

Effect of Fast Ascent, Acclimatization and Re-Exposure To 5050 m On Cerebral Autoregulation in Unacclimatized Lowlanders. A Prospective Cohort Study.

Laura C. Graf

Department of Respiratory Medicine, University Hospital of Zurich, Zurich

Sara E. Hartmann

Department of Physiology & Pharmacology, Cumming School of Medicine, University of Calgary

Mona Lichtblau

Department of Respiratory Medicine, University Hospital of Zurich, Zurich

Lara Muralt

Department of Respiratory Medicine, University Hospital of Zurich, Zurich

Patrick R. Bader

Department of Respiratory Medicine, University Hospital of Zurich, Zurich

Ivan Lopez

Safety Group, Atacama Large Millimeter Submillimeter Array, Calama

Jean M. Rawling

Department of Family Medicine, Cumming School of Medicine, University of Calgary, Calgary

Silvia Ulrich Prof

Department of Respiratory Medicine, University Hospital of Zurich, Zurich

Konrad E. Bloch Prof

Department of Respiratory Medicine, University Hospital of Zurich, Zurich

Marc J. Poulin

Department of Physiology & Pharmacology, Cumming School of Medicine, University of Calgary

Michael Furian (✉ michael.furian@usz.ch)

Department of Respiratory Medicine, University Hospital of Zurich, Zurich

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Effect of fast ascent, acclimatization and re-exposure to 5050 m on cerebral autoregulation in unacclimatized lowlanders. A prospective cohort study.

Laura C. Graf MD¹, Sara E. Hartmann PhD^{2,3}, Mona Lichtblau MD¹, Lara Muralt MD¹, Patrick R. Bader MD¹, Ivan Lopez⁴, Jean M. Rawling MD⁵, Silvia Ulrich Prof MD¹, Konrad E. Bloch Prof MD¹, Marc J. Poulin Prof PhD^{2,3}, Michael Furian PhD^{1*}

¹Department of Respiratory Medicine, University Hospital of Zurich, Zurich, Switzerland;

²Department of Physiology & Pharmacology, Cumming School of Medicine, University of Calgary, Canada; ³ Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada; ⁴ Safety Group, Atacama Large Millimeter Submillimeter Array, Calama, Chile; ⁵ Department of Family Medicine, Cumming School of Medicine, University of Calgary.

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*Correspondence

Michael Furian, Dr. sc. ETH

University Hospital Zurich, Department of Respiratory Medicine,
Raemistrasse 100, CH 8091 Zurich, Switzerland.

Phone: +41 44 255 38 28

Fax: +41 255 44 51

Email: michael.furian@usz.ch

ABBREVIATIONS LIST

ALMA	Atacama Large Millimeter / Submillimeter Array
ALMA ASF	ALMA Operation Support Facility, 2900 m
ALMA AOS	ALMA Operation Site, 5050 m
AMS	Acute mountain sickness
AMSc	Environmental symptom questionnaire, cerebral score
ARI	Cerebral autoregulation index
CA	Cerebral autoregulation
CVCi	Cerebrovascular conductance index
CVRI	Cerebrovascular resistance index
MAP	Mean arterial blood pressure
MCA	Middle cerebral artery
MCAv	Middle cerebral artery peak blood flow velocity
P _{ET} CO ₂	End-tidal partial pressure of carbon dioxide
SpO ₂	Arterial oxygen saturation measured by pulse oximetry

ABSTRACT

Cerebral autoregulation (CA) is impaired during acute high-altitude (HA) exposure and effects of acclimatization and re-exposure on CA are unknown. In 18 healthy lowlanders (11 women), we hypothesized that the cerebral autoregulation index (ARI) assessed by the percentage change in middle cerebral artery peak blood flow velocity ($\Delta\%MCAv$)/percentage change in mean arterial blood pressure ($\Delta\%MAP$) induced by a sit-to-stand maneuver, is i) reduced on Day1 at 5050m compared to 520m, ii) is improved after 6 days at 5050m, and iii) is less impaired during re-exposure to 5050m after 7 days at 520m compared to Cycle1. Participants spent 4-8h/day at 5050m and slept at 2900m similar to real-life working shifts. High/low ARI indicate impaired/intact CA, respectively. With the sit-to-stand at 520m, mean(95%CI) in ΔMAP and $\Delta MCAv$ were -26%(-41 to -10) and -13%(-19 to -7); mean \pm SE in ARI was $0.58\pm 0.63\Delta\%/\Delta\%$, respectively. On Day1 at 5050m, ARI worsened compared to 520m ($3.29\pm 0.70\Delta\%/\Delta\%$), but improved with acclimatization ($1.44\pm 0.65\Delta\%/\Delta\%$, $P<0.05$ for both). ARI was less affected during re-exposure to 5050m ($1.22\pm 0.70\Delta\%/\Delta\%$, $P<0.05$ acute altitude-induced change between sojourns). This study showed that CA i) is impaired during acute HA exposure, ii) improves with acclimatization and iii) is ameliorated during re-exposure to HA a week later.

Keywords

Acclimatization, altitude, cerebral autoregulation, sit-to-stand, re-exposure

INTRODUCTION

Recent developments had led to an increase in the number of settlements and work places at altitude, especially, astronomical observation centers and resource extraction facilities that are often situated at very high altitudes (4000-5000 m). At the Atacama Large Millimeter / Submillimeter Array (ALMA), the largest ground-based telescope station worldwide, employees sleep at 2900 m and work at 5050 m for 7 days, and recover for 7 days at their permanent residence, normally near sea level. These repeated fast ascents, brief periods of acclimatization and re-exposures to very high altitudes may have adverse effects on health, performance and safety of workers.¹⁻³

Cerebral autoregulation (CA) protects the brain by a negative feedback loop mechanism, maintaining constant cerebral blood flow and oxygen delivery independent of fluctuations in systemic blood pressure.⁴ Impaired CA results in systemic blood pressure associated cerebral blood flow fluctuations and may cause under-perfusion and inadequate oxygen delivery, or over-perfusion of capillaries with consequent disruption of the blood-brain barrier, capillary damage and micro-hemorrhages.⁵ Furthermore, impaired CA has been shown to have consequences on the cerebral function and is related to cognitive impairment.⁵

At altitude, the arterial partial pressures of O₂ and CO₂, two key factors influencing CA functionality, are reduced.⁶ Studies investigating CA functionality at different altitudes have reported persistent CA impairment with acute⁷ and prolonged high altitude exposure of up to 2 weeks compared to values reported near sea level.⁸ However, real-life working shifts as implied in ALMA require workers to sleep at 2900 m and work at

5050 m. This pattern of exposure to high altitude induces an intermittent hypobaric hypoxic exposure, which might have beneficial effects on the CA functionality as suggested for intermittent hypoxic training in patients with Alzheimer diseases.⁹ Furthermore, studies investigating the effects of repeated high altitude exposure showed milder reductions in O₂ and CO₂ when compared to previous altitude sojourns.^{2,10} However, whether these improvements in arterial blood gases might have a beneficial effect on the CA has not been studied. Therefore, the purpose of this study was to test the hypotheses that CA is impaired during acute high-altitude exposure and that acclimatization (with an intermittent schedule of daily ascents to very high altitude, but sleeping at moderate altitude), and a 2nd altitude sojourn, ameliorates CA functionality compared to the first acute high altitude exposure. Furthermore, this study assessed whether altitude exposure has sustained effects on CA functionality after descending to low altitude.

METHODS

Design and study setting

Data of the current study were collected within a prospective cohort trial with the purpose to investigate the effects of acute, prolonged and repeated altitude exposure on cognitive performance in healthy subjects.² Results of the present study have not been published elsewhere.

The ascent and assessment schedule is illustrated in Figure 1. At Santiago de Chile (520 m), participants performed a familiarization and baseline session separated by a one-day rest interval. The day after, participants traveled by plane and bus (2h each) to the ALMA Operation Support Facility (ASF; 2900 m) and spent seven consecutive nights at 2900 m. Each morning, participants were driven by car (45 min travel time) to the ALMA Operation Site (AOS; 5050 m), where they stayed 4 - 8 hours without oxygen supplementation. Measurements at 5050 m were repeated on the 1st and 6th day. Measurements were repeated on the day after descending to 520 m. This assessment schedule was repeated after a 7-day recovery period at 520 m.

Participants

Healthy, altitude-naïve men and women, aged between 18 to 30 years were recruited from the University of Calgary, Canada (N = 18, altitude of 1100 m). Participants were instructed to avoid any overnight stays at altitudes >1500 m within four weeks before the study. All participants provided written informed consent. The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary (Ethics ID: REB 15-2709) and the Cantonal Ethics Committee of Zurich (2016-00048). The main trial was registered at ClinicalTrials.gov (NCT02731456). The study has been performed in accordance with the Declaration of Helsinki.

Protocol and Measurements

Sitting values were collected and averaged over 120 stable and artifact-free heart beats at the end of a 10-minute sitting position in a comfortable chair. To assess CA

functionality, participants stood up in less than 1 second and remained in standing position for 1 minute.¹¹ The effect of standing up was measured by averaging the first 15 beats in standing position. This procedure was repeated and values were averaged within each subject.

Clinical assessments: Clinical assessment included height, weight, oxygen saturation by pulse oximetry (SpO₂) and heart rate measurements, as well as the environmental symptoms questionnaire cerebral score (AMSc) to assess acute mountain sickness (AMS).¹² The AMSc comprises 11 questions on AMS symptoms (feel sick, feel hungover, coordination off, dim vision, lightheaded, headache, dizzy, loss of appetite, feel weak, nausea, faint) rated from 0 (not at all) to 5 (extreme). A weighted AMSc score ≥ 0.7 were assumed to indicate the presence of AMS.

Transcranial Doppler ultrasound: A 2-MHz Doppler probe (TOCM, Multigon Industries, New York, USA) was placed over the temporal window to measure the peak blood flow velocity (MCAv) in the middle cerebral artery. To ensure a high standardization and reproducibility, the Doppler settings, probe position, insonation angle and depth were assessed during the familiarization period and the same settings were applied throughout the study. The cerebral autoregulation index (ARI) was defined by the ability of the CA to maintain a constant MCAv despite a rapid change in systemic blood pressure during a sit-to-stand maneuver. ARI was calculated as previously reported:¹³

$$\text{ARI, } \Delta\% \text{MCAv} / \Delta\% \text{MAP} = \frac{(\text{MCAv standing} - \text{sitting}) / \text{MCAv sitting}}{(\text{MAP standing} - \text{sitting}) / \text{MAP sitting}}$$

$$\text{ARI, } \Delta\% \text{MCAv} / \Delta \text{mmHg MAP} = \frac{(\text{MCAv standing} - \text{sitting}) / \text{MCAv sitting}}{\text{MAP standing} - \text{sitting}}$$

Therefore, higher values in ARI represent larger MAP-induced MCAv fluctuations, corresponding to worse cerebral autoregulation, whereas smaller values in ARI corresponded to intact cerebral autoregulation. Cerebrovascular resistance and conductance indexes were calculated as MAP divided by the MCAv (CVRi) or vice versa (CVCi).

Additional physiological assessments: Continuous SpO₂, heart rate and beat-by-beat systemic mean artery blood pressure (MAP) were assessed non-invasively by the finger-cuff technique (Finometer Midi, FMS, The Netherlands) and calibrated by brachialis sphygmomanometric measurements. Breath-by-breath end-expiratory partial pressure of CO₂ (P_{ET}-CO₂) and breathing frequency were assessed by capnography (Capnostream Sleep, Smiths Medical PM Inc, Waukesha, WI, USA).

Outcomes

The main outcome of this study was the ARI ($\Delta\% \text{MCAv} / \Delta\% \text{MAP}$) and the effects of acute, prolonged and re-exposure to very high altitude. Additional outcomes were changes in explanatory cerebral, respiratory and cardiac variables. No *a priori* sample size estimation has been performed.

Hypotheses

The three main hypotheses were that i) acute high-altitude exposure impairs ARI ($\Delta\% \text{MCAv} / \Delta\% \text{MAP}$), ii) 6 days of acclimatization (with an intermittent hypobaric hypoxic

protocol) improves ARI ($\Delta\%MCAv/\Delta\%MAP$) and iii) a 2nd compared to the 1st ascent to 5050 m has a lower impact on the altitude-related ARI impairment. An additional hypothesis was that CA functionality is immediately restored the day after descending to 520 m.

Data analysis

The primary outcome was tested for normality by the Shapiro Wilk test. Due to the non-normally distributed data, mixed ordered logistic regression using the interaction between altitude (520 m and 5050 m), day at altitude (1st and 6th day) and number of altitude sojourns (1st and 2nd sojourn) as fixed effects, and participants as random effects was applied. Secondary outcomes were analyzed using mixed linear regression models. To elucidate the underlying factors influencing ARI ($\Delta\% / \Delta\%$) or AMS, univariate and multivariable mixed linear regressions including baseline characteristics, SpO_2 , $P_{ET}CO_2$, MAP and MCAv were performed. Statistical significance was assumed when $P < 0.05$ and 95% confidence intervals of mean differences did not overlap zero.

RESULTS

A total of 18 healthy participants (11 women) with a mean age of 24 ± 4 years and BMI of 22.8 ± 3.1 kg/m² were included in the final analysis. Participant characteristics are presented in Table 1. Cardiorespiratory and cerebrovascular outcomes are described in Table 2.

Effect of acute altitude exposure (1st day at 5050 m compared to 520 m)

With acute exposure to 5050 m, participants had lower values in SpO₂, mean ± SE, 77.6 ± 0.8% vs. 96.5 ± 0.8%, lower values in P_{ET}CO₂, 24.5 ± 0.7 mmHg vs. 33.9 ± 0.6 mmHg and higher heart rates, 93 ± 3 bpm vs. 70 ± 3 bpm and more symptoms of AMS assessed by the AMSc score, 0.94 ± 0.09 vs. 0.12 ± 0.09 compared to 520 m (P<0.05 all comparisons). There was no acute altitude effect on MAP compared to 520 m, whereas sitting mean MCAv significantly increased from 57.9 ± 2.4 cm/s to 62.1 ± 2.4 cm/s without altering CVRi or CVCi. The sit-to-stand maneuver at 5050 m caused a stronger drop in MCAv despite a milder drop in MAP, resulting in a significantly worse ARI compared to 520 m (3.29 ± 0.70 Δ%/Δ% vs. 0.58 ± 0.63 Δ%/Δ%; 3.50 ± 0.84 Δ%/ΔmmHg vs. 0.85 ± 0.75 Δ%/ΔmmHg) (Table 2, Figure 2).

Effect of prolonged altitude exposure (6th versus 1st day at 5050 m)

With 6 days of acclimatization at 5050 m and sleeping altitude at 2900 m, participants improved their SpO₂ (83.0 ± 0.6% vs. 77.6 ± 0.6%) without altering P_{ET}CO₂ or breathing frequency, but with associated elevation in hemoglobin concentrations and lower AMS symptoms compared to the 1st day at 5050 m. With acclimatization, MAP remained unchanged and MCAv tended to further increase without altering CVRi or CVCi. Compared to the 1st day at 5050 m, the sit-to-stand test caused a similar MCAv decrease despite a stronger drop in MAP, resulting in significantly improved ARI (Δ%/Δ%) compared to the 1st day at 5050 m (Table 2, Figure 2).

Effect of descent from high altitude (520 m versus 6th day at 5050 m)

On the day after descending from 5050 m to 520 m, participants showed persistent $P_{ET}CO_2$ reductions and worse ARI ($\Delta\%/\Delta\%$) values compared to pre-ascent evaluations. After 1-week recovery period at 520 m, SpO_2 and $P_{ET}CO_2$ recovered to pre-ascent values. However, ARI ($\Delta\%/\Delta\%$) remained impaired. The worse ARI ($\Delta\%/\Delta\%$) were mainly caused by a larger drop in MCAv in relation to small changes in MAP with the sit-to-stand maneuvers (Table 2).

Effect of a second altitude sojourn (2nd compared to 1st sojourn at 5050 m)

Acute exposure during the 2nd compared to the 1st sojourn at 5050 m was accompanied with less hypoxemia and less hypocapnia. Heart rate similarly increased and breathing frequency remained unchanged as seen during the 1st sojourn at 5050 m. Compared to the 1st sojourn, MCAv did not increase during acute altitude exposure and ARI ($\Delta\%/\Delta\%$) deteriorated less compared to the 1st sojourn (Odds ratio of 0.10, 95%CI 0.01 to 0.76, $P=0.027$) (Table 2, Figure 2).

SpO_2 and $P_{ET}CO_2$ remained higher after acclimatization in the 2nd compared to the 1st sojourn at 5050 m. This was accompanied with a further increase in hemoglobin concentration. MCAv, MAP and ARI ($\Delta\%/\Delta\%$) remained stable after acclimatization (Odds ratio of 7.3, 95%CI 0.95 to 56.7, $P=0.056$) (Table 2).

When the participants descended from the 2nd sojourn at 5050 m, they persistently showed lower $P_{ET}CO_2$, lower MAP and better ARI ($\Delta\%/\Delta\%$) values compared to the values

obtained on the day after descending from the 1st sojourn (Odds ratio of 0.12, 95%CI 0.02 to 0.82, P=0.030).

Predictors for AMS and ARI ($\Delta\%/\Delta\%$)

Predictors of AMS severity at 5050 m assessed by multivariable regression analysis were acute exposure, low sitting $P_{ET}CO_2$ and high ARI ($\Delta\%/\Delta\%$) values (Table 3). Only higher MAP values remained as an independent predictor of CA impairment defined by ARI ($\Delta\%/\Delta\%$) (Table 4).

DISCUSSION

This study focused on the cerebral autoregulatory ability to protect the brain from rapid systemic blood pressure falls in maneuvers like the sit-to-stand test during acute, prolonged and repeated exposure to very high altitude (5050 m). The present findings suggest that cerebral autoregulation is impaired during acute exposure, but improved after a 7-day stay at high altitude (with a sleeping altitude of 2900 m). Strikingly, one week after altitude exposure the CA remained impaired. Moreover, novel findings of this study suggest that a 2nd altitude sojourn after one week at low altitude has a milder effect on the CA functionality, indicating that workers exposed to repeated high altitude exposures might be protected from initial cerebral autoregulatory impairments seen during the first acute high-altitude exposure. Acute exposure to 5050 m, worse ARI ($\Delta\%/\Delta\%$) and lower $P_{ET}CO_2$ values were associated with higher AMS severity.

This study used a straightforward approach to describe CA proposed by a recent meta-analysis, by calculating the percent change in MCAv divided by the percent change from baseline in MAP.¹³ The meta-analysis comprises 49 studies, whereas 41 studies used transcranial Doppler measurements to assess MCAv, a surrogate for cerebral blood flow. The average slopes proposed by the meta-analysis for a healthy population are 0.82 ± 0.77 % Δ MCAv/% Δ MAP and 0.97 ± 0.91 % Δ MCAv/ Δ mmHg MAP. Therefore, the obtained baseline values at 520 m in our cohort are within the 95% confidence intervals of the cited study (Table 2, 0.58 ± 0.63 % Δ MCAv/% Δ MAP and 0.85 ± 0.75 % Δ MCAv/mmHg MAP). Furthermore, this study used the sit-to-stand maneuver to provoke a change in MAP and MCAv. Although other interventions might result in larger changes in these variables, the current sit-to-stand maneuver showed a mean difference (95%CI) in MAP and MCAv at 520 m of -26% (-41 to -10) and -13% (-19 to -7) from sitting values, respectively. These changes are comparable with previous studies.^{11,14} The current study reports the effect of standing up by averaging 15 beats following the maneuver, and are in contrast to other studies choosing the nadir in MAP and MCAv following standing up.¹⁴ However, by averaging 15 beats, findings are less prone to artifacts, selection bias and are easily reproducible.

Several previous field studies suggest that acute high-altitude exposure impairs CA functionality.^{3,15-18} However, only a few studies have focused on the high-altitude acclimatization effect on the CA functionality. Subudhi et al. showed in 21 healthy subjects exposed to 3800 - 5260 m for 15 days that CA remained impaired compared to

measurements near sea level and compared to the 1st day at 5260 m. This was confirmed by another study exposing 11 individuals for 4 weeks to 5260 m.¹⁶ Both studies used transfer function analysis in comparison to the 2-point assessment of MCAv and MAP used in the current trial. However, these findings are in accordance with the current study showing that acclimatization does not restore sea-level values in CA. This is probably explained by the persistently increased diameter of small arteries and the MCA,¹⁹ thereby compromising the ability of the CA to further dilate small arteries due to a drop in MAP with a sit-to-stand maneuver. However, the current findings support the thesis that acclimatization at least partly mitigates CA impairment, which was not observed in the two mentioned studies. A possible explanation might be the unique intermittent hypobaric hypoxic protocol used in this study (staying at 5050 m for 8 hours and sleeping at 2900 m), which might have enhanced the sensitivity to hypoxia and hypocapnia and might have improved the CA functionality over the time course of 6 days. Although this has never been studied in detail, one trial applying 14 days of intermittent hypoxia (FiO₂ 0.10, sessions of 5 x 4 minutes per day) showed diminished cerebral blood flow fluctuation to hypocapnia and hypercapnia after the intervention,²⁰ indicating improved CA functionality. Furthermore, beneficial effects of intermittent hypoxic training on the cerebrovascular response in Alzheimer patients have been reported.⁹ This might explain the improved CA functionality with prolonged hypoxia during acclimatization. Other possible factors explaining the opposite findings of the acclimatization effect on CA between studies might be differences in the definition of

“day 1” at high altitude, duration of the high altitude stay, intervention (sit-to-stand versus rest), analysis method (2-point assessment of MCAv and MAP versus transfer function analysis) or study protocol (staying at 5050 m and sleeping at 2900 m versus staying at 5260 m). Furthermore, in healthy lowlanders, it has been shown that the functionality of cerebral autoregulation is more protective to blood pressure elevations (CA ability to vasoconstrict blood vessels) than blood pressure reductions (CA ability to vasodilate).¹³ Since spontaneous blood pressure changes assessed by transfer function analysis includes both blood pressure elevations and reductions, this might provide different information about the CA functionality than exclusive blood pressure reductions induced by a sit-to-stand maneuver. This non-linear CA functionality might partly explain previously reported opposite findings at high altitude.^{8,21} However, whether the altitude-induced CA impairment differs in the ability to protect the brain from blood pressure elevations versus blood pressure reductions has not been studied in detail.

Moreover, this study provides novel findings supporting the hypothesis that CA is less impaired during a second sojourn at very high altitude. Contrary to a previous study by Subudhi et al.¹⁰, which concluded that re-exposure to 5260 m after 7 days at sea level similarly impaired CA (based on transfer function analysis). However, they have not performed a second baseline measurement and might have missed the circumstance that the participants had persistently impaired CA after 1 week at low altitude, as seen in the current study (Table 2). This would result in a different baseline and therefore,

smaller altitude-induced difference in CA functionality. The observed smaller altitude-induced impact on CA functionality might be partly explained by preserved oxygen delivery towards the brain by elevated hemoglobin concentration and less altitude-induced hypoxemia, or by less vasodilatation of the small cerebral arteries allowing the CA to induce vasodilation in response to the sit-to-stand maneuver.

The persistent impairment of CA throughout 1-week post-altitude exposure at low altitude came as a surprise and needs further investigation. Findings on the day after the second descent to 520 m suggest already improved CA after the 2nd sojourn, indicating that CA functionality is normalized back at low altitude after repeated exposure. Nevertheless, sustained impairment of CA after repeated altitude sojourns would have an unknown impact on the safety and health of high-altitude workers and needs further investigation.

The assessment of the CA at high altitude is challenging; many influential physiological parameters change, therefore, invasive and highly sophisticated measurements would be required and large sample sizes would be needed to correct for the influences of various confounders. Altitude exposure is associated with various changes influencing the CA functionality, i.e. changes in arterial blood gases (causing vasoconstriction or vasodilation), change in plasma volume and associated elevation of hemoglobin concentration (lower blood volume with higher viscosity), change in driving pressure (difference between the MAP and the intracranial pressure) and change in cerebral blood vessel diameter.^{4,19} The findings of this study support the hypothesis that

acclimatization and re-exposure have beneficial effects on the CA against blood pressure falls. However, underlying mechanisms and physiological explanations remain speculative and further studies are needed.

CONCLUSIONS

First, this study confirms CA impairment during acute exposure to very high altitude. Further, novel findings reported here are the beneficial effects of acclimatization to very high altitude by spending the work-day at 5050 m and sleeping at 2900 m. Furthermore, we found a milder altitude-induced impact on the CA functionality during a 2nd similar cycle at high altitude but persistent CA impairment up to 1-week post-altitude exposure, which resolved after the 2nd high altitude sojourn. Taken together, these findings suggest that high altitude shift work with 1-week breaks at low altitude between work cycles, might be at risk for over and under-perfusion of brain areas during commencement of high-altitude work. Whether the improved CA functionality during the second high-altitude cycle indicates a protection also for several repeated work-shift cycles at high altitude remains to be determined.

AUTHOR CONTRIBUTION STATEMENT

MF is the guarantor of the manuscript. Concept and design: SEH, MJP, KEB and MF. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: LCG, MJP and MF. Critical revision of the manuscript: All authors. Statistical analysis: LCG, KEB, MF. Obtained funding: MJP, KEB. Supervision: KEB, MJP and MF.

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COMPETING INTERESTS

None of the authors declare any conflict of interest associated with this manuscript.

DATA AVAILABILITY STATEMENT

Anonymized data underlying this study can be requested by qualified researchers providing an approved proposal.

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FIGURES LEGENDS

Figure 1. Study design

After a familiarization session at Santiago de Chile (520 m), participants underwent baseline assessments the day preceding travelling to high altitude. Participants travelled to the ALMA Operations Support Facility (ASF - 2900 m) and stayed for one night before beginning daily sojourns to the Array Operations Site (AOS - 5050 m). Participants alternated between 2900 m (sleeping) and 5050 m (testing, 4 – 8 hours/day). After a one-week recovery period at 520 m, participants performed a second, identical altitude cycle. Arrows indicate experimental testing days and headings indicate the condition of interest.

Figure 2. Cerebral autoregulation index assessed during a sit-to-stand maneuver

Panel A: Mean arterial pressure (MAP) percentage change between standing versus sitting. Panel B: Mean middle cerebral artery peak blood flow velocity (MCAv) percent change between standing versus sitting. Panel C: Cerebral autoregulation index calculated by $\Delta\%MCAv/\Delta\%MAP$ with a sit-to-stand maneuver. Standing values were obtained by averaging 15 beats following standing up <1 second. #P<0.05 between the acute altitude-induced effect during the 2nd compared to the 1st sojourn; *P<0.05 between the acclimatization effect during the 2nd compared to the 1st sojourn; †P<0.05 between the descent effect during the 2nd compared to the 1st sojourn.

Table 1. Participant characteristics

N	18
Men, (%)	7 (39)
Women, (%)	11 (61)
Age, years	24 ± 4
Body mass index, ^{kg} / _{m²}	22.8 ± 3.1
Weight, kg	66 ± 9

Data are presented as mean ± standard deviation.

Table 2. Cardiorespiratory and cerebrovascular outcomes

		1 st sojourn				2 nd sojourn			
		Baseline, 520 m	1 st day, 5050 m	6 th day, 5050 m	Descent, 520 m	Baseline, 520 m	1 st day, 5050 m	6 th day, 5050 m	Descent, 520 m
Cardiorespiratory outcomes									
Arterial oxygenation, %		96.5 ± 0.8	77.6 ± 0.8*	83.0 ± 0.8 §	97.3 ± 0.8^	96.3 ± 0.7	81.3 ± 0.8*§	84.4 ± 0.8 §	96.8 ± 0.8 ^
Heart rate, 1/min		70 ± 3	93 ± 3*	84 ± 3 §	69 ± 3 ^	68 ± 3	89 ± 3*	84 ± 3 §	71 ± 3 ^
Breath rate, 1/min		16 ± 1	16 ± 1	17 ± 1	17 ± 1	16 ± 1	16 ± 1	18 ± 1	17 ± 1
P _{ET} CO ₂ , mmHg		33.9 ± 0.6	24.5 ± 0.7*	24.4 ± 0.7	32.2 ± 0.6 *^	33.9 ± 0.6	28.0 ± 0.7*§	26.9 ± 0.6	31.2 ± 0.6* ^
Hemoglobin conc., g/dl		-	14.9 ± 0.3	15.4 ± 0.3 §	-	-	15.2 ± 0.3 §	15.8 ± 0.3§	-
AMSc score		0.12 ± 0.09	0.94 ± 0.09*	0.16 ± 0.09§	0.03 ± 0.09	0.15 ± 0.09	0.65 ± 0.10*	0.24 ± 0.09§§	0.02 ± 0.09 ^
Cerebrovascular outcomes									
Mean arterial pressure, mmHg	sitting	87 ± 4	88 ± 4	89 ± 4	83 ± 4	81 ± 4	87 ± 4	91 ± 4	79 ± 4 ^
	stand	73 ± 4	81 ± 4	79 ± 4	81 ± 4	75 ± 4	79 ± 4	85 ± 4	69 ± 4^§
	diff	-14 (-23 to -5)	-7 (-16 to 3)	-10 (-19 to 0)	-3 (-12 to 6)	-5 (-14 to 3)	-7 (-17 to 3)	-6 (-15 to 3)	-10 (-19 to -1)
Mean MCA peak blood flow velocity cm/s	sitting	57.9 ± 2.4	62.1 ± 2.4*	65.2 ± 2.4	58.0 ± 2.4 ^	56.2 ± 2.4	57.2 ± 2.4	60.3 ± 2.4	56.9 ± 2.4
	stand	51.9 ± 2.4	54.3 ± 2.5	57.6 ± 2.4	51.9 ± 2.4 ^	50.1 ± 2.4	53.3 ± 2.5	53.7 ± 2.4	50.9 ± 2.5
	diff	-6.0 (-9.9 to -2.0)	-7.8 (-11.9 to -3.7)	-7.5 (-11.5 to -3.6)	-6.1 (-10.1 to -2.2)	-6.1 (-9.9 to -2.3)	-4.0 (-8.1 to 0.2)	-6.6 (-10.5 to -2.6)	-6.0 (-10.4 to -1.7)
		N = 15	N = 12	N = 14	N = 15	N = 16	N = 13	N = 15	N = 12
ARI, Δ%/Δ%		0.58±0.63	3.29±0.70*	1.44±0.65§	1.40±0.63 *	1.92±0.59	1.22±0.70 §	1.63±0.63	0.87±0.70 §
ARI, Δ%/mmHg		0.85±0.75	3.50±0.84*	1.35±0.77§	1.72±0.75	2.37±0.70	1.43±0.84 §	2.24±0.75	1.13±0.84
Cerebrovascular resistance index, mmHg/cm/s	sitting	1.55 ± 0.09	1.46 ± 0.09	1.42 ± 0.09	1.48 ± 0.09	1.48 ± 0.09	1.53 ± 0.10	1.57 ± 0.09	1.46 ± 0.09
	stand	1.52 ± 0.09	1.53 ± 0.10	1.43 ± 0.09	1.68 ± 0.09^	1.55 ± 0.09	1.56 ± 0.10	1.67 ± 0.09	1.42 ± 0.10^
	diff	-0.03 (-0.23 to 0.17)	0.07 (-0.15 to 0.29)	0.01 (-0.19 to 0.22)	0.20 (0.00 to 0.40)	0.08 (-0.11 to 0.27)	0.03 (-0.19 to 0.25)	0.11 (-0.09 to 0.30)	-0.04 (-0.25 to 0.18)
Cerebrovascular conductance index, cm/s/mmHg	sitting	0.67 ± 0.05	0.72 ± 0.06	0.74 ± 0.06	0.71 ± 0.06	0.71 ± 0.05	0.67 ± 0.06	0.67 ± 0.06	0.73 ± 0.06
	stand	0.70 ± 0.06	0.71 ± 0.06	0.87 ± 0.06 §	0.69 ± 0.06 ^	0.69 ± 0.05	0.67 ± 0.06	0.63 ± 0.06§	0.81 ± 0.06^
	diff	0.03 (-0.10 to 0.16)	0.00 (-0.14 to 0.14)	0.13 (0.00 to 0.26)	-0.03 (-0.16 to 0.10)	-0.20 (-0.14 to 0.10)	0.00 (-0.15 to 0.14)	-0.04 (-0.17 to 0.08)	0.08 (-0.06 to 0.22) §
Systolic MCA peak blood flow velocity, cm/s	sitting	91.4 ± 3.0	98.7 ± 3.0*	100.3 ± 3.0	95.0 ± 3.0	91.8 ± 3.0	93.5 ± 3.4	96.0 ± 3.4	93.9 ± 3.4
	stand	95.6 ± 3.0	101.9 ± 3.0*	103.5 ± 3.0	98.0 ± 3.0	95.2 ± 3.0	97.5 ± 3.4	97.0 ± 3.4	95.8 ± 3.4
	diff	4.2 (-2.0 to 10.5)	3.2 (-3.0 to 9.4)	3.2 (-3.0 to 9.4)	3.0 (-3.2 to 9.2)	3.4 (-2.7 to 9.4)	4.0 (-2.4 to 10.4)	1.0 (-5.2 to 7.2)	1.9 (-4.3 to 8.1)

Data are presented as mean ± SE or mean difference (95% CI). P_{ET}CO₂, end-tidal partial pressure of CO₂; AMSc score, environmental symptom questionnaire cerebral score; MCA, middle cerebral artery; MAP, mean arterial pressure; ARI, autoregulation index. *P<0.05 versus 520 m baseline within sojourn; §P<0.05 between 6th versus 1st day at 5050 m; §P<0.05 when comparing 2nd versus 1st sojourn effects from acute (1st day 5050 m – 520 m), prolonged (6th versus 1st day at 5050 m) or recovery (Descent 520 m – 6st day at 5050 m); ^P<0.05 between descent 520 m versus 6st day at 5050 m.

Table 3. Predictors for acute mountain sickness severity at 5050 m assessed by mixed linear regression models

Dependent variable: AMS-c score at 5050m	Univariate				Multivariable			
	Coef	SE	95% CI	P	Coef	SE	95% CI	P
Female sex	0.07	0.15	-0.23 to 0.36	0.663				
2 nd versus the 1 st sojourn	-0.28	0.17	-0.61 to 0.05	0.096	-0.21	0.21	-0.61 to 0.20	0.313
6 th versus 1 st day	-0.78	0.17	-1.10 to -0.45	<0.001	-1.00	0.19	-1.38 to -0.63	<0.001
2 nd Sojourn * 6 th day	0.36	0.24	-0.10 to 0.82	0.128	0.58	0.26	0.07 to 1.09	0.026
P _{ET} CO ₂ , mmHg	-0.05	0.02	-0.10 to 0.00	0.036	-0.09	0.03	-0.14 to -0.03	0.001
SpO ₂ , %	-0.02	0.02	-0.05 to 0.01	0.192				
MCAV, ^{cm} /s	0.00	0.01	-0.02 to 0.01	0.891				
MAP, mmHg	0.00	0.01	-0.02 to 0.01	0.684				
ARI, Δ%/Δ%	0.07	0.03	0.02 to 0.12	0.008	0.05	0.02	0.00 to 0.09	0.031
Intercept					3.19	0.72	1.79 to 4.59	<0.001

N = 18 measured at 4 different time points (1st sojourn, 1st and 6th day at 5050 m; 2nd sojourn, 1st and 6th day at 5050 m). To account for the low number of observations (a total of 51 observations due to single missing values), the 5 most significant predictors from the univariate regression were entered into the multivariable regression model. AMS-c score = acute mountain sickness-cerebral score, P_{ET}CO₂ = partial pressure of exhaled carbon dioxide, SpO₂ = oxygen saturation measured by finger pulse oximetry, MCAV = middle cerebral artery peak velocity, MAP = mean arterial pressure, ARI = autoregulation index.

Table 4. Predictors for cerebral autoregulation at 5050 m assessed by mixed ordered logistic regression models

Dependent variable: ARI, $\Delta\%/\Delta\%$, quintiles	Univariate				Multivariable			
	Odds ratio	SE	95% CI	P	Odds ratio	SE	95% CI	P
Female sex	0.87	0.43	0.33 to 2.28	0.773				
2 nd versus the 1 st sojourn	0.34	0.26	0.08 to 1.48	0.151	0.33	0.26	0.07 to 1.55	0.160
6 th versus 1 st day	0.29	0.21	0.07 to 1.19	0.087	0.29	0.24	0.06 to 1.48	0.138
2 nd Sojourn * 6 th day	5.92	6.02	0.81 to 43.47	0.081	6.53	6.73	0.86 to 49.27	0.069
P _{ET} CO ₂ , mmHg	0.96	0.09	0.80 to 1.15	0.667				
SpO ₂ , %	0.95	0.05	0.86 to 1.05	0.304	1.00	0.06	0.88 to 1.13	0.966
MCAv, cm/s	1.03	0.03	0.98 to 1.08	0.307				
MAP, mmHg	0.96	0.02	0.91 to 1.00	0.060	0.95	0.02	0.90 to 1.00	0.039

N = 18 measured at 4 different time points (1st sojourn: 1st and 6th day at 5050 m; 2nd sojourn: 1st and 6th day at 5050 m). To account for the low number of observations (a total of 53 observations due to single missing values), the 5 most significant predictors from the univariate regression were entered into the multivariable regression model. P_{ET}CO₂ = partial pressure of exhaled carbon dioxide, SpO₂ = oxygen saturation measured by finger pulse oximetry, MCAv = middle cerebral artery peak velocity, MAP = mean arterial pressure, ARI = autoregulation index.

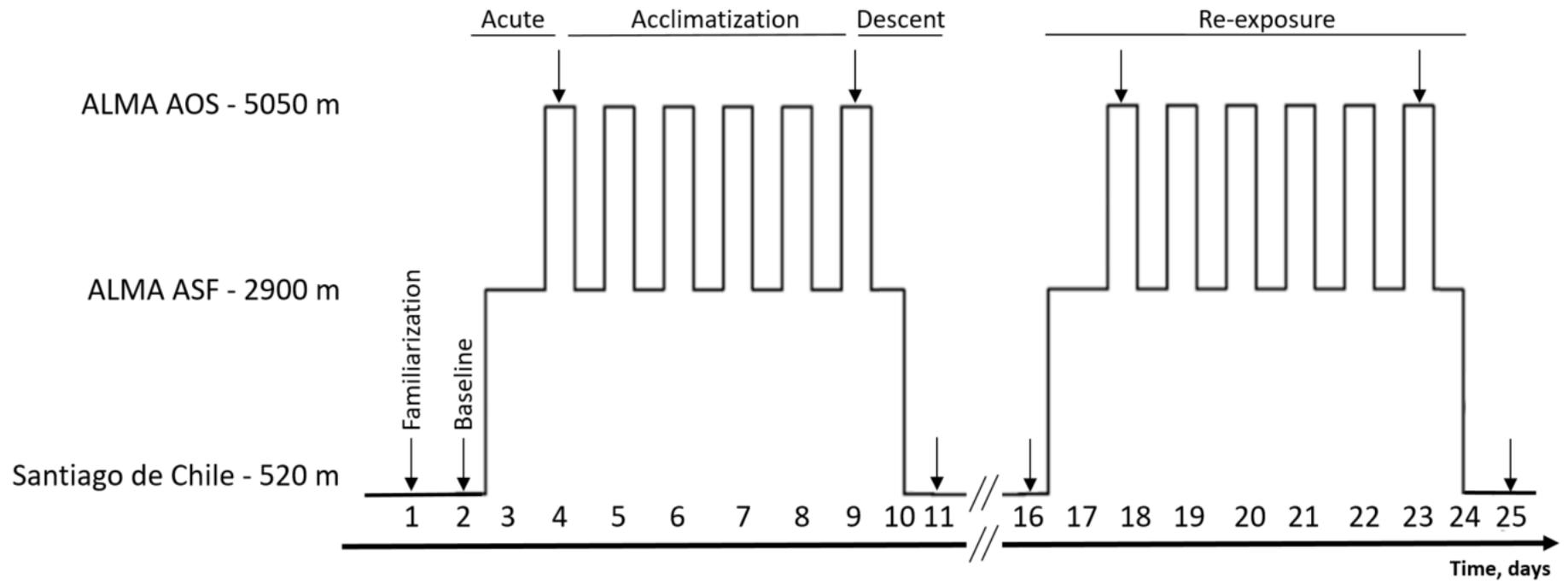


Figure 1

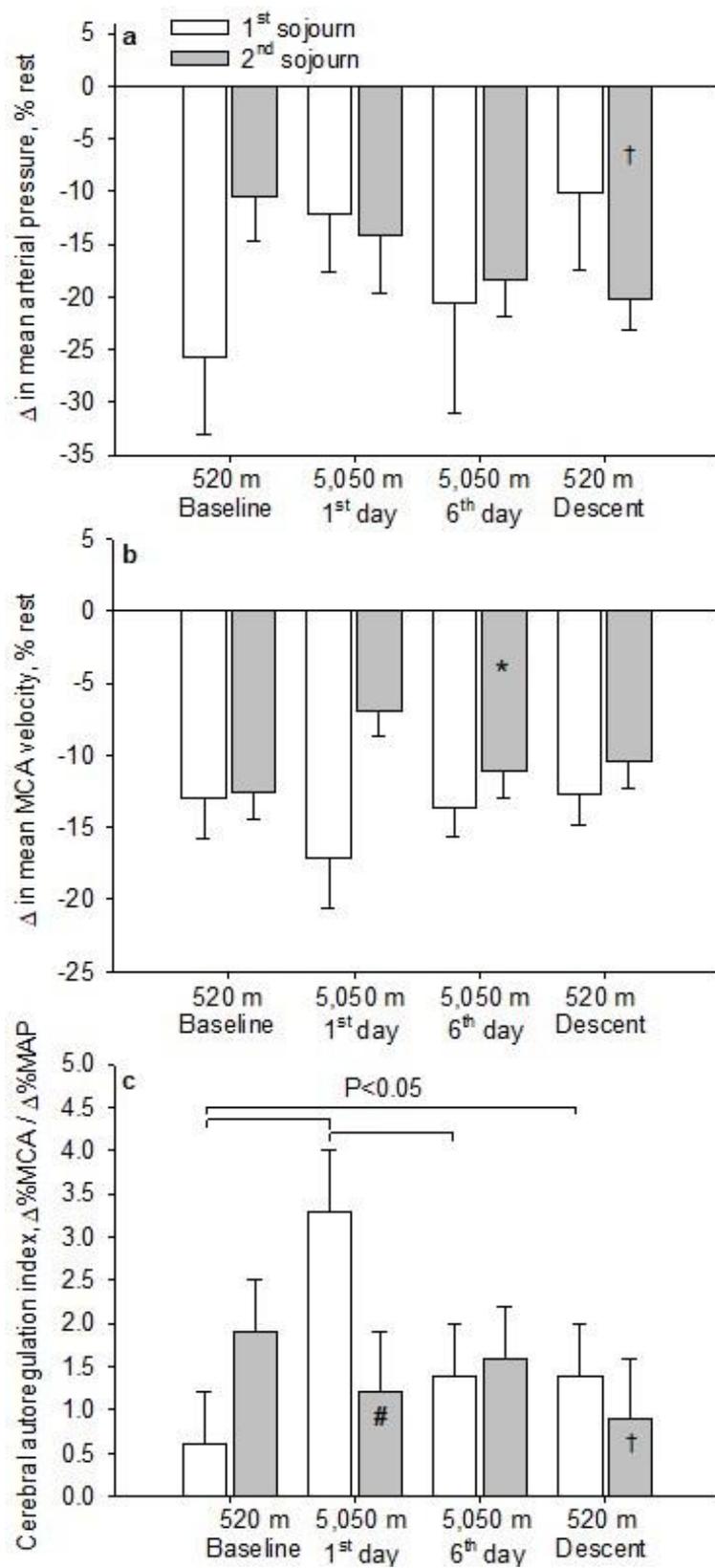


Figure 2