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Influence of high altitude on cerebral blood flow and fuel utilization during exercise and recovery

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Key points

- This study assessed the dynamic response of global cerebral blood flow (CBF) and cerebral fuel utilization during and following incremental supine exercise to exhaustion.
- Global CBF increased more during exercise and recovery at high altitude (HA) compared with sea level (SL) such that cerebral oxygen delivery (CD_{O_2}) was maintained.
- The increase in cerebral metabolic rate of oxygen during maximal exercise at HA was half the increase observed at SL.
- Arterial lactate production during exercise at the same absolute intensities was greater at HA compared with SL, but reduced at the same relative intensities.
- Cerebral carbohydrate uptake (lactate and glucose) is greater than oxygen uptake at HA compared with SL, indicating a shift towards an increased non-oxidative metabolic utilization.
- These results suggest that CBF increases to maintain CD_{O_2} during exercise at HA while changes in arterial lactate concentration and exercise intensity augment the oxidative and non-oxidative pathways to cerebral metabolism at HA.

Abstract We examined the hypotheses that: (1) during incremental exercise and recovery following 4–6 days at high altitude (HA) global cerebral blood flow (gCBF) increases to preserve cerebral oxygen delivery (CD_{O_2}) in excess of that required by an increasing cerebral metabolic rate of oxygen (CMR_{O_2}); (2) the trans-cerebral exchange of oxygen *vs.* carbohydrates (OCI; carbohydrates = glucose + ½lactate) would be similar during exercise and recovery at HA and sea level (SL). Global CBF, intra-cranial arterial blood velocities, extra-cranial blood flows, and arterial–jugular venous substrate differences were measured during progressive steady-state exercise (20, 40, 60, 80, 100% maximum workload (W_{max})) and through 30 min of recovery. Measurements ($n = 8$) were made at SL and following partial acclimatization to 5050 m. At HA, absolute W_{max} was reduced by ∼50%. During submaximal exercise workloads (20–60% W_{max}), despite an elevated absolute gCBF (∼20%, $P < 0.05$) the relative increases in gCBF were not different at HA and SL. In contrast, gCBF was elevated at HA compared with SL during 80 and 100% W_{max} and recovery. Notwithstanding a maintained CD_{O_2} and elevated absolute CMR_{O_2} at HA compared with SL, the relative increase in CMR_{O_2} was similar during 20–80% W_{max} but half that of the SL response (i.e. 17 *vs.* 27%; $P < 0.05$ *vs.* SL) at 100% W_{max}. The OCI was reduced at HA compared with SL during 20, 40, and 60% W_{max} but comparable at 80 and 100% W_{max}. At HA, OCI returned almost immediately to baseline values during recovery, whereas at SL it remained

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below baseline. In conclusion, the elevations in gCBF during exercise and recovery at HA serve to maintain CD_{O_2}. Despite adequate CD_{O_2} at HA the brain appears to increase non-oxidative metabolism during exercise and recovery.

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Abbreviations C_{a-v,O_2}, arterial–venous oxygen content differences ; C_{a,O_2}, arterial oxygen content; CD_{Glu}, cerebral glucose delivery; CD_{Lac}, cerebral lactate delivery; CD_{O_2}, cerebral oxygen delivery; CMR_{Glu}, cerebral metabolic rate of glucose; CMR_{Lac}, cerebral metabolic rate of lactate; CMR_{O_2}, cerebral metabolic rate of oxygen; C_{v,O_2}, venous oxygen content; $CVRi_{gCBF}$, cerebrovascular resistance; $CVCi_{gCBF}$, cerebrovascular conductance; F_b, breathing frequency; gCBF, global cerebral blood flow; Glu_{a-v}, cerebral arterial–venous glucose differences; HR, heart rate; ICA, internal carotid artery; Lac_{a-v}, arterial–venous lactate differences; MAP, mean arterial pressure; MCA(v), middle cerebral artery (velocity); O_2EF, relative fraction of oxygen content; OCI, oxygen–carbohydrate differences; OGI, oxygen glucose index; PCA(v), posterior cerebral artery (velocity); P_{a,O_2}, partial pressure of arterial oxygen; P_{a,CO_2}, partial pressure of arterial carbon dioxide; P_{CO_2}, partial pressure of carbon dioxide; P_{ET,CO_2}, partial pressure of end-tidal carbon dioxide; P_{ET,O_2}, partial pressure of end-tidal oxygen; P_{O_2}, partial pressure of oxygen; Q_{ICA}, internal carotid artery blood flow; Q_{VA}, vertebral artery blood flow; S_{O_2}, oxygen saturation; VA, vertebral artery; $\dot{V}_E$, minute ventilation; W_{max}, maximum achieved workload.

Introduction

Exposure to high altitude (HA) results in a reduced partial pressure of arterial oxygen (P_{aO_2}) that stimulates hyperventilation and reduces the partial pressure of arterial carbon dioxide (P_{aCO_2}). The blood vessels of the brain dilate in response to hypoxia and constrict during hypocapnia; thus, high altitude exposes the brain to competing vasoactive stimuli, the balance of which is a primary determinant for resting global cerebral blood flow (gCBF). Upon arrival at HA (>3500 m) there is an initial increase in gCBF of 20–60% – depending on the severity of hypoxia – that acts to offset the impact of the reductions in arterial oxygen content (C_{a,O_2}) to maintain cerebral oxygen delivery (CD_{O_2}; Ainslie & Subudhi, 2014). As acclimatization proceeds, increased ventilation increases P_{a,O_2} and decreases in P_{a,CO_2} act to return gCBF towards SL values (Severinghaus *et al.* 1966; Willie *et al.* 2013; Ainslie & Subudhi, 2014). Exercise too is a potent stimulus of the cerebrovasculature, producing gCBF changes that are a function of both blood gases and neuronal metabolism. However, mechanisms of CBF regulation during exercise at HA have been subject to limited study.

Imray *et al.* (2005) reported that after acute HA (5050 m) exposure (<1–2 days), middle cerebral artery velocity (MCAv) during maximal exercise was decreased compared to rest. In contrast, Huang *et al.* (1991) reported that following 18 days at 4000 m, there is no change in blood flow velocity in the internal carotid artery (ICA) during incremental exercise compared to rest. Different severities of hypoxia, different acclimatization periods, and different exercise protocols (percentage maximum work rate compared with a constant work rate at SL and HA) may contribute to these conflicting findings. In addition, the absence of concomitant robust measures of cerebral substrate delivery, metabolism and regional blood flow distribution at each exercise intensity hinders mechanistic interpretation.

Only one study has assessed the roles of arterial blood gases and cerebral metabolic rates on gCBF regulation during exercise following partial acclimatization to HA. Moller *et al.* (2002) used the Kety–Schmidt technique to measure gCBF, cerebral metabolic rates ($CMR_{O_2/Glu/Lac}$), and oxidation index of glucose and carbohydrates (OGI and OCI) during exercise (100 W), following 5 weeks at HA (5260 m), and again following return to SL. The authors observed no influence of altitude or exercise on any of these variables. Two major caveats of this study hinder interpretation. (1) Because gCBF returns to SL values as the acclimatization period is extended, this may explain the lack of a cerebral metabolic response during exercise and in response to HA; (2) Most likely because of the need for a prolonged steady-state period (∼10 min; Kety, 1945) when using the Kety–Schmidt technique, only one exercise workload (100 W) was used to assess the cerebral metabolic response to exercise at HA. A problem with this approach is that the absolute workload of 100 W would be a near-maximal intensity at high altitudes (>5000 m) in contrast to a submaximal intensity at SL (Green *et al.* 1989). Maximal intensity exercise at HA is expected to elicit either a return to baseline CBF values (Imray *et al.* 2005) or plateau ((Siebenmann *et al.* 2013). In contrast, at SL a (submaximal) workload of 100 W would elicit a ∼15–25% increase in CBF (Moraine *et al.* 1993; Imray *et al.* 2005; Subudhi *et al.* 2011; Smith *et al.* 2012); Therefore, the differential MCAv responses during incremental exercise of differing intensities at SL and HA highlights the need to make comparisons over a range of workloads.

Therefore, we wished to examine how early acclimatization to HA affects regional and global cerebral haemodynamics, cerebral metabolism and substrate delivery during incremental exercise. We hypothesized that (1) during incremental exercise and recovery following 4–6 days at 5050 m increases in gCBF will preserve delivery of oxygen (CD_{O_2}) in excess of that required by an increasing cerebral metabolic rate of oxygen (CMR_{O_2}), and (2) because of the expected elevations in gCBF early acclimatization to HA results in the trans-cerebral exchange of oxygen *vs.* carbohydrates (OCI; carbohydrates = glucose + ½lactate) which would be similar during exercise and recovery at HA and sea level (SL).

Methods

Participants

A total of 11 subjects volunteered for the study providing informed written consent. Two subjects were unable to complete the HA trial due to medical emergency evacuation prior to any of the HA testing (unrelated to any experiments). We were unable to obtain adequate blood flow measures in another subject at both SL and HA; therefore, 8 subjects were used throughout our analysis unless otherwise noted. None of the subjects were smokers, and all subjects underwent pulmonary function screening, maximal exercise stress testing and a polysomnography examination to ensure that they were free from any cardiovascular, cerebrovascular and respiratory disorders. Subjects avoided exercise, caffeine and alcoholic beverages for 12 h and fasted for 4 h prior to each session. This study was part of a research expedition conducted in April–June in 2012. As such, participants took part in a number of studies conducted during the 3 weeks at the Ev-K2-CNR Pyramid Laboratory. The experimental question addressed in this paper was *a priori* driven and the data included herein will not be duplicated in future reports. All testing was approved by the Clinical Research Ethical Review Board of the University of British Columbia and the Nepal Health Medical Research Council. All experiments conformed with the standards set forth by the declaration of Helsinki.

Study design

All variables and measurements were obtained at SL (SL: 350 m, barometric pressure (P_b) 715 ± 15 mmHg) and following 4–6 days at the Ev-K2-CNR Pyramid Laboratory, Khumbu Valley, Nepal (HA: 5050 m, $P_b = 413 \pm 4$ mmHg). Subjects spent 7 days in Kathmandu (1338 m) acclimatizing before flying to Lukla (2840 m) and trekking over 9 days (rest days: Namche Bazaar, 3440 m; Pengbouche, 3995 m; Pheriche, 4240 m). During ascent participants were given low-dose acetazolamide (125 mg, oral) twice a day to help prevent acute mountain sickness (Richalet *et al.* 2005; Basnyat *et al.* 2006). Acetazolamide was discontinued on day 8 of the trek at Pheriche; Approximately 24 h (Richalet *et al.* 2005) prior to subjects HA maximal exercise test. Subjects were familiarized with all measurements prior to beginning the study. Each subject performed an incremental maximal exercise test while pedaling on a light-weight portable supine cycle ergometer prior to both the SL and HA sessions. The maximum achieved workload (W_{max}) was recorded in order to calculate the relative workloads for each altitude. Data collection was performed within a minimum of 24 h following each maximal exercise test.

Protocol

Following instrumentation of cardio-respiratory devices, internal jugular and radial artery catheterization, and trans-cranial Doppler, subjects rested for 30 min. Baseline data (BL) were recorded and sampled during the last 5 min of this resting period prior to beginning the incremental exercise test with relative workloads of 20, 40, 60, 80, 100% W_{max}. The duration of each workload was 3 min. Steady-state blood samples were drawn during exercise at each workload (at the 2.8 min mark for each workload). Upon completion of the maximal exercise test, subjects remained supine for a 30 min recovery period. Recovery measurements and blood samples were taken at 1, 2, 4, 6, 8, 10, 15, 25, 30 min following exercise.

Cardio-respiratory variables

Electrocardiogram, intra-radial artery pressure, breathing frequency (F_b), tidal volume (TV), partial pressures of expired tidal oxygen and carbon dioxide (P_{ET,O_2} and P_{ET,CO_2}), were sampled continuously at 1 kHz via an analog-to-digital data acquisition system (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO, USA).

Intracranial and cerebral blood flow measurements

Intracranial cerebral blood velocity was measured continuously throughout each experiment in the middle (MCAv) and posterior (PCAv) cerebral arteries using a 2 MHz pulsed transcranial Doppler ultrasound (TCD) system (Spencer Technologies, Seattle, WA, USA) and recorded through the acquisition system. Identification and location of MCA and PCA was determined using standardized procedures (Willie *et al.* 2011). Bilateral TCD probes were fixed and held in place via a headband fixation device (Mark600, Spencer Technologies, Seattle, WA, USA). Our coefficients of determination for between-day MCA and PCA measurements are 3% and 2%, respectively (Smith *et al.* 2012).

Continuous diameter, velocity and blood flow recording in the left internal (Q_{ICA}) and right vertebral neck arteries (Q_{VA}) were obtained using a 10 MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (Terason 3000, Teratech, Burlington, MA, USA). The ICA was measured at least 2 cm from the carotid bifurcation, whilst ensuring there was no evidence of turbulent or retrograde flow. The VA was measured proximal to the C4 vertebral process, between the C4 and subclavian, or between the C4 and C5 vertebral processes. All VA measurements were obtained from the same location in each subject. Sample volume was positioned in the centre of each vessel and adjusted to cover the width of the vessel diameter, while precautions were taken to ensure that the angle of insonation was stable and maintained at 60 deg. Our coefficients of determination for between-day variability of baseline ICA and VA measurements are 5% and 11%, respectively (Willie *et al.* 2012).

Offline blood flow analysis of the ICA and VA was performed using edge-detection software, which allows for the integration of synchronous diameter and velocity measurements to determine the mean beat-to-beat flow at 30 Hz independent of investigator bias (Woodman *et al.* 2001). Mean blood flow was determined as half the time-averaged maximum velocity (Evans, 1985), multiplied by the cross-sectional lumen area for a minimum of ten cardiac cycles (Willie *et al.* 2012).

Arterial and jugular venous catheterization

Local anesthetic (1% lidocaine) was injected to the surrounding tissue of the radial artery and internal jugular vein under the guidance of a portable 8 MHz ultrasound unit (Nanomaxx, Sonosite, Washington, USA). A 20-gauge catheter (Arrow, Markham, Ontario, Canada) was placed into the radial artery and attached to a pressure transducer that was positioned at the level of the right atrium in the midaxillary line for the measurement of beat-to-beat arterial blood pressure and gas sampling. A jugular bulb catheter (Edwards PediaSat Oximetry Catheter, Edwards, Irvine, CA, USA) was placed in the right internal jugular vein and directed cephalad under sterile conditions while guided via ultrasound.

Arterial and jugular venous blood gas analysis

Blood gas samples were drawn into a preheparinized syringe, and analysed immediately (within 2 min). Following standardized calibration, all blood samples were analysed using an arterial blood-gas analysis system (ABL-90 CO-Ox, Radiometer, Copenhagen, Denmark) for arterial (a) and internal jugular venous (v) pH, P_{O_2}, P_{CO_2}, S_{a,O_2}, Hb, glucose and lactate.

Calculations

The average values for mean arterial pressure (MAP), MCAv, PCAv, heart rate (HR), P_{ET,O_2}, P_{ET,CO_2}, F_b, V_E were calculated offline using LabChart v7.0 (ADInstruments) during the entire 5 min of BL, 30 s prior to the blood gas samples at each workload (i.e. at steady state) and during the recovery time points.

Global cerebral blood flow (gCBF) was calculated as:

$$\mathrm{gCBF}\left(\mathrm{ml\,min^{-1}}\right) = (Q_{ICA} \times 2) + (Q_{VA} \times 2),$$

where Q_{ICA} is the blood flow from the left ICA, and Q_{VA} is the blood flow in the right VA. The total of Q_{ICA} and Q_{VA} therefore is the estimated gCBF, assuming a symmetrical blood flow between contralateral ICA and VA arteries. The Q_{ICA} and Q_{VA} were calculated offline:

$$Q = \pi r^2 v,$$

where Q is the flow, r is the radius, and v is the velocity of the blood moving through the respective vessels.

Global cerebral blood flow per unit of tissue was calculated as:

$$\mathrm{gCBF}\left(\mathrm{ml(100\ g)^{-1}\,min^{-1}}\right) = \frac{\mathrm{gCBF}}{14},$$

assuming an average brain mass of 1.4 kg.

Global cerebral blood flow during exercise at each workload was also calculated using the percentage change in MCAv and PCAv and baseline Q_{ICA} and Q_{VA}:

$$\mathrm{gCBF_{Ex}} = \left(Q_{ICA,BL} \times 2\right) + \left(Q_{ICA,BL} \times \%\Delta v_{MCA}\right) + \left(Q_{VA,BL} \times 2\right) + \left(Q_{VA,BL} \times \%\Delta v_{PCA}\right),$$

where $\mathrm{gCBF_{Ex}}$ equals the gCBF for the given workload (20, 40, 60, 80, 100% W_{max}), Q_{ICA} and Q_{VA} are the resting baseline values, and the %ΔMCAv and %ΔPCAv are the changes at the given W_{max} from resting baseline MCAv and PCAv values (Gonzalez-Alonso, 2004; Fisher *et al.* 2013). In addition, gCBF was also estimated via the *Fick principle* assuming a maintained cerebral metabolic rate of oxygen (see below).

Arterial (C_{a,O_2}) and venous (C_{v,O_2}) content of oxygen were calculated as:

$$C_{a,O_2}\left(\mathrm{ml\,dl^{-1}}\right) = \left([\mathrm{Hb}] \times 1.36 \times \frac{S_{a,O_2}\,(\%)}{100}\right) + (0.003 \times P_{a,O_2}),$$

$$C_{v,O_2}\left(\mathrm{ml\,dl^{-1}}\right) = \left([\mathrm{Hb}] \times 1.36 \times \frac{S_{v,O_2}\,(\%)}{100}\right) + (0.003 \times P_{v,O_2}),$$

where [Hb] is the concentration of haemoglobin in venous blood, 1.36 is the affinity for O_2 to hemoglobin for a given

jugular venous saturation, and 0.003 is the percentage of O_2 dissolved in the blood.

Cerebral delivery of oxygen (CD_{O_2}) was calculated as:

$$CD_{O_2}\left(\text{ml}(100\text{ g})^{-1}\text{ min}^{-1}\right) = \text{gCBF} \times C_{a,O_2},$$

where gCBF is the blood flow per unit of brain tissue.

Cerebral metabolic rate for oxygen (CMR_{O_2}) was calculated as:

$$CMR_{O_2}\left(\mu\text{mol}\,(100\text{ g})^{-1}\,\text{min}^{-1}\right) = \left[\left(\text{gCBF}\right) \times \left(C_{a,O_2} - C_{v,O_2}\right)\right] \times 0.446,$$

where CMR_{O_2} is the gCBF multiplied by the arterial jugular venous O_2 content differences, and 0.446 equals the ratio of 1 mmol of O_2 in a volume equal to 1 ml (i.e. 1/22.4 mmol). CMR_{O_2} indicates the uptake rate of oxygen by the brain.

Direct Fick measurement of cerebral blood flow (CBF) was also made. Assuming a maintained cerebral metabolic rate of oxygen from rest during exercise:

$$\text{CBF}\left(\text{ml}(100\text{ g}^{-1})\text{min}^{-1}\right) = \frac{CMR_{O_{2,BL}}}{C_{a,O_2} - C_{v,O_2}},$$

where $CMR_{O_{2,BL}}$ is the CMR_{O_2} at rest for SL and HA, and $C_{a,O_2} - C_{v,O_2}$ is the absolute arterial venous oxygen extraction at each exercise intensity and minute of recovery.

Cerebrovascular conductance (CVC) was calculated as:

$$\text{CVC}\left(\text{mmHg ml}(100\text{ g})^{-1}\text{min}^{-1}\right) = \text{MAP} \times \text{gCBF},$$

Oxygen extraction fraction (O_2EF) was calculated as:

$$O_2EF\,(\%) = \frac{C_{a,O_2} - C_{v,O_2}}{C_{a,O_2}} \times 100\%,$$

where the C_{a,O_2} and C_{v,O_2} represent the arterial and jugular venous O_2 content, respectively. The O_2EF is interpreted as being the percentage O_2 extraction across the brain.

Cerebral delivery of glucose was calculated as:

$$CD_{Glu}\left(\mu\text{mol}\,(100\text{ g})^{-1}\,\text{min}^{-1}\right) = \text{gCBF} \times \text{Glu}_a,$$

Cerebral delivery of lactate was calculated as:

$$CD_{Lac}\left(\mu\text{mol}\,(100\text{ g})^{-1}\,\text{min}^{-1}\right) = \text{gCBF} \times \text{Lac}_a,$$

where gCBF is the blood flow per unit of tissue, and Glu_a and Lac_a are the arterial concentrations of glucose and lactate, respectively.

Cerebral metabolic rate for glucose (CMR_{Glu}) was calculated as:

$$CMR_{Glu}\left(\mu\text{mol}\,(100\text{ g})^{-1}\,\text{min}^{-1}\right) = \text{gCBF} \times \left(\text{Glu}_a - \text{Glu}_v\right).$$

Cerebral metabolic rate for lactate (CMR_{Lac}) was calculated as:

$$CMR_{Lac}\left(\mu\text{mol}\,(100\text{ g})^{-1}\,\text{min}^{-1}\right) = \text{gCBF} \times \left(\text{Glu}_a - \text{Glu}_v\right),$$

where the gCBF is the blood flow per unit of brain tissue, and Glu_a and Lac_a and Glu_v and Lac_v are the arterial and venous differences of glucose and lactate in the arterial and jugular venous blood, respectively.

Oxygen glucose index (OGI) was calculated as:

$$\text{OGI} = \left(C_{a,O_2} - C_{v,O_2}\right)/(\text{Glu}_a - \text{Glu}_v).$$

The OGI indicates the ratio of oxygen to glucose taken up by the brain. OGI values at a 1:1 ratio would equal 6, as the stoichiometry for the oxidization of glucose by oxygen requires one oxygen molecule per each of the six carbon atoms found in glucose. A reduction from this value would indicate that some of the glucose was not fully oxidized, and could indicate a non-oxidative energy production.

Oxygen carbohydrate index (OCI) was calculated by:

$$\text{OCI} = \left(C_{a,O_2} - C_{v,O_2}\right)/(\text{Glu}_a - \text{Glu}_v) + \frac{1}{2}\left(\text{Lac}_a - \text{Lac}_v\right).$$

The OCI indicates the ratio of oxygen to carbohydrate (Glu and Lac) taken up by the brain. The carboxylation of lactate to pyruvate into the citric acid cycle results in only one molecule of pyruvate, compared to the two derived from the breakdown of glucose to pyruvate during glycolysis.

Cumulative molar ratio of carbohydrate uptake to oxygen uptake was calculated by:

$$\text{CMRU}(\text{mmol}\,l^{-1}) = (\text{Glu}_{a-v}) + \frac{1}{2}(\text{Lac}_{a-v}) - \frac{1}{6}(C_{a,O_2} - C_{v,O_2}).$$

where CMRU is reported in glucose equivalent units such that a score of zero indicates complete oxidation of extracted glucose and lactate. Any deviation from a score of 0 indicates either an extraction of carbohydrates in excess of oxygen (increase) or a surplus extraction of oxygen *vs.* carbohydrate (decrease). Furthermore, CMRU is cumulatively added for each subsequent measure from rest in order to demonstrate the cumulative mismatch between carbohydrate and oxygen metabolism during and following exercise.

Cumulative metabolic ratio of carbohydrate uptake to oxygen uptake was calculated by:

$$CMRU_{gCBF}\left(\mu\text{mol}\,(100\text{ g})^{-1}\,\text{min}^{-1}\right) = (\text{Glu}_{a-v}) + \frac{1}{2}\left(\text{Lac}_{a-v}\right) - \frac{1}{6}\left(C_{a,O_2} - C_{v,O_2}\right),$$

where CMRU, as calculated above, and gCBF are considered in parallel ($CMRU_{gCBF}$). This calculation is used to identify how changes in gCBF may impact HA and SL CMRU.

Table 1. Cardiorespiratory and arterial–venous variables during exercise at sea level and high altitude (5050 m)

		Rest	Exercise (%W_{max})				
Variable	Condition	BL	20	40	60	80	100
Cardio-respiratory variables							
HR (beats min^{-1})	SL	68 ± 10	101 ± 12*	125 ± 12*	143 ± 10*	164 ± 8*	176 ± 6*
	HA	68 ± 12	95 ± 9*	111 ± 10*	121 ± 9*,†	135 ± 9*,†	142 ± 11*,†
MAP (mmHg)	SL	116 ± 7	124 ± 9	137 ± 9	147 ± 9*	149 ± 11*	154 ± 11*
	HA	124 ± 9	132 ± 8	137 ± 5	142 ± 7	147 ± 8	151 ± 9*
P_{ET,O_2} (mmHg)	SL	92 ± 5	92 ± 6	97 ± 7	103 ± 5*	106 ± 3*	110 ± 4*
	HA	46 ± 2†	48 ± 3†	51 ± 2*,†	54 ± 2*,†	57 ± 3*,†	58 ± 3*,†
P_{ET,CO_2} (mmHg)	SL	40 ± 1	40 ± 1	40 ± 2	40 ± 3	38 ± 3	36 ± 3
	HA	28 ± 2†	27 ± 2†	26 ± 2†	25 ± 2†	24 ± 2*,†	23 ± 2*,†
F_b (breaths min^{-1})	SL	16 ± 3	21 ± 3*	24 ± 3*	29 ± 5*	39 ± 4*	47 ± 6*
	HA	18 ± 3	24 ± 5*	29 ± 5*,†	37 ± 7*,†	43 ± 8 *	51 ± 9*
$\dot{V}_E$ (l min^{-1})	SL	15 ± 5	29 ± 8*	46 ± 9*	67 ± 14*	102 ± 15*	127 ± 25*
	HA	18 ± 3	38 ± 10*	52 ± 14*	73 ± 19*	95 ± 23*	114 ± 19*
Arterial							
P_{O_2} (mmHg)	SL	92 ± 8	75 ± 8*	75 ± 12*	81 ± 13	85 ± 12	82 ± 12
	HA	42 ± 3†	38 ± 2*,†	38 ± 3*,†	37 ± 3*,†	37 ± 3*,†	38 ± 3†
P_{CO_2} (mmHg)	SL	38 ± 3	39 ± 2	38 ± 2	37 ± 2	34 ± 2*	34 ± 3*
	HA	23 ± 4†	23 ± 3†	23 ± 2†	22 ± 3†	22 ± 2†	20 ± 2*,†
S_{O_2} (%)	SL	98 ± 1	96 ± 1	95 ± 4	96 ± 2	96 ± 2	95 ± 3*
	HA	81 ± 4†	77 ± 3†	75 ± 4†,*	75 ± 4†,*	73 ± 5†,*	71 ± 5†,*
pH	SL	7.41 ± 0.01	7.40 ± 0.01*	7.40 ± 0.01*	7.37 ± 0.02*	7.33 ± 0.03*	7.27 ± 0.05*
	HA	7.48 ± 0.05†	7.48 ± 0.03†	7.47 ± 0.02†	7.45 ± 0.03*,†	7.42 ± 0.04*,†	7.38 ± 0.05*,†
C_{a,O_2} (ml dl^{-1})	SL	21 ± 1	21 ± 1	21 ± 1	21 ± 1	22 ± 1*	22 ± 1*
	HA	18 ± 2†	17 ± 1†	17 ± 1†	17 ± 2†	17 ± 1†	17 ± 1†
Glucose (mmol l^{-1})	SL	5.4 ± 0.3	5.4 ± 0.3	5.4 ± 0.2	5.5 ± 0.3	5.5 ± 0.3	5.4 ± 0.2
	HA	5.2 ± 0.2	5.3 ± 0.2	5.3 ± 0.2	5.3 ± 0.3	5.4 ± 0.2	5.4 ± 0.4
Lactate (mmol 1^{-1})	SL	0.7 ± 0.1	0.9 ± 0.3*	2.0 ± 0.5*	4.5 ± 1.2*	8.8 ± 1.7*	13.5 ± 2.3*
	HA	0.9 ± 0.2†	1.2 ± 0.2*,†	2.0 ± 0.5*	3.6 ± 1.3*	5.7 ± 2.0*,†	8.3 ± 2.1*,†
Venous							
P_{O_2} (mmHg)	SL	33 ± 3	32 ± 4	33 ± 3	34 ± 2	34 ± 3	35 ± 3
	HA	27 ± 2†	25 ± 1†	25 ± 1†	30 ± 5†	26 ± 2†	26 ± 2†
P_{CO_2} (mmHg)	SL	48 ± 4	49 ± 2	49 ± 2	48 ± 2	45 ± 5	46 ± 1
	HA	30 ± 3†	29 ± 2†	28 ± 2†	28 ± 2†	28 ± 2†	27 ± 2†
S_{O_2} (%)	SL	64 ± 2	64 ± 3	65 ± 3	65 ± 3	63 ± 5	61 ± 5
	HA	52 ± 4†	49 ± 2*,†	49 ± 3*,†	49 ± 3*,†	47 ± 3*,†	46 ± 2*,†
pH	SL	7.37 ± 0.01	7.36 ± 0.01	7.35 ± 0.01	7.32 ± 0.02	7.28 ± 0.03	7.23 ± 0.04
	HA	7.43 ± 0.04†	7.44 ± 0.04†	7.42 ± 0.03*,†	7.42 ± 0.03*,†	7.39 ± 0.04*,†	7.35 ± 0.05*,†
C_{v,O_2} (ml dl^{-1})	SL	14 ± 1	14 ± 1	14 ± 1	14 ± 1	14 ± 1	14 ± 1
	HA	12 ± 1†	10 ± 1*,†	11 ± 1†	11 ± 1†	11 ± 1†	11 ± 1†
Glucose (mmol l^{-1})	SL	5.0 ± 0.2	5.0 ± 0.4	5 .0 ± 0.3	5.0 ± 0.3	4.8 ± 0.5	5.0 ± 0.4
	HA	4.6 ± 0.5	4.7 ± 0.4	4.7 ± 0.4	4.8 ±	4.8 ± 0.5	4.8 ± 0.5
Lactate (mmol 1^{-1})	SL	0.6 ± 0.1	0.9 ± 0.2	1.7 ± 0.5*	4.0 ± 1.0*	6.7 ± 1.6*	10.1 ± 1.3*
	HA	0.9 ± 0.2	1.2 ± 0.2	1.9 ± 0.3*	3.1 ± 0.7	4.8 ± 1.4*,†	7.0 ± 1.7*,†
Arterial–venous differences and metabolism							
C_{a-v,O_2} (ml dl^{-1})	SL	7.1 ± 0.7	6.8 ± 0.6	6.8 ± 0.7	6.9 ± 1.1	7.6 ± 1.3	7.9 ± 1.6
	HA	6.6 ± 1.8	6.8 ± 1.2	6.2 ± 1.2	6.2 ± 1.7	6.1 ± 1.2†	6.1 ± 1.0†
O_2EF (%)	SL	34 ± 2	33 ± 3	33 ± 3	32 ± 4	34 ± 5	36 ± 6
	HA	38 ± 5†	38 ± 3†	36 ± 3†	35 ± 6	36 ± 5	36 ± 4
Glu_{a-v} (mmol l^{-1})	SL	0.4 ± 0.1	0.6 ± 0.3	0.4 ± 0.2	0.5 ± 0.3	0.7 ± 0.5	0.4 ± 0.3
	HA	0.7 ± 0.4	0.4 ± 0.2†	0.6 ± 0.3	0.8 ± 0.2	0.6 ± 0.3	0.6 ± 0.2
Lac_{a-v} (mmol l^{-1})	SL	0.04 ± 0.1	0.06 ± 0.05	0.3 ± 0.2*	0.6 ± 0.3*	2.1 ± 0.9*	3.5 ± 1.3*
	HA	-0.02 ± 0.2	0.2 ± 0.3*	0.4 ± 0.6*	0.9 ± 0.9*	1.3 ± 1.1*	1.4 ± 0.9*

Continued

Table 1. Continued

		Rest	Exercise (%W_{max})				
Variable	Condition	BL	20	40	60	80	100
Ratios							
OGI	SL	7.1 ± 1.2	7.7 ± 4.1	7.5 ± 2.7	7.5 ± 2.7	5.2 ± 2.2	8.3 ± 4.1
	HA	4.0 ± 0.5†	4.3 ± 0.8	4.3 ± 1.2†	3.9 ± 1.4†	4.6 ± 1.6	5.3 ± 2.3
OCI	SL	6.7 ± 1.0	7.4 ± 4.3	6.1 ± 2.4	4.4 ± 2.5*	1.9 ± 0.6*	1.6 ± 0.7*
	HA	4.0 ± 0.5†	3.8 ± 0.9†	3.3 ± 0.8*,†	2.4 ± 1.0*,†	2.1 ± 0.5*	2.1 ± 0.4*

HR, heart rate; MAP, mean arterial pressure; P_{ET,O_2}, partial pressure of end-tidal oxygen; P_{ET,CO_2}, partial pressure of end-tidal carbon dioxide, F_b, breathing frequency; $\dot{V}_E$, minute ventilation; P_{O_2}, partial pressure of oxygen; P_{CO_2}, partial pressure of carbon dioxide; S_{O_2}, oxygen saturation; C_{a,O_2}, arterial oxygen content; C_{v,O_2}, venous oxygen content; C_{a-v,O_2}, arterial–venous oxygen content differences; O_2EF, relative fraction of oxygen content; Glu_{a-v}, cerebral arterial–venous glucose differences; Lac_{a-v}, arterial–venous lactate differences; OGI, oxygen–glucose index; OCI, oxygen–carbohydrate differences. *Significant differences from baseline ($P < 0.003$), †significant differences between SL and HA ($P < 0.05$).

Statistical analysis

Normal distribution of variables was confirmed with the Shapiro–Wilk normality test. A two way (time × condition) repeated measures analysis of variance (ANOVA) was employed to compare all the variables measured and calculated at SL and HA during BL, exercise and recovery. A P value of <0.05 was considered statistically significant. The false discovery rate was used *post hoc* to adjust for multiple comparisons ($P < 0.003$). Values are presented as means ± SD.

Results

Subjects

Eight males completed the entire protocol (age: 30 ± 6 years; height: 167 ± 40 cm, body mass: 55–102 kg; SL $\dot{V}_{O_2,peak,supine}$: 43.1 ± 5.0 ml kg^{-1} min^{-1}). The W_{max} was reduced by 50% at HA compared with SL (150 ± 25 *vs.* 300 ± 50 W, respectively). As such, the average relative workloads equated to: 30, 60, 90, 120, 150 W at HA, and 60, 120, 180, 240, 300 W at SL for 20, 40, 60, 80 and 100% W_{max}, respectively.

Rest (Tables 1 and 3; Figs 1–5)

Following partial acclimatization at 5050 m, P_{ET,O_2}, P_{ET,CO_2}, P_{a,O_2}, P_{a,CO_2},S_{a,O_2}, C_{a,O_2}, P_{v,O_2}, P_{v,CO_2}, S_{v,O_2}, C_{v,O_2}, OGI and OCI were reduced compared to SL values ($P < 0.05$, Table 1). Resting arterial pH, arterial lactate, venous pH, and O_2EF were all elevated at HA compared with SL ($P < 0.05$). No significant differences were observed for MAP, cerebrovascular resistance or conductance (CVRi or CVCi) at either altitude. Figure 1 highlights the contribution of ICA and VA to the resting gCBF at SL and HA. At rest at HA, Q_{ICA} was elevated (∼+22%) from SL ($P < 0.05$), however, gCBF ($P = 0.056$) and Q_{VA} ($P = 0.898$) were not raised at HA compared with SL. No differences were observed in the diameter of the ICA and VA at SL and HA, nor were there differences observed for MCAv and PCAv between SL and HA at rest (Table 3; $P = 0.33$ and 0.237, respectively). Although cerebral oxygen and glucose delivery were not different at SL and HA, the cerebral lactate delivery was elevated at HA compared with SL (Fig. 5*C*; $P < 0.05$). The CMR_{O_2} and CMR_{Glu} were also elevated (∼+23% *vs.* SL; $P < 0.05$) at HA whereas CMR_{Lac} was unaltered (Fig. 5*B*; $P = 0.515$). Finally, in Fig. 1 the red lines indicate the one subject who was deemed a statistical univariate outlier (CMR_{O_2} z score >3.29 and >2 SD from the mean). Consequently, this subject was removed from the CMR_{O_2} calculations. In addition, when this subject was removed from the gCBF data set, the increase in gCBF at HA was significant (up 25%; $P = 0.02$ *vs.* SL).

Exercise (Tables 1 and 3; Figs 2–6)

Supine submaximal exercise at SL (i.e. 20 and 40% W_{max}) resulted in a reduced P_{a,O_2} followed by a return to resting values at higher intensities (Fig. 2*A*). At HA P_{a,O_2} was reduced from rest and SL at all intensities ($P < 0.003$ *vs.* rest; $P < 0.05$ *vs.* SL). Figure 2*B* illustrates a lack of any marked changes in P_{a,CO_2} during submaximal exercise at both altitudes, while similar reductions in P_{a,CO_2} from rest were observed during the highest exercise intensities (80 and 100% W_{max}) at SL and HA (down 3–4 mmHg). Moreover, the change in pH at 100% W_{max} at HA (Δ0.10; 7.38) was less than that at SL (Δ0.13; 7.27; Table 1; Fig. 2*D*). Arterial–venous differences of oxygen content (C_{a-v,O_2}) across the brain at SL and HA did not change during low-to-moderate intensity exercise (20–60% W_{max}); however, C_{a-v,O_2} at HA during 80 and 100% W_{max} was lower (∼20%; $P < 0.05$) than at SL. During the lowest exercise intensities (20 and 40%

Table 2. Cardiorespiratory and arterial–venous variables during recovery at sea level and high altitude (5050 m)

		Recovery time following exercise (min)									
	Condition	1	2	4	6	8	10	15	20	25	30
Cardio-respiratory variables											
HR (beats min^{-1})	SL	134 ± 14*	113 ± 17*	98 ± 10*	97 ± 11*	97 ± 13	93 ± 12	86 ± 14	90 ± 11	86 ± 11	84 ± 12
	HA	110 ± 12*	91 ± 14*	88 ± 14*	85 ± 14	86 ± 10	85 ± 11	80 ± 13	77 ± 9	80 ± 12	79 ± 11
MAP (mmHg)	SL	116 ± 10	113 ± 9	99 ± 7	96 ± 7	87 ± 24	96 ± 4	99 ± 7	101 ± 5	103 ± 5	104 ± 3
	HA	134 ± 6†	122 ± 8†	118 ± 9†	116 ± 17†	114 ± 19†	113 ± 8†	117 ± 10†	115 ± 10†	119 ± 8†	120 ± 6†
P_{ET,O_2} (mmHg)	SL	120 ± 6*	120 ± 6*	116 ± 5*	114 ± 6	113 ± 6	109 ± 7	106 ± 7	102 ± 8	99 ± 9	96 ± 8
	HA	59 ± 4*,†	57 ± 5*,†	57 ± 3*,†	56 ± 4*,†	55 ± 4*,†	53 ± 4†	51 ± 4†	49 ± 3†	48 ± 3†	47 ± 3†
P_{ET,CO_2} (mmHg)	SL	32 ± 6	31 ±	31 ± 5	30 ± 5	30 ± 5	30 ± 5	30 ± 5	32 ± 5	32 ± 5	33 ± 5
	HA	23 ± 3†	24 ± 3†	24 ± 3†	24 ± 3†	23 ± 3†	24 ± 3†	24 ± 3†	25 ± 3†	25 ± 3†	26 ± 2†
F_b (breaths min^{-1})	SL	29 ± 12	26 ± 11	21 ± 10	18 ± 9	20 ± 9	19 ± 8	18 ± 8	18 ± 8	16 ± 7	18 ± 7
	HA	34 ± 17*	27 ± 14	22 ± 10	21 ± 9	21 ± 9	21 ± 10	18 ± 8	18 ± 8	19 ± 9	18 ± 8
$\dot{V}_E$ (l min^{-1})	SL	69 ± 17*	46 ± 9*	34 ± 10*	26 ± 4*	24 ± 4*	22 ± 5*	18 ± 2*	18 ± 2*	15 ± 2	15 ± 2
	HA	72 ± 18*	46 ± 17*	36 ± 10*	32 ± 10*	28 ± 8*	28 ± 7*	23 ± 6	25 ± 8	21 ± 4	21 ± 4
Arterial											
P_{O_2} (mmHg)	SL	103 ± 13	112 ± 2*	109 ± 5*	109 ± 6*	103 ± 5*	101 ± 5*	98 ± 6	91 ± 7	91 ± 9	87 ± 6
	HA	46 ± 4†	52 ± 4*,†	52 ± 4*,†	52 ± 4*,†	50 ± 4*,†	50 ± 5*,†	48 ± 5*,†	43 ± 4†	43 ± 4†	43 ± 4†
P_{CO_2} (mmHg)	SL	33 ± 2*	31 ± 2*	31 ± 2*	30 ± 2*	30 ± 2*	30 ± 2*	31 ± 2*	32 ± 2*	33 ± 2*	34 ± 2*
	HA	20 ± 2*,†	20 ± 3*,†	21 ± 3*,†	20 ± 3*,†	20 ± 3*,†	20 ± 3*,†	20 ± 2*,†	21 ± 2*,†	22 ± 2†	22 ± 2†
S_{O_2} (%)	SL	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1
	HA	78 ± 5†	83 ± 3†	83 ± 2†	85 ± 2†	83 ± 2†	84 ± 3†	84 ± 4†	83 ± 3†	81 ± 3†	82 ± 4†
pH	SL	7.20 ± 0.05*	7.20 ± 0.05*	7.18 ± 0.06*	7.19 ± 0.05*	7.20 ± 0.05*	7.21 ± 0.05*	7.26 ± 0.04*	7.30 ± 0.04*	7.33 ± 0.03*	7.35 ± 0.03*
	HA	7.32 ± 0.06*,†	7.32 ± 0.05*,†	7.31 ± 0.05*,†	7.33 ± 0.07*,†	7.34 ± 0.07*,†	7.34 ± 0.07*,†	7.41 ± 0.06*,†	7.43 ± 0.04*,†	7.45 ± 0.03*,†	7.46 ± 0.03†
C_{a,O_2} (ml dl^{-1})	SL	23 ± 1*	22 ± 1*	22 ± 1*	21 ± 1	22 ± 1*	21 ± 1	21 ± 2	21 ± 2	20 ± 1	21 ± 2
	HA	19 ± 2†	20 ± 1*,†	19 ± 2†	19 ± 1†	19 ± 1†	19 ± 1†	19 ± 1†	18 ± 1†	18 ± 1†	18 ± 1†
Glucose (mmol 1^{-1})	SL	5.5 ± 0.3	5.7 ± 0.5	5.8 ± 0.6	5.8 ± 0.6	5.7 ± 0.6	5.7 ± 0.6	5.7 ± 0.7	5.8 ± 0.7	5.7 ± 0.6	5.7 ± 0.8
	HA	5.5 ± 0.6	5.5 ± 0.6	5.5 ± 0.8	5.4 ± 0.8	5.4 ± 0.8	5.4 ± 0.8	5.5 ± 0.7	5.4 ± 0.5	5.3 ± 0.5	5.3 ± 0.4
Lactate (mmol 1^{-1})	SL	16.1 ± 2.7*	15.8 ± 2.6*	15.8 ± 2.9*	14.7 ± 2.6*	13.9 ± 2.6*	12.9 ± 2.2*	10.2 ± 2.1*	8.2 ± 1.9*	6.7 ± 1.8*	5.5 ± 1.4*
	HA	9.7 ± 2.7*,†	9.4 ± 2.7*,†	8.7 ± 2.1*,†	7.5 ± 3.0*,†	7.5 ± 3.0*,†	6.9 ± 2.9*,†	5.4 ± 2.5*,†	4.3 ± 2.0*,†	3.5 ± 1.7*,†	2.9 ± 1.3*,†

Continued

Table 2. Continued

	Condition	Recovery time following exercise (min) 1	2	4	6	8	10	15	20	25	30
Venous											
P_{O_2} (mmHg)	SL	38 ± 4*	37 ± 3*	37 ± 3*	37 ± 3*	36 ± 3*	36 ± 3*	32 ± 1	32 ± 2	32 ± 2	32 ± 2
	HA	30 ± 2*	32 ± 2*	31 ± 1*	30 ± 2*	30 ± 2*	29 ± 2*	27 ± 3	26 ± 2	26 ± 1	27 ± 2
P_{CO_2} (mmHg)	SL	48 ± 1	47 ± 2	44 ± 5	45 ± 5	44 ± 2	44 ± 4*	44 ± 3*	45 ± 3*	45 ± 3	44 ± 6
	HA	26 ± 2*,†	27 ± 2*,†	28 ± 3*,†	28 ± 2*,†	28 ± 2†	45 ± 5†	28 ± 2†	29 ± 2†	29 ± 2†	29 ± 2†
S_{O_2} (%)	SL	62 ± 6	61 ± 5	59 ± 4*	59 ± 5*	57 ± 4*	59 ± 4*	55 ± 4*	58 ± 5*	58 ± 6*	61 ± 6
	HA	50 ± 3†	55 ± 3†	53 ± 3†	51 ± 3†	50 ± 4†	50 ± 4†	48 ± 4*,†	49 ± 4*,†	48 ± 2*,†	51 ± 3
pH	SL	7.17 ± 0.04	7.16 ± 0.05	7.15 ± 0.05	7.15 ± 0.05	7.16 ± 0.05	7.18 ± 0.04	7.22 ± 0.04	7.26 ± 0.03	7.28 ± 0.03	7.30 ± 0.03
	HA	7.30 ± 0.06†	7.30 ± 0.06†	7.29 ± 0.06†	7.30 ± 0.07†	7.30 ± 0.07†	7.33 ± 0.06†	7.37 ± 0.05†	7.39 ± 0.04†	7.41 ± 0.03†	7.42 ± 0.03†
C_{v,O_2} (ml dl^{-1})	SL	14 ± 2	14 ± 1	13 ± 1*	13 ± 1*	13 ± 3*	13 ± 1*	12 ± 1*	12 ± 1*	12 ± 1*	13 ± 1*
	HA	12 ± 1†	13 ± 1*	12 ± 1†	12 ± 1†	11 ± 1†	11 ± 1†	11 ± 1†	10 ± 1*,†	10 ± 1*,†	11 ± 1*,†
Glucose (mmol 1^{-1})	SL	5.0 ± 0.4	5.1 ± 0.6	5.1 ± 0.4	5.3 ± 0.7	5.3 ± 0.8	5.2 ± 0.7	5.2 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.1 ± 0.8
	HA	4.9 ± 0.6	4.9 ± 0.6	5.0 ± 0.7	5.0 ± 0.7	5.0 ± 0.8	4.9 ± 0.7	4.9 ± 0.6	4.9 ± 0.5	4.8 ± 0.5	4.8 ± 0.8
Lactate (mmol 1^{-1})	SL	12.0 ± 1.6	12.0 ± 2.0	11.4 ± 2.2	12.2 ± 3.0	12.0 ± 2.6	10.8 ± 2.4	8.6 ± 2.0	7.2 ± 1.5	5.8 ± 1.1	4.7 ± 0.9
	HA	8.2 ± 1.9	8.0 ± 2.2	7.6 ± 2.3	7.1 ± 2.4	6.5 ± 2.4	6.0 ± 2.6	4.7 ± 2.1	3.8 ± 1.6	3.2 ± 1.4	2.7 ± 1.1
Arterial–venous differences and metabolism											
C_{a-v,O_2} (ml dl^{-1})	SL	8.2 ± 2.0	8.6 ± 1.1*	8.7 ± 1.0*	8.4 ± 0.8*	8.8 ± 1.1*	8.5 ± 0.8*	9.0 ± 0.9*	8.4 ± 1.3	8.0 ± 1.4	8.3 ± 2.3
	HA	6.9 ± 1.5	6.9 ± 1.2	7.1 ± 1.3	7.8 ± 1.2*	7.6 ± 1.4*	7.8 ± 1.5*	8.0 ± 1.5*	7.7 ± 1.2*	7.5 ± 1.1	7.0 ± 1.3
O_2EF (%)	SL	36 ± 9	39 ± 5*	40 ± 4*	39 ± 4*	40 ± 5*	40 ± 4*	43 ± 4*	40 ± 5*	40 ± 5*	40 ± 7
	HA	38 ± 5	36 ± 4	38 ± 4	41 ± 4	41 ± 4	43 ± 5	44 ± 4	43 ± 5	43 ± 3	40 ± 5
$Gluc_{a-v}$ (mmol l^{-1})	SL	0.6 ± 0.2	0.6 ± 0.3	0.6 ± 0.3	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.2	0.6 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.6 ± 0.6
	HA	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.4	0.6 ± 0.4	0.6 ± 0.3	0.6 ± 0.2	0.6 ± 0.2
Lac_{a-v} (mmol l^{-1})	SL	4.1 ± 1.5*	3.8 ± 1.6*	4.1 ± 1.8*	2.5 ± 2.4*	1.9 ± 2.2*	2.0 ± 2.0*	1.6 ± 1.7*	1.0 ± 1.2*	1.0 ± 0.7*	1.0 ± 1.2
	HA	1.6 ± 0.8*,†	1.4 ± 0.8*,†	1.2 ± 0.9*,†	1.1 ± 0.7*	1.0 ± 0.8*	0.8 ± 0.8*	0.6 ± 0.6*	0.4 ± 0.5	0.3 ± 0.4	0.3 ± 0.3*
Ratios											
OGI	SL	7.9 ± 2.7	6.4 ± 3.2	7.7 ± 5.6	12 ± 13	14 ± 11	11 ± 11	8.1 ± 5.2	9.2 ± 3.8	6.9 ± 4.0	7.6 ± 4.4
	HA	4.6 ± 1.5†	4.7 ± 1.4	4.9 ± 0.8	6.9 ± 3.5	10 ± 14	10 ± 14	8.4 ± 6.4	8.4 ± 6.5	7.2 ± 5.6	7.0 ± 5.3
OCI	SL	1.4 ± 0.4*	1.5 ± 0.4*	1.5 ± 0.6*	1.8 ± 0.8*	2.3 ± 0.7*	2.1 ± 0.4*	2.4 ± 0.5*	3.0 ± 2.0	4.9 ± 3.8	6.3 ± 7.6
	HA	2.1 ± 0.6†	2.4 ± 0.6†	2.6 ± 0.6†	3.2 ± 0.9†	3.2 ± 1.0	4.8 ± 3.9	5.9 ± 4.3	5.6 ± 2.8	5.0 ± 2.2	4.8 ± 2.2

HR, heart rate; MAP, mean arterial pressure; P_{ET,O_2} partial pressure of end-tidal oxygen; P_{ET,CO_2}, partial pressure of end-tidal carbon dioxide, F_b, breathing frequency; V_E, minute ventilation; P_{O_2}, partial pressure of oxygen; P_{CO_2}, partial pressure of carbon dioxide; S_{O_2}, oxygen saturation; C_{a,O_2}, arterial oxygen content; C_{v,O_2}, venous oxygen content; C_{a-v,O_2}, arterial–venous oxygen content differences; O_2Ext, relative fraction of oxygen content; Glu_{a-v}, cerebral arterial–venous glucose differences; Lac_{a-v}, arterial–venous lactate differences; OGI, oxygen glucose index; OCI, oxygen–carbohydrate differences. *Significant differences from baseline ($P < 0.003$), †significant differences between SL and HA ($P < 0.05$).

Table 3. Cerebral blood flow and metabolism during exercise at sea level and high altitude

Variable	Condition	BL	20	40	60	80	100
MCAv (cm s^{-1})	SL	71 ± 9	75 ± 9	80 ± 10*	83 ± 12*	77 ± 12*	76 ± 14
	HA	75 ± 9	82 ± 11*	87 ± 11*	90 ± 12*	90 ± 10*,†	92 ± 11*,†
PCAv (cm s^{-1})	SL	49 ± 8	52 ± 9*	56 ± 9*	56 ± 9*	52 ± 9	52 ± 10
	HA	54 ± 10	57 ± 8*	61 ± 8*	65 ± 9*	64 ± 9*,†	64 ± 11*,†
Q_{ICA} (l min^{-1})	SL	245 ± 34	259 ± 44	261 ± 49	254 ± 60	—	—
	HA	301 ± 58†	313 ± 59†	336 ± 49†	355 ± 72†	—	—
ICA_{diam} (cm)	SL	0.53 ± 0.03	0.53 ± 0.04	0.52 ± 0.04	0.51 ± 0.03*	—	—
	HA	0.53 ± 0.06	0.52 ± 0.06	0.52 ± 0.05	0.52 ± 0.05	—	—
ICA_{vel} (cm s^{-1})	SL	37 ± 4	40 ± 2	40 ± 5	41 ± 5*	—	—
	HA	44 ± 3†	49 ± 6 *,†	53 ± 5*,†	56 ± 9*,†	—	—
Q_{VA} (l min^{-1})	SL	78 ± 31	79 ± 32	86 ± 35	—	—	—
	HA	76 ± 26	74 ± 12	—	—	—	—
VA_{diam} (cm)	SL	0.37 ± 0.07	0.37 ± 0.08	0.38 ± 0.08	—	—	—
	HA	0.38 ± 0.03	0.38 ± 0.04	—	—	—	—
VA_{vel} (cm s^{-1})	SL	23 ± 6	24 ± 6	23 ± 8	—	—	—
	HA	20 ± 2	22 ± 2	—	—	—	—
gCBF (ml (100 g)$^{-1}$ min^{-1})	SL	46 ± 9	48 ± 9*	52 ± 9*	53 ± 12*	50 ± 11*	47 ± 12
	HA	53 ± 6	58 ± 6†	62 ± 8*,†	64 ± 7*,†	64 ± 10*,†	62 ± 8*,†
$CVRi_{gCBF}$	SL	2.2 ± 0.6	2.2 ± 0.6	2.3 ± 0.7	2.5 ± 0.7	2.7 ± 0.8	2.7 ± 0.9
	HA	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.3†	1.9 ± 0.3†	2.2 ± 0.4†	2.0 ± 0.3†
$CVCi_{gCBF}$	SL	0.47 ± 0.09	0.46 ± 0.09	0.45 ± 0.09	0.43 ± 0.10	0.40 ± 0.10	0.39 ± 0.10
	HA	0.52 ± 0.04	0.52 ± 0.06	0.54 ± 0.06†	0.53 ± 0.06 †	0.52 ± 0.09†	0.51 ± 0.09†
CD_{O_2} (ml dl^{-1} min^{-1})	SL	134 ± 23	139 ± 22	150 ± 22*	159 ± 29*	153 ± 29*	156 ± 29*
	HA	137 ± 20	141 ± 20	149 ± 18	155 ± 21*	151 ± 24*	156 ± 28*
CD_{Glu} (μmol (100 g)$^{-1}$ min^{-1})	SL	248 ± 40	258 ± 39	276 ± 39*	289 ± 55*	274 ± 56	272 ± 55
	HA	283 ± 37	307 ± 33*,†	324 ± 39*,†	345 ± 49*,†	346 ± 69*,†	351 ± 84*,†
CD_{Lac} (μmol (100 g)$^{-1}$ min^{-1})	SL	30 ± 5	45 ± 11*	104 ± 18*	236 ± 43*	430 ± 84*	682 ± 188*
	HA	48 ± 7†	78 ± 23*,†	141 ± 51*	259 ± 106*	393 ± 157*	551 ± 154*
CMR_{O_2} (μmol (100 g)$^{-1}$ min^{-1})	SL	1.3 ± 0.2	1.4 ± 0.3	1.5 ± 0.3	1.6 ± 0.2*	1.6 ± 0.2*	1.7 ± 0.3*
	HA	1.7 ± 0.2†	1.8 ± 0.2†	1.9 ± 0.2*,†	1.9 ± 0.4*	1.9 ± 0.3*	2.0 ± 0.2*
CMR_{Glu} (μmol (100 g)$^{-1}$ min^{-1})	SL	20 ± 3.0	21 ± 7†	23 ± 9	25 ± 9	28 ± 8	23 ± 7
	HA	44 ± 7†	42 ± 9†	44 ± 10†	52 ± 16†	45 ± 15†	39 ± 15†
CMR_{Lac} (μmol (100 g)$^{-1}$ min^{-1})	SL	1.7 ± 4	3.0 ± 2.0	10 ± 3*	32 ± 10*	110 ± 36*	188 ± 85*
	HA	–0.9 ± 10	14 ± 20*	30 ± 40*	67 ± 62*	81 ± 77*	103 ± 61*

MCAv; middle cerebral artery velocity; PCAv, posterior cerebral artery velocity; Q_{ICA}, internal carotid blood flow; ICA_{diam}, internal carotid artery diameter; ICA_{vel}, internal carotid artery velocity; Q_{VA}, vertebral blood flow; VA_{diam}, vertebral artery diameter; VA_{vel}, vertebral artery velocity; gCFB, global cerebral blood flow; $CVRi_{gCBF}$, cerebrovascular resistance; $CVCi_{gCBF}$, cerebrovascular conductance; CD_{O_2}, cerebral oxygen delivery; CD_{Glu}, cerebral glucose delivery; CD_{Lac}, cerebral lactate delivery; CMR_{O_2}, cerebral metabolic rate of oxygen; CMR_{Glu}, cerebral metabolic rate of glucose; CMR_{Lac}, cerebral metabolic rate of lactate. *Significant differences from baseline ($P < 0.003$), †significant differences between SL and HA ($P < 0.05$).

W_{max}), O_2EF was elevated at HA (~8–12%) compared with SL, whereas at moderate and high intensities (60, 80, 100% W_{max}) O_2EF was comparable (Table 1). Absolute arterial–venous lactate differences across the brain increased progressively from rest during exercise at both SL and HA ($P < 0.003$, Table 1), and more so at SL ($P < 0.05$). Specifically, the maximal achieved arterial lactate concentration and extraction during 100% W_{max} at HA was ~half of that achieved at SL (8.2 and 1.4 *vs.* 13.5 and 3.5 mmol l^{-1}, respectively). The OGI did not change during exercise at HA or SL, but there were differences between SL and HA at 20 and 40% W_{max} (Fig. 6*A*). In contrast, the OCI was generally reduced from rest during exercise (Table 1, Fig. 6*B*). Similar to the OGI, OCI was lower at HA during 20 and 40% W_{max} compared with SL, but there were no differences observed at higher intensities.

Incremental exercise up to 60% W_{max} at both SL and HA raised gCBF, MCAv, and PCAv from resting baseline values (Fig. 3*A*–*C*; $P < 0.003$). At 100% W_{max} gCBF, MCAv and PCAv returned to baseline levels at SL, whereas at HA they remained elevated ($P < 0.003$, Table 3; Fig. 3). Similar temporal changes in gCBF were also apparent when estimated via the Fick equation at HA and SL (Fig. 3*D*). The CD_{O_2} progressively increased ($P < 0.003$ *vs.* rest, Table 3; Fig. 4*A*) during exercise at SL (~+16%) and HA (~+14%). Although the magnitude of the MAP response was similar at both altitudes during exercise, MAP was elevated above rest at 60–100% W_{max} at SL and only at 100% W_{max} at HA. Because the exercise response in MAP was similar at SL and HA, and CBF was elevated during maximal exercise intensities (>60% W_{max}) at HA, CVCi was higher at HA. However the temporal change from rest at SL and HA was comparable. An elevated CD_{Gluc} was observed at HA during all exercise intensities compared with SL (~16–30%; $P < 0.05$, Fig. 5*A*). Despite the greater increase in arterial lactate production during higher exercise intensities (80 and 100% W_{max}) at SL compared with HA ($P < 0.05$, Fig. 5*C*), the elevated gCBF resulted in similar increases in CD_{Lac} from rest at both altitudes. During exercise, although absolute CMR_{O_2} was higher at HA than SL at 20 and 40% W_{max} (+28% and 26%, respectively; $P < 0.05$), at the higher exercise intensities (i.e. 60–100% W_{max}) no statistical difference was evident (Fig. 4). Conversely, relative changes in CMR_{O_2} at HA and SL were similar from 20 to 80% W_{max}; however, during 100% W_{max} at HA the relative increase in CMR_{O_2} from rest

was almost halved (i.e. 17 *vs.* 27%; $P < 0.05$ *vs.* SL; Table 1). Incremental exercise did not elevate CMR_{Glu} from resting values at either altitude ($P > 0.003$); however, CMR_{Glu} at HA was greater (~50%) than SL across all workloads (Table 3; Fig. 5*B*). Similar progressive increases in CMR_{Lac} were observed throughout exercise at HA and SL (Fig. 5*D*).

Recovery

During recovery at SL, P_{a,O_2} was elevated from rest and returned to baseline after the 10th minute of recovery (Table 2; Fig. 2*A*). At HA, compared with rest, P_{a,O_2} was elevated from minute 2 of recovery (+ ~10 mmHg) until the 15th min (+ ~6 mmHg). Arterial pH was higher at HA compared with SL throughout recovery (Table 2; Fig. 2*D*). At SL, O_2EF was elevated from rest (34 ± 2%, Table 1) throughout the 2nd to 25th minute of recovery (39–43%; $P < 0.05$), however, it was unchanged from rest (38 ± 5%) at HA (Table 2). Glucose extraction and OGI (Fig. 6*A*) were not reliably different at HA and SL during recovery ($P > 0.003$). Lactate extraction remained elevated from rest until the 15th minute at HA (increase ~0.7 mmol l^{-1} *vs.* rest) and the 25th minute at SL (increased ~0.6 mmol l^{-1} *vs.* rest). At HA, the OCI remained reduced compared with rest at the 1st minute of recovery, and was elevated compared with SL OCI at 1st, 2nd, 4th and 6th minutes of recovery ($P < 0.003$, Table 2: Fig. 6*B*).

At HA, gCBF was greater throughout all of recovery compared to SL, but was only elevated from rest at 1st minute of recovery ($P < 0.05$; Table 4; Fig. 3*C*). At HA, MAP was greater than SL throughout recovery; however, CVRi and CVCi were not generally different between SL and HA. At SL and HA CD_{O_2} data were not different throughout recovery (Table 4; Fig. 4). The CD_{Glu} was only different between SL and HA during the last 5 min of recovery ($P < 0.05$, Table 4), while being similar to resting values throughout recovery at both altitudes ($P > 0.003$; Fig. 5*A*). Both arterial lactate concentration and CD_{Lac} remained elevated during recovery for the entire 30 min at both SL and HA ($P < 0.003$). The elevated gCBF at HA did not sufficiently compensate for the reduced arterial lactate concentration, resulting in a lower CD_{Lac} for most of recovery at HA compared with SL ($P < 0.05$, Fig. 5*C*). When compared with SL, there was a greater absolute CMR_{O_2} at HA during the entire 30 min of recovery ($P < 0.05$, Table 4, Fig. 4*B*), despite an unaltered CMR_{Glu} and CMR_{Lac} compared to rest at either altitude (Table 4,

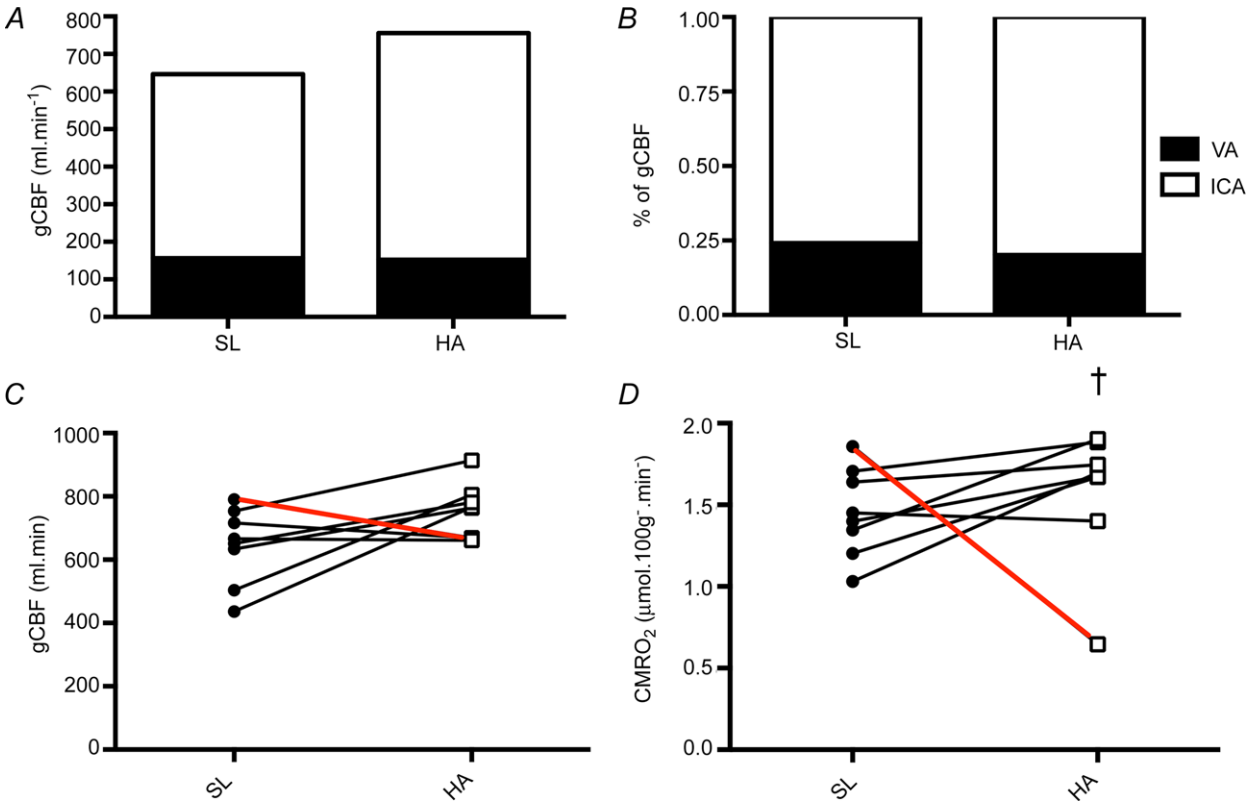

Figure 1. Baseline comparisons of CBF and $CMRO_2$ at high altitude (HA) and sea-level (SL)
Absolute (*A*) and relative (*B*) contributions of internal carotid (ICA) and vertebral (VA) artery blood flow to resting global cerebral blood flow (gCBF; *C*) as well as the resting cerebral metabolic rate of oxygen (CMR_{O_2}; *D*) at sea level (SL) and high altitude (HA). The red line indicates subject No. 5's CMR_{O_2} response to HA and illustrates the outlier response (see Results for statistical details). †Significant difference between SL and HA ($P < 0.05$).

Fig. 5*B*). However, CMR_{Glu} was higher at HA compared with SL values during the 1st, 2nd, 4th, 25th and 30th minutes of recovery, whereas CMR_{Lac} was lower at HA during 1st, 2nd and 4th minutes of recovery compared with SL ($P < 0.05$).

Cumulative metabolism

The cumulative molar ratio of carbohydrate to oxygen (CMRU) progressively rose from baseline to the end of recovery (Fig. 4; $P < 0.003$), with it being higher at rest and during submaximal exercise (20–60% W_{max}) at HA compared to SL ($P < 0.05$), but lower during recovery at HA compared to SL (interaction: $P = 0.001$). There was a similar rise in the cumulative metabolic ratio of carbohydrate to oxygen ($CMRU_{gCBF}$) from baseline to the end of recovery ($P < 0.003$). (Fig. 4)

Discussion

Our main novel findings were as follows. (1) Following partial acclimatization to HA, elevations in gCBF during and following exercise facilitate the maintenance of CD_{O_2}. Despite this maintained CD_{O_2}, CMR_{O_2} was generally elevated during submaximal exercise and recovery compared with SL. At maximal exercise, however, the increase in CMR_{O_2} at HA was approximately half that of the SL response. (2) Despite a CD_{O_2} in excess of CMR_{O_2} at HA and SL (Fig. 7), the brain appears to increase non-oxidative metabolism, as reflected by an OCI lower than six (complete oxidation of carbohydrates), during exercise and recovery. The reason for this latter finding is not obvious; however, the greater arterial lactate during exercise at HA compared with SL during similar workloads and the continued maintenance of the non-oxidative metabolism and greater arterial lactate during recovery at SL may implicate lactate availability as a key factor.

Global cerebral blood flow and delivery at high altitude: rest, exercise and recovery

The temporal changes in gCBF rest upon initial arrival and over time at HA (>3500 m) that serve to maintain CD_{O_2} have been well described in seven studies (Ainslie & Subudhi, 2014). Although isocapnic hypoxia at SL causes a greater increase in posterior blood flow comparable to anterior flow (Willie *et al.* 2012), the lack of regional changes in CBF is consistent with other studies over a comparable time frame at altitudes >5000 m (Willie *et al.* 2013; Subudhi *et al.* 2014). In contrast, only four

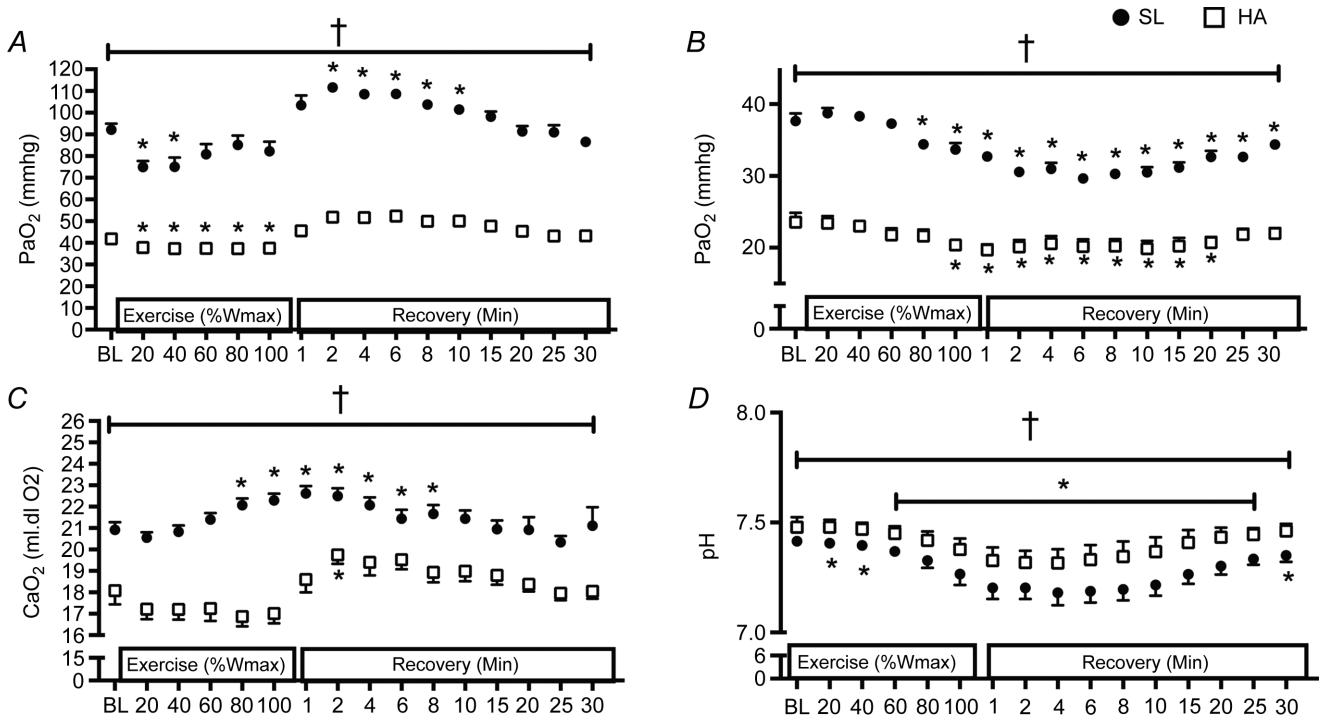

Figure 2. Arterial blood gas and acidemia during exercise and recovery at high altitude (HA) and sea-level (SL)
Arterial partial pressure of oxygen (P_{a,O_2}; *A*) and carbon dioxide (P_{a,CO_2}; *B*) as well as arterial oxygen content (C_{a,O_2}; *C*) and pH (*D*) during baseline (BL) incremental exercise (20–100% of the maximum achieved workload (%W_{max})) and 30 min of recovery at sea level (SL; •) and high altitude (HA; □). *Significant differences from BL, †significant difference between SL and HA ($P < 0.05$).

studies have monitored CBF (Möller *et al.* 2002) or velocity (Huang *et al.* 1991; Imray *et al.* 2005; Siebenmann *et al.* 2013) during exercise at HA, but none of these studies measured regional CBF distribution, oxygen delivery, or metabolism during exercise despite previous findings showcasing regional differences between specific brain regions that control motor/sensory, cerebellum and/or brainstem regions (Herholz *et al.* 1987). Nevertheless, at a global inflow level the regional distributions from the current study were not different during exercise and recovery at either altitude. This is in contrast to the larger increase in VA flow compared with ICA changes during upright exercise at SL observed by Sato *et al.* (2011).

Möller *et al.* (2002) observed gCBF to be unaltered from supine rest during both SL and HA upright exercise. Furthermore, no differences in gCBF were observed between SL and HA during exercise with similar absolute workloads (i.e. 100 W) at SL and HA. This finding is supported by Huang *et al.* (1991) who reported no difference in absolute change in ICA velocity during exercise following a prolonged exposure to HA (~18 days). However, the authors reported a larger relative increase in ICA velocity from rest during an incremental exercise bout to exhaustion following acute exposure to hypobaric hypoxia (barometric pressure and inspired P_{O_2} similar to 4300 m; ~+30%) *vs.* SL (~17%). Only limited interpretations are possible regarding gCBF because the authors did not report VA measurements or ICA diameter (Huang *et al.* 1991). Imray *et al.* (2005) reported that despite an increased MCAv following acute exposure to HA (5260 m; <1–2 days), the estimated CD_{O_2} (i.e. MCAv × arterial oxygen saturation) was reduced at maximal exercise compared to the maintained CD_{O_2} at sea level (150 m), as reflected in both a reduction in saturation and MCAv baseline measures at maximal exercise. During incremental exercise at moderate altitude (i.e. 3454 m), Siebenmann *et al.* (2013) observed an unexpected elevation in MCAv during maximal intensities when compared to the reductions observed at SL (Moraine *et al.* 1993; Sato *et al.* 2011; Smith *et al.* 2012; Fisher *et al.* 2013). Our findings support those of Siebenmann *et al.* (2013) such that gCBF during exercise at HA is increased during maximal exercise intensities compared with SL. Moreover, our study extends these previous findings from a lower elevation by incorporating both anterior and posterior regional volumetric flow. The functional relevance

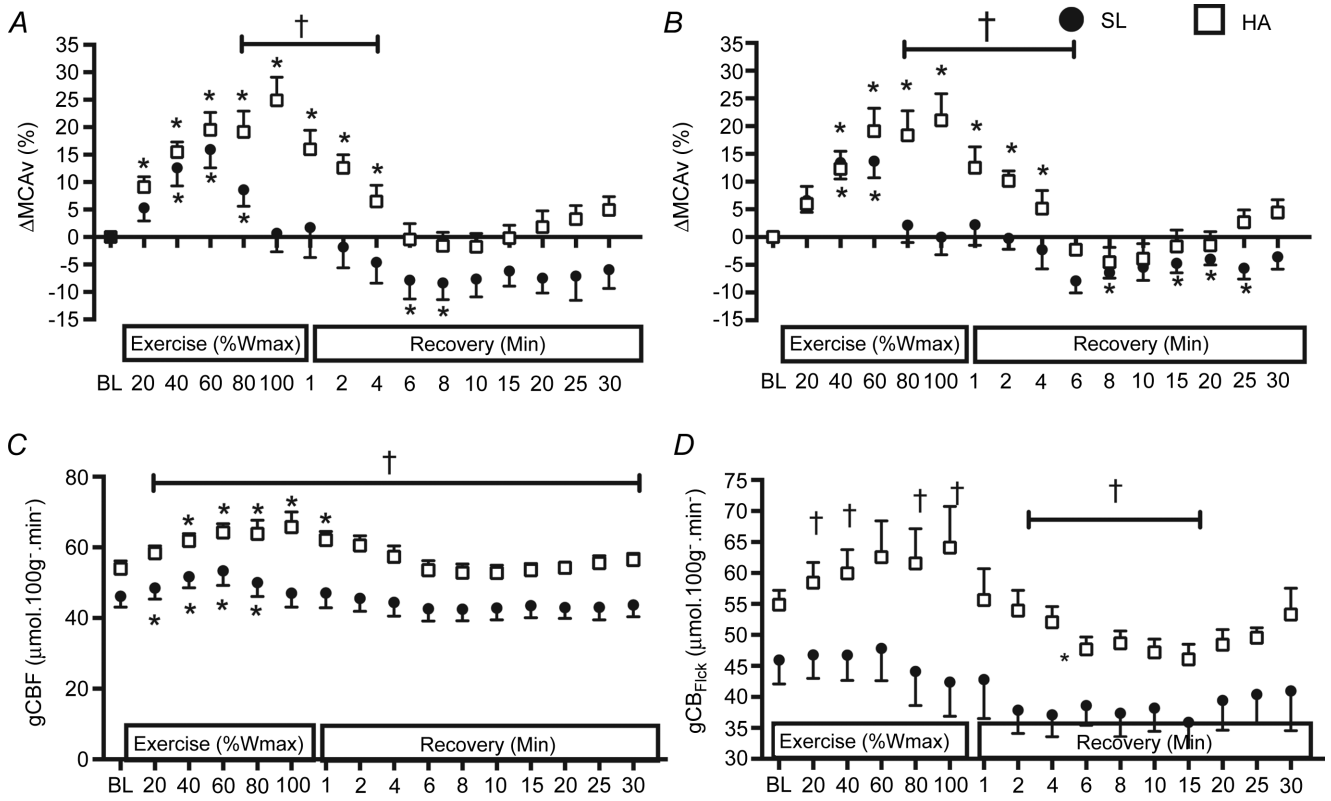

Figure 3. Cerebral blood flow measures during exercise and recovery at high altitude (HA) and sea-level (SL)
Cerebral blood flow velocity in the middle (MCAv; *A*) and posterior (PCAv; *B*) cerebral arteries, and global cerebral blood flow as measured by ultrasound (gCBF; *C*) and the Fick principle ($gCBF_{Fick}$; *D*) during baseline (BL) incremental exercise (20–100% of the maximum achieved workload (%W_{max})) and 30 min of recovery at sea level (SL; •) and high altitude (HA; □). *Significant differences from BL, †significant difference between SL and HA ($P < 0.05$).

of the 'paradoxical' elevation in gCBF at maximal exercise at HA is unknown but is likely to be beneficial for the maintenance of CD_{O_2} in excess of CMR_{O_2}, as observed during SL exercise.

At HA, the elevated gCBF during maximal exercise remained elevated above SL throughout recovery. One possible explanation for this is that during recovery fluctuations in gCBF reflect the need to preserve CD_{O_2} in excess of CMR_{O_2}.

Cerebral oxygen delivery, extraction, and metabolism during exercise

Three novel findings related to CD_{O_2}, extraction and metabolism have been revealed.

(1) Persistent maintenance of oxygen delivery during exercise. Following partial acclimatization to HA with a reduced C_{a,O_2} (Tables 1 and 2), our findings highlight a compensatory increase in gCBF during exercise at HA in order to maintain CD_{O_2} at HA in response to a reduced C_{a,O_2}. Evidence indicates that the CBF response to hypoxia appears to be determined more by oxygen content than by x. For example, studies using carbon monoxide exposure (Paulson *et al.* 1973; Todd *et al.* 1994) acute or chronic anaemia (Brown & Marshall, 1985; Brown *et al.* 1985) or haemodilution have all reported elevations in CBF independent of changes in P_{a,O_2} (Paulson *et al.* 1973; Todd *et al.* 1994; Tomiyama *et al.* 1999); thus, C_{a,O_2} (or haemoglobin) seems to regulate CBF not necessarily just P_{a,O_2}. In contrast, despite elevated limb blood flow during exercise at high altitude (5260 m) following haemodilution, O_2 delivery is not maintained (Calbet *et al.* 2002). These findings highlight a differential capacity or mechanism involving the regulation of oxygen delivery between the muscle and the brain during exercise at high altitude.

The two previous studies that have attempted to investigate CD_{O_2} during exercise at high altitude have reported that CD_{O_2} delivery is unaltered during moderate intensity exercise (Moller *et al.* 2002) and reduced (by ~18%) at maximal exercise (Imray *et al.* 2005). There are two distinct differences between the Imray *et al.* (2005) study and the current study. First, Imray *et al.* (2005)

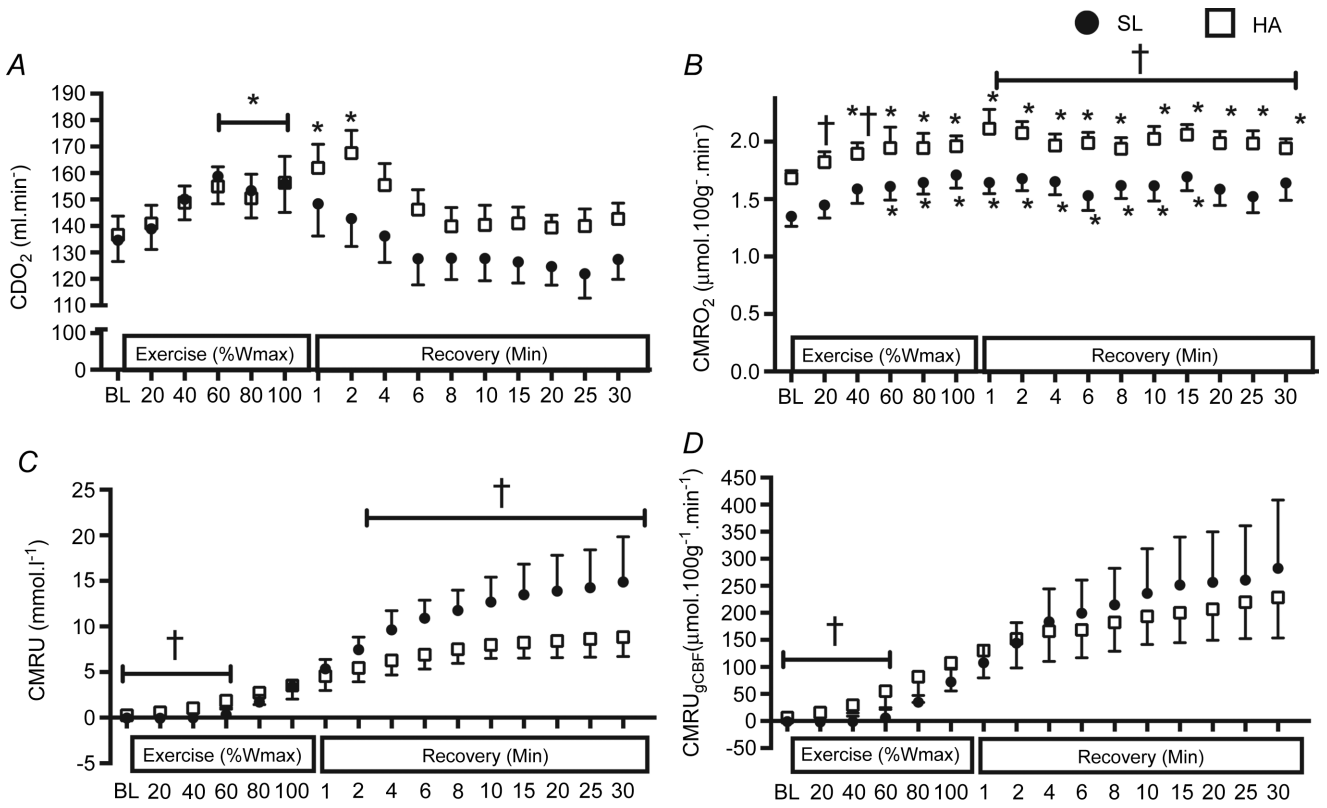

Figure 4. Cerebral oxygen delivery, metabolism and metabolic substrate utilization during exercise and recovery at high altitude (HA) and sea-level (SL)
Cerebral oxygen delivery (CD_{O_2}; *A*), cerebral metabolic rate of oxygen (CMR_{O_2}; *B*), cumulative metabolic ratio uptake (CMRU (mmol l^{-1}); *C*) and cumulative metabolic rate factored for cerebral blood flow differences ($CMRU_{gCBF}$ (mmol (100 g)$^{-1}$ min^{-1}), *D*) during baseline (BL) incremental exercise (20–100% of the maximum achieved workload (%W_{max})) and 30 min of recovery at sea level (SL; •) and high altitude (HA; □). *Significant differences from BL, †significant difference between SL and HA ($P < 0.05$).

estimated CD_{O_2} by multiplying arterial saturation (S_{a,O_2}) and MCAv, whereas we measured CD_{O_2} by measuring arterial oxygen content and utilizing a combination of volumetric flow measures (i.e. $Q_{ICA} + Q_{VA}$) and velocity measures (i.e. ΔMCAv and ΔPCAv). Second, during maximal exercise at high altitude Imray *et al.* (2005) observed a drop in MCAv similar to SL. In contrast, and generally consistent with another report at 3454 m (Siebenmann *et al.* (2013), we observed that gCBF, MCAv, and PCAv during maximal exercise continued to be elevated from resting values; such changes subsequently maintaining CD_{O_2} above rest at HA compared to levels observed during exercise at SL. The mechanisms explaining the tight control of gCBF and CD_{O_2} in excess of CMR_{O_2} during exercise are unknown, but are likely to involve one of two possible standpoints, namely that (1) gCBF and CD_{O_2} are not tightly coupled to CMR_{O_2} as indicated by a lack of linearity between increases in $gCBF/CD_{O_2}$ and CMR_{O_2} (Fox & Raichle, 1986; Fox *et al.* 1988); and (2) the coupling between delivery and metabolism may be described by an exponential relationship (Buxton & Frank, 1997). The latter is believed to be related to a limited capacity for cerebral capillary recruitment and a constant or fixed oxygen diffusion through from the capillaries to the cerebral tissues, ultimately requiring a large increase in gCBF and/or oxygen extraction to elevate CMR_{O_2} (Buxton & Frank, 1997; Mintun *et al.* 2001). For example, unlike in the skeletal muscle or the lungs, it is generally accepted that the diffusive surface area for O_2 remains constant in the brain – i.e. the brain does not increase capillary recruitment (Kuchinsky *et al.* 1992; William *et al.* 1993). Therefore, cerebral oxygen extraction can be described as being inversely proportional to CBF when metabolism is held constant, and directly proportional to metabolism when CBF is held constant.

Acclimatization to HA is a multifaceted process involving cardiorespiratory and renal compensatory changes that are most dynamic during the first few weeks of exposure (Ogoh & Ainslie, 2010; Ainslie & Subudhi, 2014). Hypoxic stimulation of the peripheral chemoreceptors leads to hyperventilation, resulting in hypocapnia and respiratory alkalosis for which renal bicarbonate excretion slowly compensates. The balance between neuronal substrate demand, blood pressure, arterial blood gases, and pH determines the volume of blood flow to the brain (Willie *et al.* 2014). Ascent to HA thus represents a complex stimulus to the cerebrovasculature, the nature of which

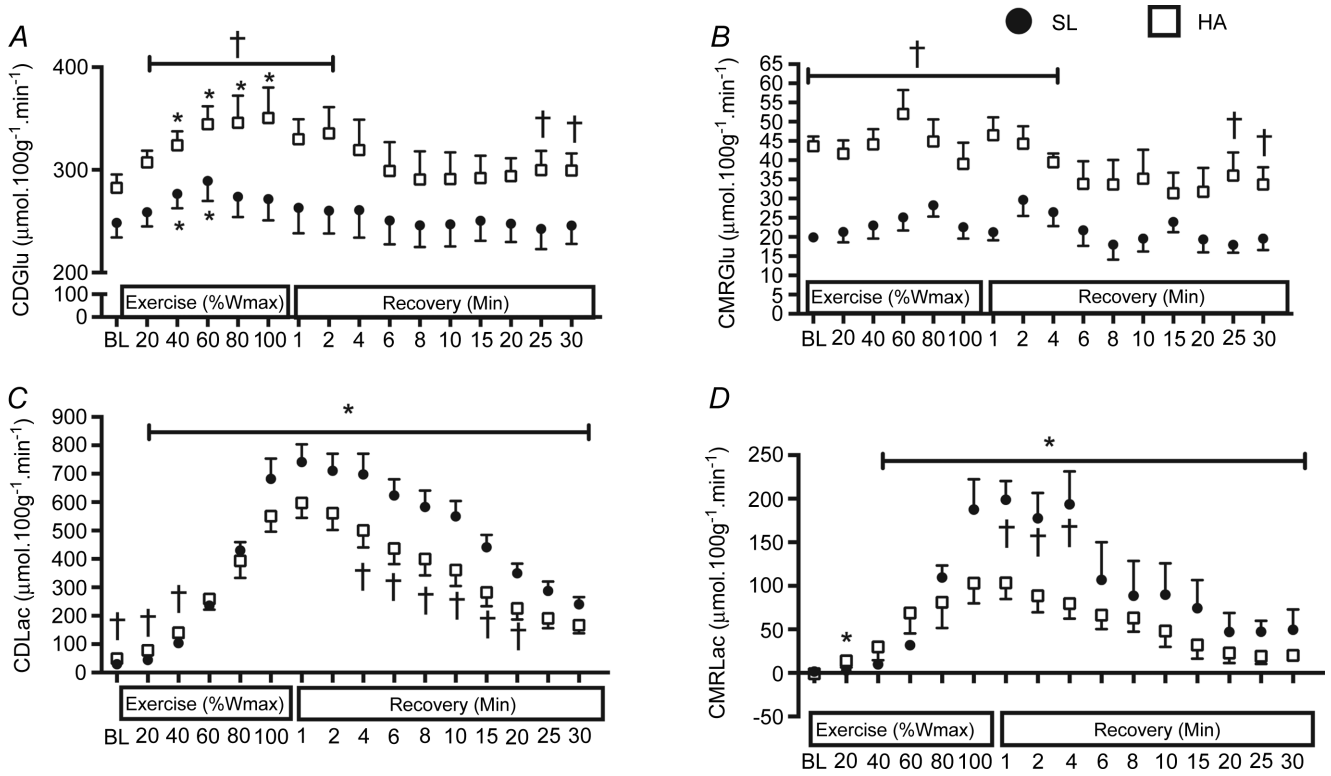

Figure 5. Cerebral metabolic substrate delivery (CD Glu and Lac) and metabolic rate (CMR Glu and Lac) during exercise and recovery at high altitude (HA) and sea-level (SL)
Cerebral delivery of glucose (CD_{Glu}; *A*) and lactate (CD_{Lac}:*C*), cerebral metabolic rate of glucose (CMR_{Glu}; *B*) and lactate (CMR_{Lac}; *D*) during baseline (BL) incremental exercise (20–100% of the maximum achieved workload (%W_{max})) and 30 min of recovery at sea level (SL; •) and high altitude (HA; □). *Significant differences from BL, †significant difference between SL and HA ($P < 0.05$).

Table 4. Cerebral blood flow and metabolism measurements during recovery at sea level and high altitude

		Recovery (min)									
Variable	Condition	1	2	4	6	8	10	15	20	25	30
MCAv (cm s^{-1})	SL	73 ± 15	70 ± 12	68 ± 12	66 ± 11*	65 ± 10*	66 ± 10	67 ± 11	66 ± 10	66 ± 12	67 ± 12
	HA	88 ± 10*,†	85 ± 9*,†	81 ± 10*,†	75 ± 8	74 ± 7	74 ± 7	75 ± 8	77 ± 10	78 ± 10	79 ± 11
PCAv (cm s^{-1})	SL	51 ± 12	49 ± 10	48 ± 11	45 ± 8*	46 ± 8*	48 ± 10	47 ± 9*	47 ± 8*	46 ± 8*	47 ± 9
	HA	61 ± 9*,†	60 ± 9*,†	58 ± 10*,†	53 ± 9	53 ± 9	52 ± 7	53 ± 4	54 ± 8	56 ± 8†	57 ± 9†
Q_{ICA} (l min^{-1})	SL		283 ± 99	267 ± 84	269 ± 85	260 ± 91	259 ± 89	259 ± 89	258 ± 80	264 ± 76	263 ± 91
	HA	350 ± 48	349 ± 71	340 ± 89	328 ± 89	323 ± 94	324 ± 94	327 ± 66	322 ± 61	330 ± 68	321 ± 66
ICA_{diam} (cm)	SL	—	—	0.53 ± 0.04	0.53 ± 0.04	0.58 ± 0.04	0.55 ± 0.06	0.52 ± 0.05	0.54 ± 0.05	0.54 ± 0.05	0.52 ± 0.07
	HA	—	—	0.55 ± 0.8	0.54 ± 0.08	0.55 ± 0.08	0.54 ± 0.54	0.55 ± 0.07	0.55 ± 0.07	0.56 ± 0.08	0.55 ± 0.08
ICA_{vel} (cm s^{-1})	SL	—	—	38 ± 7	39 ± 9	36 ± 8	36 ± 6	40 ± 4	37 ± 6	38 ± 6	41 ± 5*
	HA	—	—	48 ± 5†	47 ± 5†	45 ± 5†	46 ± 2†	46 ± 10	45 ± 8	45 ± 9	46 ± 9
Q_{VA} (l min^{-1})	SL	—	—		81 ± 35	80 ± 35	85 ± 38	76 ± 33	70 ± 31	77 ± 37	81 ± 33
	HA	—	—	—	—	—	—	—	—	—	—
gCBF (ml (100 g)$^{-1}$ min^{-1})	SL	47 ± 12	46 ± 10	44 ± 11	43 ± 10	42 ± 10	43 ± 9	43 ± 9	43 ± 9	43 ± 10	44 ± 9
	HA	62 ± 8*,†	61 ± 8†	57 ± 9†	54 ± 8†	53 ± 7†	53 ± 6†	54 ± 5†	54 ± 4†	56 ± 6†	56 ± 5†
$CVRi_{gCBF}$	SL	2.2 ± 0.7	2.2 ± 0.6	2.0 ± 0.6	2.0 ± 0.6	1.8 ± 0.6	2.0 ± 0.5	2.0 ± 0.5	2.1 ± 0.5	2.1 ± 0.6	2.1 ± 0.5
	HA	1.8 ± 0.2	1.7 ± 0.2†	1.8 ± 0.3	1.9 ± 0.3	1.8 ± 0.3	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2
$CVCi_{gCBF}$	SL	0.48 ± 0.13	0.48 ± 0.12	0.53 ± 0.15	0.53 ± 0.15	0.64 ± 0.29	0.53 ± 0.13	0.52 ± 0.10	0.50 ± 0.10	0.49 ± 0.11	0.50 ± 0.10
	HA	0.55 ± 0.06	0.59 ± 0.09	0.58 ± 0.11	0.55 ± 0.10	0.55 ± 0.09	0.55 ± 0.09	0.54 ± 0.08	0.56 ± 0.08	0.55 ± 0.07	0.56 ± 0.07
CD_{O_2} (ml.dl^{-1} min^{-1})	SL	148 ± 34	143 ± 30	136 ± 28	128 ± 28	128 ± 23	128 ± 24	126 ± 23	125 ± 20	122 ± 26	127 ± 21
	HA	162 ± 25*	168 ± 24*	155 ± 23*	146 ± 21	140 ± 20	140 ± 21	141 ± 17	140 ± 13	140 ± 18	143 ± 16
CD_{Glu} (μmol ml (100 g)$^{-1}$ min^{-1})	SL	262 ± 70	260 ± 63	261 ± 76	251 ± 65	246 ± 60	247 ± 61	250 ± 55	248 ± 50	242 ± 6	246 ± 50
	HA	330 ± 54	335 ± 73	319 ± 84	300 ± 79	291 ± 73	291 ± 74	292 ± 62	294 ± 49	299 ± 53†	299 ± 47†
CD_{Lac} (μmol (100 g)$^{-1}$ min^{-1})	SL	741 ± 178*	710 ± 169*	698 ± 204*	623 ± 162*	583 ± 163*	549 ± 153*	441 ± 122*	350 ± 97*	287 ± 93*	240 ± 72*
	HA	597 ± 148*	561 ± 167*	501 ± 171*	438 ± 156*,†	400 ± 163*,†	361 ± 150*,†	282 ± 139*,†	226 ± 111*,†	190 ± 97*	167 ± 82*
CMR_{O_2} (μmol (100 g)$^{-1}$ min^{-1})	SL	1.6 ± 0.2*	1.7 ± 0.3*	1.7 ± 0.3*	1.6 ± 0.3*	1.6 ± 0.3*	1.6 ± 0.3*	1.7 ± 0.3*	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3
	HA	2.1 ± 0.4*,†	2.1 ± 0.4*,†	2.0 ± 0.2*,†	2.0 ± 0.2*,†	2.0 ± 0.2*,†	2.0 ± 0.3*,†	2.1 ± 0.2*,†	2.0 ± 0.3*,†	2.0 ± 0.3*,†	1.9 ± 0.2*,†
CMR_{Glu} (μmol (100 g)$^{-1}$ min^{-1})	SL	21 ± 6	30 ± 11	26 ± 10	22 ± 11	18 ± 10	20 ± 9	24 ± 7	19 ± 9	18 ± 5	20 ± 8
	HA	44 ± 12†	44 ± 12†	40 ± 6†	34 ± 16	34 ± 17	35 ± 20	31 ± 14	32 ± 16	36 ± 16†	34 ± 12†
CMR_{Lac} (μmol (100 g)$^{-1}$ min^{-1})	SL	199 ± 85	178 ± 79	194 ± 100	107 ± 114	89 ± 106	89 ± 95	74 ± 85	47 ± 58	47 ± 33	50 ± 61
	HA	103 ± 61†	89 ± 51†	80 ± 46†	66 ± 42	63 ± 41	48 ± 48	32 ± 41	32 ± 41	19 ± 23	20 ± 15

MCAv, middle cerebral artery velocity; PCAv, posterior cerebral artery velocity; Q_{ICA}, internal carotid blood flow; ICA_{diam}, internal carotid artery diameter; ICA_{vel}, internal carotid artery velocity; Q_{VA}, vertebral blood flow; VA_{diam}, vertebral artery diameter; VA_{vel}, vertebral artery velocity; gCFB, global cerebral blood flow; $CVRi_{gCBF}$, cerebrovascular resistance; $CVCi_{gCBF}$, cerebrovascular conductance; CD_{O_2}, cerebral oxygen delivery; CD_{Glu}, cerebral glucose delivery; CD_{Lac}, cerebral lactate delivery; CMR_{O_2}, cerebral metabolic rate of oxygen; CMR_{Glu}, cerebral metabolic rate of glucose; CMR_{Lac}, cerebral metabolic rate of lactate. *Significant differences from baseline ($P < 0.003$), †significant differences between SL and HA ($P < 0.05$).

is not well understood, particularly in light of sustained alterations and compensations in arterial blood gases and pH. The sensitivity of CBF to CO_2 appears to rely on diffusion of molecular CO_2 into the vascular wall where the resultant shift in extracellular pH drives changes in smooth muscle tone (Lassen *et al.* 1968). That CBF is a function of extravascular pH rather than arterial pH is further supported in earlier studies showing that CBF at HA was equivalent to SL despite chronic alkalosis, indicating CBF CO_2 sensitivity is reset over time at HA (reviewed in: Ainslie & Subudhi, 2014). The implications of such adjustments are that CBF are likely to be regulated differently by P_{a,CO_2} and pH at rest and during exercise at HA.

(2) Differential changes in CMR_{O_2} and extraction during exercise. Cerebral perfusion and oxygen extraction elevations during incremental cycling exercise at SL result in a 25% increase in CMR_{O_2} at maximal intensity when estimating gCBF using relative changes in MCAv (Fisher *et al.* 2013). A similar increase in CMR_{O_2} is observed during a maximal rowing time trial (Rasmussen *et al.* 2010). These findings are similar to our results, which indicate a progressive rise in CMR_{O_2} from rest during incremental exercise, with the largest increase occurring at 100% W_{max} (up ~30%). In contrast, Trangmar *et al.* (2014) did not observe an increase in CMR_{O_2} at any point during incremental exercise to exhaustion when using ICA flow as an index for gCBF. However, Trangmar *et al.* (2014) underestimated CBF by only measuring the flow in the anterior circulation, as VA flow has been shown to progressively increase during incremental exercise up to at least 80% $\dot{V}_{O_2,peak}$ (~35–60% above baseline (Sato *et al.* 2011)). Based on our exercise data, and in agreement with others (Möller *et al.* 2002; Overgaard *et al.* 2012; Fisher *et al.* 2013), CMR_{O_2} does not appear to be altered until maximal intensity exercise is achieved at both SL and HA. Our data show a differential response, with the increase in CMR_{O_2} at HA achieved through increases in gCBF (Figs 3 and 4), whereas at SL the increase is achieved via an increased oxygen extraction (Table 3). In comparison, the HA CMR_{O_2} value is greater than SL during exercise at the same workloads (20, 60, 150 W; Fig. 6). The differences between the relative increase in CMR_{O_2} from rest to maximal exercise at HA (~17%) and SL (~27%) is most likely related to the lower absolute maximum workload achieved at HA (150 W) *vs.* SL (300 W). Collectively, these findings are consistent with the reported linear relationship between absolute intensity/frequency-dependent increases in focal CMR_{O_2} during graded motor activation (i.e. finger tapping) (Kastrup *et al.* 1999).

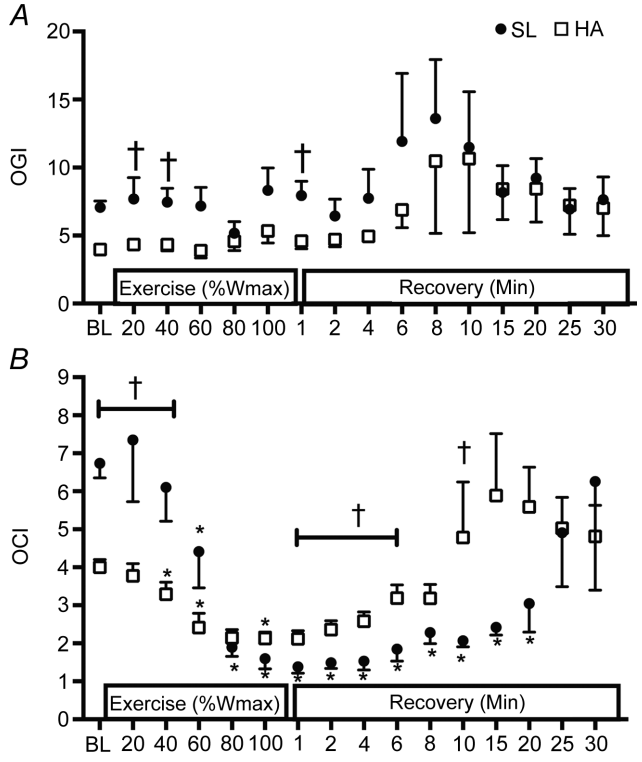

Figure 6. Cerebral oxidative ratio of glucose (OGI) and carbohydrates (OCI) during exercise and recovery high altitude (HA) and sea-level (SL)
The ratio of oxygen and glucose uptake (OGI = O_2/glucose; *A*) and ratio oxygen to carbohydrate uptake (OCI = O_2/glucose + ½lactate; *B*) as an indexes of oxidative *vs.* non-oxidative metabolism during baseline (BL) incremental exercise (20–100% of the maximum achieved workload (%W_{max})) and 30 min of recovery at sea level (SL; •) and high altitude (HA; □). *Significant differences from BL, †significant difference between SL and HA ($P < 0.05$).

(3) Non-oxidative metabolism during exercise and recovery. At HA there was a disproportionate increase in carbohydrate uptake *vs.* oxygen uptake (i.e. reduced OCI) at rest and during low-to-moderate intensity (20 to 60% W_{max}) exercise compared with SL. The disproportionate increase is believed to indicate that the brain has altered a portion of its ATP production from an oxidative to a non-oxidative pathway (Wyss *et al.* 2011). Additionally, at HA both at rest and during all exercise intensities except 100% W_{max}, CMRU and $CMRU_{gCBF}$ were higher than SL (Fig. 4). However, with increasing exercise intensity (60, 80 and 100% W_{max}) OCI was not noticeably different at HA compared with SL. During recovery, OCI at HA returned to resting values almost immediately following the cessation of exercise and was elevated above SL for much of recovery, whereas SL OCI remained below resting values for most of recovery. Furthermore, the increase in CMRU during HA recovery was approximately half of SL values. However, no reliable statistically significant difference was observed for the $CMRU_{gCBF}$ during recovery for either altitude compared to rest, nor

was there a difference between SL and HA values. The measurement of CMRU indicates the molar quantity of carbohydrate substrate that is in excess of the oxygen extraction, while $CMRU_{gCBF}$ incorporates the gCBF, providing both a convective and diffusive component to cerebral carbohydrate metabolism. Collectively, these findings indicate that the surplus of cerebral carbohydrate uptake compared with oxygen uptake during exercise at SL was greater at HA, and independent of gCBF. During recovery the elevated gCBF results in a similar contribution of non-oxidative at HA and SL (Fig. 3).

Our findings are both consistent and inconsistent with Volianitis *et al.* (2008) who despite a reduction in OCI with exercise intensity during normoxic and moderate hypoxic steady-state 2000 m rowing time trials, observed no significant difference in OCI when oxygen intake was varied. The discrepancies between the Volianitis *et al.* (2008) study and our findings may be related to the difference in the intensity of the hypoxic exposure, with their study inducing a mild ($F_{IO_2} = 0.17$) hypoxic exposure *vs.* the more severe exposure of our HA ($\sim F_{IO_2} = 0.108$ at 5050 m). Another possibility may be related to the exercise intensity, such that during the 2000 m rowing time trials, the intensity was above the submaximal intensities that elicited the differences observed in the current study. As illustrated in Fig. 6, greater amounts of arterial lactate were produced, which, in the context of the increased CMRU (Fig. 4) and reduced OCI (Fig. 5) at HA during exercise at the same workload (20 *vs.* 40%, 40 *vs.* 80%, and 60 *vs.* 100% W_{max} at SL and HA, respectively), suggests the increase in non-oxidative metabolism may be not only intensity dependent but also lactate dependent. However, Volianitis *et al.* (2011) observed no difference in OCI during a SL rowing time trial with an elevated pH and greater arterial lactate production. Our sea-level response is similar to the response observed by Dalsgaard *et al.* (2004), who reported that the CMRU increased during a 15 min exercise bout to exhaustion. Unfortunately, a hypoxic trial was not conducted. It seems likely that the combination of a greater workload and subsequent increase in the production of lactate in the current data set may explain the difference in the changes to oxidative and non-oxidative metabolism during exercise and recovery at SL and HA.

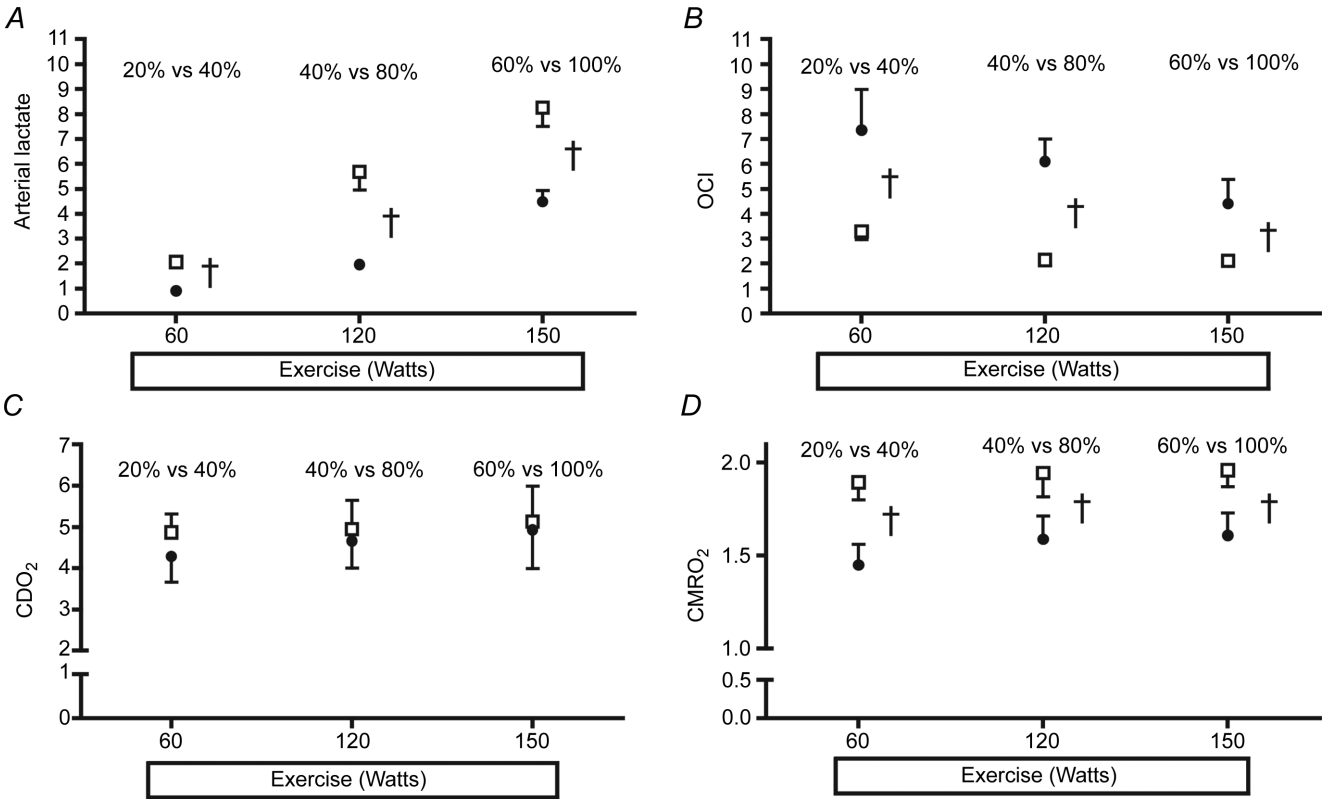

Figure 7. Comparison of lactate, carbohydrate oxidative ratio, oxygen delivery, and metabolism during exercise at similiar aboslute intensities
Arterial lactate concentration (*A*), ratio of oxygen to carbohydrate uptake (OCI = O_2/glucose + ½lactate; *B*), cerebral oxygen delivery (CD_{O_2}; *C*), and cerebral metabolic rate of oxygen (CMR_{O_2}; *D*) during incremental exercise at the same absolute workload (60, 120 and 150 W) at sea level (SL; •) and high altitude (HA; □). †Significant difference between SL and HA ($P < 0.05$).

Methodological considerations and limitations

The current study was performed in a controlled laboratory setting at sea level, as well as in a high-altitude laboratory at 5050 m following a 9 day ascent. Unfortunately, because of sickness and time constraints, we were only able to collect data in 9 out of the 12 subjects. Our data set and results only pertain to males, as no females were studied. Casey *et al.* (2014) demonstrated that, at sea level, women had an elevated hypoxic vasodilatory response in the forearm at rest and during exercise independent of baseline forearm blood volume. However, it remains unknown if any sex differences exist in the gCBF response during exercise at HA; control of menstrual phase and extent of acclimatization during these conditions would be problematic.

It is important to note, that all CBF measurements were made using either vascular ultrasound or a combination of vascular (Lewis *et al.* 2014) and transcranial (TCD) ultrasound (Gonzalez-Alonso, 2004). Each measurement of gCBF utilizes the blood flow measurements in the right ICA and left VA (Lewis *et al.* 2014; Subudhi *et al.* 2014). Despite no reported differences in blood flow between contralateral ICAs, a regional disparity (∼20%) between contralateral vertebral vessels has been observed (Schöning *et al.* 1994). However, should a disparity between contralateral VAs exist in the current study at rest, one would anticipate that the stimulus–response data would be similar during exercise. Moreover, the limitations of using TCD have been documented, with the primary concerns being related to whether or not the intracranial vessels change in diameter. Following ascent to HA the MCA diameter does increase (Wilson *et al.* 2011; Willie *et al.* 2013). Our finding at HA of an elevated Q_{ICA} flow at rest in the face of an unchanged MCAv is consistent with MCA dilatation. Although the changes in estimated gCBF were broadly consistent with the direct Fick measures, we cannot rule out dilatation of MCA during exercise considering dilatation is likely to be mediated via hypoxaemia, which was greater during exercise. However, since the reductions in P_{a,O_2} during exercise at HA were countered by a similar drop in P_{a,CO_2} and maintained pH (Fig. 2), this would seem unlikely; therefore, consistent with the direct Fick data, the stimulus–response changes in MCAv/PCAv seem valid during exercise at 5050 m. Furthermore, at both SL and HA, the observation that CVRi was not reduced supports our findings that there was no further active vasodilatation of the larger cerebral arteries (e.g. MCA and PCA) from rest during exercise.

Previous investigations of CBF and cerebral metabolism responses to HA have been compared during either similar absolute intensity exercise (Moller *et al.* 2002), or during incremental exercise tests with different durations (Imray *et al.* 2005; Seibennman *et al.* 2013). Each of the exercise intensities in the current study established steady state, allowing for comparison of both relative (Figs 2–6) and absolute exercise intensity (Fig. 6). For a given absolute workload, gCBF is elevated at HA compared with SL, such that it maintains CD_{O_2} in excess of CMR_{O_2}, while OCI is reduced as expected given the greater availability of arterial lactate at HA (∼50% more) *vs.* SL. In contrast, during exercise at HA, with similar workloads to SL, a reduced arterial lactate is reported despite reduced available oxygen (i.e. the lactate paradox; West, 1986; Kayser, 2006). It should be noted that all subjects would have been exercising for 3–6 min longer at HA for a given workload at SL. The increased time could allow greater accumulation of blood lactate and could explain part of the discrepancy between the current findings and previous investigations focusing on lactate production at HA during similar absolute workloads. We did not measure circulating catecholamines as a measure of adrenergic drive, which, if elevated at HA, may have influenced the different arterial lactate productions during exercise (Kayser, 2006), and possibly the increased non-oxidative metabolism (lower OCI) at rest and during exercise with the same workloads at HA (Fig. 7; Seifert *et al.* 2009; Seifert & Secher, 2011).

Conclusion

In conclusion, the elevations in gCBF during exercise and recovery at HA maintain an adequate CD_{O_2}-to-CMR_{O_2} ratio. Despite preservation of this ratio, as reflected by paralleled increases in CD_{O_2} and CMR_{O_2}, the brain appears to prefer non-oxidative metabolism during exercise and recovery at HA and SL, even if the contribution to total energy production is marginal.

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Additional information

Competing interests

The authors declare no conflict of interest with the present study.

Author contributions

Conception and Design of experiments: K.J.S, D.M, C.K.W, P.N.A; Collection, analysis and interpretation: K.J.S, D.M, C.K.W, N.C.S, R.L.H, K.I, M.M.T, J.D, T.A.D, N.M, P.N.A; Drafting the article or revising it critically for important intellectual content: K.J.S, D.M., C.K.W, S.J.E, N.C.S, J.D, T.A.D, P.N.A.

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