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Changes in cerebral blood flow and vasoreactivity to CO_2 measured by Arterial Spin Labeling after 6 days at 4,350 m

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ABSTRACT

Changes in cerebral perfusion and CO_2 cerebrovascular reactivity during and immediately after a sojourn at high altitude remain unclear but may be critical for acclimatization. The aim of the present study was to assess the effects of 6 days at 4,350 m on cerebral perfusion and cerebrovascular reactivity (CVR) to CO_2 by arterial spin labeling (ASL) magnetic resonance imaging at sea level and to compare it with transcranial Doppler (TCD) results at altitude. Eleven healthy male subjects, non-acclimatized to altitude, stayed for 6 days at 4,350 m (Observatoire Vallot, massif du Mont-Blanc). Prior to the stay and within 6 h after returning to sea level, subjects were investigated using pseudo-continuous ASL at 3 T during a block-design inhalation paradigm to measure basal cerebral blood flow (CBF) and CO_2 CVR. End-tidal CO_2 ($PetCO_2$), respiratory rate, heart rate and oxygen saturation were recorded during the exam. Subjects were also examined using TCD prior to and on day 5 of the stay at altitude to measure blood velocity in the middle cerebral artery (MCAv) and CO_2 CVR. CO_2 CVR was expressed as percent change in ASL CBF or TCD MCAv per mmHg change in $PetCO_2$. $PetCO_2$ was significantly decreased during and after altitude. Significant increases in TCD MCAv compared to before altitude measurements were observed on day 5 at altitude (+20.5 ± 15.5 %). Interestingly, ASL CBF remained increased in the MCA and anterior vascular territories (+22.0 ± 24.1 % and 20.5 ± 20.3 %, respectively) after altitude under normoxic conditions. TCD CVR tended to decrease on day 5 at 4,350 m (-12.3 ± 54.5 % in the MCA) while the ASL CVR was significantly decreased after altitude (-29.5 ± 19.8 % in the MCA). No correlation was observed between cerebral hemodynamic changes and symptoms of acute mountain sickness at high altitude. In conclusion, prolonged exposure to high altitude significantly increases blood flow during the altitude stay and within 6 h after returning to sea level. Decreased CO_2 CVR after prolonged

altitude exposure was also observed using ASL. Changes in cerebral hemodynamics with altitude exposure probably involve other mechanisms than the vasodilatory effect of hypoxia only, since it persists under normoxia several hours following the descent.

Key words: hypoxia, cerebral perfusion, cerebrovascular reactivity, MRI, arterial spin labeling, transcranial doppler

INTRODUCTION

Changes in cerebral blood flow (CBF) are observed during acclimatization to high altitude. The original report from Severinghaus et al. (1966) indicating an increase in CBF after several days at high altitude (3,810 m) compared to sea level was confirmed by subsequent studies (Chan et al., 2005; Fan et al., 2010; Huang et al., 1987; Lucas et al., 2011; Wolff, 2000). Others, however, failed to observe this change (Ainslie et al., 2008; Van Osta et al., 2005), probably due to differences in exposure duration and altitude levels as well as methodological considerations (see below). Increased CBF is believed to be a compensatory mechanism serving to maintain normal oxygen delivery to the brain under hypoxemic conditions. CBF changes at altitude mainly result from the opposite effects of reduced arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) partial pressures. Hypoxia is known to produce cerebral vasodilatation (at least when reaching a certain threshold, *i.e.* PaO_2< 50-60 mmHg) and a proportional increase in CBF (Ainslie, 2004; Cohen et al., 1967). However, hypoxic exposure also provokes hyperventilatory-induced hypocapnia and subsequent cerebral vasoconstriction. Hence, Poulin et al. (2002) that 48 h of poikilocapnic normobaric hypoxic exposure (end tidal O_2 partial pressure, $PetO_2$ = 60 mmHg) induces a reduction in CBF predominantly due to hypocapnia since exposure to the same hypoxic stress but under isocapnia does not induce any change in CBF. After several days at high altitude, the initial increase in extracellular pH due to hyperventilation-induced hypocapnia is progressively compensated by a change in the concentration of HCO_3^- in extracellular and cerebrospinal fluids, although cerebrospinal pH may still remain alkaline over several weeks at altitude (Brugniaux et al., 2007). Therefore, it remains to be determined how CBF is affected by a

sojourn of several days at high altitude, and the role of the opposing influences of reduced PaO_2 and $PaCO_2$ remains to be clarified.

In addition to the critical importance of changes in PaO_2 and $PaCO_2$, another factor that determines CBF is the relative degree of cerebrovascular reactivity to circulating gases (CVR). Changes in CO_2 CVR may be a key mechanism underlying ventilatory responses and acclimatization to high altitude (Ainslie et al., 2007; Lucas et al., 2011). Controversial results have been published regarding changes in CO_2 CVR following several days at high altitude, with unchanged (Ainslie and Burgess, 2008; Ainslie et al., 2007; Jansen et al., 1999) reduced (Lucas et al., 2011) or increased (Fan et al., 2010; Jensen et al., 1990) responses. These contradictory results are probably due to methodological issues (*e.g.* rebreathing *versus* steady state protocols, hypoxic *versus* hyperoxic gas mixtures) and differences in altitude exposure (e.g. preliminary acclimatization or not, measurement during *versus* after high altitude exposure).

The large majority of studies performed in this area have used transcranial Doppler ultrasound (TCD) measurements to assess middle cerebral arterial blood flow velocity (MCAv), rather than absolute measurements of CBF. Hence, most of the conclusions regarding hypoxia-induced changes in CBF rely on the assumption that the MCA diameter remains unchanged in hypoxia, despite recent results suggesting that this may not be true (Wilson et al., 2011). Limitations due to movements and changes in insonation angle are also an issue with TCD measurements, in particular for between-day comparisons. Absolute CBF can be measured with an arterial spin labeling (ASL) magnetic resonance imaging (MRI) method that magnetically tags blood water and measures its delivery to tissue capillaries, to obtain a global or regional measure of tissue perfusion in ml blood·100 g tissue^{-1}·min^{-1} (Aguirre and Detre, 2012). Only one group (Smith et al., 2012) has assessed cerebral perfusion changes with ASL following two days at high altitude and reported an increase in whole-brain CBF in hypoxia compared to normoxia.

In the present study, we used ASL measurements to clarify the regional changes in CBF and CVR induced by a prolonged stay at high altitude and the relative impact of reduced PaO_2 and $PaCO_2$ on cerebral hemodynamics. CBF and CVR were measured at sea level with TCD and ASL, on day 5 at 4,365 m of altitude with TCD, and on day 7 with ASL, 6 hours following return to sea level. Based on the current knowledge suggesting that in addition to the hypoxic vasodilator stimulus *per se* other mechanisms such as cerebral autoregulation, neuronal and endothelium-dependent pathways may influence CBF at altitude (Ainslie and Ogoh, 2010; Wilson et al., 2009), we hypothesized that CBF assessed by TCD would be increased on day 5 at 4,365 m and would remain elevated after return from high altitude when measured with ASL. This would confirm a contribution of mechanisms other than reduced PaO_2 to the altitude-induced CBF changes. We also hypothesized that reduced CO_2 CVR would be associated with high altitude acclimatization.

MATERIAL & METHODS

Subjects

Eleven healthy male subjects (28 ± 8 years old) were recruited to participate to this study and provided written informed consent. Participants were recreational climbers, taking no medication and having no history of cardiovascular, cerebrovascular and respiratory diseases. They were unacclimatized to high altitude (no night above 1,500 m or sojourn above 2,500 m of altitude over the past 3 months) and received no treatment to prevent acute mountain sickness. The study was approved by the local institutional review board and performed according to the Declaration of Helsinki (registration number: RCB2011-A00071-40, ClinicalTrials.gov ID: NCT01565603).

Experimental design

Before ascending to high altitude, subjects underwent i) a complete MRI examination including anatomical MR images as well as baseline CBF and CVR measurement using ASL and ii) a TCD exam including CBF and CVR evaluation in Grenoble (212 m). On day 1, subjects underwent helicopter transport to be dropped within 10 min at 4,350 m of altitude (ObservatoireVallot, Mont Blanc, Chamonix, France) where they stayed for 6 days. The TCD exam was repeated on day 5 of high-altitude acclimatization. On day 7, subjects were transported back to Grenoble and underwent a second and similar complete MR examination within 6 hours after returning to sea level. Because 11 subjects could not have been evaluated simultaneously during and immediately after the altitude stay, the experiment was performed over 2 weeks, a subgroup of 5 or 6 subjects being exposed to high altitude and investigated according to the same protocol during each week.

MRI examination

Before and after the altitude stay, subjects were examined using functional and anatomical MRI acquisitions at 3T (Philips Achieva TX scanner, Best, Netherlands). Acquisitions, performed with a 32-channel head-only receive array, included a pseudo-continuous ASL (pCASL) sequence (Aslan et al., 2010; Dai et al., 2008) during a block-design inhalation paradigm to measure CVR to CO_2 and basal CBF maps. Pseudo-continuous ASL acquisition parameters were: WET pre-saturation, 1650 ms label, 1525 ms post-label delay, multi-slice single-shot EPI readout (3x3x6 mm^3, 20 slices, TE 12 ms, sense-factor 2.5), TR of 4 s. A total of 180 control and tag images were acquired in 12 min. An ASL reference scan and a T_1 map were acquired for CBF quantification and a T_1 weighted morphological image was acquired as anatomical reference. Capnia was modulated during the pCASL acquisition in a 1/2/1-min paradigm (3 cycles, see figure 1) by alternating medical air and an air/CO_2 mixture (7% CO_2, 21% O_2, balance N_2) administered at 12 $l \cdot min^{-1}$ via a nonrebreathing mask with low-resistance check valves (Hudson RCI Ref 41060, Teleflex, NC, USA). This protocol is used as a matter of routine for clinical research within our Lab and typically induces an increase in end-tidal CO_2 partial pressure ($PetCO_2$) of about 10 mmHg. $PetCO_2$ was measured via nasal cannula using an MR-compatible capnometer (Maglife, Schiller medical), and recorded together with scanner triggers for synchronization in order to build a regressor representing the physiological response to hypercapnia for use in the data analysis (Figure 1). Breathing frequency, heart rate and arterial oxygen saturation (SpO_2) were also recorded during the exam. Physiologic data acquired during periods of medical air and air/CO_2 were averaged separately in the analysis ($\Delta PetCO_2$ = $PetCO_{2Hypercapnia}$ - $PetCO_{2Ambiant\ air}$).

Data were analyzed using Matlab (MathWorks Inc., Natick, MA, USA), the SPM8

software (SPM, Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/) and custom routines. Images were realigned after removing any systematic bias in realignment parameters between tag and control images. Frames exhibiting strong motion were marked for exclusion from the subsequent analysis. Structural images were segmented and all images were normalized to the template of the Montreal Neurological Institute (MNI) (Ashburner and Friston, 2005). ASL signal amplitude was scaled to express the difference between control and tag images in units of $ml \cdot 100g^{-1} \cdot min^{-1}$. The ASL signal is dependent on arterial blood T_1 (T_{1a}) and thus on hematocrit. Individual hematocrit values were measured before altitude only (47 ± 3% on average; NPT7, Radiometer, Copenhagen, Denmark). The hematocrit level was previously observed to increase by 3.7% on average in the same conditions of altitude and exposure duration (Robach et al., 2002). Therefore, in the absolute quantification of CBF we assumed T_{1a} to be 1602 ms prior to altitude exposure, corresponding to a mean hematocrit of 0.47, and T_{1a} equal 1554 ms after altitude, corresponding to a mean hematocrit of 0.51 (Gevers et al., 2012; Lu et al., 2004). Outliers in hypercapnia data were discarded and data were interpolated to the pCASL volume acquisition times, taking lag due to dead space in the sample line into account. Basal CBF was modeled with a regressor alternating between 0.5 and -0.5 for control and tag images respectively throughout the scan (Hernandez-Garcia et al., 2010; Mumford et al., 2006) (Figure 1). Hypercapnia-related perfusion increase (CVR) was modeled with a baseline-corrected capnia regressor (ctl/tag modulated for perfusion, unmodulated for BOLD) (Figure 1). CVR was expressed as percent change in perfusion per mmHg change in $PetCO_2$.

The T_1 weighted morphological images were segmented using SPM and for each scanning session a ROI was defined including all voxels with a grey-matter fraction of at least 90%. For the perfusion analyses, this ROI was subdivided into vascular territories. The vascular territories were defined as those of the left and right middle cerebral arteries (MCA) and in the anterior

(ACA) and posterior (PCA) cerebral artery territories (Figure 2). The CVR analysis was based on the same ROIs, further constrained to voxels in which significant basal perfusion was detected ($p<0.05$, false discovery rate) and excluding outliers in the CVR measurement (Thompson, 1985). ROI-average response amplitudes were computed for the two sessions before and after the altitude stay.

TCD exam

TCD measurements were performed by a trained operator using two different methods:

- MCAv at rest was assessed using a 5 to 1 MHz Transducer CX-50 (Philips, Eindhoven, Netherlands). The clinoid process of the sphenoid bone and the brain stem were initially identified. Color-coded sonography allowed recognizing the circle of Willis. The M1 segment of the right MCA was identified and manual angle correction was applied to measure mean right MCAv (in $cm \cdot s^{-1}$) by the inbuilt software. This device was used to have a better reliability for between-day comparisons of absolute TCD MCAv values at rest (Martin et al., 1995).

- A Doppler instrument operating at 2MHz (Waki^{e}, Atys Medical, Soucieu en Jarrest, France) was used to perform TCD measurements during the CVR protocol. This device could be used with a Doppler probe secured by a headband maintaining the same insonation position throughout the CVR protocol lasting for one hour. In all subjects, right middle cerebral artery was insonated through the transtemporal window at a depth of 50 to 60 mm. Mean right MCAv (in $cm.s^{-1}$) were then acquired over each heartbeat during the entire experiment. MCAv during the hypercapnic challenge was calculated as relative value, *i.e.* % change between the hypercapnic condition and the previous reference normoxic period (see below).

To assess TCD CVR, subjects inhaled gas mixtures with various inspiratory O_2 (FiO_2) and CO_2 ($FiCO_2$) fractions delivered by a modified Altitrainer 200® (SMTEC, Nyon, Switzerland) via

a face mask and were blinded for the gas mixture composition. FiO_2 and $FiCO_2$ were adjusted to reach the target values for $PetO_2$ and $PetCO_2$ according to the modified "Leiden proposal" (Teppema and Dahan, 2010). The protocol consisted of six consecutive 10-min phases. In phases 1, 3 and 5, target $PetO_2$ was 100 mmHg and $FiCO_2$ was 0 (poikilocapnic normoxia). In phases 2, 4 and 6, target $PetO_2$ was 55 mmHg (similar to the value observed at 4,350 m of altitude). Target $PetCO_2$ in phases 2, 4 and 6 was respectively 0, 5 and 12 mmHg above the value measured at the end of phase 1. These three levels thus represent isocapnic hypoxia, hypercapnic hypoxia +5 mmHg and hypercapnic hypoxia +12 mmHg, respectively. $PetO_2$ and $PetCO_2$ were continuously measured using an automated metabolic cart (Quark b2, Cosmed, Rome, Italy). MCAv was acquired continuously during the entire protocol and mean MCAv was averaged over the last minute of each period. Measurements corresponding to isocapnic hypoxia, hypercapnic hypoxia + 5 and + 12 mmHg phases were expressed as a percentage of the respective previous poikilocapnic normoxic periods and used to calculate the TCD CVR, *i.e.* the slope of the linear regression between relative MCAv values and $PetCO_2$.

Clinical examination

Clinical examination included measurements of heart rate and non-invasive blood pressure (Dinamap, GE Medical Systems Inc., Milwaukee, WI) under resting conditions. SpO_2 was measured using finger-pulse oxymetry (Biox 3740 Pulse Oximeter, Ohmeda, Louisville, CO) after 30 s of signal stabilization. Every morning at high altitude, subjects were also asked to complete self-reported questionnaires for acute mountain sickness (AMS) evaluation according to the Lake Louise Score (LLS, 5 items) (Roach et al., 1993) and the cerebral subscore of the Environmental Symptom Questionnaire (ESQ-III AMS-C, 11 items) (Sampson et al., 1983). The presence of AMS was defined as LLS > 3 and AMS-C $\geq$ 0.70.

Statistical analysis

Statistical analyses were performed using SPSSv18 on resting perfusion and CVR values obtained by ASL MRI and TCD. An ANOVA with repeated measures was first conducted to rule out a potential main effect of the hemispheric SIDE in the ASL MCA values. In absence of SIDE effect, right and left ASL MCA values were averaged. ANOVAs were further conducted to identify main effects of factor ROI (ACA, MCA, PCA), factor TIME (before and after altitude stay), and an interaction ROIxTIME. Pairwise comparisons were conducted using Wilcoxon rank tests. Correlations analyses were assessed using Spearman coefficient. All data are expressed as means ± standard deviation (SD). An omnibus significance threshold of $p<0.05$ was used.

RESULTS

Physiological and clinical data

Nine subjects presented AMS according the LLS score (peak LLS score during the altitude stay: 5.7 ± 2.5 points, on average), three of them had severe AMS with LLS > 6. AMS-C score indicated AMS in 6 subjects (peak AMS-C score during the altitude stay: 1.03 ± 0.87 points, on average).

Physiological data measured prior to the altitude exposure, on day 5 at altitude and after the altitude stay are shown in Table 1. SpO_2 was significantly lower on day 5 at altitude compared to before and after the altitude stay. $PetCO_2$ was significantly reduced on day 5 and after the altitude stay compared to before. Breathing frequency, heart rate and arterial blood pressure had increased significantly by day 5 compared to before and after the altitude stay.

No adverse reaction was detected in subjects during the hypercapnic stimuli. During the ASL CVR assessment, the hypercapnic gas mixture increased $PetCO_2$ similarly before (+10.2 ± 3.6 mmHg compared to breathing air) and after (+11.0 ± 3.6 mmHg) the altitude stay. This increase in $PetCO_2$ was also similar to the maximum hypercapnic stimulus imposed by the TCD CVR protocol (*i.e.* +12 mmHg) .

MRI and TCD data

In the MRI analysis, datasets from 3 subjects were excluded due to excessive head motion (n=1), inappropriate hypercapnic stimulus (n=1) and a technical problem (n=1), leaving 9 subjects for the ASL CBF study, and 8 subjects for the ASL CVR study. In TCD, all TCD MCAv datasets were available at rest, and one TCD CVR dataset was missing due to a technical problem, leaving 10 subjects to study TCD CVR.

Cerebral perfusion

ASL MRI. The delay between the helicopter descent and the MRI exam after the altitude stay was 6 h 30 min ± 2 h 10 min on average. Because no effect of the hemispheric side was detected, right and left MCA values were averaged. The ANOVA showed main effects of TIME ($p=0.02$) and ROI ($p<0.01$), without interaction TIMExROI. The main effect of TIME was due to significant ASL CBF increase in MCA and ACA territories (Figure 3) after altitude exposure. Increased CBF was observed in all subjects in the MCA territory (Figure 4a). Group-average ASL CBF increased by 22.0 ± 24.1 % in the MCA territory, by 20.5 ± 20.3 % in the ACA territory, and by 14.8 ± 18.4 % in the PCA territory. The main effect of ROI was due to higher CBF values in ACA compared to MCA and PCA (Figure 3).

TCD. TCD MCAv increased significantly by 20.5 ± 15.5 % on day 5 at 4,350 m (Figure 4b). An increase in TCD MCAv was observed in all subjects but one.

No correlation between altitude-induced changes in TCD MCAv and ASL CBF was detected. No correlation was observed between AMS scores and altitude-induced changes in TCD MCAv or ASL CBF.

Cerebrovascular reactivity

ASL MRI. The ANOVA for ASL CVR showed a main effect of TIME ($p=0.01$) and a trend for ROI ($p=0.06$) without interaction TIMExROI. The main effect of TIME was due to significant ASL CVR decrease in all territories (Figure 5). This result was observed in all subjects in the MCA territory (Figure 6a). To note, most of the variance of the ROI factor was due to a lower

reactivity in the MCA compared to ACA and PCA territories. No significant correlation was detected between altitude-induced ASL CBF and ASL CVR changes (Spearman ρ=-0.52, p=0.18).

TCD. TCD CVR was not significantly reduced (p=0.10) from before the altitude stay to day 5 at 4,350 m (5.2 ± 2.0 and 3.9 ± 1.2 %·mmHg^{-1}, respectively; Figure 6b). A negative correlation between altitude-induced TCD CVR and TCD MCAv changes was detected (Spearman ρ = 0.64; p<0.05).

Significant correlation between changes in TCD CVR and changes in ASL CVR was detected (Spearman ρ = 0.86; p<0.01). No correlation was observed between AMS scores during the altitude stay and changes in ASL or TCD CVR.

DISCUSSION

MCAv measured by TCD at 4,350 m on day 5 suggested an increase in CBF at altitude, in agreement with previous findings. Importantly, quantitative CBF measurements using ASL MRI showed that this perfusion increase persisted immediately after descent to sea level, under normoxic conditions. Cerebrovascular reactivity to CO_2 measured by ASL concomitantly decreased in all vascular territories. CO_2 CVR measured by TCD did not change significantly, although slightly lower values were observed at altitude compared to before altitude. Despite regional differences in amplitude, ASL changes were similar across vascular territories. No relationship was found between changes in cerebral hemodynamics and the severity of AMS during the altitude stay.

To our knowledge, this is the first study quantifying CBF and CVR before and immediately after prolonged high-altitude exposure using ASL. The majority of previous studies having investigated cerebral hemodynamic changes at high altitude used TCD, mostly because this method is relatively easy to carry and use at altitude. TCD is however a manipulator-dependent technique with poor between-day reproducibility (McMahon et al., 2007). Moreover, while this technique relies on constant MCA diameter, recent data suggest that MCA diameter may be increased at high altitude (Wilson et al., 2011). Because 2D transcranial color-coded sonography enables precise identification of the M1 segment of the right MCA and correction for the angle of insonation when determining blood flow velocities (Martin et al., 1995), this technique was used in the present study to measure basal MCAv before and during the altitude stay. Compared to TCD, ASL has the advantage to measure perfusion in absolute units and its resolution and spatial coverage allows the quantification of CBF and CVR regionally. Moreover, ASL reflects the

microcirculation in the tissue whereas TCD is a direct measurement of the velocity in the macro-circulation, usually in the MCA. ASL is not easily performed at high altitude, but the present results demonstrate its usefulness to study CBF immediately after altitude exposure to better characterize changes in cerebral hemodynamics associated with prolonged hypoxic exposure.

Only one group has measured CBF by ASL within the context of AMS and reported increased CBF after 30 min of normobaric hypoxia (Dyer et al., 2008) or 2 days at 3,800 m (Smith et al., 2012), this increase being similar in subjects with or without AMS. Such hypoxic exposures are however different from more prolonged and severe hypoxia as encountered during high-altitude stay. In the present study, ASL demonstrated a significant and widespread increase in CBF after 6 days at high altitude that was larger compared to acute normobaric hypoxic exposure (Dyer et al., 2008) but similar to the CBF increase following 2 days at lower altitude (Smith et al., 2012).

Various mechanisms can cause a change in perfusion during or immediately after a high-altitude stay. Hypoxia-induced hyperventilation reduces arterial CO_2 and therefore potentially induces cerebral vasoconstriction and reduced CBF. The large effect of hyperventilation on arterial CO_2 is shown in the present study by the reduced $PetCO_2$ values on day 5 and immediately after the altitude stay (Table 1). After several days at altitude however, the initial increase in cerebrospinal pH and consequently its vasoconstrictive effect is thought to be partly compensated (Brugniaux et al., 2007). Although we did not measure blood or cerebrospinal pH, the present results indicate that despite the potential effect of still alkaline pH, MCAv on day 5 at altitude was clearly elevated compared to sea level. After returning to sea level on day 7, subjects were still hypocapnic, although slightly less than on day 5 at altitude, and CBF remained elevated. In order to assess whether the enhanced CBF on day 7 at sea level was the consequence of a slightly increased arterial CO_2 compared to the acido-basic balance reached at altitude (*i.e.*

compared to the $PetCO_2$ observed on day 5 at altitude), we can extrapolate the CBF that would have been obtained on day 7 at the same level of capnia as was observed at altitude (on day 5), based on the measured ASL CVR. The correction for the slight difference in capnia between the two conditions only accounts for about 30% of the perfusion increase observed between the MRI exams before and after the altitude stay (results not shown). Hence, most of the increase in CBF measured immediately after altitude by ASL compared to before altitude cannot be explained by slightly reduced ventilation and reduced hypocapnia compared to the levels obtained after several days at altitude.

A significant reduction in CO_2 CVR measured by ASL immediately after the altitude stay and a similar tendency measured by TCD at altitude suggest that vasoreactivity was impaired as a consequence of altitude exposure. Similar results were recently reported by Lucas et al. (2011) using TCD and a steady-state hypercapnic protocol after several days at 5050 m. Lower CO_2 CVR has been reported in the hypocapnic compared to the hypercapnic range (Ide et al., 2003). Hence, the reduction in CO_2 CVR associated with altitude exposure in the present study could be a consequence of the reduction in baseline arterial CO_2 (Table 1). CVR is dependent on arterial CO_2 through the relationship between arterial CO_2 and pH. As stated above, after several days at high altitude, this relationship is modified and consequently arterial CO_2 remains reduced while pH progressively decreases toward normal values (Brugniaux et al., 2007). Hence, although we cannot exclude a potential effect of still alkaline pH on CO_2 CVR, the CVR reduction observed in the present study after several days at high altitude is likely due to additional mechanisms. Such a reduction in CO_2 CVR may underlie the enhanced hypercapnic ventilatory response observed at high altitude which is a critical aspect of ventilatory acclimatization (Lucas et al., 2011; Xie et al., 2006). Reduced CO_2 CVR at high altitude can affect the ventilatory response during various situations such as sleep and exercise, possibly promoting breathing instability and central sleep

apnea for instance (Ainslie and Duffin, 2009). A correlation was detected between the increase in basal perfusion and the reduction in CO_2 CVR on day 5 with TCD but not after the altitude stay with ASL. Hence, while the mechanisms underlying alterations in cerebrovascular reactivity at altitude remain to be clarified (Ainslie and Ogoh, 2010), the inconsistent correlation between perfusion and CVR changes suggests that both phenomena may not share similar underlying mechanisms and that changes in CBF associated with altitude may be due to other factors than alterations in CO_2 vasoreactivity.

It has also been shown that a significant (albeit relatively small, 3.7% on average) hematocrit increase is observed following a similar altitude stay (Robach et al., 2002). This change in hematocrit could have an effect on the ASL signal (Gevers et al., 2012; Silvennoinen et al., 2003), since a larger hematocrit leads to a decrease of the longitudinal relaxation time of the arterial blood, reducing the perfusion signal measured by ASL. To prevent this from affecting our measurements, we calculated the CBF after the altitude stay by taking into account the average increase in hematocrit observed by Robach et al. (2002) under similar conditions. We also acquired a tissue T_1 map, which was used in the CBF quantification. We did not observe any significant difference in grey matter tissue T_1 before and after altitude, suggesting that any blood relaxation time changes were not sufficient to affect overall tissue relaxation times, likely due to both the small blood volume fraction and the small amplitude of blood T_1 changes. Therefore, the changes in CBF and CVR measured by ASL were likely not the consequence of the specific effect of changes in hematocrit level on the ASL signal. As suggested by Møller et al. (2002), changes in CBF after prolonged high altitude exposure are the result of two opposite forces, one acting to increase flow because of the persistent low arterial oxygen tension, and the other acting to decrease flow as a consequence of the increased hematocrit. The increase in MCAv and ASL CBF measured in the present study indicates that the mechanisms increasing CBF following

prolonged hypoxic exposure clearly outweigh the opposing effect of the slightly increased hematocrit on blood velocity.

A significant increase in arterial blood pressure was observed on day 5 at 4,350 m, while similar values were observed before and after the altitude stay. Some studies have shown that cerebral autoregulation (*i.e.* the rapid response of the cerebral vessels to changes in mean arterial pressure in order to keep CBF within physiologically tolerable levels) is impaired at altitude (Ainslie et al., 2007; Jansen et al., 2000), especially in the presence of AMS (Bailey et al., 2009; Van Osta et al., 2005), and therefore some changes in blood pressure as observed in the present study may affect CBF. Although we cannot rule out this hypothesis which requires further investigations, the fact that CBF remained enhanced immediately after altitude while blood pressure and heart rate had returned to values similar to before the altitude stay suggests that changes in central hemodynamics and cerebral autoregulation may not be the main reasons for altitude-induced changes in cerebral perfusion. Furthermore, changes in cerebral autoregulation are not thought to be a critical factor underlying changes in CBF at altitude under resting conditions (Brugniaux et al., 2007).

Angiogenesis can occur after several days or weeks at altitude (Xu and LaManna, 2006) and could influence the CBF measured by ASL post altitude in our protocol. This phenomenon is probably still at its very early stage at the end of the altitude stay in the present study. In order to assess the contribution of angiogenesis to the increase in CBF observed here, imaging absolute CBV, vessel size and vessel density could provide additional information (Jensen et al., 2006; Troprès et al., 2001). Angiogenesis may also be characterized *in vivo* by dosing blood biomarkers such as VEGF and its soluble receptors (Batchelor et al., 2007), though this approach is not specific to the brain.

We hypothesized that other mechanisms than the reduction of arterial oxygenation underlie

the increase in CBF at high altitude and we speculated that the increased CBF at altitude (as suggested by the TCD measurement on day 5 at altitude) would persist after the subjects came back to sea level, *i.e.* when the hypoxic stimulus would not be present anymore. In accordance with this hypothesis, the ASL measurements showed that CBF was increased after the altitude stay to a similar extent than TCD MCAv at altitude. This confirms that, in addition to the hypoxic vasodilator stimulus *per se*, additional mechanisms such as angiogenesis, stimulation of neuronal pathways or release of circulating and endothelium-derived vasoactive stimuli (Ainslie and Ogoh, 2010) may significantly contribute to the larger CBF observed at altitude.

While the increase in CBF serves to maintain oxygen delivery to the brain under hypoxic conditions, its role regarding altitude acclimatization remains debated. In the present study and in accordance with recent results (Dyer et al., 2008; Smith et al., 2012; Subudhi et al., 2011), no relationship was observed between the severity of AMS symptoms at altitude and changes in CBF. Similarly, no correlation was observed between changes in CO_2 CVR and AMS symptoms. Hence, even though it has been shown by our group and others that ventilatory and cerebrovascular responses to CO_2 are critical for high altitude acclimatization (Jansen et al., 1999; Lucas et al., 2011; Nespoulet et al., 2012), we could not confirm a link between cerebral hemodynamics and the development of AMS in the present study. Further studies are needed to investigate the potential impact of changes in cerebral hemodynamics at high altitude on sleep or exercise responses for instance.

One limitation of the present study is the small sample size, due to the complexity of the logistics of an experimental protocol at high altitude combined with MRI investigations. However, the observed changes in perfusion and CVR as assessed by MRI between pre- and post-altitude sessions were clear already with this sample size and we believe that the present study provides data contributing significantly to our understanding of hemodynamic changes

associated with prolonged hypoxic exposure. Also, the slightly different protocols used to assess CO_2 vasoreactivity with ASL and TCD (in particular normoxic conditions for ASL and hypoxic conditions for TCD measurements) and difference in test scheduling (TCD CVR was measured on day 5 at altitude while ASL CVR was measured on day 7 at sea level) may affect the comparisons of CVR obtained by TCD and ASL. Because the aim of this study was to investigate changes in cerebral hemodynamics at altitude and to compare them to measurements at sea level immediately after the altitude stay, TCD measurements were performed on day 5 (days 6 and 7 at altitude were impossible due to logistical considerations) rather than on day 7 when ASL investigations were conducted. However, since altitude-induced CVR changes obtained with both techniques were significantly correlated, we believe these results indicate a consistent reduction in CO_2 vasoreactivity.

This study is the first to measure cerebral perfusion and vasoreactivity with ASL after a prolonged stay at high altitude. We demonstrated that prolonged exposure to high altitude significantly increases CBF and decreases vasoreactivity to CO_2 measured in normoxia several hours following return to sea level. Hence, these changes in cerebral hemodynamics after several days at high altitude are not only the consequences of the vasodilating effect of hypoxia but probably involve other mechanisms such as changes in cerebral autoregulation and angiogenesis. Further investigations are needed to explore these mechanisms and to determine the role of cerebral hemodynamic changes for acclimatization to high altitude.

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Tables and Figures

Table 1. Physiological parameters. Physiological parameters (Mean ± SD) before the altitude stay, on day 5 at 4,350 m, and after the altitude stay.

	SpO_2 (%)	$PetCO_2$ (mmHg)	Breathing Frequency (min^{-1})	Heart Rate (min^{-1})	Mean arterial pressure (mmHg)
Before altitude (212 m)	97.2±0.5	40.9±4.9	13.8±2.7	61.2±7.7	104.4±6.1
Day 5 at altitude (4,350 m)	87.6±1.3*,$	30.5±3.1*	19.2±2.7*,$	77.9±16.1*,$	115.6±6.7*,$
After altitude (212 m)	97.8±0.7	33.2±4.0*	14.9±2.9	63.1±8.2	105.8±8.1

Figure 1. Vasoreactivity ASL design matrix for one representative subject. The first regressor represents the average baseline MR signal. The second regressor represents the baseline ASL signal of alternating sign in control and tag images. The third regressor describes the perfusion changes during 1 min/2 min/1 min paradigm alternating air and air enriched in CO_2. The fourth regressor represents the BOLD signal changes during the vasoreactivity experiment. The last 2 regressors are calculated using the end-tidal CO_2 measured during the experiment.

Figure 2. MRI images of cerebral blood flow and ROIs. a) Cerebral blood flow map of one subject for 6 slices from the cerebellum to the superior parietal and frontal regions. The color bar indicates the quantitative blood flow measured by ASL in $ml \cdot 100g^{-1} \cdot min^{-1}$. b) Superposition of the normalized anatomical image of the same subject with vascular territories (Blue: middle cerebral artery (MCA), Green: posterior cerebral artery (PCA), Red: anterior cerebral artery (ACA)).

Figure 3. Cerebral perfusion before and after the altitude stay in vascular territories measured with ASL. (* $p<0.05$).

Figure 4. Cerebral perfusion in the middle cerebral artery (MCA) territory. a) Individual and group mean cerebral perfusion measured by ASL in $ml.100g^{-1}.min^{-1}$ in the grey matter of the MCA territory before and after the altitude stay increased in all subjects (* $p<0.05$). b) Individual and group mean blood velocity measured by 2D TCD in $cm.s^{-1}$ in the right MCA before the altitude stay and on day 5 at 4,350 m increased in 10 subjects out of 11 (* $p<0.05$).

Figure 5. Cerebrovascular reactivity (CVR) before and after the altitude stay in vascular territories measured by ASL. The mean decrease of CVR in the middle cerebral artery (MCA) territory was -29.5 ± 19.8 %, -26.9 ± 24.1 % in the anterior (ACA) territory, and -23.8 ± 23.2 % in the posterior (PCA) territory (* $p<0.05$).

Figure 6. Cerebrovascular reactivity (CVR) in middle cerebral artery (MCA) territory. a) Individual and group mean CVR measured by ASL in the grey matter of the MCA territory before and after the altitude stay was decreased in 8 subjects out of 9. b) Individual and group mean

CVR measured by TCD in the right MCA before the altitude stay and on day 5 at 4,350 m was decreased in 7 subjects out of 10, but this change did not reach significance at the group level.

Figure1

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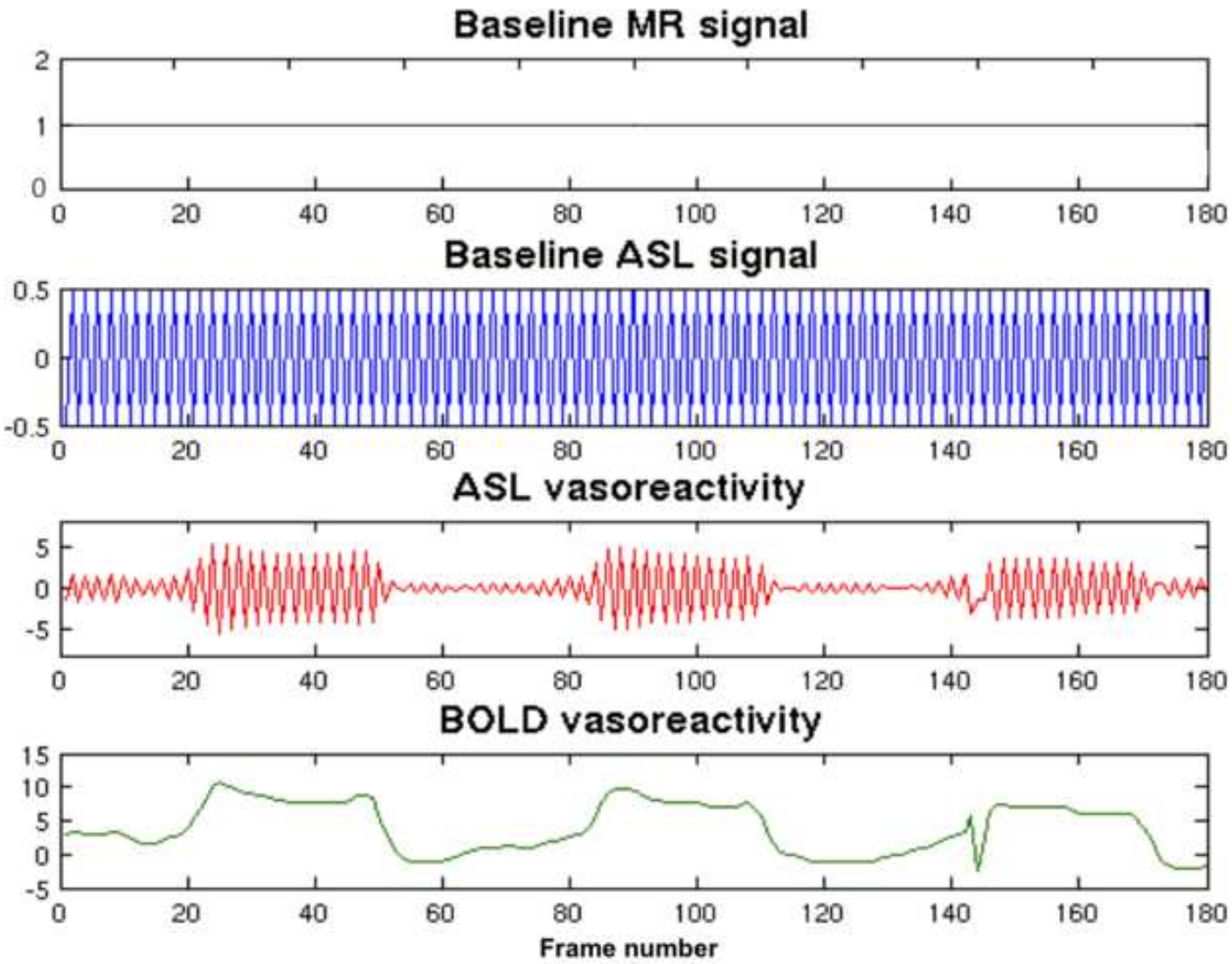


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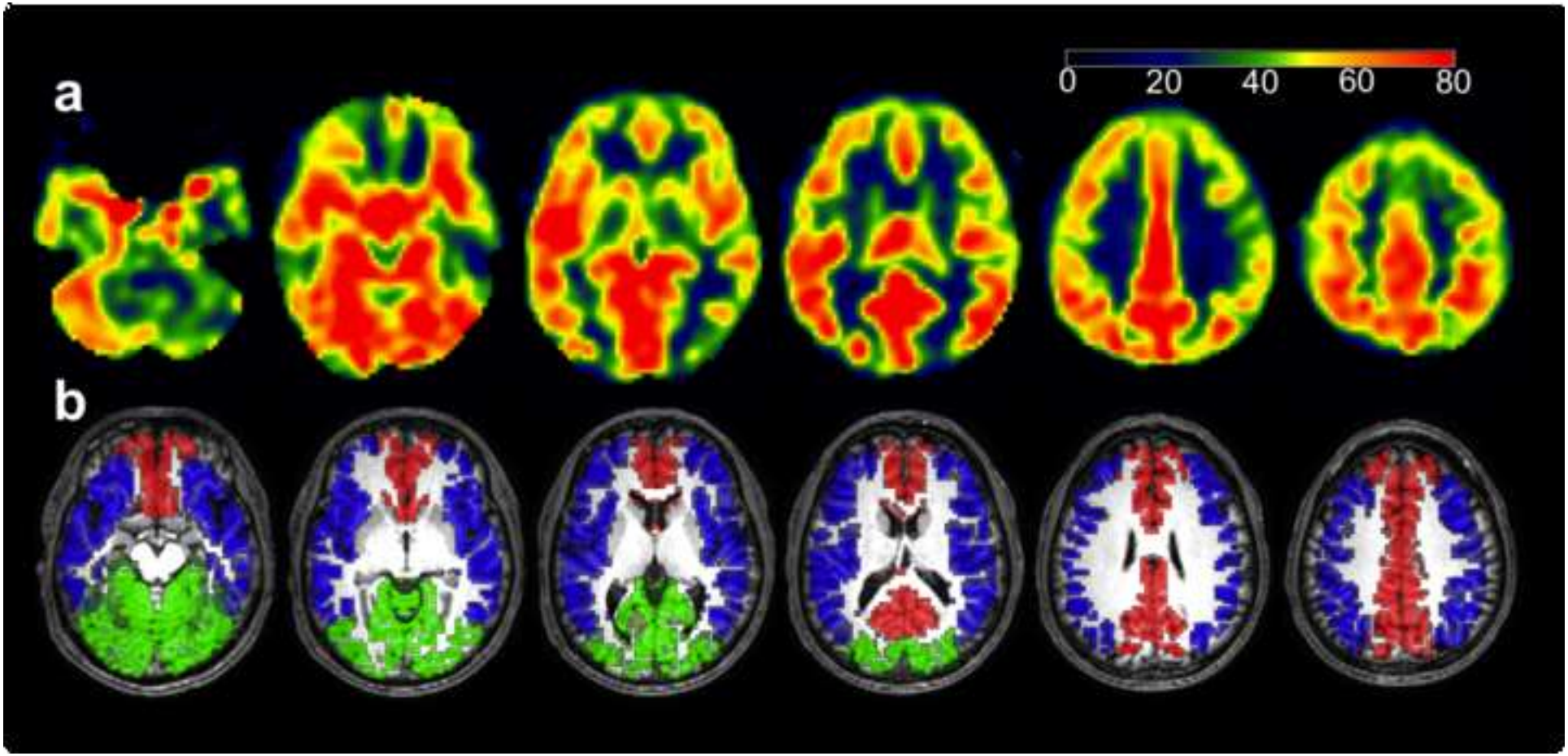


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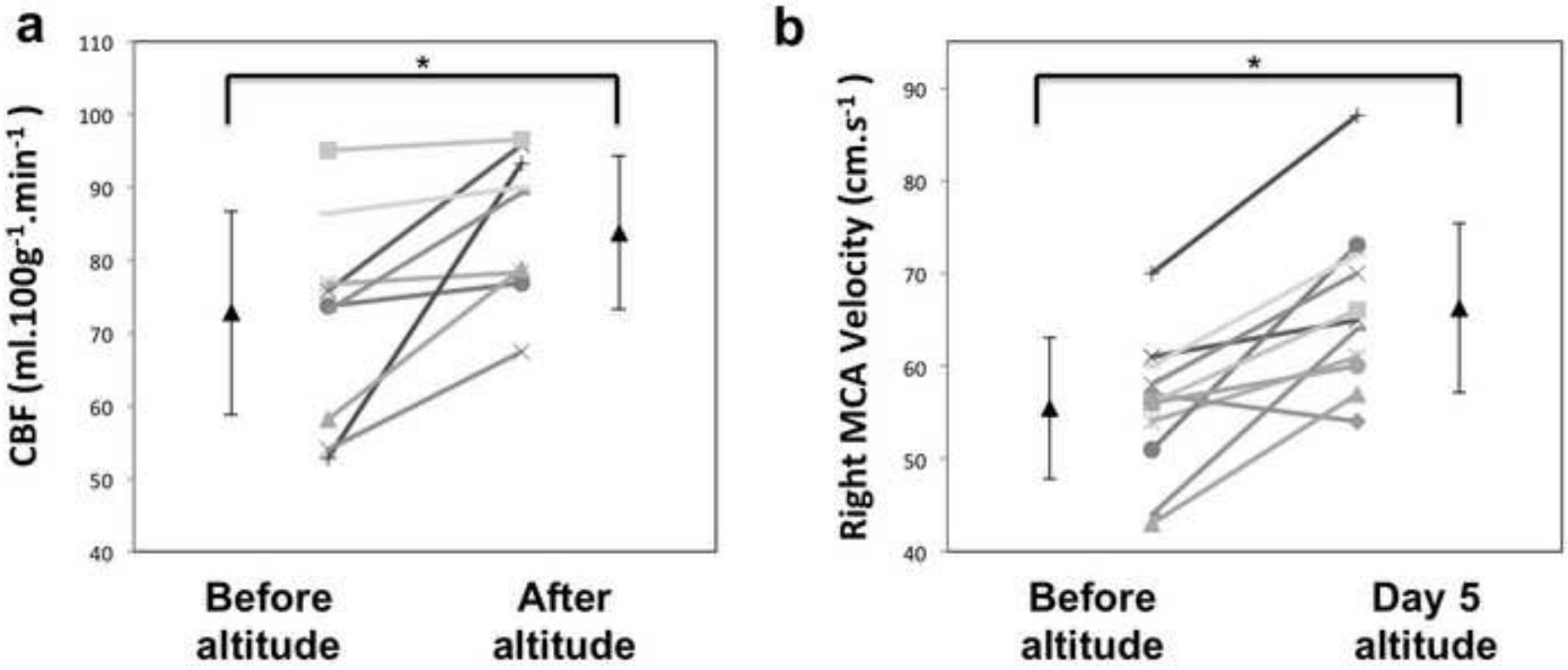


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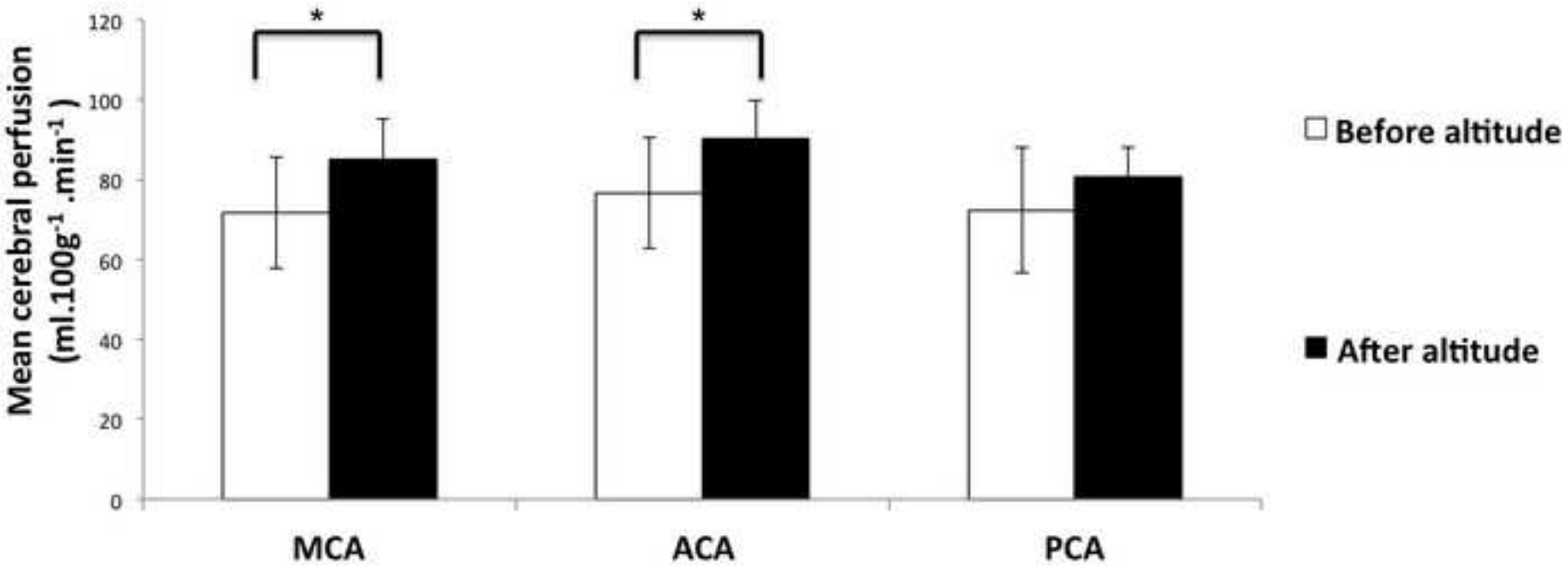


Figure5

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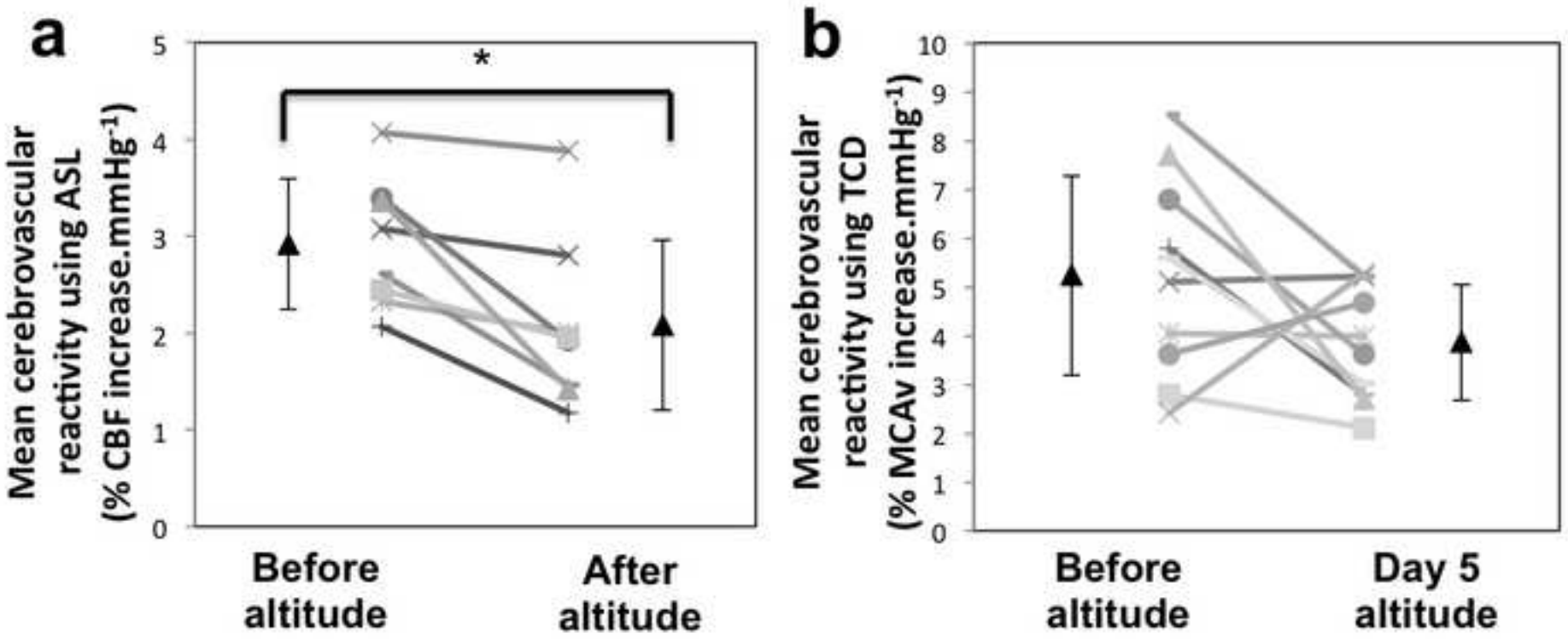


Figure6

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