been confirmed in other studies (3, 18, 24). Also, the similarity of the rise in LA

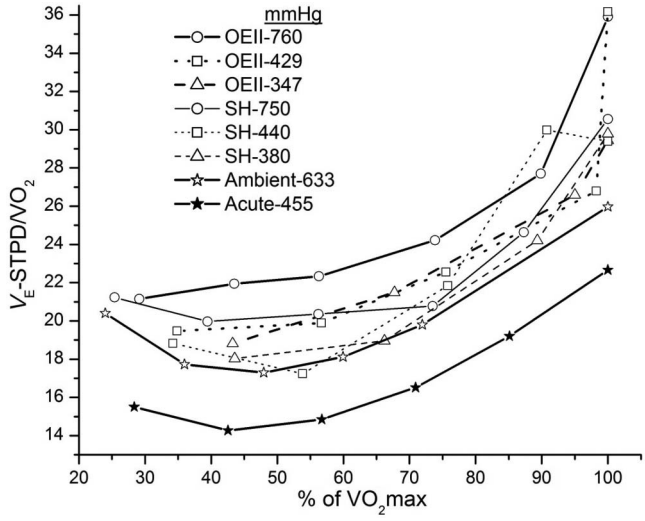

Fig. 6. V_ESTPD/VO_2 vs. percent of VO_2max for this study and from the mean data from Operation Everest (OE) and Silver Hut (SH) studies as shown in Fig. 5C and D

in relation to percent of VO_2max has been demonstrated during normoxia and normobaric hypoxia during ramp exercise (1, 23, 33). The resulting equation utilized in Table II was $HCO_3^- = 1.125 - 0.340[\exp(\text{percent of } VO_2\text{max}/0.2915)]$, with $r^2 = 0.965$ for 24 predicted vs. measured values from the two studies. The pHa was calculated from this HCO_3^- and $PACO_2$, and with measured SpO_2, the PaO_2 was calculated according to the equations of Ellis and Severinghaus (11) and base excess (BE) for fully oxygenated whole blood (18). Table II indicates that the average reduction of H^+ during exercise at 455 mmHg compared to 633 mmHg is ≈7 nmol/L, contributing to offset the chemoreceptor hypoxic drive. In acclimatized subjects, shown in column 6 at a VO_2 of 1.6 L/min, the pHa, HCO_3^-, and BE are lower than at 1.4 L/min in this study (column 4) because these have been shifted downward before exercise in the acclimatization process (32).

The breathing pattern response to exercise in poikilocapnic hypoxia in Fig. 4A shows that the increase in V_EBTPS at 455 mmHg results from the higher f_R. The relatively greater resting hypocapnia at the lower PIO_2, combined with the exercise stimulus, would favor the greater f_R and offset the contribution of V_T compared to 633 mmHg. The 28% lower gas density at 455 mmHg would also tend to favor f_R over V_T for increasing V_E (15). In agreement with our findings in Fig. 4A, Hansen et al. (14) have shown that shortly after arrival at 458 mmHg, the rise in V_EBTPS during submaximal exercise was accomplished entirely by f_R in subjects ascending abruptly with an additional contribution from V_T to increasing V_E in those that ascended gradually.

The attenuation of V_ESTPD shortly after arrival at altitude is evident in previous studies, but rarely mentioned because the focus has been on V_EBTPS. Measurements by Hansen et al. (14) indicated a 28% reduction in V_ESTPD from sea level to 458 mmHg in eight subjects during submaximal exercise 2 days after being transported to an altitude in 6 h, while the decrease in eight others who ascended gradually over 2 days was only 11%. After 15–18 days at altitude, V_ESTPD in both groups increased to near baseline. The V_ESTPD at rest showed similar trends, as did a report on resting measurements by Huang et al. (16) at the same altitude. Elliot et al. (10) reported a 14% reduction the first day after arrival at 406 mmHg at 84% VO_2max in eight subjects. Stenberg et al. (31) showed a 14% reduction upon acute

Table II. Mean measured and estimated submaximal and maximal values of the eight subjects at 633 and 455 mmHg

Variable	Submax	Max	Max (Luft et al.)	Submax	Max	Submax (Sutton et al.)
P_B (mmHg)	633	633	*630*	455	455	*428*
n	8	8	*10*	8	8	*8*
Workload (W)	**105 (1)**	**365 (44)**	***295***	**105 (0)**	**321 (41)***	***120***
VO_2 (L/min)	**1.502 (0.097)**	**4.170 (0.484)**	***3.279***	**1.433 (0.110)**	**3.525 (0.333)***	***1.598***
V_EBTPS (L/min)	**39.6 (6.5)**	**159.5 (28.1)**	***126.3***	**44.1(6.0)***	**169.0 (28.6)**	***71.8***
V_ESTPD (L/min)	**26.9 (4.4)**	**108.3 (16.6)**	***85.3***	**20.8 (2.8)***	**77.5 (14.2)***	***31.7***
V_ESTPD/VO_2	**17.9 (2.5)**	**26.7 (3.0)**	***26.0***	**14.5 (1.6)***	**22.6 (3.0)***	***19.8***
RER	**0.86 (0.07)**	**1.19 (0.04)**	***1.09***	**0.87 (0.03)**	**1.20 (0.04)**	***0.87***
$PACO_2$ (mmHg)	**35.9 (3.6)**	**33.5 (3.6)**	***29.7 (a)***	**31.0 (3.6)***	**27.7 (3.9)***	***23.9 (a)***
PAO_2 (mmHg)	**82.1 (5.1)**	**93.6 (3.4)**	*94.3 (b)*	**50.8 (4.0)***	**61.4 (3.7)***	*53.1 (b)*
SpO_2 (%)	**94.6 (2.8)**	**90.9 (2.8)**	***91.7***	**80.0 (3.1)***	**75.8 (3.5)***	***74.2***
Hb (g/dL)	16.6 (c)	18.5 (c)	***18.2***	16.6 (c)	18.1 (c)	*16.7 (c)*
HCO_3^- (mmol/L)	23.9 (d)	14.6 (d)	***14.1***	23.7 (d)	14.6 (d)	***15.7***
pHa	7.445 (e)	7.261 (e)	***7.304***	7.505 (e)	7.343 (e)	***7.440***
H^+ (nmol/L)	35.9	54.8	***49.7***	31.3	45.4	*36.3*
BE (mmol/L)	0.8 (f)	−10.7 (f)	***−9.9***	1.6 (f)	−9.3 (f)	*−6.2 (f)*
PaO_2 (mmHg)	70.4 (g)	70.2 (g)	***68.0***	39.5 (g)	43.3 (g)	***42.2***

Column 3: average measurements from Luft et al. (20). Column 6: average of acclimatized subjects from Sutton et al. (32). Bold: measured mean (±1.0 SD); *: value significantly different ($p < 0.05$) from corresponding value at 633 mmHg. $PACO_2$ and PAO_2: calculated from mixed expired gas pressures and estimated alveolar dead space (see the text). (a): arterial PCO_2; (b): PAO_2 calculated by alveolar equation with $PaCO_2$; (c): calculated as resting value (15.7 g/dL) + 0.76 × (VO_2 − 0.3); (d): HCO_3^- bicarbonate concentration calculated by equation in the text from percent of VO_2max, assuming baseline = 24.0 mmol/L; (e): calculated from HCO_3^- and $PACO_2$ by Henderson–Hasselbalch equation; hydrogen ion concentration (H^+) from pHa; (f): base excess (BE) calculated from oxygenated whole blood (18); (g): calculated from SpO_2 with equation by Ellis, corrected to pHa with equation by Severinghaus (11)

exposure to 462 mmHg in a protocol similar to ours in six subjects. Maher et al. (22) reported a 32% reduction on day 2 which returned minimally after remaining 10 days at 458 mmHg. Average data from Dill et al. (9) showed a 15% decrease at 455 mmHg in four subjects after less than 1 h. Reeves et al. (29) reported an insignificant drop in five young males on the second day after ascent from 734 to 530 mmHg, suggesting that the altitude may have been too low to induce sufficient hypocapnia because the PaO_2 measured in two subjects was near 60 mmHg, the threshold of hypoxemia required for V_E to respond (28). The range in values of V_ESTPD attenuation in these reports indicates that it depends on the magnitude of the

pressure change, the length of the time and the rate of the pressure drop before measurements are made, the subjects' hypoxic chemosensitivity, and the intensity of the exercise where measurements are made. If V_E is measured repeatedly over time at the same workload in the same subject at the reduced pressure, the time course of the V_ESTPD rise to pre-ascent levels should correlate with ventilatory acclimatization. This must be measured at a workload below 60% of VO_2max predicted for the lower pressure to avoid the additional contribution to V_E by metabolic acidosis.

Predictions of the extent of ventilatory acclimatization by V_ESTPD

Multiple linear regression equations for the prediction of V_ESTPD from VO_2 and P_B were obtained from mean data points in Figs 5A–D (excluding the two lowest pressures in C and D). The accuracy of these predictions is indicated in Table III, where predicted values are shown for 760, 633, and 455 mmHg. The predictions are more accurate for V_ESTPD than V_EBTPS as indicated by the higher SEE for the latter. The differences between acclimatized and unacclimatized subjects are consistent between the two pairs of studies evaluated at a low submaximal level of VO_2 at 1.5 L/min. For subjects acutely exposed to a simulated altitude, the V_ESTPD is reduced from the baseline altitude by the same amount (13%), even though the subjects in this study were residing at 633 mmHg and those in study 2 at near sea level. The two studies of acclimatized subjects show an increase in predicted V_ESTPD from 760 to 455 mmHg of ≈25%. Table III indicates that the degree of ventilatory acclimatization can be

Table III. Regression equations for V_ESTPD (L/min) in four studies and changes predicted for $VO_2 = 1.5$ L/min at 760, 633, and 455 mmHg

Study	Equation	*n*	SEE	P_B	V_ESTPD	V_EBTPS
This study (acclim. to 633 mmHg)	V_ESTPD = exp[2.094+ 0.557(VO_2 – L/min) + 0.000461(P_B – mmHg)]	13	3.0	760	26.6	32.2
				633	25.1	37.0
			(5.3)	455	23.1 (−13%)	48.9 (52%)
Gale et al. (12) and Wagner et al. (34) (acclim. to 750 mmHg)	V_ESTPD = exp[1.977+ 0.655(VO_2 – L/min) + 0.000441(P_B – mmHg)]	22	5.3	760	27.0	32.7
				633	25.5	37.6
			(8.0)	455	23.6 (−13%)	49.9 (53%)
Pugh et al. (27) (Silver Hut) (acclim. from 400 to 300 mmHg)	V_ESTPD = exp[2.469 + 0.747(VO_2 – L/min) − 0.000462(P_B – mmHg)]	15	9.1	760	25.5	30.9
				633	27.0	39.8
			(14.2)	455	29.3 (15%)	62.0 (101%)
Sutton et al. (32) and Cymerman et al. (5) (OEII) (acclim. from 428 to 282 mmHg)	V_ESTPD = exp[2.560 + 0.685(VO_2 – L/min) − 0.000339(P_B – mmHg)]	15	12.3	760	27.9	33.8
				633	29.2	43.0
			(23.4)	455	31.0 (11%)	65.6 (94%)

n: number of averaged data points at pressures (as shown in Fig. 5) from which equation was obtained; SEE: standard error of linear regression of measured V_ESTPD vs. predicted V_ESTPD by equation; (SEE): standard error of linear regression of measured V_EBTPS vs. predicted V_EBTPS by equation (not shown). Percentage change in V_E from 760 to 455 mmHg is in parentheses

evaluated by measuring V_E in response to a low level of work at reduced pressure; V_EBTPS is predicted to increase between 53 and 120% above sea level values at 455 mmHg depending on the progress of ventilatory acclimatization. These predictions remain to be established for acutely breathing hypoxic gas mixtures, where P_B remains constant (normobaric hypoxia) and PIO_2 is reduced.

Conclusion and Limitations

A measure of ventilatory acclimatization to hypobaric hypoxia can be approximated by comparing V_ESTPD measured serially over time at low P_B (LP) during a low submaximal workload, e.g., 100 W where $VO_2 \approx 1.5$ L/min, with V_ESTPD measured earlier at the higher P_B (HP) resident altitude. If considering only V_EBTPS, the "acclimatized" level will be reached when V_EBTPS (LP) = V_EBTPS (HP) × (HP-47)/(LP-47). For example, in this study at a VO_2 of 1.5 L/min, the V_EBTPS should have increased from the measured value of 39.6 at 633 mmHg to 56.9 L/min at 455 mmHg (+44%) if the subjects had been acclimatized, compared with the measured value of 44.1 L/min (+11%) shown in Table II, columns 1 and 4.

These observations are based on estimations and assumptions from subjects residing at 1,600 m. Differences found in sea level residents would probably be minor as the resting SaO_2 and pHa are minimally reduced at 1,600 m compared to sea level. Serial measurements of blood gases at rest and exercise following transitions in P_B during longer continuous exposures would refine this model and allow for more precise estimates of the early time course of the acid–base and ventilatory aspects of acclimatization.

Acknowledgements

The authors would like to thank James McCormick and Trisha McLain for their technical assistance in performing the experiments, as well as Dr. Jill Inouye, Dr. Daryl Macias, and Marc Beverly, PA-C, for their medical oversight during these exercise studies. The authors would also like thank the subjects for their time and energy in making this study possible.

This work was funded in part by the Research Allocations Committee, Overhead Funds Allocation Committee and Graduate and Professional Student Association at the University of New Mexico.

Conflict of interest

The authors declare no conflicts of interest.

Abbreviations

BE = base excess; deviation of total buffer base from normal (mmol/L)
f_R = ventilation frequency (breaths/min)
H^+ = concentration of hydrogen ions in blood (nmol/L)
Hb = hemoglobin concentration of whole blood (g/dL)
HbO_2 = concentration of oxygenated Hb (%)
HCO_3^- = concentration of bicarbonate ions in blood (mmol/L)
LA = lactate concentration in blood (mmol/L)
$\ln(V_E)$ = natural log of the V_E value
$PaCO_2$ = partial pressure of CO_2 in arterial blood (mmHg)
$PACO_2$ = partial pressure of CO_2 in mixed alveolar gas (mmHg)

PaO_2 = partial pressure of O_2 in arterial blood (mmHg)
PAO_2 = partial pressure of O_2 in mixed alveolar gas (mmHg)
P_B = barometric (atmospheric) pressure (mmHg)
pHa = negative common log of hydrogen ion concentration (H^+) in arterial blood
PIO_2 = partial pressure of O_2 in inspired air (mmHg)
RER = respiratory exchange ratio (VCO_2/VO_2)
SaO_2 = blood oxygen saturation, measured by oximetry (%)
SpO_2 = blood oxygen saturation, measured by pulse oximetry (%)
VCO_2 = output of CO_2 (L or mL/min)
V_E = pulmonary ventilation (L/min)
V_EBTPS = ventilation volume calculated at body temperature (37 °C), ambient pressure, saturated
V_ESTPD = ventilation volume calculated at standard temperature (0 °C), pressure (760 mmHg), dry
VO_2 = oxygen consumption (L or mL/min)
VO_2max = maximal O_2 consumption during a ramp exercise (mL/min/kg body wt)
V_T = tidal volume per breath (L or mL)
W = Watt; unit of physical power performed

REFERENCES

1. Asmussen E, von Döbeln W, Nielsen M: Blood lactate and oxygen debt after exhaustive work at different oxygen tensions. Acta Physiol. Scand. 15, 57–62 (1948)
2. Astorino TA, White AC, Dalleck LC: Supramaximal testing to confirm attainment of VO_2max in sedentary men and women. Int. J. Sports Med. 30, 279–284 (2009)
3. Beaver WL, Wasserman K, Whipp BJ: Bicarbonate buffering of lactic acid generated during exercise. J. Appl. Physiol. 60, 472–478 (1986)
4. Christensen EH: Sauerstoffaufnahme und respiratorische Funktionen in grossen Höhen. Scand. Arch. Physiol. 76, 88–100 (1937)
5. Cymerman A, Reeves JT, Sutton JR, Rock PB, Groves BM, Malconian MK, Young PM, Wagner PD, Houston CS: Operation Everest II: maximal oxygen uptake at extreme altitude. J. Appl. Physiol. 66, 2446–2453 (1989)
6. Dejours P, Kellogg RH, Pace N: Regulation of respiration and heart rate response in exercise during altitude acclimatization. J. Appl. Physiol. 18, 10–18 (1963)
7. Dempsey JA, Powell FL, Bisgard GE, Blain GM, Poulin MJ, Smith CA: Role of chemoreception in cardiorespiratory acclimatization to, and deacclimatization from, hypoxia. J. Appl. Physiol. 116, 858–866 (2014)
8. Dill DB, Myhre LG, Brown DK, Burrus K, Gehlsen G: Work capacity in chronic exposures to altitude. J. Appl. Physiol. 23, 555–560 (1967)
9. Dill DB, Myhre G, Phillips EE Jr, Brown DK: Work capacity in acute exposures to altitude. J. Appl. Physiol. 21, 1168–1176 (1966)
10. Elliott JE, Laurie SS, Kern JP, Beasley KM, Goodman RD, Kayser B, Subudhi AW, Roach RC, Lovering AT: AltitudeOmics: impaired pulmonary gas exchange efficiency and blunted ventilatory acclimatization in humans with patent foramen ovale after 16 days at 5,260 m. J. Appl. Physiol. 118, 1100–1112 (2015)
11. Ellis RK, Severinghaus JW: Determination of PO_2 from saturation. J. Appl. Physiol. 67, 902 (1989)
12. Gale GE, Torre-Bueno JR, Moon RE, Saltzman HA, Wagner PD: Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude. J. Appl. Physiol. 58, 978–988 (1985)
13. Grover RF, Reeves JT, Grover EB, Leathers JE: Muscular exercise in young men native to 3,100 m altitude. J. Appl. Physiol. 22, 555–564 (1967)
14. Hansen JE, Vogel JA, Stelter GP, Consolazio CF: Oxygen uptake in man during exhaustive work at sea level and high altitude. J. Appl. Physiol. 23, 511–522 (1967)
15. Hesser CM, Lind F, Linnarsson D: Significance of airway resistance for the pattern of breathing and lung volumes in exercising humans. J. Appl. Physiol. 68, 1875–1882 (1990)

16. Huang SY, Alexander JK, Grover RF, Maher JT, McCullough RE, McCullough RG, Moore LG, Sampson JB, Weil JV, Reeves JT: Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 56, 602–606 (1984)
17. Loeppky JA, Luft UC, Fletcher ER: Quantitative description of whole blood CO_2 dissociation curve and Haldane effect. Respir. Physiol. 51, 167–181 (1983)
18. Loeppky JA, Fletcher ER, Roach RC, Luft UC: Relationship between whole blood base excess and CO_2 content in vivo. Respir. Physiol. 94, 109–120 (1993)
19. Lovering AT, Romer LM, Haverkamp HC, Pegelow DF, Hokanson JS, Eldridge MW: Intrapulmonary shunting and pulmonary gas exchange during normoxic and hypoxic exercise in healthy humans. J. Appl. Physiol. 104, 1418–1425 (2008)
20. Luft UC, Finkelstein S, Elliott JC (1974): Respiratory gas exchange, acid–base balance, and electrolytes during and after maximal work breathing 15 mmHg P_ICO_2. In: Carbon Dioxide and Metabolic Regulations, eds Nahas G, Schaefer KE, Springer-Verlag, New York, pp. 282–293
21. MacInnis MJ, Nugent SF, MacLeod KE, Lohse KR: Methods to Estimate VO_2max upon Acute Hypoxia Exposure. Med. Sci. Sports Exerc. 47, 1869–1876 (2015)
22. Maher JT, Jones LG, Hartley LH: Effects of high-altitude exposure on submaximal endurance capacity of men. J. Appl. Physiol. 37, 895–898 (1974)
23. Ofner M, Wonisch M, Frei M, Tschakert G, Domej W, Kröpfl JM, Hofmann P: Influence of acute normobaric hypoxia on physiological variables and lactate turn point determination in trained men. J. Sports Sci. Med. 13, 774–781 (2014)
24. Ozcelik O, Kelestimur H: Effects of acute hypoxia on the estimation of lactate threshold from ventilatory gas exchange indices during an incremental exercise test. Physiol. Res. 53, 653–659 (2004)
25. Pugh LGCE: Resting ventilation and alveolar air on Mount Everest: with remarks on the relation of barometric pressure to altitude in mountains. J. Physiol. 135, 590–610 (1957)
26. Pugh LGCE: Muscular exercise on Mount Everest. J. Physiol. 141, 233–261 (1958)
27. Pugh LGCE, Gill MB, Lahiri S, Milledge JS, Ward MP, West JB: Muscular exercise at great altitudes. J. Appl. Physiol. 19, 431–440 (1964)
28. Rahn H, Otis AB: Man's respiratory response during and after acclimatization to high altitude. Am. J. Physiol. 157, 445–462 (1949)
29. Reeves JT, Grover RF, Cohn JE: Regulation of ventilation during exercise at 10,200 ft in athletes born at low altitude. J. Appl. Physiol. 22, 546–554 (1967)
30. Reeves JT, Groves BM, Sutton JR, Wagner PD, Green HJ, Cymerman A, Houston CS (1991): Adaptations to hypoxia: lessons from Operation Everest II. In: Current Pulmonology, ed Simmons DH, Mosby Year Book, St. Louis, pp. 23–50
31. Stenberg J, Ekblom B, Messin R: Hemodynamic response to work at simulated altitude, 4,000 m. J. Appl. Physiol. 21, 1589–1594 (1966)
32. Sutton JR, Reeves JT, Wagner PD, Groves BM, Cymerman A, Malconian MK, Rock PB, Young PM, Walter SD, Houston CS: Operation Everest II: oxygen transport during exercise at extreme simulated altitude. J. Appl. Physiol. 64, 1309–1321 (1988)
33. van Hall G, Lundby C, Araoz M, Calbet JA, Sander M, Saltin B: The lactate paradox revisited in lowlanders during acclimatization to 4100 m and in high-altitude natives. J. Physiol. 587(Pt.5), 1117–1129 (2009)
34. Wagner PD, Gale GE, Moon RE, Torre-Bueno JR, Stolp BW, Saltzman HA: Pulmonary gas exchange in humans exercising at sea level and simulated altitude. J. Appl. Physiol. 61, 260–270 (1986)
35. West JB: Prediction of barometric pressures at high altitude with the use of model atmospheres. J. Appl. Physiol. 81, 1850–1854 (1996)
36. West JB: Respiratory and circulatory control at high altitudes. J. Exp. Biol. 100, 147–157 (1982)
37. Westgarth-Taylor C, Hawley JA, Rickard S, Myburgh KH, Noakes TD, Dennis SC: Metabolic and performance adaptations to interval training in endurance-trained cyclists. Eur. J. Appl. Physiol. 75, 298–304 (1997)
38. White AC, Salgado RM, Astorino TA, Loeppky JA, Schneider SM, McCormick JJ, McLain TA, Kravitz L, Mermier CM: The effect of ten days of heat acclimation on exercise performance in acute hypobaric hypoxia (4350 m). Temperature 3, 176–185 (2015)