Dehydration affects cerebral blood flow but not its metabolic rate for oxygen during maximal exercise in trained humans

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Key points

- Dehydration accrued during exercise in the heat challenges systemic and locomotor muscle blood flow, but its impact on cerebral blood flow (CBF) and metabolism remains unknown.
- This study assessed whether dehydration compromises CBF and the cerebral metabolic rate for oxygen (CMRO₂) during incremental exercise to exhaustion in trained males.
- Dehydration induced an early reduction in CBF during progressive exercise, but increased O₂ extraction secured CMRO₂.
- In all hydration conditions declining CBF at high exercise intensities was correlated to decreasing arterial carbon dioxide tension and increasing jugular venous plasma noradrenaline.
- These results suggest that dehydration impairs CBF at high exercise intensities, but this circulatory strain on the human brain does not compromise CMRO₂.

Abstract

Intense exercise is associated with a reduction in cerebral blood flow (CBF), but regulation of CBF during strenuous exercise in the heat with dehydration is unclear. We assessed internal (ICA) and common carotid artery (CCA) haemodynamics (indicative of CBF and extra-cranial blood flow), middle cerebral artery velocity (MCA Vmean), arterial–venous differences and blood temperature in 10 trained males during incremental cycling to exhaustion in the heat (35°C) in control, dehydrated and rehydrated states. Dehydration reduced body mass (75.8 ± 3 vs. 78.2 ± 3 kg), increased internal temperature (38.3 ± 0.1 vs. 36.8 ± 0.1°C), impaired exercise capacity (269 ± 11 vs. 336 ± 14 W), and lowered ICA and MCA Vmean by 12–23% without compromising CCA blood flow. During euhydrated incremental exercise on a separate day, however, exercise capacity and ICA, MCA Vmean and CCA dynamics were preserved. The fast decline in cerebral perfusion with dehydration was accompanied by increased O₂ extraction (P < 0.05), resulting in a maintained cerebral metabolic rate for oxygen (CMRO₂). In all conditions, reductions in ICA and MCA Vmean were associated with declining cerebral vascular conductance, increasing jugular venous noradrenaline, and falling arterial carbon dioxide tension (Paco₂) (R² ≥ 0.41, P ≤ 0.01) whereas CCA flow and conductance were related to elevated blood temperature. In conclusion, dehydration accelerated the decline in CBF by decreasing Paco₂ and enhancing vasoconstrictor activity. However, the circulatory strain on the human brain during maximal exercise does not compromise CMRO₂ because of compensatory increases in O₂ extraction.
Introduction

Heat stress, with or without dehydration, compromises blood flow to active muscles and skin during strenuous exercise as the systemic circulation becomes compromised (González-Alonso & Calbet, 2003; González-Alonso et al. 2008; Crandall & González-Alonso, 2010). Intense exercise in the heat is also associated with a marked decline in middle cerebral artery blood velocity (MCA $V_{\text{mean}}$), suggesting attenuated cerebral perfusion (Nybo & Nielsen, 2001a,b; González-Alonso et al. 2004). Changes in MCA $V_{\text{mean}}$, however, may not reflect alterations in cerebral blood flow (CBF) as the vessel cross-sectional area remains unknown (Madsen et al. 1993; Jørgensen, 1995; Wilson et al. 2011; Willie et al. 2012). Additionally, dehydration intensifies the effect of heat stress on active muscle blood flow and increases the rate of heat storage in part by attenuating skin perfusion (Sawka et al. 1985; González-Alonso et al. 1995, 1998; Montain et al. 1998; Cheuvront et al. 2010). It remains unknown, however, whether dehydration affects CBF during maximal incremental exercise in the heat and, if so, how that is established.

On the transition from rest to moderate exercise, regional and global CBF increase to support neuronal activity (Ide & Secher, 2000; Secher et al. 2008; Ogoh & Ainslie, 2009a). However, CBF reaches a plateau or declines to baseline values prior to the attainment of maximal work rate (Madsen et al. 1993; Moraine et al. 1993; Hellström et al. 1996; Ide & Secher, 2000; Sato et al. 2011). During intense exercise, restricted cerebral perfusion could challenge the cerebral metabolic rate for oxygen (CMRO$_2$) (Nybo & Rasmussen, 2007; Rasmussen et al. 2010) and in part explain the orthostatic intolerance and reduced motor output with heat stress (Van Lieshout et al. 2003; Wilson et al. 2006; Brothers et al. 2009a; Nelson et al. 2011; Ross et al. 2012; Bain et al. 2013). Alternatively, reduced CBF can be compensated by increased oxygen extraction such that CMRO$_2$ is maintained or increased (Nybo et al. 2002; González-Alonso et al. 2004). Whether the CMRO$_2$ remains adequate during strenuous exercise in the heat with concomitant dehydration is yet unknown.

Understanding the mechanisms restricting CBF in intensely exercising humans is important for devising strategies that could ameliorate or delay its potential deleterious effects. During exercise, attenuation of CBF is in part due to cerebral vessel vasoconstriction, concomitantly with an increased systemic and regional cerebral sympathetic activity, increasing body temperature, and reduced arterial carbon dioxide tension ($P_{\text{aco2}}$) (Wilson et al. 2002; Querido & Sheel, 2007; Fan et al. 2008; Secher et al. 2008; Seifert & Secher, 2011). The cerebral vasculature is highly sensitive to changes in $P_{\text{aco2}}$, with elevations resulting in vasodilatation and reductions leading to vasoconstriction (Kety & Schmidt, 1948; Ogoh & Ainslie, 2009b; Willie et al. 2012). At rest, these responses are of importance for maintenance of a stable pH across the brain and reflect the sensitivity of the brainstem to acute changes in CO$_2$. However, $P_{\text{aco2}}$ only accounts for $\sim$7% of the CO$_2$ transported from the cerebral tissue whereas the majority of CO$_2$ is bound to haemoglobin (23%) or buffered as bicarbonate (70%). If local tissue pH balance is important for regulation of CBF, blood CO$_2$ content ($C_{\text{CO2}}$) could account for the alterations in cerebrovascular tone. It is also evident that changes in CO$_2$ are not associated with changes in conduit artery and extra-cranial (i.e. common (CCA) and external carotid artery (ECA)) tone and perfusion, as blood flow in these vessels increases progressively with exercise intensity (Hellström et al. 1996; Sato et al. 2011). Extra-cranial blood flow is likely to be controlled by thermoregulatory, rather than pH regulatory mechanisms (Fan et al. 2008; Sato et al. 2011, 2012; Bain et al. 2013; Ogoh et al. 2013); yet direct evidence for a relationship between flow and blood temperature is lacking. While evidence indicates differences in blood flow responses to exercise at the vascular beds perfusing the head, the impact of dehydration on graded exercise in the heat and the potential roles of $C_{\text{CO2}}$, $P_{\text{aco2}}$ and blood temperature in these responses have not been investigated.

The purpose of this study was to investigate cerebral and extra-cranial blood flow and CMRO$_2$ during incremental exercise to exhaustion in the heat, with and without dehydration, and to provide insights into the vascular mechanisms underpinning these responses. CBF was measured using Doppler ultrasonography, and arterial and internal jugular venous differences for oxygen, CO$_2$ and noradrenaline were measured for assessment of the exchange of these substances across the brain. We hypothesised that dehydration would accelerate the attainment
of maximal CCA blood flow but also accentuate the reduction in CBF during exercise in association with the lowering of $P_{\text{aco}_2}$ and $C_{\text{co}_2}$ and the increase in sympathetic activity, and yet increased $O_2$ extraction would maintain or enhance CMRO$_2$. 

**Methods**

**Ethical approval**

Fully informed, written consent was obtained from the participants prior to the study. All procedures were approved by the Brunel University Research Ethics Committee (RE07-11) and conformed to the guidelines of the Declaration of Helsinki.

**Participants**

Ten healthy experienced cyclists (mean ± SD; age 29 ± 5 years, stature 183 ± 5 cm, mass 78 ± 9 kg and $V_{\text{O}_2, \text{peak}}$ 59 ± 6 ml kg$^{-1}$ min$^{-1}$) participated in the study. All participants were non-smokers and free from cardio-respiratory, metabolic and neurological disease. Participants arrived at the laboratory postprandial with a normal hydration status and were required to have abstained from strenuous exercise and alcohol intake for 24 h and caffeine consumption for 12 h.

**Experimental design**

The participants visited the laboratory for three preliminary sessions followed by two experimental sessions, each separated by at least 1 week. On the first session the participants were introduced to the experimental set-up and familiarised with the methodology. Investigation of the extra-cranial arteries and MCA $V_{\text{mean}}$ Doppler spectra determined the reliability of images and identified the temporal ultrasound window and the position for the best signal-to-noise ratio. Participants performed incremental exercise on a semi-recumbent cycle ergometer (Lode Angio, Groningen, the Netherlands) with a backrest inclination of 45 deg, to establish the maximal work rate (WR$_{\text{max}}$), maximal heart rate, and $V_{\text{O}_2, \text{peak}}$. The initial work rate was 20 W for 3 min, followed by step increments of 60 W every 3 min until the limit of tolerance. Pedal cadence was maintained between 70 and 90 r.p.m. and the test was terminated when it dropped below 60 r.p.m., for more than 3 s, despite strong verbal encouragement to continue. On the second and third visits, participants cycled in an environmental chamber set at 35°C (relative humidity (RH) 50%) in the semi-recumbent position for 2 h at 55% WR$_{\text{max}}$ with heart rate and intestinal temperature recorded. No fluid consumption was permitted during exercise and body mass was recorded before and immediately post exercise.

The experimental days (visits 4 and 5) included three semi-recumbent incremental cycling exercise tests consisting of five 3 min stages of increasing intensities to WR$_{\text{max}}$ (Figs 1 and 2). In the first experimental trial, incremental cycling was completed in the following conditions: (1) in a ‘control’, hydrated state; (2) ‘dehydrated’ (DEH), ~5 min after 2 h of submaximal cycling without fluid ingestion; and (3) rehydrated (REH), after 1 h recovery with full fluid replacement. Work rates for control and REH were the same (67 ± 3, 134 ± 5, 202 ± 8, 269 ± 11 and 336 ± 14 W, corresponding to 20, 40, 60, 80 and 100% of WR$_{\text{max}}$) but in anticipation of a reduced exercise capacity when dehydrated, WR in DEH was reduced by 20% to maintain the same number of exercise stages and test duration with work rates set at 54 ± 2, 108 ± 4, 161 ± 7, 215 ± 9 and 269 ± 11 W, respectively. In the second experimental trial (i.e. euhydration trial), carried out on a separate day, participants completed the same incremental and prolonged exercise protocols, but hydration was maintained through fluid ingestion according to the body mass loss. Fluid was provided in aliquots of ~160 ml every 10 min during the 2 h of submaximal exercise and also pre- and post-incremental exercise at the same work rates. The euhydration trial was used to isolate the effect of dehydration on the observed haemodynamic responses to incremental exercise and to control for the effect of repeated exercise. In both trials, incremental exercise was performed in the heat (35°C, RH 50%) with pedal cadence maintained between 70 and 90 r.p.m. Participants were exposed to the environmental conditions for 1 h prior to commencement of the protocol.

In the dehydration trial, cerebral haemodynamics and blood samples from the brachial artery and left internal jugular vein were obtained simultaneously in the final minute of each exercise stage. Intestinal, skin and jugular venous temperatures and arterial and jugular venous pressures were recorded. The same measures were collected in the euhydration trial, except for the arterial–venous (a–v) blood sampling and jugular venous temperatures and pressures.

**Cerebral haemodynamics**

Blood flow was obtained sequentially from the right CCA and internal carotid arteries (ICA) at rest and in the final minute of each work rate using an ultrasound system (Vivid 7 Dimension, GE Healthcare, UK) equipped with a 10 MHz linear array transducer. Measurements were performed by an experienced sonographer with care taken to maintain sampling site and vessel insonation angle. Participants were seated on the cycle ergometer and encouraged to maintain a consistent head position for optimal ultrasound scanning. ICA and CCA measurements were typically taken ~1.0–1.5 cm above and ~1.5 cm below the
carotid bifurcation, respectively (Sato et al. 2011; Willie et al. 2012) with settings maintained across the protocol. Test–retest reliability was assessed during pilot studies and the coefficient of variation for CCA and ICA volume flow measurements at rest were 2.8 ± 0.9% and 4.3 ± 1.0%, and during exercise were 5.3 ± 1.6% and 5.0 ± 1.6%, respectively. For calculation of blood flow, two-dimensional brightness mode images for CCA and ICA diameter were taken, followed by pulse-wave measurements for the assessment of time-averaged mean velocity. Systolic and diastolic diameters were measured with the mean diameter calculated as systolic diameter × 1/3 + diastolic diameter × 2/3.

Time-averaged mean flow velocity (TAM \( V \); cm s\(^{-1} \)) was measured in pulse-wave mode, taken as the average of three continuous 12 s periods. Average diameter and flow velocity profiles were made from ≥15 cardiac cycles to attenuate respiration artefacts. The sample volume was maintained at the centre of the vessel lumen and adjusted to cover its width. Care was taken to ensure a consistent insonation angle below 60 deg. Mean flow velocity profiles were traced automatically and analysed offline for determination of TAM V (EchoPAC BT12, Version: 112, GE Healthcare, Norway). Blood flow (ml min\(^{-1} \)) was then calculated by mean flow velocity × cross-sectional area (CSA: \( \pi \times (\text{mean diameter}/2)^2 \)); blood flow = TAM \( V \) × CSA × 60.

Due to technical limitations, blood flow measurements were made in all work rates except the 100% stage in control and rehydration conditions. Blood flow in these stages was estimated using the individual decline in MCA \( V_{\text{mean}} \). MCA \( V_{\text{mean}} \) was measured using 2 MHz pulsed trans-cranial Doppler ultrasound (Doppler-Box, Compumedics DWL, Singen, Germany). The right MCA was insonated through the temporal ultrasound window at a depth of 45–60 mm. Signal quality was optimised according to Aaslid et al. (1982).

**Catheter placement and blood sampling**

While resting with a slight head-down tilt; catheters for blood sampling, blood pressure (mean arterial pressure, MAP), internal jugular venous pressure and blood temperature were inserted into the brachial artery of the non-dominant arm and after local anaesthesia (2% lidocaine) in the left internal jugular vein (Double Lumen Catheter, 16 gauge, 2.3 mm; Multi-Med M2716HE, Edwards Lifesciences, USA) using the Seldinger technique, and advanced to the jugular bulb. For measurement of jugular venous blood temperature, a thermistor (T204-D, PhysiTemp, Clifton, NJ, USA) was inserted through the catheter and connected to a thermocouple meter (TC-2000, Sable Systems, NV, USA). The internal jugular catheter was inserted under ultrasound guidance and catheters were regularly flushed with 0.9% saline to maintain patency. The time from catheterisation to the commencement of resting measurements was ~1 h.

**Blood variables**

Arterial and jugular venous blood samples were drawn into pre-heparinised syringes and analysed immediately for blood gas variables (ABL 800 FLEX, Radiometer, Copenhagen, Denmark) corrected for blood temperature in the internal jugular vein. The analyser was calibrated at regular intervals in accordance with manufacturer guidelines. Additional arterial and jugular venous blood was collected in 2 ml syringes and transferred to EDTA tubes, centrifuged and separated. Plasma adrenaline and noradrenaline were subsequently determined using an enzyme immunoassay kit (DEE6500 2-CAT, Demeditec Diagnostics GmbH, Kiel, Germany). Blood samples were also collected directly in stop solution (Gorman et al. 2003; Kalsi & González-Alonso, 2012). Plasma ATP was then determined using the luciferin–luciferase technique by a luminometer with three automatic injectors (Orion Microplate Luminometer, Böhringer Mannheim GmbH, Pforzheim, Germany).

**Heart rate, blood pressure and temperatures**

Heart rate was obtained from a chest strap (Polar Electro, Kempele, Finland). Arterial and internal jugular venous pressure waveforms were recorded using transducers (Pressure Monitoring Kit, TruWave, Edwards Lifesciences, Germany) zeroed at the level of the right atrium in the midaxillary line (arterial) and at the level of the tip of the catheter (jugular venous). Arterial pressure waveforms were sampled at 1000 Hz, amplified (BP amp, ADInstruments, Oxford, UK) and connected to a data acquisition unit (Powerlab 16/30, ADInstruments) for offline analysis. Intestinal temperature was measured using an ingestible telemetry pill (HQInc., Palmetto, FL, USA) and mean skin temperature from four sites (standard weightings of chest, abdomen, thigh and calf; Ramanathan, 1964) was obtained using a wired thermo-couple system (TC-2000, Sable Systems, Las Vegas, NV, USA).

**Calculations**

Cerebral vascular conductance (CVC) indices were calculated by dividing blood flow in the ICA and CCA, and MCA \( V_{\text{mean}} \) by cerebral perfusion pressure (difference between MAP and jugular venous pressure). Arterial oxygen content was used to quantify \( \text{O}_2 \) delivery through the MCA and ICA, respectively. CMRO\(_2\) and \( \text{CO}_2 \) production indices were calculated as \( 2 \times \text{CMRO}_2 \) flow multiplied by the arterial–venous (a–v) \( \text{O}_2 \) difference.
and/or venous–arterial (v–a) CO₂ difference. Whole blood CO₂ content was also calculated (Douglas et al. 1988).

**Data analysis**

A one-way repeated-measures ANOVA was used for the assessment of changes over time (i.e. rest and increasing exercise intensities). Where significant differences were found, appropriate post hoc analysis were made using the Dunn–Sidak correction. Where applicable, measured variables between conditions were analysed using a two-way repeated-measures ANOVA in which condition (control, DEH and REH) and exercise phase (rest, 20, 40, 60, 80 and 100%) were the main factors. Multiple regression for within-subject repeated measures was used for the analysis of the relationship between blood flow and blood gas variables and temperatures (Bland & Altman, 1995; Slinker & Glantz, 2008). Statistical significance was set at \( P < 0.05 \) and all analyses were made using IBM SPSS Statistics (Version 20, IBM Corporation, Armonk, NY, USA).

**Results**

**Hydration and temperature**

In the dehydration trial (Fig. 1), body mass in DEH was lower compared to control (75.8 ± 2.7 vs. 78.2 ± 2.7 kg, corresponding to a 3.1 ± 0.3% body mass loss, \( P < 0.01 \)), and was restored in REH (77.7 ± 2.9 kg). DEH was accompanied by an increased arterial and venous haemoglobin concentration ([Hb]) (\( P < 0.01 \); Table 1), indicative of a reduction in blood volume, whereas REH restored these responses. Prior to exercise, intestinal and internal jugular venous temperatures were higher in DEH compared to control (38.3 ± 0.1 vs. 36.8 ± 0.1 and 37.7 ± 0.1 vs. 36.5 ± 0.1°C, respectively, both \( P < 0.001 \); Fig. 6C), but were restored to control values in REH (36.5–36.8°C). In DEH, both intestinal and blood temperature remained elevated and increased with work rates to a peak of 38.2 ± 0.1°C (\( P < 0.01 \); Fig. 6C). In control, intestinal and internal jugular venous temperature increased progressively to 37.4 ± 0.1 and 37.9 ± 0.1°C, with similar responses observed during REH. Mean skin temperature (\( T_{sk} \)) was unchanged across exercise intensities and between incremental conditions (33.8 ± 0.3, 32.6 ± 0.4 and 33.1 ± 0.3°C in control, DEH and REH, respectively). Heart rate followed the same pattern, with peak values being similar in all three conditions (179 ± 4, 184 ± 2 and 179 ± 3 beats min⁻¹ in control, DEH and REH, respectively).

In the euhydration trial, body mass was the same at the start of each of the three incremental cycling tests. Prior to exercise, intestinal temperature was higher in the second and third test, compared to the first control test (37.8 ± 0.2 and 37.2 ± 0.1 vs. 37.0 ± 0.1°C; \( P < 0.05 \)). During exercise, intestinal temperature increased with exercise intensity and reached 37.8 ± 0.1, 37.5 ± 0.1 and 37.4 ± 0.1°C, at exhaustion. Similarly to the dehydration trial, mean \( T_{sk} \) was unchanged across exercise intensities and between incremental tests (33.3 ± 0.2, 32.7 ± 0.3 and 33.3 ± 0.2°C, respectively). Heart rate was elevated prior to the second test compared to the first, but peak heart rate was not different (176 ± 2, 176 ± 3 and 177 ± 3 beats min⁻¹, in the first, second and third tests, respectively).

**Brain haemodynamics and metabolism**

In control in the dehydration trial, ICA blood flow and MCA \( V_{mean} \) increased by ~17 ± 2% from rest to sub-maximal exercise and thereafter declined to resting values (both \( P < 0.05 \); Fig. 3A and D). Conversely, during DEH, ICA blood flow did not increase from rest to moderate exercise, but declined to below resting values at \( W_{Rmax} \) (−11% vs. rest, \( P < 0.05 \)). ICA blood flow responses to REH were similar to control. In all conditions, the decline in blood flow at high exercise intensities was associated with reductions in vessel diameter and blood velocity. In contrast to ICA blood flow, CCA blood flow did not change during low intensity exercise in control, but increased progressively with further increases in exercise intensity (rest = 0.47 ± 0.02 vs. 0.60 ± 0.02 1 min⁻¹, \( P < 0.01 \)) (Fig. 3C). During DEH, CCA blood flow was elevated (\( P < 0.05 \)) at the start of exercise and did not change throughout incremental exercise. CCA blood flow responses to REH incremental exercise were similar to control. The increases in CCA blood flow in control and REH were associated with increases in blood velocity (\( P < 0.05 \)). In the euhydration trial, ICA and CCA blood flow, and MCA \( V_{mean} \) were similar at rest and during incremental exercise.

At rest, ICA \( O_2 \) delivery, a–v \( O_2 \) and v–a \( O_2 \) difference, and CMRO₂ and brain rate of CO₂ production (\( V_{CO_2} \)) indices were not significantly different across the three experimental conditions of the dehydration trial. From rest to sub-maximal exercise (40% \( W_{Rmax} \)) in control, ICA \( O_2 \) delivery increased, v–a \( CO_2 \) difference decreased, while the a–v \( O_2 \) difference was unchanged (Fig. 3B, E and F). When exercise intensity became strenuous (≥60%), ICA \( O_2 \) delivery declined to baseline values, as with ICA blood flow, and v–a \( CO_2 \) and a–v \( O_2 \) difference increased progressively to exhaustion (≈32% increase vs. rest, \( P < 0.05 \)). Additionally, there was a progressive increase in brain \( V_{CO_2} \) index up to \( W_{Rmax} \) (Fig. 3G). During DEH, ICA \( O_2 \) delivery remained constant up to 60% \( W_{Rmax} \), before declining to below resting values. Moreover, v–a \( CO_2 \) difference, a–v \( O_2 \) difference and brain \( V_{CO_2} \) index were elevated at \( W_{Rmax} \) (\( P < 0.05 \)). ICA \( O_2 \) delivery was somewhat restored in REH whereas v–a \( CO_2 \) and a–v \( O_2 \) difference, and brain \( V_{CO_2} \) index were
similar to control. Overall, these responses resulted in a maintained CMRO₂ index at rest and throughout exercise to exhaustion (Fig. 3H). Brain a–v lactate concentration ([La]) difference was maintained at sub-maximal exercise intensities in control conditions before increasing at WRₘₐₓ, resulting in net uptake of [La] by the brain (Fig. 4A and C). Conversely, in DEH and REH, a–v [La] was unchanged. Brain a–v glucose concentration ([Glu]) difference was stable in all conditions (except WRₘₐₓ in control conditions), resulting in a stable uptake of glucose across exercise intensities (Fig. 4B and D).

**Blood pressure and vascular conductance**

At rest and during incremental exercise in the dehydration trial, MAP was lower in DEH compared to control whereas jugular venous pressure was not different across incremental exercise conditions (P < 0.01; Fig. 5A). Brain perfusion pressure was therefore lower in DEH compared to control (P < 0.01). Concurrently, ICA, CCA and MCA vascular conductances were higher in DEH, compared to control and REH, at rest (P < 0.01; Fig. 5B–D). However, in all incremental exercise conditions, ICA and MCA vascular conductances were not different at sub-maximal exercise intensities before declining at WRₘₐₓ (P < 0.05). During control, CCA vascular conductance declined from rest to sub-maximal exercise intensities before recovering to baseline values at WRₘₐₓ, whereas in DEH CCA vascular conductance continued to decline. In contrast to the haemodynamic alterations seen in the dehydration trial, in the euhydration trial MAP and ICA, CCA and MCA vascular conductance were similar at rest and throughout the three exercise tests.

**Cerebral blood flow, PₐCO₂, CₐCO₂ and temperature**

At rest, PₐCO₂ was not different across conditions. The transition from rest to exercise resulted in an increase in PₐCO₂ in all incremental exercise conditions that continued up to 40% WRₘₐₓ in control, whereas in DEH and REH PₐCO₂ was unchanged above 20% WRₘₐₓ. Beyond sub-maximal intensities PₐCO₂ rapidly declined, by 6–7 mmHg, to below resting values in control (and REH), and by 3 mmHg in DEH (P < 0.05; Fig. 6A). Venous CO₂ tension (PₐCO₂) increased from rest to 60% WRₘₐₓ in control conditions before declining to baseline values at WRₘₐₓ, whereas in DEH and REH PₐCO₂ was unchanged throughout exercise (Table 2).

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**Figure 1. Experimental protocol**

Schematic representation of the experimental protocols. Participants completed 2 trials (i.e. dehydration and euhydration trials) separated by at least 1 week. Each trial consisted of 3 incremental cycle ergometer exercise tests until volitional exhaustion. The incremental exercise consisted of five, 3 min stages at 20, 40, 60, 80 and 100% of WRₘₐₓ. In the dehydration trial, WRₘₐₓ was approximately 20% lower when participants were dehydrated compared to when they were euhydrated or rehydrated (269 ± 11 vs. 336 ± 14 W). In the euhydration trial, however, WRₘₐₓ was the same in the 3 incremental exercise tests.
(\(C_{aCO_2}\)) was lower in DEH compared to control and REH (479 ± 22 vs. 507 ± 17 and 495 ± 6 ml l\(^{-1}\); Fig. 6B). From rest to WR\(_{\text{max}}\), \(C_{aCO_2}\) declined to below resting values in control (and REH; \(P < 0.05\)), but a similar decline was not apparent in DEH. Jugular venous CO\(_2\) content (\(C_{vCO_2}\)) declined from rest to WR\(_{\text{max}}\) (581 ± 15 to 463 ± 11 ml l\(^{-1}\); \(P < 0.05\)) in control conditions, whereas in DEH and REH \(C_{vCO_2}\) was unchanged throughout exercise (~553 ± 4 ml l\(^{-1}\)).

**Relationships between cerebral blood flow and \(P_{CO_2}\), \(C_{CO_2}\), pH and temperature**

At rest and throughout incremental exercise in all conditions, ICA blood flow (\(R^2 = 0.41\); Fig. 6D) and MCA \(V_{\text{mean}}\) (Coefficient of determination, \(R^2 = 0.42\); Fig. 6E) were correlated to changes in \(P_{aCO_2}\) (both \(P < 0.01\)). In contrast, only non-significant correlations were observed for \(C_{atCO_2}\) (\(R^2 = 0.16\)), \(P_{vCO_2}\) (\(R^2 = 0.15\)) and \(C_{vCO_2}\) (\(R^2 = 0.19\); \(P = 0.15–0.85\)). Also, CCA (\(R^2 = 0.05\)) and ICA (\(R^2 = 0.13\)) blood flow, in all conditions, were not correlated to jugular venous pH (both \(P > 0.05\)). Lastly, CCA blood flow in control and REH was correlated to changes in jugular venous temperature (\(R^2 = 0.68\); \(P < 0.001\); Fig. 6F), but not in DEH (\(R^2 = 0.00\); \(P = 0.74\)).

**Plasma catecholamines and ATP**

At rest in DEH, arterial and jugular venous noradrenaline concentration ([NA]) was higher than control and rehydration (13 ± 4 vs. 3 ± 1 and 3 ± 1 nmol l\(^{-1}\) and 12 ± 4 vs. 2 ± 0.2 and 6 ± 2 nmol l\(^{-1}\), respectively; \(P < 0.05\)). From rest to WR\(_{\text{max}}\), arterial and jugular venous [NA] increased exponentially in all conditions to a peak of 43 ± 10, 69 ± 19 and 82 ± 21 nmol l\(^{-1}\), and 36 ± 8, 39 ± 10 and 27 ± 5 nmol l\(^{-1}\) in dehydration, control and rehydration, respectively. The a–v [NA] differences and exchange across the brain remained stable in the three trials (Fig. 7). The reductions in ICA vascular conductance were correlated to an increased jugular venous [NA] (control \(R^2 = -0.79\), dehydration and rehydration \(R^2 = -0.66\); \(P < 0.05\)). On the other hand, arterial and jugular venous adrenaline concentration ([A]) was not different among conditions at rest (1.1 ± 0.3 vs. 0.8 ± 0.2 and

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**Figure 2. Experimental arrangement and ultrasound recording**

Photo depicting one of the participants in the study performing an incremental cycling test on a semi-recumbent cycle ergometer (Lode Angio, Groningen, the Netherlands) with a backrest inclination of 45 deg, while measurements of ICA and CCA blood flow were obtained at each stage. Representative images of real time ICA blood velocity recordings at rest, submaximal and peak exercise are shown.
Table 1. Blood responses to incremental cycling exercise

|                  | Incremental cycling exercise (%WRmax in Control) | 20% | 40% | 60% | 80% | 100% |
|------------------|-----------------------------------------------|-----|-----|-----|-----|------|
| **Hb (g l⁻¹)**   | Control                                       | 141 ± 5 | 145 ± 4* | 147 ± 4* | 149 ± 4* | 154 ± 4* | 158 ± 4* |
|                  | Dehydration                                   | 154 ± 4* | 148 ± 3 | 154 ± 3* | 149 ± 3 | 152 ± 4* | 156 ± 4* |
|                  | Rehydration                                   | 140 ± 3 | 143 ± 3 | 142 ± 3 | 146 ± 3* | 149 ± 3* | 147 ± 3* |
| **S\textsubscript{O}₂ (%)** | Control                                       | 98.5 ± 0.2 | 97.7 ± 0.1 | 97.8 ± 0.2* | 97.5 ± 0.3* | 97.3 ± 0.4* | 96.6 ± 0.4* |
|                  | Dehydration                                   | 64.7 ± 1.0 | 66.0 ± 1.5 | 68.7 ± 1.0* | 67.0 ± 1.1 | 64.9 ± 1.5 | 61.0 ± 2.1 |
|                  | Rehydration                                   | 67.5 ± 0.8 | 63.2 ± 1.2* | 64.0 ± 0.9 | 63.9 ± 1.3 | 63.4 ± 2.0 | — |
| **PO\textsubscript{2} (mmHg)** | Control                                       | 97.2 ± 0.5* | 97.4 ± 0.2* | 97.2 ± 0.1* | 97.2 ± 0.3* | 97.0 ± 0.7* | — |
|                  | Dehydration                                   | 9.0 ± 0.3 | 39.6 ± 2.3 | 39.6 ± 2.3 | 39.6 ± 2.3 | 39.6 ± 2.3 | 39.6 ± 2.3 |
|                  | Rehydration                                   | 9.0 ± 0.3 | 39.6 ± 2.3 | 39.6 ± 2.3 | 39.6 ± 2.3 | 39.6 ± 2.3 | 39.6 ± 2.3 |
| **PC\textsubscript{O}₂ (ml l⁻¹)** | Control                                       | 192 ± 6 | 195 ± 6 | 199 ± 5* | 201 ± 5* | 206 ± 5* | 211 ± 6* |
|                  | Dehydration                                   | 127 ± 4 | 131 ± 5 | 138 ± 5 | 137 ± 4 | 136 ± 5 | 131 ± 5 |
|                  | Rehydration                                   | 191 ± 4 | 189 ± 4 | 191 ± 4 | 195 ± 4* | 200 ± 3* | 203 ± 5* |
| **pH**           | Control                                       | 7.39 ± 0.01 | 7.38 ± 0.01* | 7.36 ± 0.01* | 7.36 ± 0.01* | 7.36 ± 0.01* | 7.31 ± 0.01* |
|                  | Dehydration                                   | 7.33 ± 0.01 | 7.32 ± 0.02 | 7.32 ± 0.01 | 7.32 ± 0.01 | 7.32 ± 0.01 | 7.26 ± 0.01* |

Values are means ± SEM for 10 subjects. Control, dehydation and rehydration incremental exercise tests are represented. *Different from rest, \( P < 0.05 \). †Different from previous intensity, \( P < 0.05 \). \( P_{\text{O}_2} \), partial pressure of \( \text{O}_2 \); \( S_{\text{O}_2} \), \( \text{O}_2 \) saturation of the blood; \( C_{\text{O}_2} \), \( \text{CO}_2 \) content of the blood.

0.8 ± 0.2 nmol l⁻¹ and 1.0 ± 0.3 vs. 0.7 ± 0.1 and 0.6 ± 0.1 nmol l⁻¹, respectively. Yet, from rest to \( \text{WR}_{\text{max}} \) in dehydration, control and rehydration conditions, [A] increased to a peak of 5.5 ± 1.9, 9.1 ± 2.2 and 7.7 ± 2.8 nmol l⁻¹ in arterial and 6.5 ± 2.4, 8.5 ± 3.6 and 3.3 ± 1.1 nmol l⁻¹ in venous plasma, respectively (all \( P < 0.05 \)). Lastly, arterial plasma [ATP] increased in a curvilinear manner from similar values at rest (1058 ± 177 vs. 938 ± 128 and 1027 ± 199 nmol l⁻¹) to \( \text{WR}_{\text{max}} \) and was higher in dehydration compared to control and rehydration at maximal intensities (1641 ± 189 vs. 1403 ± 221 and 1274 ± 188 nmol l⁻¹; \( P < 0.05 \)).

**Discussion**

The novel findings of the present study were threefold. Firstly, during exercise in control conditions cerebral perfusion increased from rest to moderate exercise in the heat, before declining to baseline values prior to exhaustion. Secondly, dehydration accelerated the declines in blood flow and \( \text{O}_2 \) delivery to the brain during incremental cycling exercise to exhaustion in association with a blunted perfusion pressure, reductions in \( P_{\text{aCO}_2} \), and increases in internal jugular venous [NA]. In contrast to the evident cerebral circulatory strain during the intense exercise stages, common carotid artery blood flow increased from rest to peak exercise in the control and rehydration conditions and remained unchanged with dehydration, indicating that the increase in blood flow to extra-cranial tissues was related to the increase in temperature (jugular blood). Finally, compensatory increases in brain \( \text{O}_2 \) extraction maintained CMRO\(_2\) throughout exercise in association with a stable or increasing \( \text{CO}_2 \) production. Collectively these findings

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suggest that the circulatory strain on the human brain during maximal exercise in the heat, even with dehydration, does not compromise CMRO$_2$.

**Hydration and perfusion of the head**

The current study demonstrates that CBF, blood velocity and O$_2$ delivery are attenuated prior to the attainment of maximal work rate and that dehydration accelerates this restriction in cerebral perfusion. The decline in cerebral perfusion is in agreement with investigations in humans during graded incremental exercise (Moraine *et al*. 1993; Hellström *et al*. 1996; Sato *et al*. 2011) and intense constant load exercise, with and without heat stress (Nybo & Nielsen, 2001$b$, 2002; González-Alonso *et al*. 2004). We have extended these findings by obtaining direct measurements of anterior CBF under conditions...
that challenge the cardiovascular system to its capacity and examined the functional consequences of a diminished flow on CMRO$_2$ during strenuous exercise.

The common carotid artery forms a major part of the extra-cranial circulation through to the ECA. During all incremental exercise conditions extra-cranial perfusion (CCA and calculated ECA flow: CCA – ICA) increased or was maintained. Strikingly, at rest prior to the dehydration test CCA blood flow was elevated by 25% whereas ICA blood flow was only modestly increased (~6%), indicating a substantially augmented ECA blood flow compared to control when participants’ jugular venous and core temperatures were elevated by 1.2–1.5°C. Additionally, ECA blood flow increased by ~50% from baseline to 80% WR$_{\text{max}}$ (217 ± 30 to 307 ± 22 ml min$^{-1}$) and achieved a similar peak value across interventions. These findings are consistent with an elevated extra-cranial blood flow with graded exercise in normothermic conditions (Hellström et al. 1996; Sato et al. 2011) and with passive heating at rest (Fan et al. 2008; Ogoh et al. 2013). Heat stress, with and without concomitant dehydration, results in a distinct cardiovascular strain (Sawka et al. 1979; Montain & Coyle, 1992a,b; González-Alonso et al. 1997; González-Alonso, 1998) and promotes redistribution of blood flow to the skin vascular beds for thermoregulatory purposes (Crandall et al. 2008; Crandall & González-Alonso, 2010; Johnson & Kellogg, 2010). Given that the ECA supplies the majority of the cutaneous circulation of the face and neck, an elevated blood flow to these regions is important for local convective heat exchange. Collectively these findings show contrasting blood flow adjustments across the different vascular beds of the head during strenuous exercise in the heat with both dehydration and euhydration.

**Mechanisms of cerebral and extra-cranial blood flow control**

In all incremental exercise conditions attenuation in cerebral perfusion was coupled to a decline in cerebral vascular conductance, indicative of vasoconstriction and

![Figure 4. Brain lactate and glucose uptake during incremental exercise](image-url)

**Figure 4. Brain lactate and glucose uptake during incremental exercise**

Brain a–v lactate [La] and glucose [Glu] concentration differences (A and B) and [La] and [Glu] uptake/exchange (C and D) during the 3 incremental tests. Exchange was calculated as the product of 2 × ICA blood flow and a–v difference. Data are means ± SEM for 7 subjects. ∗P < 0.05 vs. rest; ∗∗P < 0.05 vs. sub-maximal exercise.
Table 2. Blood gases and metabolite responses to incremental exercise in different hydration states

| Incremental cycling exercise (% WR_{max} in Control) | Rest | 20% | 40% | 60% | 80% | 100% |
|----------------------------------------------------|------|-----|-----|-----|-----|------|
| $P_{CO_2}$ (mmHg)                                  |      |     |     |     |     |      |
| Control                                            | 39 ± 1 | 42 ± 1$^*$ | 43 ± 1$^*$ | 42 ± 1$^*$ | 40 ± 1$^*$ | 36 ± 1$^{*\text{†}}$ |
| v                                                  | 50 ± 1 | 52 ± 1 | 52 ± 1 | 53 ± 1$^*$ | 52 ± 1 | 50 ± 1$^\dagger$ |
| Dehydration                                       | 37 ± 2 | 39 ± 1 | 39 ± 1 | 40 ± 2 | 37 ± 1$^\dagger$ | — |
| v                                                  | 49 ± 1 | 50 ± 1 | 48 ± 2 | 47 ± 3 | 48 ± 2 | — |
| Rehydration                                       | 38 ± 1 | 39 ± 1 | 39 ± 1 | 39 ± 1 | 36 ± 1$^\dagger$ | 33 ± 1$^\dagger$ |
| v                                                  | 49 ± 1 | 49 ± 1 | 49 ± 1 | 50 ± 1$^*\text{†}^2$ | 48 ± 2$^\dagger$ | 45 ± 4$^\dagger$ |
| $[HCO_3^-]$ (mmol l$^{-1}$)                        |      |     |     |     |     |      |
| Control                                            | 23.5 ± 0.7 | 24.0 ± 0.6 | 23.1 ± 0.7$^\dagger$ | 23.0 ± 0.6 | 22.2 ± 0.6 | 18.7 ± 0.8 |
| v                                                  | 23.6 ± 0.8 | 23.1 ± 1.1 | 23.6 ± 0.6 | 23.6 ± 0.7 | 23.2 ± 0.8 | 19.3 ± 0.3 |
| Dehydration                                       | 23.9 ± 0.7 | 23.7 ± 1.0 | 23.0 ± 0.9 | 23.1 ± 1.3 | 23.7 ± 1.1 | — |
| v                                                  | 23.6 ± 0.8 | 23.1 ± 1.0 | 21.6 ± 1.6 | 23.4 ± 1.6 | 26.5 ± 0.6 | — |
| Rehydration                                       | 22.5 ± 0.6 | 22.4 ± 0.6 | 22.4 ± 0.6 | 22.2 ± 0.7 | 21.6 ± 0.7 | 19.2 ± 0.9 |
| v                                                  | 23.1 ± 0.6 | 22.7 ± 0.6 | 22.7 ± 0.7 | 23.0 ± 0.7 | 20.5 ± 1.9 | 21.2 ± 0.4 |
| ABE (mmol l$^{-1}$)                                 |      |     |     |     |     |      |
| Control                                            | −1.1 ± 0.9 | −0.3 ± 0.7 | −1.3 ± 0.8$^\text{†}$ | −1.5 ± 0.8 | −2.7 ± 0.7 | −7.4 ± 1.0 |
| v                                                  | 0.7 ± 1.0 | 0.3 ± 1.2 | 1.0 ± 0.7 | 1.0 ± 0.9 | 0.4 ± 1.0 | −4.3 ± 0.5 |
| Dehydration                                       | −1.7 ± 0.9 | −1.7 ± 1.3 | −1.9 ± 1.2 | −2.0 ± 1.7 | −1.4 ± 1.3 | — |
| v                                                  | 0.6 ± 0.9 | 0.0 ± 1.2 | −2.0 ± 2.1 | −1.1 ± 2.2 | 2.7 ± 1.4 | — |
| Rehydration                                       | −2.4 ± 0.7 | −2.3 ± 0.8 | −2.4 ± 0.8 | −2.8 ± 0.9 | −3.7 ± 0.9 | −6.9 ± 1.0 |
| v                                                  | 0.1 ± 0.8 | −0.4 ± 0.8 | −0.3 ± 0.8 | 0.0 ± 0.8 | −3.4 ± 2.4 | −2.6 ± 0.8 |
| Lactate (mmol l$^{-1}$)                             |      |     |     |     |     |      |
| Control                                            | 0.8 ± 0.1 | 1.3 ± 0.1$^*$ | 1.7 ± 0.1$^*$ | 2.8 ± 0.2$^*$ | 5.6 ± 0.4$^*$ | 11.3 ± 0.7$^*$ |
| v                                                  | 0.9 ± 0.1 | 1.3 ± 0.1$^*$ | 1.6 ± 0.1$^*$ | 2.6 ± 0.2$^*$ | 5.0 ± 0.4$^*$ | 10.1 ± 0.6$^*$ |
| Dehydration                                       | 2.1 ± 0.2 | 1.9 ± 0.2$^*$ | 1.6 ± 0.2$^*$ | 1.7 ± 0.2$^*$ | 2.6 ± 0.2$^*$ | — |
| v                                                  | 2.2 ± 0.2 | 1.9 ± 0.2$^*$ | 1.7 ± 0.2$^*$ | 1.7 ± 0.2$^*$ | 2.4 ± 0.2$^*$ | — |
| Rehydration                                       | 3.3 ± 0.3 | 2.9 ± 0.2$^*$ | 2.5 ± 0.2$^*$ | 2.8 ± 0.2 | 4.8 ± 0.2$^*$ | 8.8 ± 0.3$^*$ |
| v                                                  | 3.3 ± 0.3 | 2.9 ± 0.2$^*$ | 2.5 ± 0.2$^*$ | 2.9 ± 0.2$^*$ | 4.3 ± 0.2$^*$ | 8.2 ± 0.3$^*$ |
| Glucose (mmol l$^{-1}$)                             |      |     |     |     |     |      |
| Control                                            | 6.0 ± 0.2 | 6.0 ± 0.2 | 6.0 ± 0.2 | 5.9 ± 0.2 | 5.8 ± 0.2 | 5.7 ± 0.2 |
| v                                                  | 5.4 ± 0.2 | 5.4 ± 0.2 | 5.4 ± 0.2 | 5.3 ± 0.2 | 5.2 ± 0.2 | 5.0 ± 0.2 |
| Dehydration                                       | 6.0 ± 0.2 | 5.6 ± 0.3$^*$ | 5.2 ± 0.3$^*$ | 5.0 ± 0.3$^*$ | 4.7 ± 0.2$^*$ | — |
| v                                                  | 5.4 ± 0.2 | 4.9 ± 0.2$^*$ | 4.6 ± 0.2$^*$ | 4.2 ± 0.2$^*$ | 4.0 ± 0.3$^*$ | — |
| Rehydration                                       | 12.0 ± 0.7 | 11.2 ± 0.8$^*$ | 10.6 ± 0.8$^*$ | 9.7 ± 0.7$^*$ | 8.3 ± 0.7$^*$ | 6.6 ± 0.9$^*$ |
| v                                                  | 11.0 ± 0.5 | 10.0 ± 0.5$^*$ | 9.4 ± 0.5$^*$ | 8.6 ± 0.5$^*$ | 7.4 ± 0.5$^*$ | 6.2 ± 0.5$^*$ |

Values are mean ± SEM for 10 participants. $P_{CO_2}$, partial pressure of CO$_2$; $[HCO_3^-]$, sodium bicarbonate; ABE, acid–base excess; lactate and glucose for arterial (a) and internal jugular venous (v) blood. Rehydration values at 100% are $n = 5$. $^*$ Different from rest, $P < 0.05$. $^\dagger$ Different from previous intensity, $P < 0.05$.

thus diminished vessel diameter (Fig. 5B and D). Alterations in $P_{CO_2}$ and blood CO$_2$ content increased sympathetic nerve activity and concurrent changes in the intra- and extravascular milieu of vasoconstrictor and vasodilator signals may all play a role in restricting CBF (Paulson et al. 1990; Iide & Secher, 2000; Secher et al. 2008; Ogoh & Ainslie, 2009b). During strenuous exercise cerebral perfusion was associated with the decrease in $P_{CO_2}$, (Fig. 6A, D and E). Given that free CO$_2$ accounts for only a minor portion of the CO$_2$ in blood, we reasoned that C$_{CO_2}$ would indicate whether plasma and/or blood CO$_2$ is important for the decline in cerebral perfusion. In contrast to the prominent association with $P_{aCO_2}$, the correlation with arterial or jugular venous blood C$_{CO_2}$ was non-significant, indicating that the cerebral circulation is sensitive to changes in free blood $P_{CO_2}$ rather than to changes in CO$_2$ bound to haemoglobin or buffered as bicarbonate in the arterial or venous vasculature. There is also controversy in regards to the role of cerebral venous versus arterial $P_{CO_2}$ in regulation of brain blood flow (Peebles et al. 2007). The current study shows that the relationship between brain flow and $P_{aCO_2}$ was not significant because of the maintenance or minimal changes in jugular $P_{CO_2}$. Furthermore, the impact of arterial $P_{O_2}$ and HbO$_2$ saturation on CBF is negligible in the present conditions because the changes in these variables during incremental exercise were too small to activate the oxygen-sensitive pathways of local CBF control (Willie et al. 2012). CO$_2$ readily crosses the blood–brain barrier, altering the extracellular pH, and there is compelling evidence to suggest that pH has an independent effect on cerebral vessel vasoconstriction (Kontos et al. 1977a,b). However, there was no relationship between blood flow to the brain and jugular venous pH. Jugular venous pH may
Figure 5. Cerebral vascular conductance and perfusion pressure during incremental exercise in different hydration states

Mean arterial and jugular venous pressures (A), internal carotid, common carotid and middle cerebral artery vascular conductance indices (B–D) for control (open circles), dehydration (filled circles) and rehydration (open squares) conditions. Values are mean ± SEM. *P < 0.05 vs. rest, †P < 0.05 vs. sub-maximal exercise (i.e. ~40% WRmax). Significance for control and rehydration were similar in panels A, B and D.
during light exercise (Miyazawa et al. 2012). Whilst $P_a\text{CO}_2$ may not play an important role in the regulation of blood flow to the extra-cranial circulation, mechanisms involving temperature-sensitive pathways seem to do so. We observed for the first time a strong correlation between increases in common carotid artery blood flow and internal jugular venous temperature during control and REH incremental exercise (Fig. 6F). Additionally, with a rising blood temperature during incremental exercise in all three exercise conditions (up to 1.1°C), the plasma concentration of the potent intravascular vasodilator ATP increased in arterial blood; a potential mechanism for

**Figure 6. Relationships between cerebral perfusion and blood CO$_2$ and temperature**

Left panel: $P_a\text{CO}_2$ (A), arterial CO$_2$ content ($C_a\text{CO}_2$, B), and jugular venous temperature responses to incremental exercise (C). Right panel: ICA blood flow and MCA $V_{mean}$ group mean correlations with $P_a\text{CO}_2$ (D and E), and CCA blood flow group mean correlation to jugular venous temperature (F) in control (open circles), dehydration (filled circles) and rehydration (open squares). *$P < 0.05$ vs. rest, $#P < 0.05$ vs. sub-maximal exercise (i.e. ~40% WR$_{max}$). Unless presented, significance for control and rehydration were similar (i.e. panels B and C).

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the temperature-related increase in regional perfusion (Pearson et al. 2011; González-Alonso, 2012; Kalsi & González-Alonso, 2012). Irrespective of the mechanisms, the progressive increase in extra-cranial perfusion may be an important pathway by which heat is locally dissipated to regulate temperature of the tissues within the head (Sato et al. 2011). Collectively, these data suggest that cerebral perfusion is restricted with a declining cerebral vascular conductance via a net increase in vasoconstrictor activity. Alterations in $P_{aCO_2}$ are the primary mechanism for regulation of cerebrovascular tone, but not extra-cranial vessel conductance.

![Graph showing brain noradrenaline (NA) exchange during incremental exercise.](image)

Figure 7. Brain noradrenaline (NA) exchange during incremental exercise

Brain a–v noradrenaline concentration [NA] difference (A) and exchange (B) across the brain. Exchange was calculated as the product of $2 \times$ ICA blood flow and a–v difference. Values are means ± SEM for 7 subjects.

Is brain oxygen consumption compromised with dehydration during maximal incremental exercise?

An important question is whether central nervous system activity, and thus cerebral metabolic demand, rise sufficiently during strenuous exercise to increase CMRO$_2$ and whether reductions in flow result in a compromised CMRO$_2$. A major finding of the present study was that CMRO$_2$ was not compromised throughout incremental exercise across exercise conditions in spite of an attenuated perfusion at maximal intensities. This response was met by an increased $O_2$ extraction during maximal exercise, a response enhanced with dehydration. Our findings of an enhanced $O_2$ extraction and a maintained CMRO$_2$ are similar to observations during constant load sub-maximal (Ide & Secher, 2000; Nybo et al. 2002; González-Alonso et al. 2004; Secher et al. 2008) and maximal exercise (Scheinberg et al. 1954; González-Alonso et al. 2004). Nevertheless, the possibility exists that CMRO$_2$ is somewhat suppressed during maximal exercise and dehydration due to reduced $O_2$ supply. In this light, strenuous exercise with hyperthermia increases CMRO$_2$, a response attributed to the requirement of an increased neuronal activity associated with mental effort and the $Q_{10}$ effect of temperature on brain metabolism (Nybo et al. 2002). A marked reduction in $O_2$ supply might lower intracellular $P_{O_2}$ to an extent that affects metabolic fluxes and challenges cerebral metabolism and motor function (Gjedde et al. 2005; Nybo & Rasmussen, 2007; Rasmussen et al. 2007, 2010; Seifert et al. 2009). However, in spite of the 20% reductions in perfusion observed across conditions from submaximal to maximal exercise, it is unlikely that the capillary to intracellular $P_{O_2}$ gradient was reduced to the extent that would compromise CMRO$_2$, given that fractional oxygen extraction increased from 34% at rest to 39% at maximal exercise and was thereby within the range of adequate cerebral tissue oxygenation (Gjedde et al. 2005). This notion is consistent with the parallel observations that brain glucose uptake was well-maintained across exercise intensities and hydration conditions and lactate uptake was maintained or elevated (Fig. 4). Whilst it is difficult to speculate on the alterations within the deep structures of the brain, the current data suggest that brain oxygen consumption is not reduced during intense exercise in the heat, with and without concomitant dehydration.

Methodological considerations

There are several methodological considerations in the present study. Firstly, blood flow measurements were made in the right CCA and ICA, whereas the vessels on the left-hand side of the anterior circulation and the vessels of posterior circulation were not measured. In regard to the anterior circulation, side-to-side blood flows at rest
and during exercise are similar (Schöning et al. 1994; Sato et al. 2011; Willie et al. 2012). Secondly, blood flow measurements were made by one sonographer. Upon the transition from CCA to ICA ultrasound scans, a temporal lag and minor shift in sample area may occur. Care was taken to ensure a consistent measuring site for each participant and the use of duplex ultrasound allowed the continued monitoring of sample position. Thirdly, in contrast to previous literature observing the right internal jugular vein, we obtained venous blood samples from the left internal jugular vein. Asymmetry may exist in the venous drainage of the brain with the often larger right internal jugular vein draining the hemispheres and the left internal jugular vein draining the subcortical areas (Seifert & Secher, 2011). However, similar resting values for blood parameters and a–v O₂ difference values are reported in the two jugular veins (Gibbs et al. 1942; Munck & Lassen, 1957). Moreover, comparable a–v O₂ difference dynamics is observed during incremental exercise based on right jugular vein blood samples (Ide et al. 1999). We therefore assumed equal blood flow and O₂ extraction in the left and right sides of the brain to estimate the CMRO₂ index. Thirdly, the CMRO₂ index underestimates the global CMRO₂ because blood flow through the posterior circulation is not considered. The posterior portion of the brain is supplied by the two vertebral arteries (VAs) that anastomose to form the basilar artery before joining the circle of Willis, and their contribution to total brain blood flow is ~20% at rest (Zauner et al. 1997). VA flow increases progressively with graded exercise intensities, in contrast to the anterior circulation (ICA) (González-Alonso et al. 2004; Sato et al. 2011, 2012). Thus, if we assume that VA blood flow increases, or follows the same pattern as the ICA, CMRO₂ would remain unchanged during exercise in the conditions of the present study. Finally, we were unable to obtain satisfactory ultrasound images during the final stage (100%) in control and rehydration conditions. Blood flow in these stages, used for the calculation of CMRO₂, was estimated using the percentage decline in MCA \( V_{\text{mean}} \) from the 80 to 100% work rate. This assumption has been used to assess changes in flow and CMRO₂ during maximal exercise (Fisher et al. 2013).

**Conclusion**

The present findings demonstrate that dehydration restricts CBF during strenuous exercise. The blunted CBF was associated with a decline in vascular conductance and \( P_{\text{aCO}_2} \) and an increase in systemic and jugular venous noradrenaline, indications of an enhanced vasoconstrictor activity. Cerebral oxygen extraction was increased during strenuous exercise, more so when perfusion was challenged with dehydration. In contrast, extra-cranial perfusion increased, mirrored by increases in blood temperature. Thus, reductions in cerebral perfusion and cerebral vascular conductance during maximal exercise in different hydration states does not appear to negatively impact CMRO₂ because of compensatory increases in cerebral oxygen extraction.

![Figure 8. Jugular venous [NA] during incremental exercise and relationship of ICA vascular conductance and jugular venous [NA]](image)

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Additional information

Competing interests

All authors declare no conflict of interests associated with this work.

Author contributions

Experiments were performed at the Centre for Sports Medicine and Human Performance, Brunel University, London. S.J.T. and J.G.-A. were involved in the conception and design of the experiments. All authors were involved in data collection, analysis and interpretation of data. S.J.T. drafted the article and it was critically revised for important intellectual content by S.T.C., K.K.K., C.G.S., N.H.S. and J.G.-A. All authors approved the final version of the manuscript.

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