# Chemoreceptor responsiveness at sea level does not predict the pulmonary pressure response to high altitude

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None of the authors declare a conflict of interest.

**Abstract:** The hypoxic ventilatory response (HVR) at sea level (SL) is moderately predictive of the change in pulmonary artery systolic pressure (PASP) to acute normobaric hypoxia. However, because of progressive changes in the chemoreflex control of breathing and acid-base balance at high altitude (HA), HVR at SL may not predict PASP at HA. We hypothesized that resting peripheral oxyhemoglobin saturation ($SpO_2$) at HA would correlate better than HVR at SL to PASP at HA. In 20 participants at SL, we measured normobaric, isocapnic HVR ($L/min \cdot -\%SpO_2^{-1}$) and resting PASP using echocardiography. Both resting $SpO_2$ and PASP measures were repeated on day 2 (n=10), days 4-8 (n=12), and 2-3 weeks (n=8) after arrival at 5050m. These data were also collected at 5050m on life-long HA residents (Sherpa; n=21). Compared to SL, $SpO_2$ decreased from 98.6 to 80.5% ($P<0.001$), while PASP increased from 21.7 to 34.0mmHg ($P<0.001$) after 2-3 weeks at 5050m. Isocapnic HVR at SL was not related to $SpO_2$ or PASP at any time point at 5050m (all $P>0.05$). Sherpa had lower PASP ($P<0.01$) than lowlanders on days 4-8 despite similar $SpO_2$. Upon correction for hematocrit, Sherpa PASP was not different from lowlanders at SL, but lower than lowlanders at all HA time points. At 5050m, whilst $SpO_2$ was not related to PASP in lowlanders at any point (all $R^2=<0.05$; $P>0.50$), there was a weak relationship in the Sherpa ($R^2=0.16$; $P=0.07$). We conclude that neither HVR at SL nor resting $SpO_2$ at HA correlates with elevations in PASP at HA.

**Introduction:**

The initial increase in ventilation in response to hypoxia (i.e. hypoxic ventilatory response; HVR) is highly variable[1]. In response to a decreased partial pressure of oxygen ($PO_2$) at high altitude (HA), pulmonary artery pressure (PAP) increases primarily through hypoxic pulmonary vasoconstriction (HPV)[2]. In some studies, a blunted HVR is characteristic of high altitude pulmonary edema (HAPE) susceptible subjects who exhibit marked elevations in PAP[3–9]. The latter findings highlight a link between HVR and PAP at altitude.

Animal studies have clearly demonstrated that higher peripheral chemoreceptor responsiveness attenuates HPV[10,11]. For example, following mechanical ventilation of the lungs with 100% $N_2$, stimulation of the carotid chemoreceptors via arterial hypoxemia reduces pulmonary vascular resistance in cats and dogs[12,13]. This neural modulation of PAP in hypoxia has been studied recently in humans by interpolating the pulmonary artery systolic pressure (PASP) response to hypoxia at a specific peripheral oxyhemoglobin saturation ($SpO_2$=85%).[14] Between-individual variability in HVR (indicative of peripheral chemoreceptor responsiveness) at SL was moderately correlated ($R^2$=0.38) with PASP in normobaric hypoxia.[14] This finding is consistent with the aforementioned reports linking HVR to HAPE susceptibility, and HAPE to excessive HPV. Furthermore, individuals with a blunted HVR will consequently have a lower alveolar $PO_2$ and thus a greater stimulus to HPV at any given altitude[14]. However, the issue with extrapolating variability in HVR at SL to predict changes in PAP at HA is that, in addition to acid-base adjustments, HVR represents a reflex arc with three components: (1) afferent input, (2) central integration, and (3) efferent output[15], all of which are likely changing, resulting in an overall change in HVR at HA[16,17]. Due to the myriad of physiologic changes at HA related to the HVR[18–20] and HPV[21], we hypothesized that resting $SpO_2$ at HA would correlate better than variability in HVR at SL to PASP at HA (i.e., by virtue of $SpO_2$ reflecting alveolar $PO_2$ and hence HPV). We also reasoned that chronic adaptation to HA, as seen in the Sherpa, would result in higher resting $SpO_2$ and lower PASP than that of lowlanders at HA.

## Methods

*Study Participants and Design*

All experimental procedures and protocols were approved by the Clinical Research Ethics Board at the University of British Columbia, University of Otago, and the Nepal Health Medical Research Council, and conformed to the Declaration of Helsinki. Twenty Caucasian lowlanders (34±7 years, 5 females) and twenty-one Nepalese male highland Sherpa (31±13 years) provided informed consent and volunteered to participate in the study. One to two months prior to departure, Caucasian participants underwent a transthoracic echocardiographic assessment at or close to SL (see below), and then again at day two (n=10; from 2008), 4-8 days (5.2±0.8; further referred to as day five; n=12; 10 from 2008, two from 2012), and between 2 to 3 weeks (16±0.7 days; n=8; from 2012) after arrival at the Ev-K2-CNR Pyramid Research Laboratory (Lobuche, Nepal; 5050m) in the absence of acute mountain sickness (AMS) symptoms. Sherpa were assessed at 5050m only. All participants were free from respiratory and cardiovascular disease and were not taking any prescription medications. The native Sherpa participants originated from, and were residents of, the Khumbu Valley at an altitude greater than 3000m and self-identified to be of Sherpa ethnicity. None of the Sherpa had travelled below 2800m for at least 6 months prior to testing. Height, body mass, blood pressure, and $SpO_2$ were recorded prior to each transthoracic echocardiographic assessment (see below "*Transthoracic Echocardiography"*). Peripheral and central chemoreflex sensitivities were also assessed on a different day at SL (see below "*Chemoreflex testing"*). Prior to each experiment, participants abstained from exercise and alcohol for 24h, and caffeine for 12h.

In different participants, SL data were collected in February 2008 (n=10) in Dunedin (New Zealand; at ~10m) and in April 2012 (n=10) in Kelowna (Canada; altitude 344m). The HA experiments were completed over 2 weeks (2008) and 3 weeks (2012) at the Ev-K2-CNR Pyramid Laboratory, Khumbu region, Nepal in April-May of 2008 (New Zealand group) and 2012 (Canada group). After travel to Nepal and seven nights in Kathmandu (~1400m), participants flew to Lukla (2800m) and began an 8-11 day ascent to the Pyramid Research Laboratory (5050m). A cautious ascent profile was adopted, with ≤700m net gain per day and at least two days with no net change in altitude. Participants were given low-dose acetazolamide (125mg, oral) twice per day as an acute mountain sickness prophylactic[22]. Acetazolamide was discontinued at ~4300m (Pheriche), at least one day before ascending to the laboratory, to allow sufficient time (e.g., ≥48 hours) for the drug to clear participants' system prior to the first data collection session at 5050m[23,24]. Previously, pre-treatment of acetazolamide has resulted in an

almost negligible difference of PASP (~2mmHg; no statistical analyses were performed) 48hours after final drug treatment when compared to individuals that received placebo treatment[25]. Although unlikely to alter our findings, we were unable to rule out the possibility of persisting physiological sequelae secondary to acetazolamide treatment during our day two testing. Participants spent 1 to 3 days at Pheriche before the final ascent. Expedition members participating in this study had a minimum of 48h between this and other studies involving pharmaceutical interventions or exercise, to minimize contamination. Some of the data presented here (e.g., chemosensitivity responses, pulmonary pressures) have been reported previously in other studies from these expeditions[26–29]; however, the research question addressed here is distinct, and combining data from these two expeditions provides a novel data set, with greater power to address the research question[30].

*Transthoracic Echocardiography*

All echocardiographic images were recorded on a commercially available portable ultrasound system (Vivid I, GE Healthcare, Australia-2008 & Vivid Q, GE Medical Systems, Israel Ltd-2012). Images were captured by the same highly trained cardiac sonographer within each expedition (Yeoman, D.J., 2008 & Stembridge, M., 2012) while the participant lay in the left lateral decubitus position. Following 10 minutes of supine rest, an apical four chamber view was visualized for the recording of the systolic tricuspid regurgitation jet velocity (TRV) using continuous wave Doppler with the atrio-ventricular pressure gradient calculated using the simplified Bernoulli equation ($4TRV^2$). PASP was then calculated with the addition of right atrial pressure estimated from the collapsibility of the inferior vena cava on inspiration[31]. Heart rate was recorded via 3-lead electrocardiogram.

*Chemoreflex testing*

The respiratory chemoreflex responses to both hypoxia (an index of peripheral chemoreflex sensitivity; HVR) and hypercapnia (an index of central chemoreflex sensitivity; HCVR) were assessed at SL in the 2008 and 2012 studies; however, these tests differed slightly between investigations. Specifically, in the 2008 experiments, isocapnic hypoxia was induced for approximately 4-9 minutes via a 6-L rebreathing bag and soda lime reservoir. The isocapnic hypoxia was terminated when either: 1) partial pressure of end-tidal oxygen ($P_{ET}O_2$) reached 45mmHg at SL; 2) ventilation ($\dot{V}_E$) exceeded 100L/min; or 3) the participant reached the end of their tolerance. In the 2012 experiments, isocapnic hypoxia ($P_{ET}O_2$ = 47mmHg) was maintained over 10 minutes via end-tidal forcing, as described in depth elsewhere[29,32]. Despite the different methods, in a sub-group of participants (n=6) who underwent both tests, the peak

HVR between tests was comparable ($R^2$=0.46; P<0.05) and not significantly different from one another (P=0.6), indicating they both reflected similar chemoreflex phenomena. In 2012, a subgroup (n=8) of participants at SL underwent 10 minutes of poikilocapnic hypoxia (11% $O_2$) to simulate 5050m. Although acute poikilocapnic hypoxia testing is more complicated than the commonly used isocapnic hypoxic tests, due to the interactive effects of hypoxia and concomitant hypocapnia, they are more representative of the uncontrolled breathing environment at HA, and therefore, more applicable to such scenarios.

In 2008, HCVR was assessed from a 4-min steady state hyperoxic hypercapnia gas mixture (7% $CO_2$; 93% $O_2$) after a 5-min room air baseline. In 2012, HCVR was assessed using end-tidal forcing where the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was clamped initially at baseline and then elevated in a stepwise fashion at +5, +10, and +15mmHg from individual baseline values while $P_{ET}O_2$ was maintained at individual baseline values (~100mmHg). In a sub-group of participants (n=7) who underwent both tests, the relationship ($R^2$) between HCVR tests was 0.53 (P<0.01).

In both the 2008 and 2012 experiments, all respiratory parameters were acquired at 200Hz using an analog-to-digital converter (PowerLab/16SP ML 880; ADInstruments, Colorado Springs, CO, USA) interfaced with a personal computer and analyzed with commercially available software (LabChart, ADInstruments). Throughout all procedures, participants breathed through a mouthpiece (with nose-clip) or facemask with an attached bacteriological filter, and a two-way non-rebreathing valve (2600 series, Hans Rudolph, Shawnee, KS, USA). Respired gas was sampled at the mouth and analyzed for $P_{ET}O_2$ and $P_{ET}CO_2$ by a calibrated gas analyzer (ML206; ADInstruments). Respiratory flow was measured near the mouth using a pneumotachograph (HR 800L, HansRudolph) and a differential pressure amplifier (ML141, ADInstruments).

*Calculations*

For the 2008 studies, isocapnic HVR was calculated as the slope of the linear regression between $\dot{V}_E$ and $SpO_2$, while HCVR was calculated as $\Delta\dot{V}_E/\Delta P_{ET}CO_2$ from baseline to steady state. For the 2012 studies, isocapnic HVR was calculated as $\Delta\dot{V}_E/\Delta SpO_2$ from baseline to the peak ventilation during hypoxia. Peak poikilocapnic HVR was calculated in a similar manner, while delayed poikilocapnic

HVR was calculated as $\Delta\dot{V}_E/\Delta SpO_2$ from baseline to the average of minutes 10-15 of hypoxia. The HCVR was calculated as the linear regression slope between $\dot{V}_E$ and $P_{ET}CO_2$.

To account for differences in hematocrit (HCT) between groups we estimated PASP after correction of HCT to sea level values (45%). First, we calculated pulmonary vascular resistance (PVR) in all of our subjects using the following equation[31]:

PVR = TRV/RVOT VTI · 10 + 0.16

Where TRV is tricuspid regurgitation velocity (m/s), and RVOT VTI is the right ventricular outflow tract velocity time integral (cm), and PVR is pulmonary vascular resistance expressed in woods units. Once this was determined for both lowlanders and Sherpa at high altitude, we calculated PVR at a HCT of 45% in all individuals using the following equation[33]:

$$PVR(45\%) = PVR(HCT\%)\,\frac{1-\varphi^{1/3}}{0.234}$$

Where $\varphi$ represents the hematocrit at HA. As pressure is proportional to resistance, we infer the calculated %change in PVR to be representative of the %change effect of hematocrit on PASP, and as such adjusted PASP values to a 45%HCT estimate in all groups. For the day two group we used a HCT value of 45.7%[27], while day five, 2-3 weeks, and Sherpa HCT were 49.4%[27], 49.4%[29], and 53.9%[29], respectively.

*Statistical Analyses*

Comparison of lowlanders at SL, day two, day five, and 2-3 weeks at altitude, as well as Sherpa were performed using a 1-factor ANOVA. The relationship between variables ($SpO_2$, HVR, HCVR, & PASP) was assessed using least squares linear regression following conformation of a Gaussian distribution. Alpha was set *a priori* to 0.05. All statistical analyses were performed using Prism (Version 5.0b, 2008) and SPSS (IBM Statistics, Version 21, 2012).

**Results**

*Baseline Characteristics*

Consistent with previous reports of HVR and HCVR at 4300m[34,35], we found no significant sex differences for chemoreflexes at sea level and both PASP and $SpO_2$ at HA; therefore, data for males and females were pooled for statistical analysis. At HA, $SpO_2$ decreased from its SL value of 98.6±1.1% to 79.5±2.9% (P<0.001) on day two, 83.4±1.9% (P<0.001) on day five, and 80.5±1.6% (P<0.001) after 2-3 weeks acclimatization at 5050m; at these time points, PASP increased from 21.7±2.1mmHg at SL to 36.6±4.6mmHg (P<0.001), 35.7±5.5mmHg (P<0.001), and 34.0±4.5mmHg (P<0.001), respectively. Isocapnic HVR at SL was 1.61±0.94 (L/min · -$SpO_2^{-1}$), while peak and delayed poikilocapnic HVR were 0.46±0.23 and 0.14±0.08 (L/min · -$SpO_2^{-1}$), respectively. HCVR at SL was 3.00±1.49 (L/min · mmHg $P_{ET}CO_2^{-1}$). Correction of lowlander PASP to a HCT of 45% indicated that independent of blood viscosity PASP still significantly increased from 21.7±2.1mmHg at sea level to 35.9±4.5mmHg (P<0.001) on day two, 31.9±5.0mmHg (P<0.001) on day five, and 30.4±41mmHg (P<0.01) after 2-3weeks acclimatization.

*Relationship between chemoreflexes and PASP at HA*

Elevations in PASP at 5050m after 2-3 weeks acclimatization were unrelated to SL isocapnic HVR ($R^2$<0.01; P=0.97; Figure 1), SL peak poikilocapnic HVR ($R^2$=0.16; P=0.38), and SL delayed poikilocapnic HVR ($R^2$=0.13; P=0.42). Variability in the HCVR was also unrelated to the changes in PASP ($R^2$=0.08; P=0.50). Poikilocapnic HVR (peak & delayed) and isocapnic HVR (see Figure 1) were unrelated to $SpO_2$ after 2-3 weeks acclimatization. These relationships remained insignificant when ventilatory tests were related to PASP and $SpO_2$ values on day two and day five at 5050m. Furthermore, incorporating individual variability at SL and HA via calculation of delta scores (i.e., HA-SL) did not render any significant relationships.

Sherpa had higher $SpO_2$ (82.8±3.3 vs. 79.5±2.9%; P<0.01) but lower PASP (29.8±5.9 vs. 36.6±4.6mmHg; P<0.01) compared to lowlanders on day two at 5050m. However, on day five, although Sherpa had comparable $SpO_2$ (82.8±3.3 vs. 83.4±1.9%; P=0.56), PASP was still lower compared with lowlanders (29.8±5.9 vs. 35.65±5.5mmHg; P<0.01). After 2-3 weeks acclimatization, Sherpa and lowlander $SpO_2$ were not different (82.8±3.3 vs. 80.5±1.6%; P=0.07); however, PASP still tended to be lower in the Sherpa (29.8±5.9 vs. 34.0±4.5mmHg; P=0.06). Upon correction for HCT to 45% Sherpa

PASP was reduced to 23.7±4.7mmHg, which was not different from lowlanders at sea level (P=0.09), but significantly lower than lowlanders at all HA time points (all P<0.01). Regression analysis revealed similar non-significant correlations between HA $SpO_2$ and PASP in lowlanders on day two at altitude ($R^2$=0.03; P=0.61), day five ($R^2$=0.05; P=0.51), and after 2-3weeks acclimatization ($R^2$=0.03; P=0.69), and in Sherpa ($R^2$=0.16; P=0.07). On examination of the group regressions, the slopes for lowlanders on day two, day five, after 2-3 weeks acclimatization and Sherpa were -0.29, 0.67, -0.49 and -0.74mmHg · -%$SpO_2^{-1}$, respectively (Figure 2).

**Discussion**

The primary finding of this study is the lack of correlation between both peripheral and central chemosensitivity at SL and PASP at HA, contrary to previous findings during SL hypoxia.[14] Furthermore, at any time point, there was no relationship between HA $SpO_2$ and resting PASP at 5050m in SL dwellers. Consistent with our second hypothesis, Sherpa had higher $SpO_2$ and lower PASP than lowlanders on day two at HA. Early acclimatization eliminated the difference in $SpO_2$ between Sherpa and lowlanders while PASP was generally lower in the native highlanders.

Changes in peripheral chemoreceptor responsiveness[19,36,37], central processing [18,20,38], and the consequent efferent output[18] all effect the ventilatory response to hypoxia at altitude[16,17]. The further effect of changes in acid-base balance, as well as the complex nature of breathing at HA have been reviewed in detail[15]. Therefore, although SL HVR has been correlated with PASP during normobaric hypoxia ($SpO_2$=85%; n=15)[14], the lack of correlation (of both isocapnic and poikilocapnic HVR) to PASP at HA is perhaps not surprising due to the aforementioned changes, in addition to changes in lung diffusion capacity[39], which occur upon exposure to altitude. Moreover, as HVR rapidly increases within the first week of exposure to HA[16,17], and full ventilatory acclimatization may take up to 4-6 weeks at 5050m[15], it is further not surprising that SL HVR was unrelated to PASP at all HA time points. Although a blunted HVR has been reported in some studies to related to HAPE susceptibility[40,41], we did not include any AMS/HAPE susceptible subjects by design and ensured safe ascent and acclimatization. As most studies derive their relationships via the use of two distinct phenotypes (i.e. AMS susceptible and non-susceptible who often have a blunted and brisk HVR[40–43], respectively), having a singular phenotype within our participant group may preclude any relationship between HVR and PASP. However, this does not undermine the significance that biological variability in SL HVR does not predict the marked variability in PASP at HA in a homogenous group.

An inverse relationship between $SpO_2$ and PAP was reported as early as 1957 at 4540m[44]. As a reduction in alveolar $PO_2$ is the primary stimulus for HPV[2,45], we reasoned that $SpO_2$ at HA would correlate more strongly to PASP than SL HVR. However, we acknowledge that the regulation of elevations in PAP upon exposure to HA involves the complex interaction of multiple factors and hence, likely explains the unremarkable correlation found between $SpO_2$ and PASP in lowlanders and Sherpa. This is evidenced by incomplete restoration of normal PAP in lowlanders[3,46] and Sherpa[29] upon

alleviation of alveolar hypoxia. Our findings are consistent with earlier reports that Sherpa have higher resting $SpO_2$ than lowlanders upon initial arrival to high altitudes (i.e., >4000m; day two in this investigation). Similar $SpO_2$ between Sherpa and lowlanders after 1-3 weeks acclimatization is likely due to progressive ventilatory acclimatization and consequent elevations in resting ventilation. Previous studies have reported a significant[47] and trending[48] inverse relationship between $SpO_2$ and PAP; however, this is not a consistent finding[28,44]. Furthermore, PASP has been reported as both lower[48] and the same[28,29] in Sherpa than lowlanders at HA, with the differing results likely due to duration of time at altitude prior to assessment[29] and small sample sizes. Our data, which includes a larger sample size of Sherpa than previous investigations, showed that despite similar $SpO_2$ to lowlanders after ~5 days acclimatization, Sherpa continued to have lower PASP. Therefore, several other key factors that act to regulate PAP at HA in addition to alveolar $PO_2$ [2,45] must be interacting in a different manner between Sherpa and lowlander populations. These factors likely include pulmonary vascular remodeling to life at HA[49], genetic adaptations, higher circulating nitric oxide in Sherpa as compared to lowlanders[50], and blood viscosity[29]. To provide insight into this latter point, we corrected both lowlander and Sherpa PASP values to a sea level HCT (45%). After correction, PASP in Sherpa fell within sea level norms at ~24mmHg therefore indicating that hematocrit and subsequently viscosity are predominantly responsible for their elevated PASP at 5050m. This further provides evidence suggesting a differential regulation of PASP between lowlanders and high altitude natives, and indicates that we and others[28,29,48] have likely underestimated the difference in HPV between lowlanders and Sherpa without consideration of changes in HCT[33].

In conclusion, as the multiple factors regulating breathing differ between SL and HA, the utility of SL chemoreflex tests, both poikilocapnic and isocapnic, to predict changes in PASP at HA is limited in otherwise healthy individuals.

**Acknowledgments:**

These studies were carried out within the framework of the Ev-K2-CNR Project in collaboration with the Nepal academy of Science and Technology, as foreseen by the Memorandum of Understanding between Nepal and Italy, and thanks to contributions from the Italian National Research Council. The work in this project was supported by a Canada Research Chair, NSERC Discovery Grant, Otago Medical Research Foundation, and the Department of Physiology (University of Otago). The authors are grateful to the other members of both research expeditions for their invaluable help with logistical planning and implementation of this research study. CKW is supported by a Vanier Canada graduate scholarship, and KJS and NCS by the NSERC Alexander Graham Bell Canada Graduate Scholarship and Heart and Stroke Foundation of Canada doctoral and post-doctoral fellowship, respectively. JD is supported by a Woolf Fisher scholarship. We are extremely grateful to Professor Greg Atkinson for advice and assistance with the statistical analysis.

**Figures:**

**Figure 1**. The relationship between sea level isocapnic HVR and both $SpO_2$ (A) and PASP (B) in lowlanders within day two (closed circles, solid line), day five (open circles, dashed line) and after 2-3 weeks acclimatization (filled squares, dashed line). HVR was unrelated to $SpO_2$ on day two ($R^2$=0.24; P=0.14), day five ($R^2$=0.12; P=0.27) and after 2-3weeks acclimatization ($R^2$=0.10; P=0.46). The relationship between sea level isocapnic HVR with PASP at high altitude on day two ($R^2$=0.03; P=0.64), day five ($R^2$=0.25; P=0.12), and after 2-3 weeks acclimatization ($R^2$<0.01; P =0.97) were also insignificant. HVR, hypoxic ventilatory response; PASP, pulmonary artery systolic pressure; $SpO_2$, peripheral oxyhemoglobin saturation.

**Figure 2**. The influence of peripheral oxyhemoglobin saturation ($SpO_2$) on PASP at high altitude in lowlanders on day two (closed circles, thin solid line), day five (open circles, dashed line), after 2-3 weeks altitude (filled squares, thick solid line), as well as in Sherpa (open squares, dotted line). Regression analysis revealed non-significant correlations between high altitude $SpO_2$ and PASP on day two ($R^2$=0.03; P=0.61), day five ($R^2$=0.05; P=0.51), and after 2-3weeks acclimatization ($R^2$=0.03; P=0.69), and in Sherpa ($R^2$=0.16; P=0.07). PASP, pulmonary artery systolic pressure; HA, high altitude; $SpO_2$, peripheral oxyhemoglobin saturation.

**References:**


1. Hirshman C, McCullough R, Weil J V. Normal values for hypoxic and hypercapnic ventilatory drives in man. *J Appl Physiol*. 1975;38(6):1095-1098.

2. Motley HL, Cournand A, Werko L, Himmelstein A, Dresdale D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am J Physiol*. 1947;150(2):315-320.

3. Maggiorini M, Mélot C, Pierre S, et al. High-Altitude Pulmonary Edema Is Initially Caused by an Increase in Capillary Pressure. *Circulation*. 2001:2078-2083. doi:10.1161/01.CIR.103.16.2078.

4. Maggiorini M, Brunner-La Rocca H-P, Peth S, et al. Both Tadalafil and Dexamethasone May Reduce the Incidence of high altitude pulmonary edema: A randomized trial. *Ann Intern Med*. 2006;145:497-507.

5. Swenson ER, Maggiorini M, Mongovin S, et al. Pathogenesis of High-Altitude Pulmonary Edema: Inflammation is not an etiological factor. *JAMA*. 2002;287(17):2228-2235.

6. Grünig E, Mereles D, Hildebrandt W, et al. Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. *J Am Coll Cardiol*. 2000;35(4):980-7.

7. Kawashima a, Kubo K, Kobayashi T, Sekiguchi M. Hemodynamic responses to acute hypoxia, hypobaria, and exercise in subjects susceptible to high-altitude pulmonary edema. *J Appl Physiol*. 1989;67(5):1982-9.

8. Hultgren HN, Grover RF, Hartley LH. Abnormal Circulatory Responses to High Altitude in Subjects with a Previous History of High-Altitude Pulmonary Edema. *Circulation*. 1971;44(5):759-770. doi:10.1161/01.CIR.44.5.759.

9. Bartsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med*. 1991;325(18):1284-1289.

10. Levitzky M. Chemoreceptor stimulation and hypoxic pulmonary vasoconstriction in concious dogs. *Respir Physiol*. 1979;(February):151-160.

11. Levitzky M, Newell J, Krasney J, Dutton R. Chemoreceptor influence on pulmonary blood flow during unilateral hypoxia in dogs. *Respir Physiol*. 1977.

12. Daly I de B, Daly M de B. The effects of stimulation of the carotid sinus baroreceptors on the pulmonary vascular bed. *J Physiol*. 1959:220-226.

13. Fitzgerald RS, Dehghani G a, Sham JS, Shirahata M, Mitzner W a. Peripheral chemoreceptor modulation of the pulmonary vasculature in the cat. *J Appl Physiol*. 1992;73(1):20-9.

14. Albert T, Swenson E. Peripheral chemoreceptor responsiveness and hypoxic pulmonary vasoconstriction in humans. *High Alt Med Biol*. 2014;15(1):15-20.

15. Ainslie P, Lucas S, Burgess K. Breathing and sleep at high altitude. *Respir Physiol Neurobiol*. 2013.

16. White D, Gleeson K, Pickett C, Rannels A, Cymerman A, Weil J. Altitude acclimatization: influence on periodic breathing and chemoresponsiveness during sleep. *J appl Physiol*. 1987;63(1):401-412.

17. Sato M, Severinghaus JW, Powell FL, Xu F, Spellman M. Augmented hypoxic ventilatory in men at altitude. *J Appl Physiol*. 1992:101-107.

18. Dwinell M, Powell F. Chronic hypoxia enhances the phrenic nerve response to arterial chemoreceptor stimulation in anesthetized rats. *J Appl Physiol*. 1999:817-823.

19. Barnard P, Andronikou S, Pokorski M, Smatresk N, Mokashi a, Lahiri S. Time-dependent effect of hypoxia on carotid body chemosensory function. *J Appl Physiol*. 1987;63(2):685-91.

20. Gallman E, Millhorn D. Two long-lasting central respiratory responses following acute hypoxia glomectomized cats. *J Physiol*. 1988:333-347.

21. Swenson ER. Hypoxic pulmonary vasoconstriction. *High Alt Med Biol*. 2013;14(2):101-10. doi:10.1089/ham.2013.1010.

22. Basnyat B, Gertsch JH, Holck PS, et al. Acetazolamide 125mg BD is not significantly different from 375 mg BD in the prevention of acute mountain sickness: the prophylactic acetazolamide dosage comparison for efficacy (PACE) trial. *High Alt Med Biol*. 2006;7(1):17-28. doi:10.1038/kisup.2013.30.

23. Ritschel W, Paulos C, Arancibia A, Agrawal M, Wetzelsberger K, Lucker P. Urinary excretion of acetazolamide in healthy volunteers after short- and long-term exposure to high altitude. *J Clin Pharmacol*. 1998;38:533-539.

24. Richalet J-P, Rivera M, Bouchet P, et al. Acetazolamide: a treatment for chronic mountain sickness. *Am J Respir Crit Care Med*. 2005;172(11):1427-33. doi:10.1164/rccm.200505-807OC.

25. Ke T, Wang J, Swenson ER, et al. Effect of acetazolamide and gingko biloba on the human pulmonary vascular response to an acute altitude ascent. *High Alt Med Biol*. 2013;14(2):162-7. doi:10.1089/ham.2012.1099.

26. Donnelly J, Cowan DC, Yeoman DJ, et al. Exhaled nitric oxide and pulmonary artery pressures during graded ascent to high altitude. *Respir Physiol Neurobiol*. 2011;177(3):213-7. doi:10.1016/j.resp.2011.04.008.

27. Lucas SJE, Burgess KR, Thomas KN, et al. Alterations in cerebral blood flow and cerebrovascular reactivity during 14 days at 5050 m. *J Physiol*. 2011;589(Pt 3):741-53. doi:10.1113/jphysiol.2010.192534.

28. Stembridge M, Ainslie PN, Hughes MG, et al. Ventricular structure, function and mechanics at high altitude: chronic remodelling in Sherpa verses short-term lowlander adaptation. *J Appl Physiol*. 2014. doi:10.1152/japplphysiol.00233.2014.

29. Foster GE, Ainslie PN, Stembridge M, et al. Resting pulmonary haemodynamics and shunting: a comparison of sea-level inhabitants to high altitude Sherpas. *J Physiol*. 2014;592(Pt 6):1397-409. doi:10.1113/jphysiol.2013.266593.

30. Ainslie PN. On the nature of research at high altitude: packing it all in! *Exp Physiol*. 2014;99(5):741-2. doi:10.1113/expphysiol.2013.077362.

31. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and t. *J Am Soc Echocardiogr*. 2010;23(7):685-713. doi:10.1016/j.echo.2010.05.010.

32. Querido JS, Ainslie PN, Foster GE, et al. Dynamic cerebral autoregulation during and following acute hypoxia: role of carbon dioxide. *J Appl Physiol*. 2013;114(9):1183-90. doi:10.1152/japplphysiol.00024.2013.

33. Naeije R, Vanderpool R. Pulmonary hypertension and chronic mountain sickness. *High Alt Med Biol*. 2013;14(2):117-25. doi:10.1089/ham.2012.1124.

34. Muza SR, Rock PB, Fulco CS, et al. Women at altitude: ventilatory acclimatization at 4,300m. *J Appl Physiol*. 2001;91:1791-1799.

35. Bhaumik G, Sharma RP, Dass D, et al. Hypoxic ventilatory response changes of men and women 6 to 7 days after climbing from 2100 m to 4350 , altitude and after descent. *High Alt Med Biol*. 2003;4(3):341-348.

36. Nielsen a M, Bisgard GE, Vidruk EH. Carotid chemoreceptor activity during acute and sustained hypoxia in goats. *J Appl Physiol*. 1988;65(4):1796-802.

37. Vizek M, Pickett CK, Weil J V. Increased carotid body hypoxic sensitivity during acclimatization to hypobaric hypoxia. *J Appl Physiol*. 1987;63(6):2403-10.

38. Dwinell MR, Huey K a, Powell FL. Chronic hypoxia induces changes in the central nervous system processing of arterial chemoreceptor input. *Adv Exp Med Biol*. 2000;475:477-84.

39. Agostoni P, Swenson ER, Bussotti M, et al. High-altitude exposure of three weeks duration increases lung diffusing capacity in humans. *J Appl Physiol*. 2011;110(6):1564-71. doi:10.1152/japplphysiol.01167.2010.

40. Hackett PH, Roach RC, Schoene RB, Harrison GL, Mills WJ. Abnormal control of ventilation in high-altitude pulmonary edema. *J Appl Physiol*. 1988;64(3):1268-72.

41. Hohenhaus E, Paul a., McCullough RE, Kücherer H, Bärtsch P. Ventilatory and pulmonary vascular response to hypoxia and susceptibility to high altitude pulmonary oedema. *Eur Respir J*. 1995;8(11):1825-1833. doi:10.1183/09031936.95.08111825.

42. Moore LG, Harrison GL, McCullough RE, et al. Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. *J Appl Physiol*. 1986;60(4):1407-12.

43. Milledge JS, Beeley JM, Broome J, Luff N, Pelling M, Smith D. Acute mountain sickness susceptibility, fitness and hypoxic ventilatory response. *Eur Respir J*. 1991;4(8):1000-3.

44. Rotta A, Cánepa A, Hurtado A, Velasquez T, Chavez R. Pulmonary circulation at sea level and at high altitudes. *J Appl Physiol*. 1956;9(3):328-336.

45. Euler U, Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol Scand*. 1946;12(1937).

46. Kronenberg RS, Safar P, Lee J, et al. Pulmonary Artery Pressure and Alveolar Gas Exchange in Man during Acclimatization to 12 , 470 ft. *J Clin Invest*. 1971;50(10).

47. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation*. 2007;115(9):1132-46. doi:10.1161/CIRCULATIONAHA.106.624544.

48. Faoro V, Huez S, Vanderpool R, et al. Pulmonary circulation and gas exchange at exercise in Sherpas at high altitude. *J Appl Physiol*. 2014;116:919-926. doi:10.1152/japplphysiol.00236.2013.

49. Welsh DJ, Peacock AJ. Cellular Responses to Hypoxia in the Pulmonary Circulation. *High Alt Med Biol*. 2013;14(2). doi:10.1089/ham.2013.1016.

50. Beall CM, Laskowski D, Strohl K, et al. Pulmonary nitric oxide in mountain dwellers. *Nature*. 2001;414(6862):411-2. doi:10.1038/35106641.