Cerebral blood flow, frontal lobe oxygenation and intra-arterial blood pressure during sprint exercise in normoxia and severe acute hypoxia in humans

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Abstract
Cerebral blood flow (CBF) is regulated to secure brain \(O_2\) delivery while simultaneously avoiding hyperperfusion; however, both requisites may conflict during sprint exercise. To determine whether brain \(O_2\) delivery or CBF is prioritized, young men performed sprint exercise in normoxia and hypoxia (\(P_{\text{IO}_2}=73\) mmHg). During the sprints, cardiac output increased to \(\sim22\) L/min\(^{-1}\), mean arterial pressure to \(\sim131\) mmHg and peak systolic blood pressure ranged between 200 and 304 mmHg. Middle-cerebral artery velocity (MCAv) increased to peak values (\(\sim16\)% after 7.5 s and decreased to pre-exercise values towards the end of the sprint. When the sprints in normoxia were preceded by a reduced PETCO\(_2\), CBF and frontal lobe oxygenation decreased in parallel (\(r=0.93, P<0.01\)). In hypoxia, MCAv was increased by 25\%, due to a 26\% greater vascular conductance, despite 4–6 mmHg lower PaCO\(_2\) in hypoxia than normoxia. This vasodilation fully accounted for the 22\% lower CaO\(_2\) in hypoxia, leading to a similar brain \(O_2\) delivery during the sprints regardless of \(P_{\text{IO}_2}\). In conclusion, when a conflict exists between preserving brain \(O_2\) delivery or restraining CBF to avoid potential damage by an elevated perfusion pressure, the priority is given to brain \(O_2\) delivery.

Keywords
Exercise, high altitude, hypertension, cerebral blood flow, cerebral haemodynamics

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Introduction
Cerebral vascular conductance is continuously adjusted to maintain cerebral oxygen delivery compensating for changes in both arterial \(O_2\) content (CaO\(_2\)) and blood pressure.\(^1,2\) When CaO\(_2\) and/or blood pressure is reduced cerebral vascular conductance is increased.

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During exercise arterial blood pressure (i.e. cerebral perfusion pressure) increases as a function of exercise intensity, and may surpass the limits of cerebral autoregulation during forceful muscular contractions. This imposes a high wall tension in the cerebral arterial tree, which if unchecked could cause cerebrovascular damage. Although during exercise in hypoxia the brain can compensate for a lower CaO₂ by increasing O₂ extraction, this capacity is markedly lower relative to other tissues. Therefore, to maintain brain oxygen delivery at rest cerebral blood flow is increased in hypoxia. During dynamic exercise (i.e. cycling, running) in hypoxia the brain faces the combined challenges of reduced CaO₂, hypocapnia and increased arterial blood pressure. Moreover, arterial blood pressure increases with exercise intensity while CaO₂ is progressively reduced due to an impairment of pulmonary gas exchange in hypoxia. This may lead to inadequate brain oxygenation, central fatigue, and impaired neural muscle activation.

During exercise in severe acute hypoxia (i.e. equivalent to altitudes above 4500 m) cerebral vascular conductance is much higher than in normoxia, implying that the diameter of the resistance vessels should be greater. According to the Laplace Law, the same blood pressure causes a greater wall tension the higher the diameter of vessels. Therefore, the haemodynamic risks for the cerebrovascular system will be greater during high-intensity exercise in hypoxia than in normoxia, unless the level of vasodilation is limited during high-intensity exercise in hypoxia.

During sprint exercise on the cycle ergometer maximal muscle contractions of the lower extremities are coordinated with intense static contractions by the arm muscles to stabilize the trunk. This likely elicits a marked arterial blood pressure elevation, however, the intra-arterial blood pressure response to sprint exercise has not been measured in humans. Moreover, it remains unknown how cerebral blood flow is regulated when a reduced CaO₂ is combined with a high arterial blood pressure as during sprint exercise in severe acute hypoxia.

Therefore, the main aim of this study was to determine the responses of cerebral blood flow and brain oxygenation during sprint exercise and the immediate post-exercise period in humans. We also aimed to determine what is prioritized during sprint exercise: oxygen delivery or the avoidance of hyperperfusion? We hypothesized that cerebral blood flow would be reduced during sprint exercise, and this would depend on the degree of hypocapnia and increase in blood pressure. We further hypothesized that in severe acute hypoxia brain oxygen delivery would be reduced and consequently brain oxygenation would be compromised, leading to lower exercise performance than in normoxia. This information is crucial to provide a better understanding of the physiological responses to high-intensity exercise, currently recommended as a preventive and therapeutic tool in medicine.

**Methods**

**Subjects**

This study was part of a larger project designed to address the mechanisms limiting whole body exercise performance in humans. The present investigation consisted of two studies, one a ‘non-invasive’ study (Study I) and another one with invasive procedures (Study II). Twenty physically active young men (age: 24.7 ± 4.7 years, height: 176.3 ± 6.2 cm, body mass: 75.9 ± 9.2 kg, body fat: 18.8 ± 5.1%, VO₂max: 3.6 ± 0.6 L min⁻¹ or 48.2 ± 6.8 mL kg⁻¹ min⁻¹) volunteered to participate in Study I. Another 11 comparable subjects (age: 21.5 ± 2.0 years, height: 173.8 ± 8.0 cm, body mass: 72.3 ± 9.3 kg, body fat: 16.1 ± 4.9%, VO₂max: 3.6 ± 0.3 L min⁻¹ or 50.7 ± 4.0 mL kg⁻¹ min⁻¹) volunteered to participate in Study II. Subjects received full oral and written information about the experiments and written consent was obtained from each participant. The studies were performed in accordance with the current version of the Helsinki Declaration and approved by the Ethical Committee of the University of Las Palmas de Gran Canaria (CEIH-2010-01 and CEIH-2009-01). Subjects were requested to refrain from ingesting caffeine and taurine-containing beverages and to avoid exercise 24 h before all the experiments.

**General overview**

After a familiarization process including incremental and sprint exercise (Excalibur Sport 925900, Lode, Groningen, The Netherlands), body composition (Lunar iDXA, General Electric, Wisconsin and Hologic QDR-1500, Hologic Corp., software version 7.10, Waltham, MA) and VO₂max were first measured in both studies. On a subsequent day, subjects performed an isokinetic all-out 30 s sprint performed on the cycle ergometer (called Wingate test) at 80 rpm, while MCAv and frontal lobe oxygenation were assessed. During the Wingate test, subjects were required to sprint as fast and hard as possible from the start to the end of the sprint, while being verbally encouraged to give their maximal effort. With the ergometer set in isokinetic mode the resistance offered was continuously adjusted by an automatic servocontrol system that only allows a pedaling rate of 80 (±1) rpm, such that if the subject applies less force on the pedals then the resistance of the ergometer is reduced and vice versa. By using the same pedaling rate in all subjects and conditions we intended...
to reduce the variability due to differences in pedalling cadence.

In Study II leg VO\textsubscript{2}, intra-arterial blood pressures, as well as leg blood flow and cardiac output were also measured.

Power output and oxygen uptake (Study I and II)

In Study I, after 3 min recording resting values, subjects started to warm up (2 min at 60 W; 2 min at 100 W and 1 min at 150 W) followed by 5 min at 20 W at 30 rpm. Thirty seconds before the end subjects stopped pedalling and prepared for Wingate. At the fifth minute, subjects began to sprint as hard and fast as possible with the cycle-ergometer set to isokinetic mode at 80 rpm. This warm up resulted in a small reduction of CO\textsubscript{2} end-tidal pressure (P\textsubscript{ETCO2}) and cerebral blood flow before the start of the sprints. Once the sprint exercise finished, recovery values were recorded for 1 min.

In Study II, the warm up consisted of 3 min unloaded pedalling before the Wingate test and P\textsubscript{ETCO2} and PaCO\textsubscript{2} were similar to that recorded at rest. In both studies, power output during the sprint is reported as instantaneous peak power (W\textsubscript{peak-i}), and as the mean power output achieved during the full duration of the sprints (W\textsubscript{mean-30}). Oxygen uptake was measured with a calibrated metabolic cart (V\textsubscript{max N29}; Sensormedics, Yorba Linda, CA, USA). Respiratory variables were analysed breath-by-breath and averaged every 5 s during the sprint and every 20 s during the incremental exercise tests. The highest 20-s averaged VO\textsubscript{2} recorded in normoxia was taken as the VO\textsubscript{2}\textsubscript{max}. The same criterion was applied to determine the VO\textsubscript{2}\textsubscript{max} in hypoxia.

Cerebral blood flow and oxygenation (Study I and II)

The mean blood flow velocity in the middle cerebral artery (MCA\textsubscript{v\textsubscript{mean}}), insonated through the trans-temporal window as described elsewhere,\textsuperscript{9,28} was determined as an estimate of cerebral blood flow. In Study I, two Doppler 2 MHz transducers were applied bilaterally over the middle transtemporal window\textsuperscript{29} (Multi Box, DWL, Singen, Germany). Since both Doppler probes yield similar readings these were averaged for further analysis to reduce variability. In Study II, only one Doppler probe was placed on the right side. To minimize potential movement artefacts the Doppler probes where kept in place with a head harness (Figure 1) and subjects were instructed to avoid head movements.

Cerebral oxygenation was assessed using near-infrared spectroscopy (NIRS, NIRO-200, Hamamatsu, Japan) employing spatial resolved spectroscopy to obtain the tissue oxygenation index (TOI) using a path-length factor of 5.92.\textsuperscript{30} The NIRS optodes were placed on the right frontoparietal region at 3 cm from the midline and 2–3 cm above the supraorbital crest, to avoid the sagittal and frontal sinus areas. With this optode placement the tissue oxygenation of the superficial frontal cerebral cortex is recorded. This region is irrigated by the anterior cerebral artery, which, like the MCA, receives its flow from the internal carotid artery. Both MCA and anterior cerebral arteries...
communicate through the circle of Willis. In Study I, an additional optode was placed in the lateral aspect of the thigh at middle length between the patella and the anterosuperior iliac crest, over the middle portion of the m. Vastus lateralis. In Study II, the optodes were placed ipsilaterally to the Doppler probe, that is over the right frontal cortex region of the forehead.

**Invasive experiments (Study II)**

The experimental protocol for invasive experiments is illustrated in Figure 1. On the experimental day, subjects reported to the laboratory at 07:00 after an overnight fast from 22:00 h. After catheterization (see below) subjects performed three incremental exercise tests: the first two in normoxia or hypoxia (in random order), and a third one always in hypoxia (P_{O2} = 73 mmHg), followed by a 2-h resting period, as previously reported. Thereafter, the subjects performed in random order two isokinetic Wingate tests, one in normoxia (P_{O2} = ~143 mmHg) and another in hypoxia (P_{O2} = ~73 mmHg, Altitrainer200, SMTEC, Switzerland) interspaced by a 90 min resting period. No warm up was performed before the Wingate tests apart from 3 min of unloaded pedalling. Subjects breathed hypoxic gas for 4 min before the start of the Wingate in hypoxia. At the end of the Wingate test recovery was always performed in normoxia. Part of the results on oxygen transport and pulmonary gas exchange obtained during the invasive experiments has been reported. Since 7 ml (kg body mass)^{-1} of carbon monoxide (CO) was administered at exhaustion during the last incremental exercise test, a small amount of CO was present in blood at the start of the Wingate test.

**Catheterization and preparation (Study II)**

Prior to the exercise tests, both femoral veins and one femoral artery were catheterized under local anaesthesia (2% lidocaine). Catheters and thermistors were used to obtain blood samples, to measure venous and arterial blood temperatures, and to determine leg blood flow (LBF) and cardiac output using the constant infusion thermodilution method.

**Blood sampling (Study II)**

Prior to the sprint exercise a blood sample was obtained simultaneously from the right femoral artery and the left femoral vein. Then, during the sprint blood was sampled every 5 s from the left femoral vein and every 10 s from the right femoral artery and used for determination of blood gases and haemoglobin concentrations (ABL90, Radiometer, Copenhagen, Denmark). Blood gases and pH were corrected for blood temperature as previously reported.

**Statistical analysis**

Sample size calculation was performed based on previous studies, assuming an effect size of 1.2 for the effect of severe hypoxia on cerebral blood flow using free online software G*Power, setting type I error and power to 5% and 80%, respectively. This resulted in a calculated group size of eight subjects. Variables were normally distributed as shown by the Shapiro–Wilks test. Two-way repeated-measures ANOVA for oxygenation (two levels: normoxia vs. hypoxia) and time (six levels: 0, 5, 10, 15, 20, 25, and 30 s) was used to analyse the responses observed during the sprints. The post exercise recovery period was divided in three 5 s averages, which were analysed using also two-way repeated-measures ANOVA for oxygenation (two levels: normoxia vs. hypoxia) and time (three levels: 5, 10, and 15). The Mauchly’s test of sphericity was run before the ANOVAs, and in the case of violation of the sphericity assumption the degrees of freedom were adjusted according to the Huynh and Feldt test. Pairwise comparisons at specific time points were performed with the Student t-test, and adjusted for multiple comparisons with the Holm–Bonferroni method. The relationship between variables was determined using linear regression analysis. Values are reported as the mean ± standard deviation (unless otherwise stated). P < 0.05 was considered significant. All statistical analysis was performed using SPSS v.15.0 for Windows (SPSS Inc., Chicago, IL).

**Results**

**Study I**

The responses of ergometric and cardiorespiratory variables are depicted in Figures 2 and 3. During the sprint, subjects reached 92%, 76%, 86%, 77%, 89% and 99% of maximal heart rate (HR), pulmonary ventilation (V_{E}), O_{2} uptake (VO_{2}), CO_{2} production (VCO_{2}), V_{E}/VO_{2} and V_{E}/VCO_{2} observed during incremental exercise to exhaustion. Middle cerebral artery velocity followed a decreasing curvilinear pattern during the sprint (MCA_{v} = 44.2 - 0.265 t + 0.0026 t^2, where MCA_{v} is in cm s^{-1} and t is in s, R^2 = 0.81, P < 0.001; n = 7, each point representing the mean of 20 subjects). From the values recorded just before the start of the sprint to the end of the sprint the MCA_{v} was reduced by 10% (P < 0.05). During the sprints there was dissociation between the changes in MCA_{v} and P_{ET}CO_{2}. Frontal lobe cerebral oxygenation (FLO) paralleled the MCA_{v}, that is, it was progressively reduced during
the sprint following a curvilinear pattern (FLO = 68.0 − 0.136 \( t \) + 0.0004 \( t^2 \), where FLO is the TOI of the frontal lobe in % and \( t \) is the time in s, \( R^2 = 0.97, P < 0.001, n = 7 \), each point representing the mean of 20 subjects). This resulted in a reduction of TOI from 67.9 ± 7.1 to 64.7 ± 7.9 (\( P < 0.05 \)). While only small changes in frontal lobe oxygenation were observed during the sprint, Vastus lateralis tissue oxygenation was reduced to minimal values in just 15 s (Figure 3(e)).

With the interruption of contractile activity, 2.5 s after stopping, \( V_E \) was reduced by 21 L min\(^{-1} \) and \( VO_2 \) by 390 mL min\(^{-1} \). During the first 20–30 s of the recovery, \( V_E \) and \( VCO_2 \) remained almost unchanged, to slowly decrease thereafter. At 2.5 s of the recovery,
the MCAv dropped to 32 cm s\(^{-1}\), that is 18% less than observed at the end of exercise. Thereafter, MCAv increased markedly to reach maximal values of 51 cm s\(^{-1}\) at 40 s after the end of exercise that is about 15 s after the peak values of P\(_{ET\text{CO}_2}\) observed during the recovery. Thereafter, MCAv decreased towards the values observed before the start of the sprint. In general, frontal lobe oxygenation reproduced the same pattern observed for MCAv, except at the end of exercise when, despite an abrupt reduction in MCAv, frontal lobe oxygenation remained unchanged.

There was a strong linear association between MCAv and frontal lobe oxygenation during the sprint exercise \((r = 0.93, P < 0.01; n = 7,\) each point representing the mean of 20 subjects) (Figure 3(f)). During recovery the association was less strong but was statistically significant \((r = 0.43, P < 0.05; n = 12,\) each representing the mean of 20 subjects).

**Study II**

*Power output and systemic haemodynamics.* In study II, good MCAv recordings were obtained in eight subjects,
while a complete set of haemodynamic data during both
Wingate test was obtained in nine subjects. Peak power
output was not statistically different between normoxia
and hypoxia (973 ± 300 and 906 ± 377 W, respectively,
$P = 0.36$). However, the mean power output was reduced
by 7%, from 494 ± 47 W in normoxia to 461 ± 52 W in
hypoxia ($P < 0.05$), as previously reported.$^{26}$

Figure 4 depicts the main hemodynamic variables
assessed in a representative subject during a Wingate
test in normoxia and hypoxia. As shown in
Figure 5(a), heart rate was higher during the first 10 s
of the sprint in hypoxia, being similar in both conditions
during the last 20 s. Peak cardiac output was 23.2 ± 2.5
and 21.0 ± 2.5 L min$^{-1}$ in normoxia and hypoxia,
respectively ($P < 0.05$), as previously reported.$^{26}$ Blood
pressure responses are depicted in Figure 5(b). Systolic
blood pressure increased during the sprint to mean
values close to 200 mmHg ($F_{O_2}$ effect: $P = 0.38$; time
effect: $P < 0.001$; $F_{O_2} \times$ time interaction: $P = 0.24$),
while diastolic blood pressure remained at the level
observed just before the start of the sprint (80–
90 mmHg) ($F_{O_2}$ effect: $P = 0.38$; time effect: $P = 0.12$;
$F_{O_2} \times$ time interaction: $P = 0.09$; time effect: $P = 0.004$;
$F_{O_2} \times$ time interaction: $P = 0.34$). The highest
systolic blood pressure values recorded were 222 ± 27
(range: 202–304) and 211 ± 24 (range: 200–259) mmHg, in normoxia and hypoxia, respectively
($P = 0.197$). The highest systolic blood pressure values
recorded during the sprints were linearly related to the
peak power output expressed in absolute (i.e. in watts)
($r = 0.625$, $P = 0.006$) and relative values (i.e. W kg$^{-1}$
body mass; $r = 0.678$, $P = 0.002$) (Figure 6).

The systolic blood pressure response to sprint exercise
in normoxia was linearly related to the response
observed in hypoxia ($r = 0.81$, $P < 0.01$). At the end of
the sprint in normoxia and hypoxia, the MAP was rap-
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flow and brain oxygenation during sprint exercise and
the immediate post-exercise period. Second, we asked if
oxygen delivery or the avoidance of hyperperfusion is
prioritized during sprint exercise. We have shown that
cerebral blood flow is exquisitely adjusted to maintain a
normoxic brain oxygen delivery in severe acute
hypoxia, both at rest and during sprint exercise. Moreover, our findings demonstrate that cerebral
oxygen delivery is prioritized during sprint exercise
when a conflict exists between preserving brain
oxygen delivery or restraining cerebral blood flow to
avoid potential damage by an elevated blood pressure.

Figure 4. Raw data obtained from one of the volunteers during 30 s sprints in normoxia (red lines) and severe acute hypoxia
($P_{O_2} = 73$ mmHg, blue lines). (a) Intra-arterial blood pressure (FA); (b) blood pressure in the femoral vein (FV); (c) middle-cerebral
artery velocity (MCAv); (d) smoothed MCAv (1 s averages); (e) frontal lobe tissue oxygenation index (TOI); (f) heart rate (HR). The
first vertical arrow indicates the start of the sprint, and the second the end of the sprint, i.e., the start of the recovery.
BP: blood pressure; BS: blood sample; FV: femoral vein; FA: femoral artery.
Figure 5. Haemodynamic and cerebral blood flow responses to sprint exercise in normoxia (red circles) and severe acute hypoxia (blue circles; \( F_{O2} = 73 \text{ mmHg}; \) study II). (a) heart rate (HR), \( n = 9 \); (b) blood pressures, \( n = 9 \); (c) middle-cerebral artery mean velocity (MCAvmean), \( n = 8 \); (d) cerebrovascular conductance (CVC) index, calculated as the quotient MCAv/MAP, \( n = 8 \); (e) arterial partial pressure of carbon dioxide (PaCO2), \( n = 9 \); (f) Oxygen delivery index, calculated as the product of arterial oxygen content \((CaO2) \times MCAv, n = 8\); (g) frontal lobe tissue oxygenation index (TOI), \( n = 9 \).

BP: blood pressure; MAP: mean arterial pressure. During exercise the Doppler signal was lost in three subjects.

* \( P < 0.05 \) normoxia versus hypoxia, at the same time point; \( \dagger P < 0.05 \) time effect compared to immediately before the start of the sprint; the error bars represent the standard error of the mean.
Cardiorespiratory responses to sprint exercise pose a challenge to the brain circulation

During all-out 30 s sprinting peak power output values are reached within the first 5 s. At the end of the sprint VO\textsubscript{2} reaches between 80% and 90% of maximum\textsuperscript{34} and cardiac output approaches peak values.\textsuperscript{26} This requires a strong central command activation of the medullary vasomotor and cardiorespiratory centres.\textsuperscript{35} As a part of these integrated responses arterial blood pressure was markedly increased in our study, with mean peak systolic values maintained close to 200 mmHg for the duration of sprint exercise. The blood pressure response we observed is similar or slightly lower than elicited by arm cranking at near-maximal intensities\textsuperscript{3} and slightly higher than observed close to exhaustion during incremental cycle\textsuperscript{3} or rowing exercise.\textsuperscript{36} The combined increase of mean arterial pressure and cardiac output facilitates muscle perfusion in active muscles, but may pose a challenge to the integrity of the blood brain barrier and the brain parenchyma in case of regional or global cerebral hyperperfusion.\textsuperscript{8,37}

Due to the increase in mean arterial pressure, without opposing mechanisms cerebral blood flow would have been increased by \(\sim 20\%\)\textsuperscript{3}–\(25\%\) during the sprints, compared to the levels immediately before the start of the sprints. Thus, vasoconstrictor mechanisms must have efficiently opposed to the increase in perfusion pressure in order to avoid brain hyperperfusion during the sprints. The risk of vascular damage during hyperperfusion increases when accompanied by high blood pressure.\textsuperscript{5,8} Animal studies in lambs have shown a marked sympathetic nerve activity in the superior cervical ganglia in response to hypertension,\textsuperscript{38} accompanied by vasoconstriction of pial arteries via sympathetic activation combined with a myogenic response preventing or blunting the increase of cerebral blood flow.\textsuperscript{39,40} Other studies have proposed a role for the carotid and vertebral arteries in sympathetic regulation of cerebral blood flow. Small reductions in their diameter at the entry of the cranium, where they are more tortuous produce a substantial increase in their vascular resistance to limit brain perfusion.\textsuperscript{1,41,42} Sympathetic and myogenic responses have not been thought to be very important\textsuperscript{1} but they are probably the most rapid mechanism that could be recruited to prevent an excessive increase of cerebral blood flow during sprint exercise that combines a fast increase of cardiac output with a quick and sustained elevation of blood pressure from the start to the end of the sprint.

Recently, Willie et al.\textsuperscript{1} combined the results of numerous studies in healthy humans that have reported steady-state changes in mean arterial pressure (MAP) and cerebral blood flow (CBF). From this, they calculated that the slope of the %ΔCBF/%ΔMAP relationship above and below resting mean arterial pressure, has mean values of 0.81±0.77 in the hypotensive range and 0.21±0.47 in the hypertensive range. In our experiments the %ΔCBF/%ΔMAP lied close to 1.08 during the sprint. This is 5-fold higher than observed in other experimental setups, in which the increase in mean arterial pressure occurred more gradually and was not accompanied by an elevation of cardiac output.\textsuperscript{1} A %ΔCBF/%ΔMAP value close to 1 indicates lack of autoregulation at the start of the sprint or a delayed response, exposing the cerebral circulation to the potential harmful effects of a high blood pressure combined with increased blood flow.\textsuperscript{5,7,8} The greater degree
of hyperventilation and, hence, lower $P_{ET}CO_2$, before the start of the sprint exercise in Study I, might have prevented the initial increase in cerebral blood flow during the sprints performed in normoxia in Study I.

A peculiarity of sprint exercise relative to steady-state exercise is the fast, almost instantaneous, reduction of mean arterial pressure upon the cessation of exercise. Several factors to explain the reduction in mean arterial pressure include: a deactivation of the central command, lowered metaboreflex and mechanoreflex feedback after cessation of exercise, and fast reduction of cardiac output caused by the combination of lower central command and venous return.43,44 These post-sprint events pose a substantial challenge to brain $O_2$ delivery homoeostasis. According to the estimations by Willie et al.,1 with a 26% drop of mean arterial pressure in just 2.5 s, cerebral blood flow should be reduced by 21%. Indeed, this is in good agreement with the 18% drop in MCAv we observed 2.5 s after the end of the sprint in Study I.

**Brain $O_2$ delivery is the main variable determining the regulation of cerebral blood flow during sprint exercise**

Brain function is so dependent on $O_2$ that flow arrest leads to loss of consciousness within 5–10 s.45 Therefore, a continuous supply of $O_2$ is required to maintain the cerebral metabolic rate (CMRO$_2$). Sprint exercise causes hypocapnia, which may contribute to the reduction of cerebral blood flow during sprint exercise in normoxia. In fact, the lowest values of MCAv were observed 10 s after the nadir in $P_{ET}CO_2$, what corresponds to the expected 5–10 s shift in the MCAv response due to the circulating time.33

For the $PaCO_2$ drop observed during the sprints in severe hypoxia (10 mmHg), a 25% lower cerebral blood flow has been reported in resting humans with the Ketty–Schmidt method.46 However, the vasoconstrictor effect of hypocapnia was completely abrogated during the sprint exercise in severe hypoxia, as reflected by the 25% higher MCAv during the sprint in hypoxia compared to the sprints in normoxia, in Study II. Likewise, the reduction in MCAv observed in normoxia in Study I, was less than expected from the reduction in $P_{ET}CO_2$.

The decline of cerebral blood flow during sprint exercise in Study I and during the last 15 s of the sprint in Study II occurred in a context for which an increased brain oxygen demand is expected10 due to the intense neuronal activity required to activate the muscles and cardiorespiratory medullary centres, and to process all afferent signals reaching the CNS.16,47 This neural activity is expected to enhance cerebral blood flow locally by a feed-forward mechanism,48 that is likely counterbalanced or adjusted by neurovascular coupling to provide a good regional match between $O_2$ supply and the $O_2$ demand generated by neural activity.16,49,50 Nevertheless, frontal lobe oxygenation was reduced during sprint exercise implying that $O_2$ extraction likely increased to preserve the appropriate flux of $O_2$ from the brain capillaries to the neurons.9 We interpret our results to mean that during the sprint performed in normoxia, the priority was given to the avoidance of brain hyperperfusion over the maintenance of $O_2$ delivery, by allowing a small decline in cerebral blood flow. However, during sprint exercise in severe acute hypoxia, despite a similar perfusion pressure as in the sprints performed in normoxia, cerebral blood flow was increased to account for the reduction in $CaO_2$ to maintain $O_2$ delivery at levels similar to those observed during the sprint in normoxia. Study II demonstrates that the most critical variable regulated is brain oxygen delivery, to the extent that a greater level of brain perfusion is tolerated despite the increase in perfusion pressure and the reduction in $PaCO_2$ during sprint exercise in severe hypoxia. This secures brain function under conditions of low oxygenation at the expense of increasing haemodynamic risks.51,52

**Cerebral blood flow drops markedly upon cessation of sprint exercise**

At the end of the sprints in normoxia (Study I) MCAv was abruptly lowered by $\sim 18 \text{ cm s}^{-1}$ what is more than the 4–5 cm s$^{-1}$ reduction observed after moderate intensity cycle ergometer exercise in the semi-recumbent position.43 The inability to maintain cerebral perfusion during the first seconds of recovery after sprint exercise likely reflects some impairment of cerebral autoregulation as previously reported for post-exercise recovery in the semi-recumbent position.43 Nevertheless, 20 s after the end of the sprint MCAv and frontal lobe oxygenation values were similar to pre-exercise values indicating a fast re-establishment of normal cerebral perfusion and oxygenation (Figure 3(b)). Our invasive data indicate that, compared to the values observed during the sprint, MAP is 50–60 mmHg lower 12.5 s after cessation of sprint exercise, remaining at this level during the first minute of recovery. Thus, myogenic relaxation (i.e. autoregulation) combined with the vasodilatory effects of increased $PaCO_2$ and neurovascular coupling efficiently counteract the reduction in perfusion pressure that occurs abruptly upon cessation of exercise, although with a small delay.

**Methodological considerations**

This study has two main methodological limitations related with the use of NIRS to measure brain
oxygenation and transcranial Doppler to assess brain blood flow. Although the frontal lobe NIRS signal is contaminated by noise from the skin,\textsuperscript{53} it has been shown that frontal lobe NIRS oxygenation tracks well changes in brain \(O_2\) delivery, during carotid surgery,\textsuperscript{54,55} postural changes from supine to standing,\textsuperscript{56} head-up tilt induced presyncope,\textsuperscript{57} lower-body negative pressure,\textsuperscript{58} systemic hypoxia,\textsuperscript{59} exercise,\textsuperscript{60} prolonged apnoea\textsuperscript{61} and return of spontaneous circulation during chest compressions.\textsuperscript{62,63}

Since the assessment of cerebral blood flow by inert gasses or dye injection requires steady-state haemodynamic conditions, these techniques cannot be applied to sprint exercise.\textsuperscript{64} The usage of transcranial Doppler is not without limitations,\textsuperscript{65} but it does provide a measure of cerebral blood flow\textsuperscript{16,44} that agrees well with the \(^{133}\text{Xenon} \) clearance method.\textsuperscript{66} The use of transcranial Doppler to measure cerebral blood flow is based on the assumption that the diameter of the MCA does not change with the intervention. This seems to be the case for small fluctuations of \(P_{\text{ETCO}_2}\) (± 8 mmHg).\textsuperscript{65} Therefore, it is reasonable assuming that the diameter of the MCA was not changed in Study I by the 6 mmHg decrease and increase in \(P_{\text{ETCO}_2}\), during the sprint and recovery, respectively, assuming that \(P_{\text{ETCO}_2}\) is a good surrogate of \(P_{\text{PaCO}_2}\).\textsuperscript{31}

In contrast to hypocapnia, hypoxia may elicit an augmentation of the MCA diameter.\textsuperscript{21} After 3 h of exposure to acute hypoxia (\(F_\text{IO}_2=0.12\)), the MCA diameter determined with magnetic resonance angiography was increased from 3.04 to 3.27 mm.\textsuperscript{21} Using the mean MCA\textsubscript{v} values recorded during the sprint in normoxia and hypoxia (i.e. 57.9 and 72.5 cm\textsuperscript{s}\textsuperscript{-1}, respectively), we have calculated that our subjects experienced a similar level of MCA vasodilatation in acute hypoxia as observed by Wilson et al.,\textsuperscript{21} the estimated cerebral blood flow would have been 35% greater in hypoxia than normoxia. This compares with an estimated 25% increase in cerebral blood flow calculated assuming no change in MCA diameter. Actually, the experimentally observed 25% increase in cerebral blood flow was sufficient to account for the 22% lower \(\text{CaO}_2\) in hypoxia, indicating that in our experimental conditions most likely the diameter of MCA remained unchanged.

Finally, we only examined blood flow responses in MCA and we cannot rule out the possibility of a different response in other main cerebral arteries. During sub-maximal exercise, blood flow through the vertebral arteries increases more than through the internal carotid artery and MCA.\textsuperscript{67} Nevertheless, MCA and internal carotid artery flows increase in the same proportion.\textsuperscript{67} Thus, the haemodynamic risk to the brain barrier could be even higher in the vascular bed irrigated by the vertebral and basilar arteries, particularly in hypoxia.\textsuperscript{12}

## Conclusion

During maximal sprint cycle exercise lasting 30 s blood pressure increases markedly and cardiac output reaches values close to maximum at the end of the sprint, regardless of \(F_\text{IO}_2\). When the sprint is performed in normoxia and \(P_{\text{ETCO}_2}\) has been reduced immediately before the beginning of the sprint cerebral blood flow decreases progressively during the sprint. Consequently, frontal lobe oxygenation also decreases in parallel to the changes of cerebral blood flow, indicating that during sprint exercise in normoxia the priority is given to limit brain hyperperfusion even at the expense of a small drop in cerebral blood flow. When the same exercise is performed in severe acute hypoxia, cerebral blood flow is increased to account for the reduction in arterial oxygen content, indicating that the main variable regulated during sprint exercise is oxygen delivery to the brain, which achieves values similar to those observed during sprint exercise in normoxia, regardless of \(P_{\text{PaO}_2}\), \(P_{\text{PaCO}_2}\) and mean arterial pressure. At the end of sprint exercise, mean blood pressure is dramatically reduced by 50–60 mmHg within the first 15 s, causing a drop in cerebral blood flow, which is partly blunted likely by autoregulatory mechanisms. The fast and marked changes in cardiac output and blood pressure during the sprint and the immediate recovery period challenge the regulation of brain circulation. It remains to be determined whether the combination of hypoxia and sprint exercise may be harmful for the integrity of the brain vasculature. New studies are required to establish the safety of sprint exercise for the integrity of the brain vascular tree in patients with hypertension, reduced arterial compliance, dysautonomy or a fragile vasculature.

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Authors’ contributions
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