



What Is the Point of the Peak? Assessing Steady-State Respiratory Chemoreflex Drive in High Altitude Field Studies

Christina D. Bruce, Gary Saran, Jamie R. Pfoh,
Jack K. Leacy, Shaelynn M. Zouboules,
Carli R. Mann, Joel D. B. Peltonen,
Andrea M. Linares, Alexandra E. Chiew,
Ken D. O'Halloran, Mingma T. Sherpa,
and Trevor A. Day

Abstract

Measurements of central and peripheral respiratory chemoreflexes are important in the context of high altitude as indices of ventilatory acclimatization. However, respiratory chemoreflex tests have many caveats in the field, including considerations of safety, portability and consistency. This overview will (a) outline

commonly utilized tests of the hypoxic ventilatory response (HVR) in humans, (b) outline the caveats associated with a variety of peak response HVR tests in the laboratory and in high altitude fieldwork contexts, and (c) advance a novel index of steady-state chemoreflex drive (SS-CD) that addresses the many limitations of other chemoreflex tests. The SS-CD takes into account the contribution of central and peripheral respiratory chemoreceptors, and eliminates the need for complex equipment and transient respiratory gas perturbation tests. To quantify the SS-CD, steady-state measurements of the pressure of end-tidal ($P_{ET}CO_2$ (Torr)) and peripheral oxygen saturation (SpO_2 ; %) are used to quantify a stimulus index (SI; $P_{ET}CO_2/SpO_2$). The SS-CD is then calculated by indexing resting ventilation (L/min) against the SI. SS-CD data are subsequently reported from 13 participants during incremental ascent to high altitude (5160 m) in the Nepal Himalaya. The mean SS-CD magnitude increased approximately 96% over 10 days of incremental exposure to hypobaric hypoxia, suggesting that the SS-CD tracks ventilatory acclimatization. This novel SS-CD may have future utility in fieldwork studies

C. D. Bruce · G. Saran · J. R. Pfoh · S. M. Zouboules
C. R. Mann · J. D. B. Peltonen · A. M. Linares
A. E. Chiew · T. A. Day (✉)
Department of Biology, Faculty of Science and
Technology, Mount Royal University,
Calgary, AB, Canada
e-mail: tday@mtroyal.ca

J. K. Leacy
Department of Biology, Faculty of Science and
Technology, Mount Royal University,
Calgary, AB, Canada

Department of Physiology, University College Cork,
Cork, Ireland

K. D. O'Halloran
Department of Physiology, University College Cork,
Cork, Ireland

M. T. Sherpa
Kunde Hospital, Khunde, Solukhumbu, Nepal

assessing ventilatory acclimatization during incremental or prolonged stays at altitude, and may replace the use of complex and potentially confounded transient peak response tests of the HVR in humans.

Keywords

Hypoxic ventilatory response · Peripheral chemoreceptors · Central chemoreceptors · High altitude · Steady-state chemoreflex drive

2.1 Introduction

2.1.1 Respiratory Chemostimuli, Chemoreceptors and Chemoreflexes

Blood gases (O_2 and CO_2) are maintained at relatively constant values, in part through the coordination and interaction between central (brainstem) and peripheral (carotid body) chemoreceptors. Central chemoreceptors, located at various loci throughout the brainstem, detect the accumulation of $PCO_2/[H^+]$ in brain tissue (Guyenet and Bayliss 2015). Peripheral chemoreceptors are found within the carotid bodies, located bilaterally at the bifurcation of the common carotid arteries. The carotid bodies detect rapid changes in both O_2 and CO_2 in a synergistic fashion (Fitzgerald and Parks 1971; Lahiri and DeLaney 1975; López-Barneo et al. 2016).

In reduced preparations, intact animals and humans, chemoreflexes resulting from chemoreceptor stimulation can be measured in a variety of ways, depending upon the model system, context and experimental question (Duffin 2011; Teppema and Dahan 2010; Powell 2006, 2012). For example, in humans, the central chemoreflex can be elicited and measured by administering increases in CO_2 in a background of hyperoxia (>300 Torr PO_2), in a step-wise (steady-state) or incremental (rebreathing) fashion. The resulting linear response in ventilation quantifies the responsiveness. The relative hyperoxia silences the peripheral chemoreceptors to the increases in CO_2 , isolating the central chemoreceptors. The

peripheral chemoreflex can be elicited through tests exploiting both temporal domain and stimulus specificity (Pedersen et al. 1999; Smith et al. 2006). Because the carotid bodies detect rapid changes in blood gases, transient changes in O_2 and CO_2 are likely representative of the peripheral chemoreflex. In addition, because the central chemoreceptors are thought to limit their responsiveness to $PCO_2/[H^+]$, responses to changes in O_2 , particularly in isocapnic conditions, likely represent the peripheral chemoreflex.

2.1.2 Hypoxic Ventilatory Response (HVR) Tests

Exposure to acute normobaric or prolonged hypobaric hypoxia presents a profound and sometimes life-threatening stressor. Many organ systems interact to coordinate and mount an acute response, including the sympathetic nervous system (SNS), cardiovascular and respiratory systems. In response to carotid body stimulation, a SNS response is elicited, increasing cardiac output and peripheral resistance, with a subsequent increase in mean arterial pressure, the driving force for maintaining blood flow to tissues. The respiratory system mounts a robust hypoxic ventilatory response (HVR), which can be measured and quantified in many ways (e.g., Teppema and Dahan 2010). A number of these tests with relevant caveats are outlined below.

2.1.2.1 Steady-State Isocapnic and Poikilocapnic Hypoxia Tests

Using chambers, large breathing bags with pre-mixed gas concentrations or more sophisticated dynamic end-tidal forcing (DEF) systems, participants can be exposed to single or multiple steady-state reductions in the fraction of inspired (F_I) O_2 . In the case of acute normobaric hypoxia in the isocapnic state, a large peak response is elicited within minutes, followed by hypoxic ventilatory decline (HVD; e.g., Powell et al. 1998; Steinback and Poulin 2007), possibly due to increases in brainstem blood flow and CO_2 washout from central chemoreceptors

(Berkenbosch et al. 1995; Hoiland et al. 2015) or other central or peripheral mechanisms (e.g., Honda 1995; Long et al. 1993; Poulin and Robbins 1998; Robbins 1995). In the poikilocapnic state, where CO₂ is allowed to drift downward as a result of the ventilatory response, the peak response is much smaller. In this poikilocapnic context, steady-state ventilation is similar to baseline conditions after approximately 10 min, likely due in part to the CO₂-O₂ stimulus interaction at the carotid body, and a new steady-state is achieved between hypoxia, hypocapnia and ventilation (e.g., Steinback and Poulin 2007; Pfoh et al. 2017). In either case, even though the hypoxic exposure is steady-state in nature, the response is quantified by visually identifying the peak in ventilation (e.g., Hoiland et al. 2015; Pfoh et al. 2016; Steinback and Poulin 2007), making these tests essentially peak response tests. In the context of high altitude ascent, these tests require sophisticated equipment that lacks portability (e.g., DEF system, gas tanks, gas analyzers, calibration gases). In the case of isocapnic hypoxia tests, it is an open question as to what level is appropriate to clamp the CO₂ at. Because of carotid body acclimatization, and the associated increase in ventilation, participants become incrementally more hypocapnic with ascent and acclimatization, departing from their sea level values during baseline measurements at altitude. In addition, because of the renal compensations (outlined below), there is a reduction in buffering capacity, and a given change in CO₂ will represent a larger relative chemoreceptor stimulus (e.g., Eger et al. 1968; Fan et al. 2010). Thus, participants simply cannot tolerate levels of CO₂ that would be eucapnic at sea level, prior to ascent. Because of these changes in CO₂ and bicarbonate, it is difficult to isolate the hypoxic responsiveness alone given the significant changes in other relevant variables.

2.1.2.2 Transient Hypoxic or Hyperoxic Tests

Given the reported temporal domain (i.e., fast) and stimulus specificity (i.e., hypoxia) of the carotid chemoreceptors, transient tests of the peripheral chemoreflex have been developed and

utilized (Chua and Coats 1995; Edelman et al. 1973; Pfoh et al. 2016). Briefly, participants are exposed to multiple breaths of 100% N₂ to elicit a transient HVR. We recently compared a transient 100% N₂ test (TT-N₂) to both steady-state isocapnic and poikilocapnic HVR tests (SS-ISO and SS-POI respectively), and showed that (a) all three tests had different magnitudes, (b) the TT-HVR and SS-ISO test were moderately correlated with each other, within-individual and (c) the TT-N₂ had very little confounding sympathetic, cardiovascular and cerebrovascular responses, which are well-described with the SS-ISO (e.g., Steinback and Poulin 2008; Steinback et al. 2009). However, even though the TT-N₂ and SS-ISO tests are moderately correlated, the TT-N₂ was smaller in magnitude than that of SS-ISO tests and had a lot of within-individual variability between trials (Pfoh et al. 2016). From a fieldwork perspective, the TT-N₂ has similar limitations as the SS-ISO, given that a gas tank (100% N₂) and a calibrated gas analyzer is required, which limit portability. In addition, all hypoxic tests may be dangerous and uncomfortable for participants who are already hypoxic during baseline conditions at altitude, depending on the testing altitude.

In an attempt to overcome the portability and safety caveats of steady-state and transient hypoxic tests, we also recently characterized a transient hyperoxic withdrawal test (TT-O₂) in the context of steady-state hypoxia in the laboratory, and compared it to the TT-N₂ and a non-peak response SS-POI test (following 10-min of steady-state hypoxia). The TT-O₂, originally developed by Dejours (1962), requires only a 100% O₂ tank (readily available in cities prior to ascending to altitude), a spirometer and a pulse oximeter. Unlike the Dejours method, which only quantified a change in ventilation following transient 100% O₂ exposure, we indexed the ventilatory change against the change in peripheral oxygen saturation (SpO₂), providing normative values for this test in unacclimatized hypoxic conditions (Pfoh et al. 2017).

Unfortunately, these various steady-state and transient peak response tests described above have different magnitudes (Pfoh et al. 2016,

2017), are not well-correlated with each other (Pfoh et al. 2016, 2017), nor are their magnitudes related with oxygenation while in steady-state hypoxia (Pfoh et al. 2017), within-individuals. In addition, Milledge et al. (1988) found no relationship between the HVR prior to ascent with the severity of acute mountain sickness (AMS) symptoms upon rapid ascent to 5200 m. Thus, the validity and utility of peak response tests should be questioned with respect to assessing ventilatory acclimatization, oxygenation and avoiding AMS during exposure to chronic hypobaric hypoxia.

2.1.3 The Problem: Caveats for Tests of the HVR in High Altitude Fieldwork Contexts

Testing the HVR at altitude is often performed to assess ventilatory acclimatization (e.g., Forster et al. 1971; Sato et al. 1992; Smith et al. 1986). As a result of prolonged exposure to hypoxia, (e.g., high altitude ascent), ventilatory acclimatization ensues, increasing ventilation for a given combination of O₂ and CO₂. Similar to exposure to acute hypoxic conditions, during ascent to altitude, a new steady-state is achieved between hypoxia, hypocapnia and ventilation. Despite the competing nature of hypoxia (stimulatory) and hypocapnia (inhibitory), steady-state ventilation is eventually higher at rest than sea level due to carotid body plasticity (Smith et al. 1986).

Unfortunately, commonly applied peak response tests of the HVR utilized in many laboratory and field studies at altitude suffer from a number of important caveats, confounds and limitations, summarized below:

1. HVR tests typically require sophisticated equipment, lacking portability in many fieldwork contexts. These include feedback control systems, laptop computers, gas tanks (e.g., 100% O₂, 100% CO₂, 100% N₂, pre-mixed gases), gas analyzers, and calibration gas tanks. Although possible in some high altitude regions, these are not trivial considerations when intending to ascend to high altitude laboratories, lodges or base camps.
2. It may be dangerous and uncomfortable to make participants more hypoxic when already hypoxic at rest while at altitude when carrying out HVR tests.
3. HVR tests are contaminated by chronic changes in CO₂ and arterial/CSF bicarbonate associated with ventilatory and renal acclimatization. Prolonged hypoxia-induced hypocapnia and respiratory alkalosis induces a compensatory metabolic acidosis through the renal excretion of bicarbonate (Dempsey et al. 2014; Krapf et al. 1991), potentially making central chemoreceptors more sensitive to changes in CO₂ due to the reduction in buffering capacity for a given change in CO₂ (Dempsey et al. 2014; Sato et al. 1992; Fan et al. 2010). These steady-state changes in resting CO₂ and acid-base homeostasis likely affect the magnitude of the peripheral chemoreflex independent from changes in O₂. These changes also likely affect the resting central chemoreceptor activation at altitude. Thus, it is difficult to make meaningful comparisons to unacclimatized sea level values.
4. The assumption of stimulus specificity (i.e., hypoxia) of the peripheral chemoreceptors may be incorrect. Recent studies have demonstrated the existence of central (i.e., brainstem) chemosensors that are both sensitive to hypoxia and elicit a hypoxic ventilatory response (Angelova et al. 2015; Curran et al. 2000; Gourine and Funk 2017).
5. Previous studies have demonstrated that the magnitude of different tests of the HVR are not well-correlated with each other, nor are they correlated with oxygenation (SpO₂ or P_{ET}O₂) while being exposed to steady-state hypoxia, within-individuals (Pfoh et al. 2016, 2017). If the HVR (broadly defined) is an intrinsic mechanism that protects oxygenation when hypoxic, then any valid test of the HVR should capture these relationships. Our previous study demonstrated that peak response tests are not (a) related to each other in magnitude and (b) are not related to oxygenation.

Thus, our observations should give investigators pause when considering the utility and validity of HVR tests in assessing ventilatory acclimatization when participants are exposed to prolonged hypoxia.

6. The assumption that separate tests of the central and peripheral chemoreflexes are distinct and can isolate chemoreceptors is also likely incorrect. For example, steady-state isocapnic tests have well-described sympathetic, cardiovascular and cerebrovascular effects, which may confound the resulting ventilatory response. Steady-state poikilocapnic tests, where CO₂ is reduced as a result of the HVR, causes a withdrawal of central chemoreceptor stimulation. In addition, prolonged hypoxic stimulation and hypocapnia causes renal compensation, likely affecting the responsiveness of central chemoreceptors through a reduction of PCO₂/[H⁺] buffering capacity. Lastly, there is a potential interaction between central and peripheral chemoreceptors, whereby the activation or withdrawal of stimulation of one chemoreceptor compartment may affect the sensitivity of the other compartment's resulting chemoreflex to a transient perturbation. On balance, experimental evidence suggests that in intact animals and humans, the interaction between chemoreceptors is likely simple addition (e.g., Forster and Smith 2010; Smith et al. 2010; Wilson and Teppema 2016). However, the interaction has not been tested in chronic hypoxia, and the interaction may be state-dependent and different than previously demonstrated when tested below eupneic levels of CO₂ (i.e., hypocapnia; e.g., Day and Wilson 2009; Wilson and Day 2013). Thus, HVR tests are likely contaminated by a host of integrative responses that confound the isolation of peripheral chemoreceptors in humans.
7. Lastly, peak HVR tests, whether steady-state or transient, do not represent the steady-state ventilatory strategy that an individual utilizes against a given combination of O₂, CO₂ and acid-base chemostimuli while at rest at altitude. Thus, it is difficult to interpret what a peak ventilatory response to a transient stimulus represents in this context.

Given the many caveats, confounds and limitations outlined above, ultimately these considerations raise doubts about the feasibility and ability of specific transient peak response tests to isolate and quantify specific peripheral chemoreflex responsiveness in human participants in the context of high altitude ascent and acclimatization.

2.1.4 The Solution? A Novel Index of Steady-State Respiratory Chemoreflex Drive

In response to the many challenges outlined above, and faced with a need for a feasible and portable metric to assess respiratory chemoreflexes in high altitude fieldwork studies, we recently developed a novel index of steady-state chemoreflex drive (SS-CD). The SS-CD takes into account the prevailing CO₂ and O₂ chemostimuli and the activation state of both central and peripheral chemoreceptors through their cumulative effect on resting ventilation (Pfoh et al. 2017). To make the SS-CD measurement and calculation, only three portable devices are required (see Fig. 2.1):

1. A spirometer for a measurement of steady-state minute ventilation (\dot{V}_I ; L/min)
2. A capnograph to measure the pressure of end-tidal (P_{ET})CO₂ (Torr)
3. A pulse oximeter to measure peripheral oxygen saturation (SpO_2 ; %)

First, steady-state representative measurements of $P_{ET}CO_2$ and SpO_2 are used to quantify a stimulus index:

$$SI = P_{ET}CO_2 / SpO_2$$

The SS-CD is then calculated by indexing resting ventilation (\dot{V}_I ; L/min) against the SI:

$$SS-CD = \dot{V}_I / SI$$

In the context of respiratory chemoreflex activation state, the SI is applied to assess the steady-state prevailing $P_{ET}CO_2$ and SpO_2 . The SS-CD

A. Portable Respirometer (Ventilation; L/min) **B. Portable Capnograph ($P_{ET}CO_2$; Torr)** **C. Portable Pulse Oximeter (SpO_2 ; %)**



Fig. 2.1 Three portable devices to measure and calculate steady-state respiratory chemoreflex drive in humans in fieldwork contexts. (a) Portable respirometer to measure minute ventilation (V_I , L/min; picture from <http://bit.ly/2F8xxRJ>). (b) Portable capnograph to measure the pressure of end-tidal ($P_{ET}CO_2$; Torr; picture from <http://bit.ly/2BsmxA2>). (c). Portable pulse oximeter to

measure peripheral arterial oxygen saturation (SpO_2 , %; picture from <http://bit.ly/2BuOabJ>). These three devices, or others like them, make up a portable system that can be used to quantify resting steady-state respiratory chemoreflex drive in the laboratory, clinic or fieldwork contexts. All devices are non-invasive, do not require power, can be used simultaneously and require only a short-duration spot-check (i.e., a few minutes)

then gives the investigator insight into the steady-state ventilation against the prevailing chemostimuli, eliminating the need for transient gas challenges or peak response tests. This test can then be applied during incremental ascent or at multiple time points during acclimatization to a single altitude.

The strength of the SI lies not only in its simplicity of measurement and calculation, but also in the fact that both chemostimuli have well-documented linear relationships with ventilation. For example, CO_2 is linearly related to ventilation, as demonstrated by both steady-state and rebreathing tests (Duffin 2011; Nielsen and Smith 1952). In addition, although the relationship between O_2 and ventilation is curvilinear (e.g., Loeschcke and Gertz 1958; Weil et al. 1970), indexing ventilation against SpO_2 linearizes the relationship (e.g., Rebeck and Campbell 1974). Thus, CO_2 is proportionally and linearly related to ventilation, and SpO_2 is inversely and linearly related to ventilation, justifying the calculation of SI as $P_{ET}CO/SpO_2$ (Pfoh et al. 2017). Also by way of validation, we used this SI methodology previously in other contexts, specifically when quantifying cerebrovascular responsiveness to breath holding, where both CO_2 and O_2

are changing simultaneously at the metabolic rate (Bruce et al. 2016).

We recently compared the SS-CD between breathing room air and breathing steady-state normobaric hypoxia (~20 min of ~13.5% $F_{I}O_2$; ~90 Torr $P_{i}O_2$ in Calgary). Despite resting ventilation and the stimulus index being statistically higher in hypoxia, due to the competing effects of hypoxia and hypocapnia, there were no statistical differences in SS-CD between room air (i.e., baseline) and after 20 min of steady-state hypoxia (Pfoh et al. 2017). This demonstration is consistent with the fact that in response to acute poi-kilocapnic hypoxia, ventilation is not appreciably higher following the peak response, and HVD leads to a new steady-state following approximately 10-min, where ventilation is similar to baseline values breathing room air (e.g., Steinback and Poulin 2007).

Following this previous study comparing SS-CD while breathing room air and acute normobaric hypoxia in a laboratory setting, we aimed to assess the SS-CD during incremental ascent to high altitude. Specifically, we hypothesized that the SS-CD would track ventilatory acclimatization during incremental ascent over 10 days to high altitude hypoxia.

2.2 Methods and Materials

2.2.1 Participant Recruitment and Ethics

Participants were recruited on a voluntary basis to undergo serial measurements from a large group of participants (31) on a research expedition during a trek to Everest base camp (5300 m) in the Nepal Himalaya. Inclusion criteria included adult participants over 18 years of age who planned to trek the entire journey and those who were willing to provide free, informed, verbal, written and ongoing consent. In this study, we recruited 13 participants for inclusion (23.0 ± 3.1 years; BMI 24.0 ± 2.7 kg/m²; 5 males). This study abided by the Canadian Government Tri-Council policy on research ethics with human participants (TCPS2) and the Declaration of Helsinki, except registration in a database. Ethical approval was received in advance through the Mount Royal University Human Research Ethics Board (Protocol 100012) and was harmonized with the Nepal Health Research Council (Protocol 109-2017). All participants were recruited via verbal communication and provided written and informed consent prior to voluntary participation in the study. Although this study took place in the context of a large research expedition to altitude, the specific study design, research question and data collection were planned *a priori*.

2.2.2 Study Protocol and Ascent Profile

Participants had baseline measurements performed at a low altitude of 1045 m (Calgary) or 1400 m (Kathmandu, Nepal), and these data were combined. They were then flown to 2800 m (Lukla) before beginning the trek. During the trek, all measurements were made on rest days (i.e., no altitude gain) following one night at each altitude, which occurred upon reaching altitudes of 3440 m (Namche; Day 3), 3820 m (Debuche; Day 5), and 4370 m (Pheriche; Day 7) and 5160 m (Gorak Shep; Day 10). Prior to

measurements at 5160 m (Gorak Shep), participants trekked to ~5300 m (Everest base camp) and back (approximately 5 h of walking), after which measurements were taken at rest in the afternoon. No participants were taking prophylactic acetazolamide (Diamox) at any time during the trek.

2.2.3 Measurements

All data were collected between 06:00 and 17:00 on non-trekking days. Participants were seated in lodge bedrooms or dining rooms and provided with white noise through head phones to minimize distraction. They were instrumented to measure resting ventilation (V_I ; L/min), the pressure of end-tidal (P_{ET})CO₂ and peripheral oxygen saturation (SpO₂). Ventilatory data were collected using a 16-channel PowerLab system (Powerlab/16SP ML880; AD Instruments; ADI; Colorado Springs, CO, USA) and analyzed offline using commercially available software (ADI LabChart Pro software version 8). Participants were instrumented with a mouthpiece, personal bacteriological filter, and nose clip. Respiratory flow was measured through the use of a calibrated pneumotachometer (HR 800 L flow head and spirometer amplifier; ADI ML141). Instantaneous inspired ventilation ($V_{I,}$ L/min) was calculated as the product of breath-by-breath inspired volume (calculated from the integral of the flow signal) and respiratory rate (calculated by 60/period of the flow signal). P_{ET} CO₂ was measured using a portable, calibrated capnograph (Masimo EMMA, Danderyd, Sweden) with a personal mouthpiece and nose clip and SpO₂ was measured with a portable finger pulse oximeter (Masimo SET® Rad-5, Danderyd, Sweden).

2.2.4 Data Analysis and Statistics

Resting ventilation at each altitude was analyzed from a one-minute representative mean bin near the end of a 10-min baseline period, whereas P_{ET} CO₂ and SpO₂ measures were obtained after

Table 2.1 Baseline variables at rest during incremental ascent to high altitude in the Nepal Himalaya over 10 days

Variable/Day	0	3	5	7	10
Altitude (m)	1400	3440	3820	4370	5160
Atmospheric pressure (mm Hg)	648	509	486	454	411
Pressure of inspired O ₂ (mm Hg)	136	107	102	95	86
V _I (L/min)	12.1 ± 0.6	14.4 ± 1.0	13.9 ± 0.9	14.3 ± 1.0	16.4 ± 1.3*†
P _{ET} CO ₂ (Torr)	32.3 ± 1.5	26.8 ± 0.8*	25.8 ± 0.8*	21.8 ± 0.8*†	18.4 ± 0.6*†
SpO ₂ (%)	96.5 ± 0.3	91.6 ± 0.7*	90.8 ± 0.9*	87.5 ± 0.8*†	78.0 ± 2.0*†
SI (P _{ET} CO ₂ /SpO ₂)	0.34 ± 0.02	0.30 ± 0.01*	0.29 ± 0.01*	0.25 ± 0.01*†	0.24 ± 0.01*
SS-CD (V _I /SI)	36.8 ± 2.7	48.6 ± 3.9	48.9 ± 3.8	57.7 ± 5.3*	70.4 ± 6.7*†

Baseline data obtained from a one-minute bin near the end of a 10-minute room-air baseline, following at least one night at each altitude. The first measurement was made in Calgary (1045 m) or Kathmandu (1400 m), and each successive day during ascent is listed, with representative altitude, atmospheric pressure, and approximate pressure of inspired O₂. V_I minute ventilation, P_{ET}CO₂ partial pressure of end-tidal carbon dioxide, SpO₂ oxygen saturation via peripheral pulse oximetry, SI stimulus index (P_{ET}CO₂/SpO₂; Torr/%), SS-CD steady-state chemoreflex drive (V_I/SI)

*denotes different than 1400 m, P < 0.001

†denotes different than previous altitude, P < 0.001

These data n = 13, except V_I, SI and SS-CD: 1045/1400 m, n = 13; 3440 m, n = 10; 3820, n = 11; 4370 m, n = 11; 5160 m, n = 10

Data reported as mean ± SEM

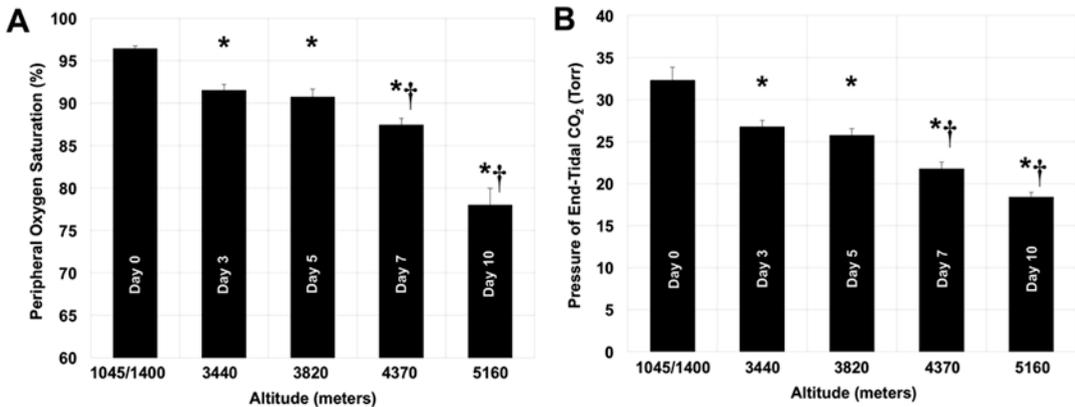


Fig. 2.2 Measures of peripheral oxygen saturation (SpO₂; %) and pressure of end-tidal CO₂ (P_{ET}CO₂; Torr) with ascent. Note the incremental decline in SpO₂ and P_{ET}CO₂ with incremental ascent, demonstrating hypoxia, and concomitant hypocapnia due to the hypoxic

ventilatory response. The relative altitude and measurement day during ascent is labeled for each value. * denotes different than 1045/1400 m, P < 0.001. †denotes different than previous altitude, P < 0.001. These data, n = 13. Error bars represent mean ± SEM

steady-state was achieved. Data in Table 2.1 and Figs. 2.2 and 2.3 are presented as mean ± standard error of the mean (SEM). A one-factor repeated measures ANOVA was utilized to test for differences in P_{ET}CO₂, SpO₂, V_I, SI (P_{ET}CO₂/SpO₂) and SS-CD (V_I/SI) at each altitude. Statistical significance was assumed at P < 0.05 (SigmaPlot v14, Systat).

2.3 Results

Table 2.1 illustrates resting ventilation (V_I), the pressure of end-tidal (P_{ET})CO₂, peripheral oxygen saturation (SpO₂), stimulus index (SI) and measurement of steady-state chemoreflex drive (SS-CD) during incremental ascent to high altitude. All variables changed in predictable

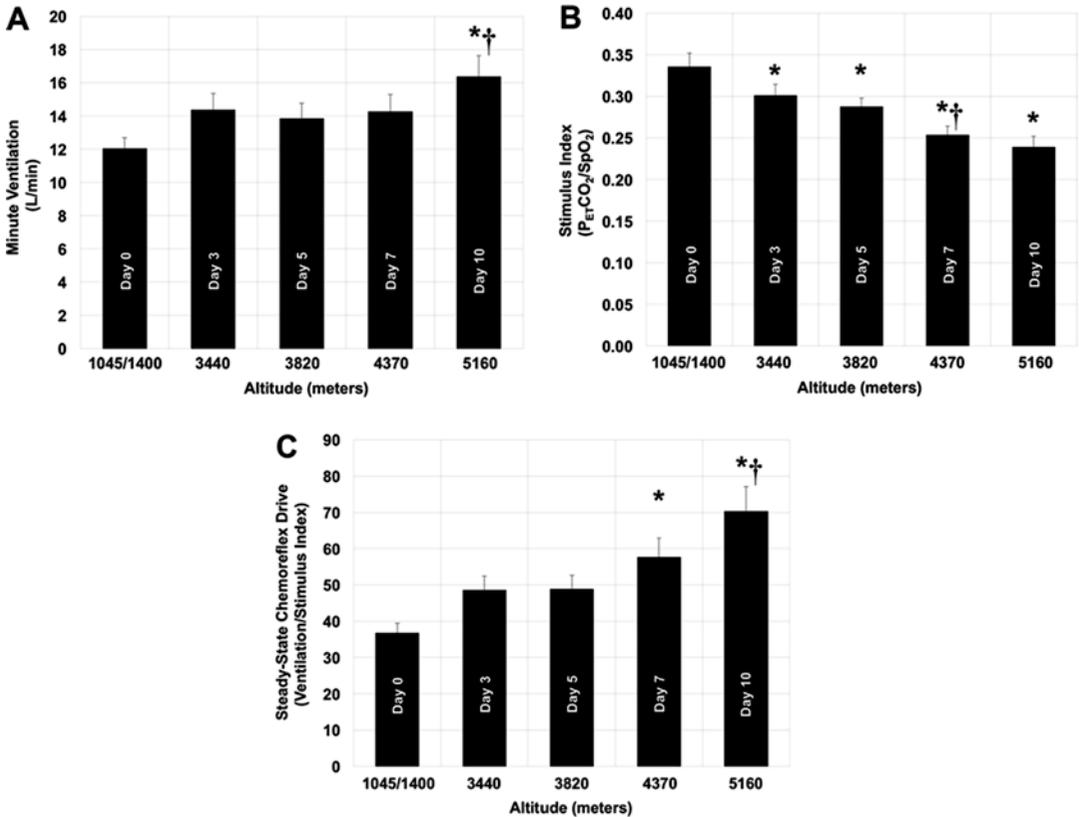


Fig. 2.3 Steady-state chemoreflex drive during incremental ascent to high altitude. These ventilatory (V_I) data in A. were derived from a one-min mean bin following 10-min of rest at each location, following at least one night at each respective altitude. The SI data in B. ($P_{ET}CO_2/SpO_2$) was calculated from data in Fig. 2.2. SS-CD in C. is calculated as V_I/SI at each location. The

relative altitude and measurement day during ascent is labeled for each value. * denotes different than 1045/1400 m, $P < 0.001$. † denotes different than previous altitude. These data: 1045/1400 m, $n = 13$; 3440 m, $n = 10$; 3820 m, $n = 11$; 4370 m, $n = 11$; 5160 m, $n = 10$. Error bars represent mean \pm SEM

ways with incremental ascent. Figure 2.2 illustrates the reductions in SpO_2 and $P_{ET}CO_2$ with ascent, illustrating hypoxia and concomitant hypocapnia due to the HVR. Following 10 days of incremental ascent, SpO_2 and $P_{ET}CO_2$ were $78.0 \pm 2.0\%$ and 18.4 ± 0.6 Torr at 5160 m, respectively, significantly lower than 1045/1400 m. Figure 2.3 illustrates resting V_I , SI and SS-CD during ascent to altitude. Following 10 days of incremental ascent, V_I , SI and SS-CD were 16.4 ± 1.3 L/min, 0.24 ± 0.01 and 70.4 ± 6.7 respectively, significantly different than 1045/1400 m. The mean SS-CD was approximately 96% larger (i.e. almost double) at 5160 m compared to 1045/1400 m, indicating

appreciable ventilatory acclimatization in these participants.

2.4 Discussion

Following the development and validation of the SS-CD during exposure to normobaric hypoxia in a laboratory setting, we aimed to characterize the SS-CD during incremental and more prolonged exposure to high altitude. We found that the SS-CD index increased in magnitude with incremental ascent to altitude over 10 days to a maximum of 5160 m. On average, SS-CD increased 96% in this time frame, suggesting

appreciable ventilatory acclimatization. This finding suggests that the SS-CD tracks the well-described ventilatory acclimatization during exposure to high altitude hypoxia.

The SS-CD captures the overall resting chemoreflex drive to prevailing chemostimuli. Thus, this index includes contributions from both central and peripheral respiratory chemoreceptors and the prevailing O₂, CO₂ and acid-base status. Indeed, given the many considerations outlined above, the methodological and technical simplicity of the SS-CD illustrates its strength, and underlies its potential broad utility. Although the equipment we used here for measuring ventilation required a calibrated flow head, spirometer amplifier and a laptop with data acquisition hardware and software, we suggest that the same measures can be made using more portable respirometers (see Fig. 2.1), increasing the portability and utility in austere conditions.

There are many contexts where tests approximating the specific central and/or peripheral chemoreflex magnitude may be important, including mechanistic studies of cardiorespiratory control in animal models and humans. As with all experimental studies, the utility of any methodology lies in the experimental question. However, the novel SS-CD index outlined here may have future utility in assessing ventilatory acclimatization during incremental or prolonged stays at altitude, and may replace the use of complex and potentially confounded transient peak response tests of the HVR in some experimental or clinical contexts.

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