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The influence of short-term high-altitude acclimatization on cerebral and leg tissue oxygenation post orthostasis

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Abstract

Purpose: Orthostasis at sea level decreases brain tissue oxygenation and increases risk of syncope. High altitude reduces brain and peripheral muscle tissue oxygenation. This study determined the effect of short-term altitude acclimatization on cerebral and peripheral leg tissue oxygenation index (TOI) post-orthostasis.

Method: Seven lowlanders completed a supine-to-stand maneuver at sea level (450 m) and for 3 consecutive days at high altitude (3,776 m). Cardiorespiratory measurements and near-infrared spectroscopy-derived oxygenation of the frontal lobe (cerebral TOI) and vastus lateralis (leg TOI) were measured at supine and 5 min post-orthostasis.

Results: After orthostasis at sea level, cerebral TOI decreased (mean Δ% [95% CI]: -4.5%, [-7.5, -1.5], $P < 0.001$) whilst leg TOI was unchanged (-4.6%, [-10.9, 1.7], $P = 0.42$). High altitude had no effect on cerebral TOI following orthostasis (day 1 to 3: -2.3%, [-5.3, 0.7]; -2.4%, [-5.4, 0.6]; -2.1%, [-5.1, 0.9], respectively, all $P > 0.05$) whereas leg TOI decreased (day 1 to 3: -12.0%, [-18.3, -5.7]; -12.1%, [-18.4, -5.8]; -10.2%, [-16.5, -3.9], respectively, all $P < 0.001$). This response did not differ with days spent at high altitude, despite evidence of cardiorespiratory acclimatization (increased peripheral oxygen saturation [supine: $P = 0.01$; stand: $P = 0.02$] and decreased end-tidal carbon dioxide [supine: $P = 0.003$; stand: $P = 0.01$]).

Conclusion: Cerebral oxygenation is preferentially maintained over leg oxygenation post-orthostasis at high altitude, suggesting different vascular regulation between cerebral and peripheral circulations. Short-term acclimatization to high altitude did not alter cerebral and leg oxygenation responses to orthostasis.

Keywords: *altitude, blood pressure, heart rate, hypoperfusion, hypoxia, tissue oxygenation*

Declarations

Funding

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Conflicts of interest/Competing interests (include appropriate disclosures)

No conflict of interest, financial or otherwise, are declared by the authors.

Ethics approval and consent to participate

All study procedures were approved by the ethical committee of the Mount Fuji Research Institute in Japan (ECMFRI-01-2014) and performed in accordance with the Declaration of Helsinki 2013, with written informed consent obtained from all study participants.

Availability of data and material (data transparency)

All relevant data are within the paper. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability (software application or custom code)

Not applicable.

Authors' contributions

The M.H., K.A., and K.O. conceived and designed the study. M.H., K.A., and K.O. performed the experiments. M.H., K.O., A.T.F., G.M.K.R., and S.J.O. analyzed data and interpreted results. M.H., G.M.K.R., and A.T.F. prepared tables and figures. M.H. drafted the first manuscript. M.H., K.A., K.O., A.T.F., G.M.K.R., and S.J.O. critically revised the manuscript, and all authors approved the final version of the manuscript.

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Abbreviations

ANOVA: Analysis of variance

BP: blood pressure

DBP: diastolic blood pressure

HR: Heart rate

MAP: Mean arterial pressure

NIRS: near-infrared spectroscopy

$P_{ET}CO_2$: partial pressure of end tidal carbon dioxide

SBP: Systolic blood pressure

SD: standard deviation

SpO_2: peripheral arterial oxygen saturation

TOI: tissue oxygenation index

Introduction

In the upright stand position the cerebral arteries are positioned above the heart resulting in a hydrostatic arterial pressure gradient between the heart and the brain, causing a reduction in cerebral perfusion pressure (Rosner and Coley 1986). Consequently, the brain is prone to incidents of hypoperfusion that may lead to orthostatic intolerance (Van Lieshout et al. 2003). Orthostatic tolerance is reduced during exposure to severe (10% O_2) normobaric hypoxia (Rowell and Seals 1990) and to hypobaric hypoxia at moderate (ca. 2,800 m) (Nicholas et al. 1992), and high (ca. 6,000 m) altitudes (Westendorp et al. 1997). As impaired orthostatic tolerance is associated with syncope or collapse (Van Lieshout et al. 2003), this is of concern to mountaineers and others working and visiting high altitude, for whom falls may be life threatening (Firth et al. 2008). Short-term acclimatization at high altitude could be a strategy to reduce orthostatic intolerance. However, evidence of high-altitude acclimatization effect on orthostatic intolerance is limited.

To evaluate tolerance to orthostasis, measurements of cerebral tissue oxygenation index (TOI) by near-infrared spectroscopy (NIRS) have been commonly used (Mehagnoul-Schipper et al. 2000; Mehagnoul-Schipper et al. 2003). Cerebral TOI is determined by arterial oxygen content, oxygen consumption, and total blood volume at the target tissue (i.e., directly below the probes). Moreover, previous research has suggested that cerebral TOI is a sensitive and robust indicator of orthostatic intolerance (Kuriyama et al. 2000). Although it is well established that a common cause of syncope is initial (< 1 min) orthostatic hypotension (Wieling et al. 2007), the potential risk of syncope during the later phase (> 1 min) should also be considered. Previous studies have demonstrated that blood pressure (BP) and middle cerebral artery blood flow velocity fall acutely from supine to stand within 10 s, but recovers within 30 s (Thomas et al. 2010; Thomas et al. 2009; van Lieshout et al. 2001). However, cerebral oxygenation remains lower after 5 min of stand (van Lieshout et al. 2001), suggesting a possibility of syncope incidents even after initial orthostatic hypotension phase. Moreover, it has been suggested that orthostatic intolerance is fundamentally due to a critical fall in cerebral perfusion, rather than systemic BP *per se* (Van Lieshout et al. 2003). Thus, evaluations of cerebral TOI and BP after initial orthostatic hypotension phase could provide further understanding to orthostasis.

Orthostatic tolerance is positively related to the strength of sympathetic-driven peripheral vasoconstriction (Brown and Hainsworth 2000; Claydon and Hainsworth 2004). Enhanced muscle sympathetic nerve activity is accompanied by reductions in peripheral oxygenation during lower body negative pressure during normoxia (Hansen et al. 2000; Hansen et al. 1996; Vongpatanasin et al. 2011) and hypoxia (Hansen et al. 2000). Therefore, the reduced peripheral oxygenation reported to orthostasis may be part of an adaptive response to maintain cerebral oxygenation and prevent orthostatic intolerance. This study aimed to investigate the cerebral and peripheral tissue oxygenation response to orthostasis at sea level and high altitude. We hypothesized that with acute exposure to high altitude (day 1), following the initial hypotension phase (5 min post-orthostasis) cerebral tissue oxygenation would be maintained at the expense of peripheral tissue oxygenation. Secondly, we hypothesized that following short-term high-altitude acclimatization (3 days) there would be an attenuated reduction in peripheral oxygenation post-orthostasis compared to acute exposure (day 1).

Methods

Participants

This study was approved by the ethical committee of the Mount Fuji Research Institute in Japan (ECMFRI-01-2014) and performed in accordance with the *Declaration of Helsinki 2013*, with written informed consent obtained from all study participants. Seven healthy male lowlanders [mean ± standard deviation (SD): age 46 ± 15 years; height 173 ± 6 cm; body mass 68 ± 5 kg] voluntarily participated in this study. All participants were free from cardiovascular disease, were not taking medications, and did not engage in regular exercise. Additionally, none of the participants had been exposed to an altitude higher than 1,500 m within six months before the study. Before the study commenced participants abstained from strenuous physical activity and alcohol for 24 h, and from caffeinated beverages for 12 h. They also abstained from strenuous exercise, alcohol and caffeine for the following four study days.

Study locations and procedures

Measurements were taken at sea level followed by three consecutive days at high altitude (3,776 m; day 1, day 2, and day 3). The sea level study was conducted at the Mount Fuji Research Station (450 m above sea level, ambient barometric pressure ca. 720 mmHg), and the high altitude study at the Mount Fuji Summit Hut (3,776 m above sea level, ambient barometric pressure ca. 490 mmHg, **Figure 1**). All participants were familiarized with the experimental protocol and supine-to-stand maneuver before beginning the study. Sea level measurements were performed 2 weeks before ascent to high altitude. On the day of ascent, all participants reached the Self-Defense Forces base camp in the morning by vehicle (1,280 m above sea level, ambient barometric pressure ca. 655 mmHg). Participants ascended to the top of Mount Fuji (3,776 m) within 3 h by riding on a bulldozer, arriving at approximately 9:00 AM. All studies were performed between 14:00 and 17:00. After three nights at high altitude the participants walked down the mountain and returned to sea level.

Experimental protocol and measurements

Each participant rested in the supine position for 30 min before they were asked to stand quickly and assume an erect and immobile posture. Participants were requested not to speak, to breathe normally, and to remain as still as possible to reduce any influence of the skeletal muscle pump when in the stand position. Stand position was determined once the participant maintained a stable balance.

Heart rate (HR), peripheral arterial oxygen saturation (SpO_2), and partial pressure of end tidal carbon dioxide ($P_{ET}CO_2$) were continuously measured during supine and stand. $P_{ET}CO_2$ was measured in 5 participants due to equipment fault. HR was recorded using a commercial HR monitor (Polar RS800CX, Polar Electro Japan, Tokyo, Japan). SpO_2 was monitored by finger pulse oximetry (PULSOX-300i; Konica Minolta, Tokyo, Japan) on the right index finger. $P_{ET}CO_2$ was measured using a CO_2 monitor (OLG-2800, Nihon Kohden, Tokyo, Japan). Systolic BP (SBP) and diastolic BP (DBP) were measured at 1-min intervals during supine and stand using the oscillometric method on the upper left arm (HEM-7200; Omron, Tokyo, Japan).

Cerebral and peripheral hemodynamics were measured continuously using NIRS (NIRO-300; Hamamatsu Photonics KK, Hamamatsu, Japan) throughout the supine-to-stand maneuver (Al-Rawi et al. 2001). NIRS has been utilized for continuous monitoring of cerebral oxygenation by evaluating the concentrations of oxyhemoglobin and deoxyhemoglobin at the measurement site using spatially resolved spectroscopy (Houtman et al. 1999; Mehagnoul-Schipper et al. 2000; Mehagnoul-Schipper et al. 2003). TOI provides a measure of tissue oxygen saturation and is calculated as the ratio of oxygenated to total tissue hemoglobin [TOI = oxyhemoglobin / total hemoglobin (oxyhemoglobin + deoxyhemoglobin)]. A probe holder containing an emission probe and detection probe was attached to the right side of the forehead (with a distance of 3 cm between the probes) to measure TOI at the frontal lobe (cerebral TOI). Two further probes were attached to the lower third of the vastus lateralis muscle (10–12 cm above the knee joint) to measure peripheral oxygenation (leg TOI) (Koga et al. 2007). Pen marks were made on the skin to indicate the margins of the probe holder and electrodes so that the probe could be positioned at exactly the same place each day.

Data analysis

Continuous measurements of cerebral TOI, leg TOI, HR, $P_{ET}CO_2$, and SpO_2 were averaged from the final 5 min of supine rest and from the final 10 s of standing following the maneuver (i.e., 4’50”–5’00” min). Incremental measurements of SBP and DBP were taken every minute at supine rest with the average reported. During standing, one measurement of SBP and DBP was taken 5 min following the maneuver. Mean arterial pressure (MAP) was calculated: [MAP = (SBP-DBP)/3+DBP]. To evaluate the effects of high-altitude acclimatization (i.e., from day 1 to day 3 at high altitude) to orthostasis, cerebral TOI and leg TOI are presented as the percent change from supine to stand for each day spent at high altitude.

Statistical analysis

A sample size estimation for the primary analysis (cerebral TOI) indicated that 4 participants were needed to produce an 80% chance of obtaining statistical significance at the 0.05 level (G Power 3.1) (Faul et al. 2009) for a meaningful Cohen's F effect size of 0.92 for a 2×4 repeated measures analysis of variance (ANOVA). The effect size was calculated based on a minimum important difference of 4.4% determined by the difference in cerebral TOI between orthostatic symptomatic and asymptomatic persons (Harms et al. 2000), a standard deviation of the difference of 2.4% from the same study (Harms et al. 2000), and a correlation of repeated measures of $r = 0.76$, based on data from a previous study (Al-Rawi et al. 2001). A minimum 6 participants were set as the target for recruitment to account for possible dropout. All data were expressed as mean ± SD. Statistical analysis was performed using GraphPad Prism 7 commercial software (MDF Co., Ltd, Tokyo, Japan), with statistical significance accepted at $P < 0.05$. Two-way repeated measures ANOVA with Bonferroni post-hoc tests were used to assess differences between day (sea level, day 1, day 2, and day 3) and posture (supine and stand) for all cardiorespiratory and oxygenation measures. One-way repeated-measures ANOVA was used to determine differences in the percentage change in cerebral TOI and leg TOI between days. To assess the effect of acclimatization to high altitude, one-way repeated-measures ANOVA (day 1 to day 3) with linear trend analysis were conducted on cardiorespiratory and oxygenation measures. This is because we sought to observe the overall slope and fit of the response in physiological responses during sojourn at high altitude. This linear trend analysis approach was particularly advantageous to reduce the number of comparisons made (Horiuchi et al. 2016; Horiuchi et al. 2017).

Results

Cardiorespiratory variables

Supine cardiorespiratory variables demonstrated expected responses to acute hypoxia and provide evidence of altitude acclimatization over the three days. Specifically, compared to sea level, SpO_2 was lower on day 1 at high altitude and then increased on subsequent days at altitude (**Table 1**). Further, linear trend analysis identified that SpO_2 ($P = 0.01$) and MAP ($P < 0.001$) increased, and $P_{ET}CO_2$ ($P = 0.003$) decreased, linearly with sojourn at high altitude. HR also tended to linearly increase with days at altitude ($P = 0.06$, **Table 1 and 2**). The supine-to-stand maneuver increased MAP on day 2 at high altitude (P = 0.02), HR at sea level and all days at high altitudes (all P < 0.05), SpO_2 on all days at high altitude (all P < 0.05), and decreased $P_{ET}CO_2$ on day 1 (P = 0.02) and day 2 (P = 0.01) at high altitude (**Table 1**).

Cerebral tissue oxygenation index

Compared to sea level, supine cerebral TOI decreased on day 1 at high altitude (P < 0.01, **Figure 2A**), and did not recover during the sojourn at high altitude (P = 0.36, **Table 2**). Cerebral TOI was lower after the supine-to-stand maneuver at sea level (supine-to-stand mean Δ% [95% CI]: - 4.5%, [-7.5, -1.5], P < 0.001, **Figure 2A and 2C**). In contrast, altitude had no effect on cerebral TOI after the supine-to-stand maneuver (day 1 Δ%: -2.3%, [-5.3, 0.7], P = 0.34; day 2 -2.4%, [-5.4, 0.6], P = 0.22; day 3 -2.1%, [-5.1, 0.9], P = 0.49; **Figure 2A and 2C**). Linear trend analysis of day 1 to 3 revealed that short-term acclimatization did not alter cerebral oxygenation change to orthostasis (P = 0.86).

Peripheral leg tissue oxygenation index

Supine leg TOI was unchanged at high altitude compared to sea level (P = 0.32, **Figure 2B and Table 2**). Leg TOI was maintained after the supine-to-stand maneuver at sea level (Δ% -

4.6% [-10.9, 1.7], $P = 0.42$, **Figure 2B and 2D**). In contrast, leg TOI was lower after the supine-to-stand maneuver on all days at high altitude (day 1 Δ%: -12.0%, [-18.3, -5.7]; day 2 -12.1%, [-18.4, -5.8]; day 3 -10.2%, [-16.5, -3.9]; all $P < 0.001$, **Figure 2B and 2D)**. Linear trend analysis of day 1 to 3 revealed that short-term acclimatization did not alter leg oxygenation change to orthostasis ($P = 0.37$).

Discussion

The principle finding of this study is that after orthostasis at high altitude cerebral TOI was protected against the reduction that was observed at sea level. Indeed, the non-significant mean difference in cerebral TOI after orthostasis at high altitude can be considered trivial as it was less than the minimum important difference (4.4%) that was calculated from the difference in cerebral TOI between orthostatic symptomatic and asymptomatic persons (Harms et al. 2000). A reduction in cerebral TOI (4.5%) was achieved after orthostasis at sea level in this study. Peripheral (leg) TOI was in contrast reduced after orthostasis at high altitude but not at sea level. These data highlight that cerebral oxygenation is preferentially maintained compared to leg oxygenation during orthostasis at high altitude. This reciprocal response was unchanged during the 3-day high altitude sojourn that led to cardiorespiratory altitude acclimatization adaptations including a progressive recovery of SpO_2. These results indicate a different vascular regulation between the cerebral and peripheral circulations to orthostasis during short-term high-altitude acclimatization.

In agreement with previous studies (Cheung et al. 2014; Sanborn et al. 2015), high altitude hypoxia reduced cerebral TOI during supine rest compared to sea level (**Figure 2A**). Since TOI is calculated as the ratio of oxyhemoglobin to total tissue hemoglobin (Al-Rawi et al. 2001), changes in TOI could be due to alterations in cerebral blood flow (oxygen delivery) or oxygen extraction. Oxyhemoglobin is mainly included in the artery and cerebral blood flow (arterial inflow) increases within the first 6–12 hours at high altitude, remaining elevated for several days compared with sea level as first reported (Severinghaus et al. 1966). Subsequent studies have confirmed these results (Jensen et al. 1990; Lucas et al. 2011; Subudhi et al. 2014; Willie et al. 2014). Thus, TOI reductions in the present study may be explained by increases in deoxyhemoglobin in the brain that is consistent with a previous research (Cheung et al. 2014). Indeed, it was reported that hypoxia causes an increase in the volume of cerebral deoxyhemoglobin by increasing oxygen extraction (Rasmussen et al. 2007). The absence of a further reduction in cerebral oxygenation to orthostasis suggests that the cerebrovascular perfusion is preferentially maintained compared to peripheral perfusion e.g. leg TOI. There are several possibilities to explain these results. We found significant reductions in the leg TOI 5 min post-orthostasis. This may indicate that sympathetic-induced vasoconstriction occurred at the peripheral arteries, which could be an adaptive response to ensure the maintenance of cerebral TOI. Indeed, during 3-day acclimatization at high altitude, MAP, which is observed along with increases in muscle sympathetic nerve activity (Hansen et al. 1996), progressively increased irrespective of posture (P < 0.05, respectively, **Table 1 and 2**). Combined, this suggests the maintenance of cerebral TOI to orthostasis at high altitude is dependent on peripheral vasoconstriction to maintain MAP, with compromising consequences for oxygenation of peripheral tissues. These interpretations are supported by a previous study that has reported reductions in peripheral oxygenation with enhanced muscle sympathetic nerve activity during lower body negative pressure (i.e., simulated orthostasis) in hypoxia (Hansen et al. 2000).

The absence of a further decrease in cerebral oxygenation after orthostasis at high altitude may be due to a redistribution of cardiac output (cardiac output = stoke volume × HR) since changes in cerebral oxygenation to orthostasis is also cardiac output dependent (van Lieshout et al. 2001). Stroke volume decreases during short-term (5 days) exposure high altitude (Kanstrup et al. 1999), and hence, increased HR compensates to maintain cardiac output for sufficient oxygen delivery to peripheral tissues. Indeed, HR at high altitude was significantly higher than sea level and the supine-to-stand maneuver significantly increased HR throughout the days. Thus, it is also possible that the increase in HR from supine to stand could compensate to maintain cardiac output and support the maintenance of cerebral TOI.

However, we acknowledge that this hypothesis is speculative and warrants future investigation with a measurement of stroke volume and cardiac output.

In the present study, cerebral TOI did not recover, but SpO_2 progressively increased irrespective of posture during the sojourn at high altitude. While SpO_2 assessed by pulse oximeter has been widely used to evaluate systemic hypoxemia (Kohyama et al. 2015), our data and that of others (Sanborn et al. 2015) demonstrate that SpO_2 may not represent cerebral oxygenation. The finding that cerebral TOI responses are divergent from peripheral (leg) TOI and SpO_2 not only has implications for our understanding of physiological responses to high altitude, but also for future research design in the field.

Methodological considerations

NIRS was used to provide a non-invasive measure of tissue oxygenation. As near infrared light passes through skin before absorption into the tissue the potential exists for blood flow outside of the tissue to influence NIRS derived measurements. A limitation of the present study is that skin blood flow was not measured. Nevertheless, previous research using the same NIRS device as in the present study, reported that a change in cerebral TOI was predominantly associated with internal carotid artery blood flow, and not external carotid artery or skin blood flow during carotid vessel clamping (Al-Rawi et al. 2001). Further, a more recent study demonstrated that cerebral oxygenation during acute hypotension periods in hypoxia (simulated orthostasis) was not associated with skin blood flow (Horiuchi et al. 2020). To aid clarity of interpretation future studies should measure where practically possible tissue oxygenation and skin blood flow simultaneously. The present study was completed in a field environment to enable the investigation of high-altitude acclimatization. A limitation of this scenario was that we were not able for logistical reasons to measure other cardiac and cerebrovascular responses, including skin blood flow. These additional measures would have provided a more complete assessment and understanding of the physiological mechanisms that underpin the divergent cerebral and leg oxygenation responses observed.

Conclusions

Cerebral oxygenation post-orthostasis at high altitude was protected against the reduction observed at sea level, whereas peripheral (leg) oxygenation was only reduced post-orthostasis at high altitude. This reciprocal response highlights divergent vascular regulation in cerebral and peripheral circulations and may suggest an adaptive response to preferentially maintain cerebral oxygenation during orthostasis at high altitude. Short-term acclimatization to high altitude did not alter the cerebral and peripheral oxygenation response to orthostasis.

References

Al-Rawi PG, Smielewski P, Kirkpatrick PJ (2001) Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. Stroke 32 (11):2492-2500

Brown CM, Hainsworth R (2000) Forearm vascular responses during orthostatic stress in control subjects and patients with posturally related syncope. Clinical autonomic research : official journal of the Clinical Autonomic Research Society 10 (2):57-61

Cheung SS, Mutanen NE, Karinen HM, Koponen AS, Kyrolainen H, Tikkanen HO, Peltonen JE (2014) Ventilatory chemosensitivity, cerebral and muscle oxygenation, and total hemoglobin mass before and after a 72-day mt. Everest expedition. High altitude medicine & biology 15 (3):331-340. doi:10.1089/ham.2013.1153

Claydon VE, Hainsworth R (2004) Salt supplementation improves orthostatic cerebral and peripheral vascular control in patients with syncope. Hypertension 43 (4):809-813. doi:10.1161/01.HYP.0000122269.05049.e7

Faul F, Erdfelder E, Buchner A, Lang AG (2009) Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 41 (4):1149-1160. doi:10.3758/BRM.41.4.1149

Firth PG, Zheng H, Windsor JS, Sutherland AI, Imray CH, Moore GW, Semple JL, Roach RC, Salisbury RA (2008) Mortality on Mount Everest, 1921-2006: descriptive study. BMJ 337:a2654. doi:10.1136/bmj.a2654

Hansen J, Sander M, Hald CF, Victor RG, Thomas GD (2000) Metabolic modulation of sympathetic vasoconstriction in human skeletal muscle: role of tissue hypoxia. The Journal of physiology 527 Pt 2:387-396. doi:10.1111/j.1469-7793.2000.00387.x

Hansen J, Thomas GD, Harris SA, Parsons WJ, Victor RG (1996) Differential sympathetic neural control of oxygenation in resting and exercising human skeletal muscle. The Journal of clinical investigation 98 (2):584-596. doi:10.1172/JCI118826

Harms MP, Colier WN, Wieling W, Lenders JW, Secher NH, van Lieshout JJ (2000) Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. Stroke 31 (7):1608-1614

Horiuchi M, Endo J, Dobashi S, Kiuchi M, Koyama K, Subudhi AW (2016) Effect of progressive normobaric hypoxia on dynamic cerebral autoregulation. Experimental physiology 101 (10):1276-1284. doi:10.1113/EP085789

Horiuchi M, Endo J, Handa-Kirihra Y (2020) Relationship Between Cerebral Oxygenation and Skin Blood Flow at the Frontal Lobe during Progressive Hypoxia: Impact of Acute Hypotension. Adv Exp Med Biol 1232:69-75. doi:10.1007/978-3-030-34461-0_10

Horiuchi M, Oda S, Uno T, Endo J, Handa Y, Fukuoka Y (2017) Effects of Short-Term Acclimatization at the Summit of Mt. Fuji (3776 m) on Sleep Efficacy, Cardiovascular Responses, and Ventilatory Responses. High altitude medicine & biology 18 (2):171-178. doi:10.1089/ham.2016.0162

Houtman S, Colier WN, Hopman MT, Oeseburg B (1999) Reproducibility of the alterations in circulation and cerebral oxygenation from supine rest to head-up tilt. Clin Physiol 19 (2):169-177. doi:10.1046/j.1365-2281.1999.00159.x

Jensen JB, Wright AD, Lassen NA, Harvey TC, Winterborn MH, Raichle ME, Bradwell AR (1990) Cerebral blood flow in acute mountain sickness. Journal of applied physiology 69 (2):430-433. doi:10.1152/jappl.1990.69.2.430

Kanstrup IL, Poulsen TD, Hansen JM, Andersen LJ, Bestle MH, Christensen NJ, Olsen NV (1999) Blood pressure and plasma catecholamines in acute and prolonged hypoxia: effects of local hypothermia. Journal of applied physiology 87 (6):2053-2058. doi:10.1152/jappl.1999.87.6.2053

Koga S, Poole DC, Ferreira LF, Whipp BJ, Kondo N, Saitoh T, Ohmae E, Barstow TJ (2007) Spatial heterogeneity of quadriceps muscle deoxygenation kinetics during cycle exercise. Journal of applied physiology 103 (6):2049-2056. doi:10.1152/japplphysiol.00627.2007

Kohyama T, Moriyama K, Kanai R, Kotani M, Uzawa K, Satoh T, Yorozu T (2015) Accuracy of pulse oximeters in detecting hypoxemia in patients with chronic thromboembolic pulmonary hypertension. PLoS One 10 (5):e0126979. doi:10.1371/journal.pone.0126979

Kuriyama K, Ueno T, Ballard RE, Cowings PS, Toscano WB, Watenpaugh DE, Hargens AR (2000) Cerebrovascular responses during lower body negative pressure-induced presyncope. Aviation, space, and environmental medicine 71 (10):1033-1038

Lucas SJ, Burgess KR, Thomas KN, Donnelly J, Peebles KC, Lucas RA, Fan JL, Cotter JD, Basnyat R, Ainslie PN (2011) Alterations in cerebral blood flow and cerebrovascular reactivity during 14 days at 5050 m. The Journal of physiology 589 (Pt 3):741-753. doi:10.1113/jphysiol.2010.192534

Mehagnoul-Schipper DJ, Vloet LC, Colier WN, Hoefnagels WH, Jansen RW (2000) Cerebral oxygenation declines in healthy elderly subjects in response to assuming the upright position. Stroke 31 (7):1615-1620

Mehagnoul-Schipper DJ, Vloet LC, Colier WN, Hoefnagels WH, Verheugt FW, Jansen RW (2003) Cerebral oxygenation responses to standing in elderly patients with predominantly diastolic dysfunction. Clinical physiology and functional imaging 23 (2):92-97

Nicholas R, O'Meara PD, Calonge N (1992) Is syncope related to moderate altitude exposure? Jama 268 (7):904-906

Rasmussen P, Dawson EA, Nybo L, van Lieshout JJ, Secher NH, Gjedde A (2007) Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 27 (5):1082-1093. doi:10.1038/sj.jcbfm.9600416

Rosner MJ, Coley IB (1986) Cerebral perfusion pressure, intracranial pressure, and head elevation. J Neurosurg 65 (5):636-641. doi:10.3171/jns.1986.65.5.0636

Rowell LB, Seals DR (1990) Sympathetic activity during graded central hypovolemia in hypoxemic humans. The American journal of physiology 259 (4 Pt 2):H1197-1206. doi:10.1152/ajpheart.1990.259.4.H1197

Sanborn MR, Edsell ME, Kim MN, Mesquita R, Putt ME, Imray C, Yow H, Wilson MH, Yodh AG, Grocott M, Martin DS (2015) Cerebral hemodynamics at altitude: effects of hyperventilation and acclimatization on cerebral blood flow and oxygenation. Wilderness & environmental medicine 26 (2):133-141. doi:10.1016/j.wem.2014.10.001

Severinghaus JW, Chiodi H, Eger EI, 2nd, Brandstater B, Hornbein TF (1966) Cerebral blood flow in man at high altitude. Role of cerebrospinal fluid pH in normalization of flow in chronic hypocapnia. Circ Res 19 (2):274-282. doi:10.1161/01.res.19.2.274

Subudhi AW, Fan JL, Evero O, Bourdillon N, Kayser B, Julian CG, Lovering AT, Roach RC (2014) AltitudeOmics: effect of ascent and acclimatization to 5260 m on regional cerebral oxygen delivery. Experimental physiology 99 (5):772-781. doi:10.1113/expphysiol.2013.075184

Thomas KN, Burgess KR, Basnyat R, Lucas SJ, Cotter JD, Fan JL, Peebles KC, Lucas RA, Ainslie PN (2010) Initial orthostatic hypotension at high altitude. High altitude medicine & biology 11 (2):163-167. doi:10.1089/ham.2009.1056

Thomas KN, Cotter JD, Galvin SD, Williams MJ, Willie CK, Ainslie PN (2009) Initial orthostatic hypotension is unrelated to orthostatic tolerance in healthy young subjects. Journal of applied physiology 107 (2):506-517. doi:10.1152/japplphysiol.91650.2008

van Lieshout JJ, Pott F, Madsen PL, van Goudoever J, Secher NH (2001) Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. Stroke 32 (7):1546-1551

Van Lieshout JJ, Wieling W, Karemaker JM, Secher NH (2003) Syncope, cerebral perfusion, and oxygenation. Journal of applied physiology 94 (3):833-848. doi:10.1152/japplphysiol.00260.2002

Vongpatanasin W, Wang Z, Arbique D, Arbique G, Adams-Huet B, Mitchell JH, Victor RG, Thomas GD (2011) Functional sympatholysis is impaired in hypertensive humans. The Journal of physiology 589 (Pt 5):1209-1220. doi:10.1113/jphysiol.2010.203026

Westendorp RG, Blauw GJ, Frolich M, Simons R (1997) Hypoxic syncope. Aviation, space, and environmental medicine 68 (5):410-414

Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME (2007) Initial orthostatic hypotension: review of a forgotten condition. Clinical science 112 (3):157-165. doi:10.1042/CS20060091

Willie CK, Smith KJ, Day TA, Ray LA, Lewis NC, Bakker A, Macleod DB, Ainslie PN (2014) Regional cerebral blood flow in humans at high altitude: gradual ascent and 2 wk at 5,050 m. Journal of applied physiology 116 (7):905-910. doi:10.1152/japplphysiol.00594.2013

Figure captions

Figure 1. Illustration of the study procedure. TOI; tissue oxygenation index, $P_{ET}CO_2$; partial pressure of end-tidal carbon dioxide, BP; blood pressure, HR; heart rate, SpO_2; peripheral arterial oxygen saturation.

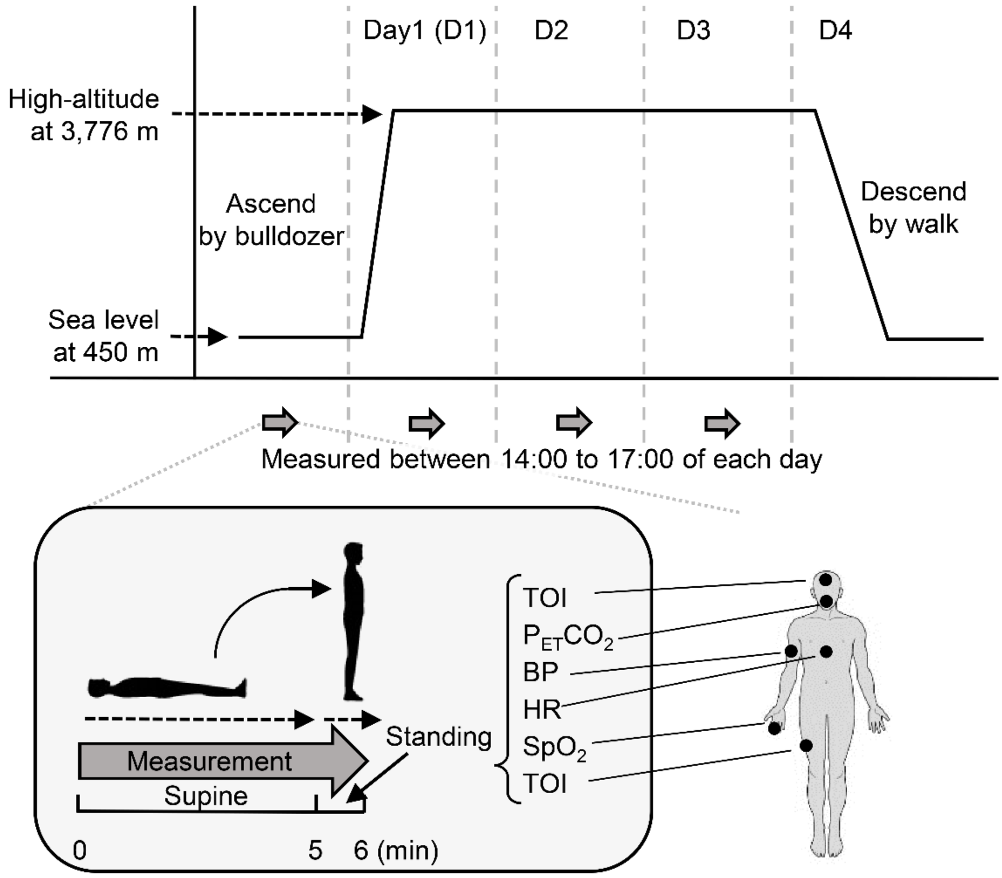

Figure 2. Cerebral total oxygenation index (TOI [%, panel A]), leg TOI (%, panel B), and change in cerebral TOI (Δ%, panel C) and leg TOI (Δ%, panel D) after the supine-to-stand maneuver at sea level (SL) and each day at high altitude (day 1, day 2, and day 3). Data are presented as resting supine (blue circles), standing 5 min after the supine-to-stand maneuver (red squares) and change from supine to stand (green triangles). * $P < 0.05$ supine versus stand for that day, † $P < 0.05$ versus another day for stand posture only, ‡ $P < 0.05$ versus another day for both postures. Values are presented as mean ± standard deviation.

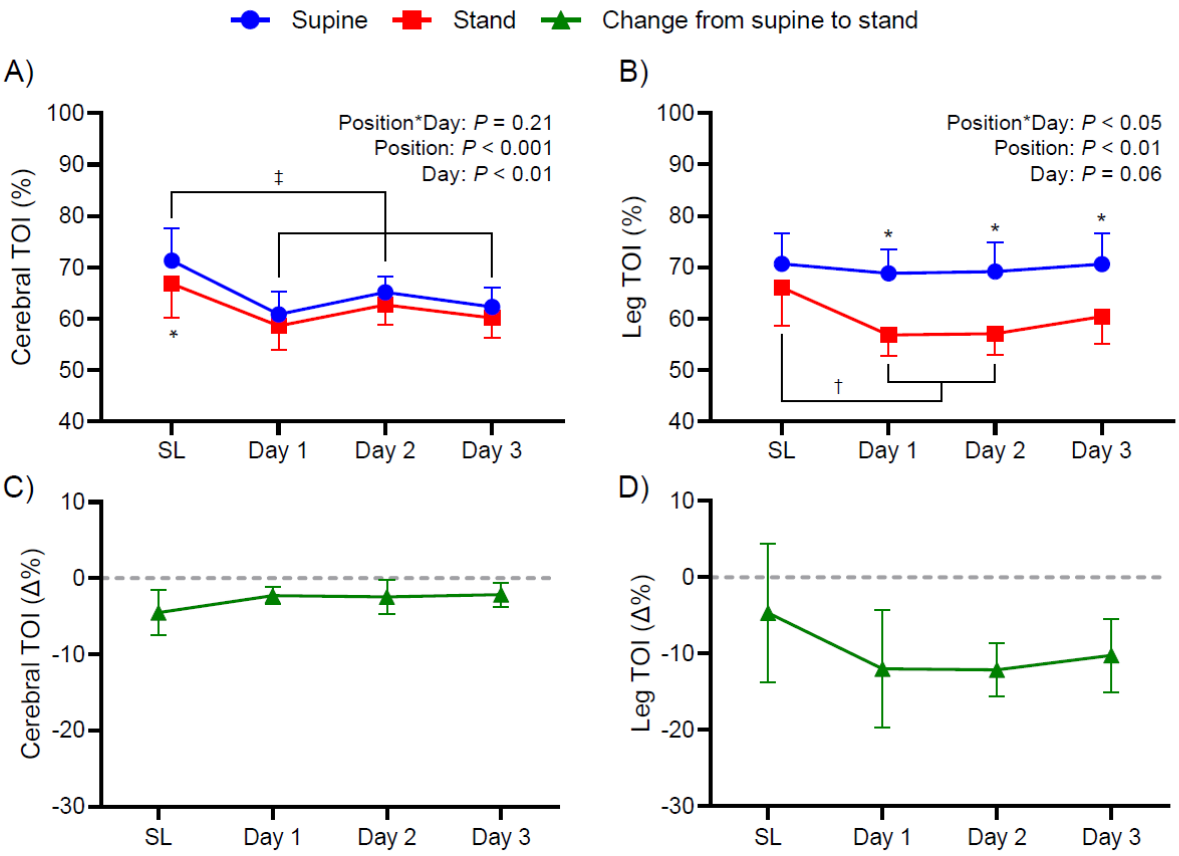

Table 1. Supine and 5 min post-orthostasis standing cardiorespiratory responses at sea level and for 3 days whilst acclimatizing to high altitude.

		Sea level	Day 1	Day 2	Day 3	Two-way ANOVA *P* values		
						Day	Posture	Interaction
MAP, mmHg	Supine	87 (8)	87 (8)	95 (8)	98 (9)*	< 0.001	0.002	0.26
(n=7)	Stand	92 (9)	89 (7)	103 (10)$^{*\#}$	105 (10)*			
HR, bpm	Supine	64 (10)	72 (11)	75 (10)*	76 (15)*	0.01	0.001	0.39
(n=7)	Stand	81 (12)$^{\#}$	86 (20)$^{\#}$	87 (16)$^{\#}$	89 (18)$^{\#}$			
SpO_2, %	Supine	96 (1)	82 (5)*	84 (6)*	86 (4)*	< 0.001	0.02	0.002
(n=7)	Stand	96 (2)	86 (4)$^{*\#}$	86 (5)$^{*\#}$	88 (4)$^{*\#}$			
$P_{ET}CO_2$, mmHg	Supine	36.7 (3.3)	35.6 (2.2)	35.2 (2.3)	30.6 (4.6)*	0.001	0.001	0.54
(n=5)	Stand	33.6 (1.5)	31.4 (3.0)$^{\#}$	30.4 (2.3)$^{\#}$	27.4 (3.4)*			

Values are mean (standard deviation). MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; SpO_2, peripheral oxygen saturation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide *, $P < 0.05$ vs. sea level at each position. $^{\#}$, $P < 0.05$ between supine and stand at that day.

Table 2. Linear trend analysis of each variable for 3 days whilst acclimatizing to high altitude

		F values (degree of freedom)	*P* value
Cerebral TOI	Supine	F (1,12) = 0.92	0.36
	Stand	F (1,12) = 1.64	0.22
Leg TOI	Supine	F (1,12) = 1.09	0.32
	Stand	F (1,12) = 3.48	0.09
MAP	Supine	F (1,12) = 21.53	< 0.001
	Stand	F (1,12) = 17.99	0.001
HR	Supine	F (1,12) = 4.16	0.06
	Stand	F (1,12) = 0.52	0.49
SpO_2	Supine	F (1,12) = 9.34	0.01
	Stand	F (1,12) = 7.41	0.02
$P_{ET}CO_2$	Supine	F (1,8) = 17.04	<0.01
	Stand	F (1,8) = 9.80	0.01

TOI, tissue oxygenation index; MAP, mean arterial pressure; HR, heart rate; SpO_2, peripheral arterial oxygen saturation; $P_{ET}CO_2$, partial pressure of end tidal carbon dioxide.