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Cerebral homeostasis and orthostatic responses in residents of the highest city in the world

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Permanent residence at high-altitude and chronic mountain sickness (CMS) may alter the cerebrovascular homeostasis and orthostatic responses. Healthy male participants living at sea-level (LL; n = 15), 3800 m (HL_{3800m}; n = 13) and 5100 m (HL_{5100m}; n = 17), respectively, and CMS highlanders living at 5100 m (n = 31) were recruited. Middle cerebral artery mean blood flow velocity (MCAv), cerebral oxygen delivery (CDO₂), mean blood pressure (MAP), heart rate variability and spontaneous cardiac baroreflex sensitivity (cBRS) were assessed while sitting, initial 30 s and after 3 min of standing. Cerebral autoregulation index (ARI) was estimated ($\Delta\text{MCAv}_{\%baseline}/\Delta\text{MAP}_{\%baseline}$) in response to the orthostatic challenge. Altitude and CMS were associated with hypoxemia and elevated hemoglobin concentration. While sitting, MCAv and LF_{power} negatively correlated with altitude but were not affected by CMS. CDO₂ remained preserved. BRS was comparable across all altitudes, but lower with CMS. Within initial 30 s of standing, altitude and CMS correlated with a lesser ΔMAP while ARI remained unaffected. After 3 min standing, MCAv, CDO₂ and cBRS remained preserved across altitudes. The LF/HF ratio increased in HL_{5100m} compared to LL and HL_{3800m} from sitting to standing. In contrary, CMS showed blunted autonomic nervous activation in responses to standing. Despite altitude- and CMS-associated hypoxemia, erythrocytosis and impaired blood pressure regulation (CMS only), cerebral homeostasis remained overall preserved.

Abbreviations

ARI	Cerebral autoregulation index
CA	Cerebral autoregulation
cBRS	Spontaneous cardiac baroreflex sensitivity
CDO ₂	Cerebral oxygen delivery
CMS	Chronic mountain sickness
CMS _{mild}	Highlanders with mild chronic mountain sickness
CMS _{mod.-sev.}	Highlanders with moderate-to-severe chronic mountain sickness
CVC	Cerebrovascular conductance
CVR	Cerebrovascular resistance
EE	Excessive erythrocytosis
HF	High frequency
HL _{3800m}	Highlanders living at 3800 m
HL _{5100m}	Highlanders living at 5100 m
HRV	Heart rate variability
LF	Low frequency

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MAP	Mean artery pressure
MCAv	Middle cerebral artery blood flow velocity
PB	Barometric pressure
PI	Pulse interval
SBP	Systolic blood pressure
SL	Sea-level residents
SpO ₂	Arterial oxygen saturation assessed by finger oximetry

The Peruvian high-altitude city of La Rinconada, with an estimated population of 40,000–60,000 permanent inhabitants, is the highest city in the world and is situated at 5100–5300 m. Most of the residents migrated from the Altiplano region (~4000 m); however, despite their high-altitude origins, these highlanders experience the full impact of chronic severe hypoxia and low arterial oxygenation (hypoxemia) associated with the approximately 47% lower barometric pressure at 5100 m compared to sea level¹. Additionally, Andean high-altitude residents are prone to developing chronic mountain sickness (CMS), a syndrome involving excessive erythrocytosis (EE, defined by hemoglobin concentration values ≥ 21 g/dl for men or ≥ 19 g/dl for women), severe hypoxemia, neurological disorders² and other signs and symptoms leading to reduced quality of life and premature death³. In La Rinconada, the CMS prevalence has been reported to be 14%⁴.

Since CMS is associated with neurological symptoms^{2,5}, understanding the cerebral homeostasis during the manifestation process of CMS (before CMS manifestations, as well as during the progression of CMS) is of high clinical relevance to better recognize, prevent and treat CMS in highlanders who are unable to relocate to lower altitudes. Since cerebral functioning requires continuous supply of oxygen, this vulnerable organ is particularly challenged under chronic hypoxic conditions and with CMS⁶. Surprisingly, despite severe hypoxemia and impaired cardiac baroreflex sensitivity reported in Andean highlanders with CMS^{7,8}, quantitative data are not available to support the dogma that cerebrovascular homeostasis and reactivity is impaired. One prospective study conducted at 3600 m (La Paz, Bolivia) has reported impaired cerebrovascular reactivity in response to CO₂ and O₂ alterations but preserved cerebral oxygen delivery in highlanders with and without CMS when compared to a low altitude control group from the United Kingdom⁵. Another study conducted at 4338 m (Cerro de Pasco, Peru) found no differences in the response of the cerebral circulation to hypoxia and hypocapnia between highlanders with and without CMS, either at high altitude or within 24 h of arriving at sea level⁹. However, neither study compared cerebrovascular homeostasis to ethnically matched populations living at lower altitudes or tried to distinguish between different CMS severities, while albeit in a different context, generic differences can affect susceptibility to cerebrovascular diseases¹⁰. Therefore, for the interpretation and contextualization of revealed differences in the cerebrovascular homeostasis and reactivity, comparisons of ethnically matched control groups living at different altitudes is paramount, especially when investigating the adaptation of Andeans, a genetically adapted high-altitude population.

Therefore, the purpose of the current study was to investigate the cerebrovascular homeostasis and reactivity in relation to the living altitude of Andean male highlanders and to elucidate the role of CMS on its functionality. We hypothesized that at 5100 m, (1) highlanders free from CMS, present impaired cerebrovascular homeostasis and reactivity in comparison to highlanders at 3800 m and lowlanders; and that (2) in highlanders at 5100 m, CMS compared to non-CMS further deteriorates cerebrovascular homeostasis and reactivity.

Methods

Design and setting

This cross-sectional study took place in Lima (sea-level, barometric pressure [PB] = 760 mmHg), Puno (3800 m, PB = 480 mmHg) and La Rinconada (5100–5300 m, PB = 405 mmHg), Peru, and was part of the *Expedition 5300* research program, which investigates the (patho)physiological consequences of long-term exposure to very high altitude^{4,11–13}. The study was approved by the ethics committee of the Universidad Nacional Mayor de San Marcos (CIEI-2019-002) and was performed in accordance with the Declaration of Helsinki. Participants in all three locations were recruited through street and radio advertisements and word of mouth.

Participants

Due to the higher risk of CMS manifestation in men compared to women and due to the challenging field conditions of recruitment, this study was conducted in men only⁴.

Non-smoking Peruvian males, permanently living (i) in Lima at <1000 m (SL), (ii) in Puno at 3800 m (HL_{3800m}) or (iii) La Rinconada at 5100–5300 m (HL_{5100m}), aged between 18 and 60 years, without any regular intake of medication and no documented medical history of cardiorespiratory, metabolic, or neurological diseases were included in this study.

At 5100 m highlanders were categorized into no (HL_{5100m}), mild (CMS_{mild}) and moderate-to-severe (CMS_{mod.-sev.}) CMS groups based on the Qinghai CMS questionnaire score (< 6; 6 to 10; and > 10, respectively)³. All participants gave their written informed consent prior to participation in this study.

Protocol overview

Medical history was assessed, and all participants had clinical examinations assessing heart rate, blood pressure and arterial oxygen saturation (SpO₂). Hemoglobin concentration ([Hb]; HemoCue Hb201+, HemoCue AB, Ängelholm, Sweden) was determined from a cubital venous blood sample while the patients were resting in the supine position and prior to the experimental procedure. To diagnose CMS, highlanders completed the Qinghai CMS questionnaire as described above.

Thereafter, participants were instructed to quietly sit in a comfortable chair for 10 min prior to instrumentation and the start of the protocol, which consisted in an active orthostatic challenge. After 5 min of baseline, participants were given a count down and instructed to stand up in one steady move within 1 s and without any assistance from their arms. They subsequently kept this upright position for a further 3 min. The experimental procedure is illustrated in Fig. 1. Participants were instructed not to talk, move or fall asleep during the sitting period as well as the active tilt test.

Continuous beat-by-beat blood pressure was measured by finger cuff photoplethysmography (ADInstruments, Oxford UK) and oxygen saturation by finger pulse oximetry throughout the test. The changes in the vertical distance between the hand and the heart were accounted for by the height correction unit non-invasive blood pressure monitor.

Middle cerebral artery (MCA) blood flow velocity (MCAv) was measured through insonation of the temporal window with a 2 MHz pulsed Doppler ultrasound transducer (Multi-Dop-T, DWL, Elektronische Systeme, Singen, Germany). Throughout the procedures, the placement and angle of the ultrasound transducer were held constant using a headset (DiaMon, DWL, Elektronische Systeme, Singen, Germany). In this position the systolic (sMCAv), mean (mMCAv) and diastolic (dMCAv) MCAv were averaged over the time periods illustrated in Fig. 1. Cerebrovascular conductance (CVC, sMCAv/mean arterial pressure [MAP]) and resistance (CVR, MAP/sMCAv) indices were calculated. An index of cerebral O₂ delivery (CDO₂) was calculated as the product of oxygen content (CaO₂; 1.39 × hemoglobin concentration × SpO₂/100) × sMCAv⁵.

Data collection and analysis

Throughout the protocol, analogue signals were sampled and continuously recorded at 1 kHz, using an analogue to digital converter (Powerlab/16SP ML795, ADInstruments, Oxford UK), and stored for offline analysis (Chart version 7.2.2, ADInstruments, Oxford, UK). Sitting values were analyzed in the last 30 s of the 5-min baseline period (except HRV and cBRS – see below). The effect of the orthostatic challenge was assessed by identifying and averaging a 1-s interval around the nadir of the sMCAv and MAP, respectively. Standing values were analyzed in the last 30 s of the 3 min standing period (except HRV and cBRS – see below).

The cerebral autoregulation index (ARI)

The ARI was defined by the ability of the CA to maintain a constant sMCAv despite a change in MAP and was calculated for the orthostatic challenge when the direction of Δ sMCAv / Δ MAP were positively correlated¹⁴ as follows:

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

$$\text{ARI}(\Delta\% \text{sMCAv} / \Delta \text{mmHg MAP}) = \frac{((\text{sMCAv standing} - \text{sitting}) / \text{sMCAv sitting}) \times 100}{\text{MAP standing} - \text{sitting}}.$$

Therefore, higher ARI values represent larger MAP-induced MCAv fluctuations corresponding to impaired CA, whereas smaller values in ARI correspond to efficient CA.

Heart rate variability (HRV)

HRV parameters were calculated with the HRV LabChart Module (ADInstruments Ltd, Oxford, UK) during the last 2.5 min of the sitting and standing phases by applying the Lomb-Scargle periodogram for spectral analysis¹⁵ (Fig. 1). Spontaneous breathing was allowed, and ectopic beats and artefacts were visually and automatically detected and deleted but not replaced, since the Lomb-Scargle periodogram is capable of dealing with gaps and unevenly spaced samples¹⁶. These 2.5-min intervals allowed to analyse absolute and normalized low frequency (LF) (0.04–0.15 Hz) and high frequency (HF, 0.15–0.60 Hz) power as well as the LF/HF ratio¹⁷. The HF band was post-hoc extended from an upper limit of 0.40 Hz to 0.60 Hz and to address for chronic hyperventilation observed in highlanders at 5100 m. This extension allowed to compare HF activity between all altitudes.

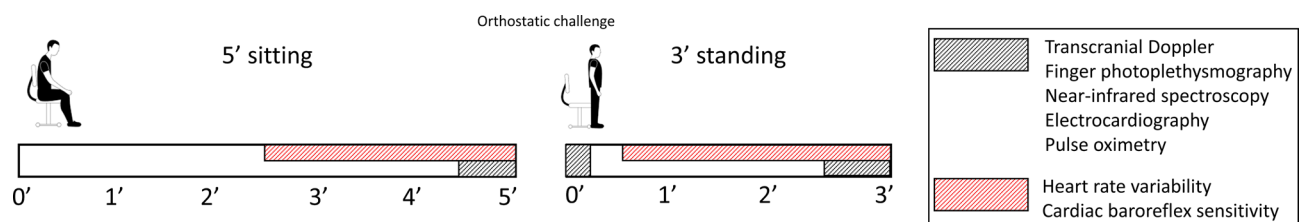


Figure 1. Experimental procedure. Participants remained seated in a comfortable chair for at least 10 min. After 5 min of baseline, participants were given a count down and instructed to stand up in one steady move within 1 s without any assistance from their arms. They subsequently kept this upright position for 3 more minutes. Red shaded areas indicate the 2.5-min intervals for heart rate variability and cardiac baroreflex sensitivity assessments. Gray shaded areas indicate the 30-s intervals for other physiological measurements.

Spontaneous cardiac baroreflex sensitivity

The cardiac baroreflex sensitivity (cBRS) was calculated using the sequence technique described by Kardos et al.¹⁸ In brief, during the last 2.5 min while sitting and standing (Fig. 1), the time series of systolic blood pressure (SBP) and pulse interval (PI) were automatically scanned. Only simultaneous increments in PI and SBP (+PI/+SBP) or decrements in PI and SBP (-PI/-SBP) over a minimum of 3 consecutive beats were included in the analysis, and if the minimum change in the rise or fall of SBP exceeded 1 mmHg and the correlation coefficient was >0.85 for each individual sequence. In case of at least 3 valid sequences of PI/SBP within the 2.5 min, they were averaged and the linear correlation between PI/SBP was computed. The obtained value represented the cBRS. In accordance to the approach described by Kardos et al.¹⁸, cBRS was calculated for lag 0 and 1 of the PI interval and the lag with the largest number of valid sequences was included in the analysis.

Outcomes

Main outcomes of interest were the cerebrovascular indices while sitting, in response to the orthostatic challenge and while standing for 3 min (Fig. 1), in relation to the altitude of residence and CMS severity. Additional outcomes were obtained from cBRS and HRV analyses, giving insights into the mechanisms and allowing a comprehensive interpretation of the main outcomes.

Statistical analysis

This study being part of the larger research program falling under the umbrella of *Expedition 5300*, therefore no formal sample size estimation was performed for this substudy. Demographic characteristics are presented as mean \pm standard deviation (SD), whereas values and their precision obtained from regression analyses are presented in mean \pm standard error (SE). To analyse absolute and percentage changes from baseline values of continuous outcomes, linear mixed regression analyses were applied with the dependent variable in absolute number or in percent from baseline. Dependent variables were tested for normality (Shapiro Wilk test), and visually verified with Kernel density plots. In case of non-normal distribution, log transformation (CVC, CVR, ARI, Total power, LF_{power}, normalized LF, HF_{power}, LF/HF, cBRS) or 1/sqrt (sMCAv) was applied. Independent variables were altitude (sea level, 3800 m and 5100 m), CMS severity (no, mild and moderate to severe) and intervention (sitting, orthostatic challenge and standing), and the interaction between altitude*intervention*CMS severity as fixed effects and participants as random effects. Single missing values were not replaced. Statistical significance was assumed with P values <0.05 and when the 95% confidence intervals of the mean difference did not include zero (STATA 16, StataCorp LLC, Texas, USA).

Results

Participants

Among a total of 76 male participants included in this study, 15 were SL, 13 HL_{3800m} and 48 were highlanders living at 5100 m, respectively. Highlanders at 5100 m had been living in La Rinconada for 15 ± 8 years, and 17 (35%) were categorized as HL_{5100m}, 11 (23%) CMS_{mild} and 20 (42%) CMS_{mod.-sev.} respectively (Table 1). All participants had similar anthropometric characteristics (height and weight) but HL_{5100m} were significantly older and had elevated hemoglobin than HL_{3800m} and SL groups. At 5100 m, CMS_{mod.-sev.} had the highest hemoglobin concentrations.

Cardiovascular and cerebrovascular homeostasis while sitting

In HL_{5100m}, living at 5100 m was associated with hypoxemia, lower PetCO₂ and higher mean and diastolic blood pressure compared to SL (Table 2). Systolic MCAv and CVC was lower, and CVR higher with the altitude of residence while CDO₂ was slightly reduced in HL_{5100m} compared to HL_{3800m} (P=0.028) but comparable to SL (P=0.253, Table 2). Frequency domain analysis of the HRV revealed altitude-dependent decrements in LF

	Participants without CMS			Highlanders living at 5100 m		
	SL	HL _{3800m}	HL _{5100m} ¹	HL _{5100m} ¹	CMS _{mild}	CMS _{mod.-sev.}
N	15	13	17	17	11	20
Age, years	30 \pm 10	33 \pm 11	42 \pm 8* [‡]	42 \pm 8	45 \pm 8	44 \pm 7
Weight, kg	70.2 \pm 14.1	68.7 \pm 7.2	69.9 \pm 6.1	69.9 \pm 6.1	71.2 \pm 11.6	69.3 \pm 8.5
Height, cm	169 \pm 5	167 \pm 5	166 \pm 6	166 \pm 6	164 \pm 6	163 \pm 5
Hb, g/dL	13.9 \pm 2.3	18.9 \pm 2.0*	22.1 \pm 2.3* [‡]	22.1 \pm 2.3	22.1 \pm 1.6	23.9 \pm 1.6 ^{††}
CMS score	1 \pm 2	1 \pm 1	4 \pm 1* [‡]	4 \pm 1	8 \pm 1 [‡]	13 \pm 2 ^{††}

Table 1. Participants characteristics. Values are presented as mean \pm standard deviation. SL sea-level residents, HL_{3800m} highlanders living at 3800 m, HL_{5100m} highlanders living at 5100 m without the diagnosis of chronic mountain sickness (CMS), CMS_{mild} highlanders living at 5100 m with mild CMS, CMS_{mod.-sev.} highlanders living at 5100 m with moderate-to-severe CMS, Hb hemoglobin concentration. CMS severity was classified using the Qinghai CMS questionnaire. Rating ranges from no CMS with scores of 0 to 5; mild CMS with scores of 6 to 10; and moderate to severe CMS, > 10 points. ¹These are the same participants. *P < 0.05 vs. SL; [‡]P < 0.05 vs. HL_{3800m}; [†]P < 0.05 vs. HL_{5100m}; ^{††}P < 0.05 vs. CMS_{mild}.

	Participants without CMS			Highlanders living at 5,100 m		
	SL	HL _{3800m}	HL _{5100m} ^a	HL _{5100m} ^a	CMS _{mild}	CMS _{mod.-sev.}
Oxygen saturation, %	98 ± 1	93 ± 2*	84 ± 5* [‡]	84 ± 5	82 ± 4	81 ± 6 [‡]
PetCO ₂ , mmHg	38 ± 5	27 ± 3*	24 ± 3* [‡]	24 ± 3	23 ± 4	26 ± 4
Cardiovascular parameters						
Blood pressure systolic, mmHg	123 ± 2	128 ± 3	125 ± 2	125 ± 2	127 ± 3	131 ± 2
Blood pressure diastolic, mmHg	68 ± 3	78 ± 3*	79 ± 3*	79 ± 3	79 ± 4	74 ± 3
MAP, mmHg	83 ± 3	90 ± 3	91 ± 3*	91 ± 3	91 ± 3	87 ± 2
Heart rate, bpm	72 ± 3	79 ± 3	71 ± 3 [‡]	71 ± 3	72 ± 3	73 ± 2
Cerebrovascular parameters						
MCAv systolic, cm/s	105.4 ± 5.2	85.2 ± 5.4*	68.4 ± 4.7* [‡]	68.4 ± 4.7	64.5 ± 5.9	65.1 ± 4.4
MCAv mean, cm/s	64.4 ± 3.2	54.1 ± 3.3*	42.9 ± 2.9* [‡]	42.9 ± 2.9	39.8 ± 3.6	39.6 ± 2.7
MCAv diastolic, cm/s	43.9 ± 2.4	38.6 ± 2.5	30.2 ± 2.2* [‡]	30.2 ± 2.2	27.5 ± 2.7	26.9 ± 2.0
CVC index, cm/s/mmHg	0.75 ± 0.06	0.58 ± 0.04*	0.46 ± 0.03* [‡]	0.46 ± 0.03	0.43 ± 0.04	0.44 ± 0.03
CVR index, mmHg/cm/s	1.33 ± 0.10	1.71 ± 0.13*	2.18 ± 0.15* [‡]	2.18 ± 0.15	2.32 ± 0.19	2.28 ± 0.14
CDO ₂ , ml/cm/s	1203 ± 75	1314 ± 78	1087 ± 68 [‡]	1087 ± 68	1003 ± 85	1055 ± 64
Autonomic regulation of cardiovascular function						
Total power, ms ²	1925 ± 271	1496 ± 282	974 ± 244*	974 ± 244	1068 ± 294	680 ± 218
LF power, ms ²	390 ± 108	295 ± 85	138 ± 34* [‡]	138 ± 34	157 ± 47	112 ± 25
Normalized LF, nu	37 ± 6	38 ± 6	28 ± 4	28 ± 4	40 ± 7	37 ± 5
HF power ms ²	610 ± 204	418 ± 145	305 ± 92	305 ± 92	190 ± 69	162 ± 44
Normalized HF, nu	61 ± 6	57 ± 6	66 ± 5	66 ± 5	53 ± 7	58 ± 5
LF/HF	0.64 ± 0.19	0.71 ± 0.21	0.45 ± 0.12	0.45 ± 0.12	0.83 ± 0.26	0.69 ± 0.16
cBRS, msec/mmHg	18.3 ± 3.3	12.5 ± 2.4	15.5 ± 2.7	15.5 ± 2.7	10.4 ± 2.4	8.3 ± 1.4 [‡]

Table 2. While sitting—Cardiovascular and cerebrovascular homeostasis. SL sea-level residents, HL_{3800m} highlanders living at 3800 m, HL_{5100m} highlanders living at 5100 m without the diagnosis of chronic mountain sickness (CMS), CMS_{mild} highlanders living at 5100 m with mild CMS, CMS_{mod.-sev.} highlanders living at 5100 m with moderate-to-severe CMS, PetCO₂ end-tidal partial pressure of CO₂, MAP mean arterial pressure, MCAv systolic middle cerebral artery peak blood flow velocity measured by transcranial Doppler ultrasound, CVC cerebrovascular conductance index, CVR cerebrovascular resistance index, CDO₂ calculated cerebral oxygen delivery as the product of (1.39 × hemoglobin concentration × SpO₂/100) × systolic MCAv, LF low frequency, HF high frequency, cBRS cardiad baroreflex sensitivity. ^aThese groups represent the same population but are presented twice to account for the two hypotheses for altitude and CMS effects. *P < 0.05 vs. SL.; [‡]P < 0.05 vs. HL_{3800m}; [‡]P < 0.05 vs. HL_{5100m}.

(P = 0.005 between HL_{5100m} vs. SL), a trend in lower HF power (P = 0.123 between HL_{5100m} vs. SL) and unchanged LF/HF ratio (P = 0.383 between HL_{5100m} vs. SL). Cardiac BRS was similar across all altitudes.

At 5100 m, the CMS_{mod.-sev.} was associated with more pronounced hypoxemia but similar degree of hypocapnia (lower end-tidal partial pressure of CO₂) compared to HL_{5100m} and CMS_{mild} (Table 2). Blood pressure and cerebrovascular indices such as sMCAv, CVC, CVR and CDO₂ were unaffected by CMS (Table 2) and no differences were found in HRV. In contrast cBRS was markedly reduced in CMS_{mod.-sev.} compared to HL_{5100m}.

Cardiovascular and cerebrovascular responses to an orthostatic challenge

In SL, HL_{3800m} and HL_{5100m}, the orthostatic challenge induced a transient drop in blood pressure. In contrast, the orthostatic challenge elevated the HR, but, these elevations were lower in HL_{5100m} compare to SL and HL_{3800m} (Table 3). However, when expressed in Δpercent from sitting, HL_{3800m} showed a similar or milder reduction in MAP (% sitting) compared to HL_{5100m} and SL, respectively (Table 3). The orthostatic challenge induced a similar fall in sMCAv across SL, HL_{3800m} and HL_{5100m} when expressed in percent change from sitting (Table 3) and resulted in lower CVC and increased CVR compared to sitting position. The calculated ARI expressed as Δ% sMCAv/Δ%MAP and Δ% sMCAv/ΔmmHg MAP were similar in those groups.

At 5100 m, the orthostatic challenge induced a decrease in MAP in HL_{5100m} (P < 0.05), while MAP did not change significantly in CMS_{mild} (P = 0.285) or CMS_{mod.-sev.} (P = 0.396, Table 4). Although MAP changes differed across CMS groups with the orthostatic challenge, heart rates moderately increased and a similar decrease in absolute and percent change from baseline in the sMCAv was observed (Table 4). The calculated ARI was not altered by CMS severity (Table 4).

Cardiovascular and cerebrovascular homeostasis while standing

Despite persistently reduced sMCAv in HL_{5100m} compared to SL and HL_{3800m} (Table 5), no differences in CDO₂ were observed. When expressed as a Δpercent from sitting, the changes in sMCAv while standing was similar between SL, HL_{3800m}, HL_{5100m} (Fig. 2B). Unlike what was observed while sitting, HRV-derived total power and

	Absolute changes			Normalized changes (% baseline)		
	SL	HL _{3800m}	HL _{5100m}	SL	HL _{3800m}	HL _{5100m}
Cardiovascular response						
BP systolic, mmHg	-7.5 (-13.2 to -1.9)	-5.7 (-12.2 to 0.9)	-5.3 (-10.5 to 0.0)	-6 (-11 to -1)	-5 (-11 to 1)	-5 (-9 to 0)
BP diastolic, mmHg	-8.2 (-12.6 to -3.8)	-2.2 (-6.9 to 2.5)	-4.3 (-8.4 to -0.1)	-13 (-20 to -7)	-2 (-9 to 5)*	-5 (-11 to 1)
MAP, mmHg	-10.2 (-14.7 to -5.6)	-4.0 (-8.9 to 0.9)	-6.0 (-10.3 to -1.7)	-13 (-18 to -7)	-4 (-10 to 2)*	-6 (-11 to -1)
Heart rate, bpm	10 (6 to 13)	9 (6 to 13)	4 (0 to 7)**	15 (10 to 21)	13 (7 to 19)	5 (0 to 11)*
Cerebrovascular response						
MCAv systolic, cm/s	-5.8 (-11.0 to -0.7)	-1.1 (-5.3 to 3.1)*	-1.4 (-4.0 to 1.2)*	-6 (-10 to -1)	-1 (-6 to 3)	-2 (-6 to 2)
MCAv mean, cm/s	-12.3 (-15.0 to -9.5)	-8.3 (-11.1 to -5.4)	-5.7 (-8.2 to -3.2)*	-34 (-41 to -26)	-28 (-36 to -20)	-24 (-31 to -17)
MCAv diastolic, cm/s	-14.6 (-17.4 to -11.8)	-11.7 (-14.6 to -8.8)	-7.8 (-10.4 to -5.3)**	-19 (-24 to -14)	-14 (-20 to -9)	-12 (-17 to -8)
ARI, Δ% <i>s</i> MCAv/ Δ%MAP	1.07 ± 0.41	2.03 ± 0.81	1.03 ± 0.36	NA	NA	NA
ARI, Δ% <i>s</i> MCAv/ ΔmmHgMAP	1.31 ± 0.50	2.20 ± 0.88	1.14 ± 0.40	NA	NA	NA
CVC index, cm/s/mmHg	-0.05 (-0.10 to 0.01)	-0.06 (-0.10 to -0.02)	0.03 (-0.06 to 0.00)	-4 (-11 to 3)	-10 (-17 to -3)	-6 (-12 to 1)
CVR index, mmHg/cm/s	0.09 (-0.02 to 0.19)	0.02 (0.05 to 0.34)	0.14 (-0.01 to 0.30)	8 (-1 to 19)	12 (2 to 22)	7 (-1 to 16)
CDO ₂ , ml/cm/s	-221 (-283 to -159)	-200 (-264 to -136)	-141 (-197 to -85)	-19 (-24 to -14)*	-14 (-20 to -9)	-12 (-17 to -8)

Table 3. Orthostatic challenge—Participants without chronic mountain sickness. Values are presented as mean ± standard error or mean changes (95% confidence intervals) during standing up compared to sitting. *SL* sea-level residents, *HL_{3800m}* highlanders living at 3800 m, *HL_{5100m}* highlanders living at 5100 m without the diagnosis of chronic mountain sickness, *BP* blood pressure, *MAP* mean arterial pressure, *sMCAv* systolic middle cerebral artery peak blood flow velocity measured by transcranial Doppler ultrasound, *ARI* cerebral autoregulation index, *CVC* cerebrovascular conductance index, *CVR* cerebrovascular resistance index, *CDO₂* calculated cerebral oxygen delivery as the product of (1.39 × hemoglobin concentration × SpO₂/100) × *sMCAv*. *P < 0.05 vs. SL; **P < 0.05 vs. HL_{3800m}.

	Absolute changes			Normalized changes (% baseline)		
	HL _{5100m}	CMS _{mild}	CMS _{mod-sev}	HL _{5100m}	CMS _{mild}	CMS _{mod-sev}
Cardiovascular response						
BP systolic, mmHg	-5.3 (-10.5 to 0.0)	5.4 (-0.9 to 11.7)*	0.1 (-4.6 to 4.9)	-5 (-9 to 0)	4 (-1 to 10)*	1 (-4 to 5)
BP diastolic, mmHg	-4.3 (-8.4 to -0.1)	4.5 (-0.7 to 9.6)*	-0.7 (-4.6 to 3.2)	-5 (-11 to 1)	5 (-2 to 13)*	-1 (-7 to 5)
MAP, mmHg	-6.0 (-10.3 to -1.7)	2.9 (-2.4 to 8.3)*	-1.8 (-5.9 to 2.2)	-6 (-11 to -1)	3 (-3 to 9)*	-2 (-7 to 3)
Heart rate, bpm	4 (0 to 7)	5 (1 to 10)	5 (2 to 8)	5 (0 to 11)	8 (1 to 15)	6 (1 to 11)
Cerebrovascular response						
MCAv systolic, cm/s	-1.5 (-5.3 to 2.3)	0.2 (-4.5 to 5.0)	1.1 (-2.4 to 4.7)	-2 (-6 to 2)	1 (-5 to 6)	2 (-2 to 5)
MCAv mean, cm/s	-7.8 (-10.4 to -5.3)	-7.4 (-10.5 to -4.2)	-7.4 (-9.8 to -5.1)	-24 (-31 to -17)	-28 (-37 to -19)	-23 (-30 to -17)
MCAv diastolic, cm/s	-5.7 (-8.2 to -3.2)	-4.8 (-8.0 to -1.7)	-4.6 (-6.9 to -2.2)	-12 (-17 to -8)	-12 (-18 to -7)	-11 (-16 to -7)
ARI, Δ% <i>s</i> MCAv/ Δ%MAP	1.03 ± 0.36	3.85 ± 3.26	1.01 ± 0.40	NA	NA	NA
ARI, Δ% <i>s</i> MCAv/ ΔmmHgMAP	1.14 ± 0.40	4.48 ± 3.08	1.15 ± 0.46	NA	NA	NA
CVC index, cm/s/mmHg	-0.03 (-0.06 to 0.00)	-0.07 (-0.10 to -0.03)	-0.04 (-0.07 to -0.01)	-6 (-12 to 1)	-15 (-23 to -7)	-8 (-14 to -2)
CVR index, mmHg/cm/s	0.14 (-0.01 to 0.30)	0.43 (0.20 to 0.65)	0.23 (0.07 to 0.38)	7 (-1 to 16)	19 (9 to 30)	12 (4 to 20)
CDO ₂ , ml/cm/s	-141 (-197 to -85)	-124 (-194 to -55)	-123 (-176 to -70)	-12 (-17 to -8)	-12 (-18 to -7)	-11 (-16 to -7)

Table 4. Orthostatic challenge—Highlanders living at 5100 m. Values are presented as mean ± standard error or mean changes (95% confidence intervals) during standing up compared to sitting. *SL* sea-level residents, *HL_{3800m}* highlanders living at 3800 m, *HL_{5100m}* highlanders living at 5100 m without the diagnosis of chronic mountain sickness, *BP* blood pressure, *MAP* mean arterial pressure, *sMCAv* systolic middle cerebral artery peak blood flow velocity measured by transcranial Doppler ultrasound, *ARI* cerebral autoregulation index, *CVC* cerebrovascular conductance index, *CVR* cerebrovascular resistance index, *CDO₂* calculated cerebral oxygen delivery as the product of (1.39 × hemoglobin concentration × SpO₂/100) × *sMCAv*; #P < 0.05 vs. HL_{5100m}.

LF were similar between groups while standing, mainly due to a larger increase in LF in HL_{5100m} compared to HL_{3800m} and SL (Fig. 2D and F). The cBRS did not differ between altitudes.

At 5100 m, MCAv metrics, CDO₂ and HRV-derived values were not different between HL_{5100m}, CMS_{mild} and CMS_{mod-sev} while standing (Table 5). When expressed in Δpercent from sitting, however, CMS_{mild} and CMS_{mod-sev} showed no increase in LF (Fig. 3D), no decrease in HF (Fig. 3E) and, therefore, no increase in LF/HF compared

	Participants without CMS			Highlanders living at 5100 m		
	SL	HL _{3800m}	HL _{5100m} ^a	HL _{5100m} ^a	CMS _{mild}	CMS _{mod.-sev}
Cerebrovascular parameters						
MCAv systolic, cm/s	90.0 ± 6.0	79.2 ± 5.2	66.4 ± 3.5* [‡]	66.4 ± 3.5	62.2 ± 3.9	64.6 ± 3.1
MCAv mean, cm/s	60.0 ± 3.2	51.5 ± 3.3	42.3 ± 2.9* [‡]	42.3 ± 2.9	38.1 ± 3.6	39.3 ± 2.7
MCAv diastolic, cm/s	42.0 ± 2.4	36.3 ± 3	29.1 ± 2.2* [‡]	29.1 ± 2.2	25.5 ± 2.7	25.7 ± 2.0
CDO ₂ , ml/cm/s	1130 ± 75	1249 ± 78	1072 ± 68	1072 ± 68	959 ± 85	1045 ± 64
Autonomic regulation of cardiovascular function						
Total power, ms ²	1215 ± 271	1558 ± 282	1295 ± 244	1295 ± 244	935 ± 294	916 ± 218
LF power, ms ²	363 ± 100	303 ± 87	202 ± 50	202 ± 50	218 ± 65	154 ± 34
Normalized LF, nu	56 ± 9	43 ± 7	54 ± 8	54 ± 8	48 ± 8	39 ± 5
HF power ms ²	251 ± 84	306 ± 106	154 ± 46	154 ± 46	176 ± 64	188 ± 51
Normalized HF, nu	42 ± 6	51 ± 6	44 ± 5	44 ± 5	47 ± 7	55 ± 5
LF/HF	1.45 ± 0.42	0.99 ± 0.30	1.32 ± 0.35	1.32 ± 0.35	1.24 ± 0.39	0.82 ± 0.19
Heart rate, bpm	76 ± 3	83 ± 3	74 ± 3 [‡]	74 ± 3	74 ± 3	74 ± 2
cBRS, msec/mmHg	9.1 ± 1.6	9.5 ± 1.8	8.6 ± 1.5	8.6 ± 1.5	11.3 ± 2.4	11.2 ± 1.9

Table 5. While standing—Cardiovascular and cerebrovascular homeostasis. Values are presented as mean ± standard error. SL sea-level residents, HL_{3800m} highlanders living at 3800 m, HL_{5100m} highlanders living at 5100 m without the diagnosis of chronic mountain sickness (CMS), CMS_{mild} highlanders living at 5100 m with mild CMS, CMS_{mod.-sev.} highlanders living at 5100 m with moderate-to-severe CMS, MAP mean arterial pressure, MCAv middle cerebral artery blood flow velocity measured by transcranial Doppler ultrasound, CVC cerebrovascular conductance index, CVR cerebrovascular resistance index, CDO₂ calculated cerebral oxygen delivery as the product of (1.39 × hemoglobin concentration × SpO₂/100) × mean MCAv, LF low frequency, HF high frequency, cBRS cardiac baroreflex sensitivity. ^aThese groups represent the same population but are presented twice to account for the two hypotheses for altitude and CMS effects. *P < 0.05 vs. SL; [‡]P < 0.05 vs. HL_{3800m}.

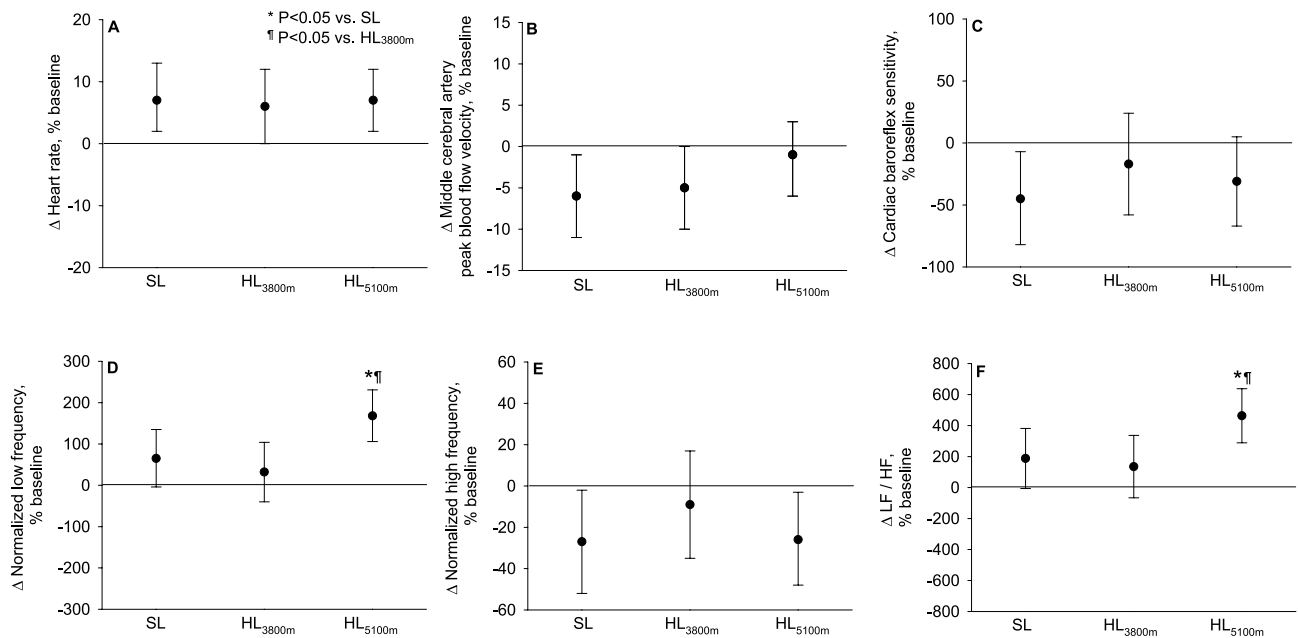


Figure 2. Physiological changes while standing expressed in percentage from sitting values in healthy lowlanders and highlanders. Panel (A) heart rate; Panel (B) middle cerebral artery peak blood flow velocity; Panel (C) cardiac baroreflex sensitivity; Panel (D) normalized low frequency power; Panel (E) normalized high frequency power; Panel (F) ratio between low frequency (LF) and high frequency (HF). Dots represent the mean change, whiskers the 95% confidence interval. Significant changes from resting are present when the 95% confidence interval does not include the value zero. *P < 0.05 indicate significant different changes compared to lowlanders; [†]P < 0.05 indicate significant different changes compared to highlanders at 3800 m.

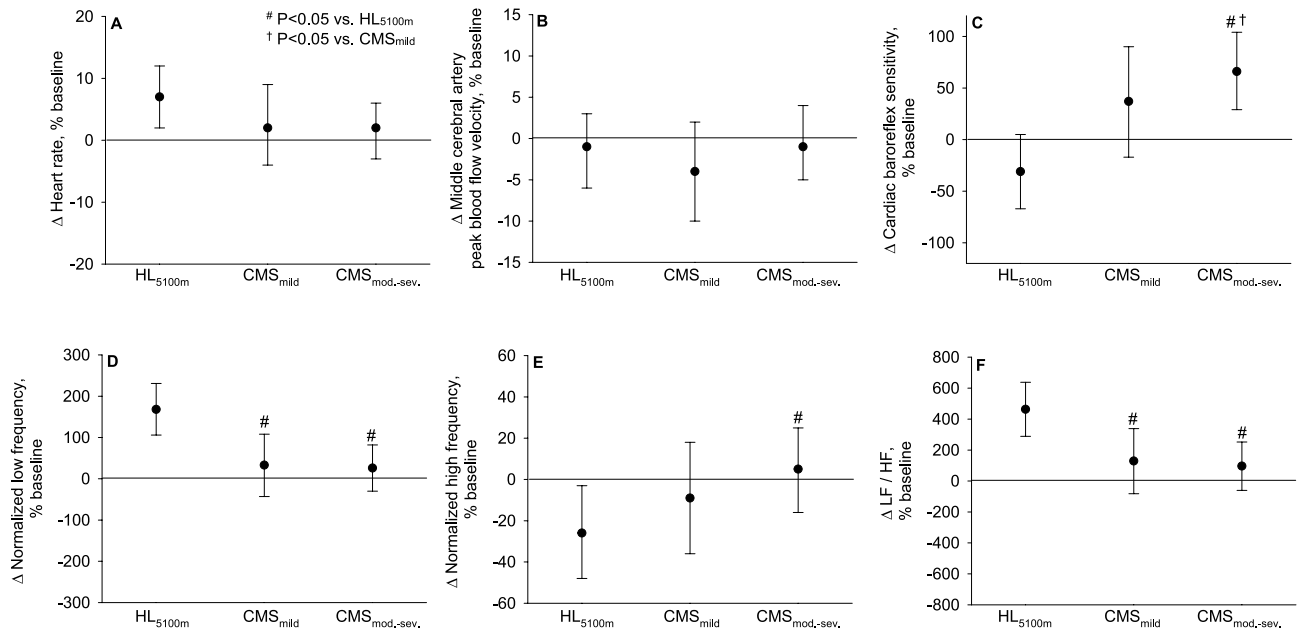


Figure 3. Physiological changes while standing expressed in percentage from sitting in highlanders living at 5100 m. CMS chronic mountain sickness. Panel (A) heart rate; Panel (B) middle cerebral artery peak blood flow velocity; Panel (C) cardiac baroreflex sensitivity; Panel (D) normalized low frequency power; Panel (E) normalized high frequency power; Panel (F) ratio between low frequency (LF) and high frequency (HF). Dots represent the mean change, whiskers the 95% confidence interval. Significant changes from resting are present when the 95% confidence interval does not include the value zero. * $P < 0.05$ indicate significant different changes compared to highlanders without CMS; † $P < 0.05$ indicate significant different changes compared to highlanders with mild CMS.

to HL_{5100m} (Fig. 3F). The cBRS remained unchanged in HL_{5100m} and CMS_{mild} during standing but increased in CMS_{mod.-sev.} compared to HL_{5100m} ($P = 0.011$) and CMS_{mild} ($P < 0.001$) (Fig. 3C).

Discussion

Main findings

This comprehensive study assessed for the first time the cerebrovascular homeostasis at three different altitudes and in highlanders with different CMS scores severity.

Preserved cerebral homeostasis and CDO₂ while sitting was achieved by elevated CaO₂ to compensate for reduced cerebral perfusion in HL_{3800m} and HL_{5100m} compared to SL (Table 2). Interestingly, although HL_{5100m} already showed pathological hemoglobin concentrations (> 21 g/dl, Table 1), these highlanders did not develop any CMS-related neurological symptoms (i.e. headache, tinnitus). Moreover, HL_{5100m} had maintained cerebrovascular and cardiovascular responsiveness during the orthostatic challenge (Table 3) and during standing (Fig. 2) compared to HL_{3800m} and SL residents. While standing, this was achieved by altered orthostatic hypotension, elevated sympathetic nervous system activation and maintained cardiac baroreceptor sensitivity (Table 5).

While sitting, CMS_{mild} and CMS_{mod.-sev.} presented comparable cerebrovascular homeostasis and CDO₂ compared to HL_{5100m}, albeit using different strategies (Table 2). Indeed, CMS_{mod.-sev.} maintained their CDO₂ due to further excessive erythrocytosis, which was associated with altered blood pressure regulation, and ventilatory (unchanged level of PetCO₂ despite severe hypoxemia) and autonomic cardiovascular function (Tables 1 and 2). Interestingly, in CMS_{mild} and CMS_{mod.-sev.}, the cerebrovascular reactivity in response to the orthostatic challenge was comparable to HL_{5100m}; however, their baroreflex sensitivity and sympathetic/parasympathetic activity in response to standing for 3 min were impaired (Table 5, Fig. 3). Despite unaltered cerebrovascular homeostasis and reactivity in highlanders with vs. without CMS, this pathology has been traditionally associated with neurological symptoms; therefore, other underlying mechanisms might be involved in its manifestation and expression, e.g. cerebral edema¹⁹.

Effect of altitude

As mentioned above, our findings in HL_{5100m}, while sitting showed maintained cerebral homeostasis and CDO₂ compared to SL residents (Table 2). Only one study by Bailey et al.⁵ looked at cerebral homeostasis while resting in Andean highlanders with and without CMS living at 3600 m, La Paz, Bolivia, and compared their results to UK lowlanders. By using the same CDO₂ equation as in our study, they showed reduced CDO₂ in highlanders compared to lowlanders (850 vs. 983 ml/cm/s, $P < 0.05$). However, the CDO₂ in highlanders reported by Bailey et al. was lower than those in the present study (1314 and 1087 ml/cm/s in HL_{3800m} and HL_{5100m}, respectively). This discrepancy is caused by the higher sMCAv and hemoglobin concentrations found in our populations (Tables 1

and 2) (54.1 cm/s and 18.9 g/dl at 3800 m; 42.9 cm/s and 22.1 g/dl at 5100 m compared to 39 cm/s and 17.2 g/dl at 3600 m reported by Bailey et al.). Interestingly, in the cited study, they employed transfer function analysis to investigate static CA while resting quietly. They reported no difference in coherence, phase and gain in the very low and low frequency bands between highlanders and lowlanders, suggesting maintained CA functionality. However, based on the exaggerated oxidative-inflammatory nitrosative stress and corresponding decrease in vascular NO bioavailability combined with reduced CDO₂, they concluded that the cerebrovascular function is impaired in highlanders compared to lowlanders while resting. The differences between the cited study and our findings could be due to the chosen control group and, therefore, the comparator for the definition of “normal” CA functionality. In our study, an ethnically matched control group was chosen, therefore, comparisons of CA functionality in Peruvian highlanders compared to Peruvian lowlanders was not influenced by any factors related to ethnicity.

We found altered orthostatic hypotension but similar physiological changes in HL_{3800m} and HL_{5100m} compared to SL (Table 3). Interestingly, highlanders were less prone to hypotension during the orthostatic challenge, which has been reported previously²⁰. Gulli et al. examined orthostatic tolerance and hypotension by using head-up tilting in highlanders living in Cerro de Pasco (4338 m), Peru, and compared their results to Ethiopian highlanders and UK sea-level controls. Similar to our results, Andean highlanders had no drop in systemic blood pressure with tilting (114 mmHg supine to 116 mmHg while tilted for 20 min), whereas Ethiopian highlanders as well as the lowlanders had slight decrements in blood pressure. On another hand, Gulli et al. also showed impaired autonomic cardiovascular activation in response to 20 min of 60 degree head-up tilting in Peruvian highlanders. This was mainly shown by an absence of LF-increase and HF-decrease in response to tilting by using autoregressive monovariate model with automated time series analysis. These results are in contrast with the present findings showing a normal rise in LF and drop in HF frequency after standing for 3 min compared to sitting. The passive vs active nature of the tilt test, the analysis method of the autonomic cardiovascular activity and more generally different study design between Gulli et al. and the present work most likely contribute to the discrepancy in the results.

In accordance with previous reports in lowlanders, the orthostatic challenge by standing-up is normally associated with reduced cBRS²¹ and elevated sympathetic activity²². We observed the same pattern of responses across altitudes, except for HL_{5100m} who had pronounced LF activation when standing up (Fig. 2). This latter might be necessary to achieve comparable peripheral, cardiac and cerebrovascular responses under severe hypoxic conditions compared to normoxia²³. One potential underlying factor might be the hypoxia-related dilatation of blood vessels²⁴ requiring higher sympathetic activity levels to vasoconstrict, but further studies are required to clarify these cardiovascular responses.

Effect of CMS

Although CMS_{mild} and CMS_{mod.-sev.} were associated with further hypoxemia and excessive erythrocytosis (Table 1), CDO₂ remained comparable to HL_{5100m} (Table 2). The underlying cause for the comparable CDO₂ most likely was the excessive hemoglobin concentration, while sMCAv remained stable and SpO₂ was only mildly reduced (Table 2). Indeed, Bailey et al.⁵ also found similar CDO₂ values between highlanders with and without CMS at 3600 m. Similarly, comparisons of CA functionality showed no difference between highlanders with and without CMS at 3600 m⁵, or, indeed at 5100 m, in the present study. These results suggest that other, yet to be established, CMS-related alterations explain neurological symptoms traditionally associated with CMS. In contrary, previous findings by Appenzeller et al.²⁵ showed no response in cerebral blood velocity to an exogenous NO donor in Peruvian highlanders compared to reduced cerebral blood volumes in Ethiopian low- and highlanders, indicating impaired CA functionality in Peruvian highlanders. Unfortunately, owing to the small sample size, and methodological limitations (change in MCA diameter due to exogenous NO donor), this latter study did not separate analyses by CMS (4 out of 9 participants had CMS); therefore, the authors could not conclude about the possible role of CMS in the impaired CA functionality.

Aside from the maintained CDO₂ in highlanders with CMS, CMS has clear deleterious effects on the cardiovascular and sympathetic/parasympathetic activity. The observed lower cBRS and therefore, lower blood pressure regulation while sitting (Table 2) is in accordance with a previous report comparing highlanders with hematocrit values > 65% and high CMS scores (cBRS 3.9 ± 2.1 ms/mmHg) to highlanders with hematocrit < 60% and lower CMS scores (cBRS 11.2 ± 8.5 ms/mmHg)⁸. Mechanisms behind the compromised blood pressure regulation might be impaired vascular compliance, lower cBRS sensitivity or, as previously shown negative correlation between blood volume and cBRS activity^{26,27}.

When rapidly standing-up (Table 4), CMS was associated with altered orthostatic hypotension as suggested by the absence of decrease or even the increase in blood pressure but comparable ARI and sMCAv in comparison to HL_{5100m}. However, it remains debatable whether the observed increase in blood pressure in response to the orthostatic challenge is an adequate response²⁸. Blood pressure falls are thought to be the consequence of gravitationally driven redistribution of blood from the central circulation to the periphery and predominantly venous vasculature²⁹. Highlanders living at 5100 m have large blood volumes¹¹, and therefore a postural change might not cause the classically observed blood volume shift, blood vessel dilatation and blood pressure fall³⁰. Although no study has examined the effect of hypervolemia on blood pressure regulation and orthostatic hypotension at high-altitude, our findings are in accordance with the widely accepted theory that hypovolemia causes orthostatic intolerance by exaggerated hypotension³¹. Despite hypervolemia and potentially limited capability to dilate the peripheral venous vasculature causing a minimal blood volume shift, the hydrostatic pressure still was likely to increase due to the orthostatic challenge. As seen in the elevation of heart rate in CMS_{mild} and CMS_{mod.-sev.} during the orthostatic challenge (Table 4), the potential hydrostatic shift caused sympathetic excitation and parasympathetic inhibition through reduced pressure on the arterial baroreflex

receptors, as described previously³². Assuming that these sympathetic/parasympathetic alterations affect the cerebral vasculature³², then cerebrovascular vasoconstriction, decrease in MCAv and increase in CVR would be the consequences – which we observed in CMS compared to HL_{5100m} (Table 4, reduction in mean and diastolic MCAv), despite no change in MAP with the orthostatic challenge.

While standing (Fig. 3), CMS_{mild} and CMS_{mod.-sev.} were associated with blunted autonomic cardiovascular activity (no change in heart rate, LF, HF or LF/ HF ratio), indicating that the impaired system was not able to adapt to the postural changes. This pattern was uniquely observed in CMS_{mild} and CMS_{mod.-sev.}, however, challenging to comprehend. Indeed, excessive erythrocytosis cannot be the driving factor behind this observation, since HL_{5100m} have comparable hemoglobin concentrations (at least compared to CMS_{mild}), however, they are solely asymptomatic. Moreover, in a previously published paper in the same participants, we found no difference in hematocrit, blood viscosity or blood volume between HL_{5100m} and CMS_{mild}^{11,12}. Therefore, the reduced sympathetic/parasympathetic activation has another origin. For instance, we observed no change or even increased cBRS sensitivity in response to standing in CMS, which suggests impaired blood pressure regulation, possibly through reduced cBRS sensitivity. Indeed, it could be hypothesized that the failure to activate cBRS in highlanders with CMS might have resulted in the failure of the baroreflex to activate the classical autonomic nervous system.

The selfish brain theory in CMS?

It seems to be appropriate to highlight that the brain is the most important and valuable organ in the human body and, due to its inability to store resources such as oxygen and glucose, constantly demands supply from the body^{33,34}. The simple rationale is that when the brain dies, the organism dies, therefore, the better alternative is to extract as much resources as possible from the body – whatever the cost. In terms of highlanders living in the highest city in the world, being severely hypoxemic and suffering from CMS causing further hypoxemia, the brain is chronically under stress of not receiving enough oxygen to keep functioning. In our comprehensive study, we have insights, that the oxygen delivery to the brain is maintained by pathologically high hemoglobin concentrations especially in CMS¹¹, as well as pathological alterations in several body functions. These consequences might be the direct cause of the brain-pull, maybe being the ultimate cause of CMS symptoms, impaired body functions, organ damage and premature death. However, it is certain that without this “selfish” behaviour, the brain would suffer substantial damage. Therefore, whether the observed changes in ventilatory, systemic and autonomic cardiovascular activation are “beneficial” or “detrimental” differ by what should be more prioritized – the brain or the body?

Limitations

This study was conducted only in men, although, CMS can also manifest in women just to a much lower extent⁴. The rationale behind studying only men was the unpredictable and challenging recruitment procedure of highlanders living in La Rinconada as well as the complexity and multidimensionality of the study, not allowing to sufficiently characterize women related to their hormonal profile, menstrual cycle phase and pre-/postmenopause. Although this cross-sectional study conducted at different altitudes and in highlanders with and without CMS provides original data regarding the physiological effects of permanent high-altitude residence and CMS, longitudinal studies are warranted to further elucidate the (lack of) adaptations of the cerebral, cardiovascular and autonomic systems, as well as blood pressure regulation in highlanders. Furthermore, whether the observed CMS-related specificities are continuous or related to the CMS severity classifications (no, mild, moderate-to-severe), and whether hypervolemia and baroreflex function play an important role, requires further investigation. The chosen examination techniques were adapted and carefully chosen according to the challenging field conditions in La Rinconada. In absence of any hospital nearby, non-invasive over invasive measurements for assessing cerebral regulation and autonomic cardiovascular activation were preferred. Furthermore, assessed TCD indexes of the MCA and calculated CDO₂ provide only partial insights into cerebral homeostasis, while potentially confounding factors such as differences in the MCA diameter among populations due to hypervolemia or PetCO₂ differences remain to be elucidated. Standing-up as an orthostatic stress was chosen to simulate ecological condition with results directly applicable to daily life, however, the relatively mild change in blood pressure might have masked physiological responses potentially revealed with higher stress levels, i.e. exercise. As per Table 1, one can notice that dwellers from La Rinconada were overall older than those residing at lower altitudes, which could in and of itself influence cerebrovascular function. However, the present results were not modified by the inclusion of age as covariate.

Conclusion

In conclusion, we showed in male residents without symptoms of CMS living at sea-level, 3800 m and 5100 m, that the cerebral oxygen delivery and cerebrovascular reactivity are comparable during sitting and an orthostatic stress. This was achieved by ventilatory compensation, altered orthostatic hypotension, elevated sympathetic activation while standing and maintained blood pressure regulation through cardiac baroreflex function. At 5100 m, male highlanders with CMS showed comparable CDO₂ and cerebral reactivity compared to highlanders living at 5100 m free of CMS. However, CMS, especially moderate-to-severe CMS, was associated with highly excessive erythrocytosis, absent of ventilatory compensation for severe hypoxemia, impaired blood pressure regulation and impaired sympathetic/parasympathetic activation. Whether these various pathological consequences developed due to CMS and maladaptation to chronic hypoxia or whether in some individuals the “selfish” brain under chronic oxygen deprivation caused the observed CMS symptoms and body dysfunction remains to be elucidated.

Data availability

Data available: Yes, Data types: De-identified participant data, How to access data: michael.furian@usz.ch, When available: With publication, Who can access the data: Anonymized data underlying this study can be requested by qualified researchers providing an approved proposal.

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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