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AlSalahi, Sultan E; Junejo, Rehan T; Bradley, Christopher; Balanos, George; Siebenmann, Christoph; Fisher, James P

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RESEARCH PAPER

The middle cerebral artery blood velocity response to acute normobaric hypoxia occurs independently of changes in ventilation in humans

Sultan E. AlSalahi[1] | Rehan T. Junejo[2] | Chris Bradley[1] | George M. Balanos[1] | Christoph Siebenmann[3] | James P. Fisher[4]

[1] School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of BirminghamEdgbaston, Birmingham, UK

[2] Department of Life Sciences, Manchester Metropolitan University, Manchester, UK

[3] Institute of Mountain Emergency Medicine, EURAC Research, Bolzano, Italy

[4] Department of Physiology, Faculty of Medical & Health Sciences, University of Auckland, Auckland, New Zealand

Correspondence
James P. Fisher, Department of Physiology, Faculty of Medical & Health Sciences, University of Auckland, Park Road, Grafton, Auckland 1142, New Zealand.
Email: jp.fisher@auckland.ac.nz

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Abstract

Hypoxia induces ventilatory, cardiovascular and cerebrovascular adjustments to defend against reductions in systemic oxygen delivery. We aimed to determine whether the ventilatory response to moderate acute hypoxia increases cerebral perfusion independently of changes in arterial oxygenation. Eleven young healthy individuals were exposed to four 15 min experimental conditions: (1) normoxia (partial pressure of end-tidal oxygen, P_{ETO_2} = 100 mmHg), (2) hypoxia (P_{ETO_2} = 50 mmHg), (3) normoxia with breathing volitionally matched to levels observed during hypoxia (hyperpnoea; P_{ETO_2} = 100 mmHg) and (4) hypoxia (P_{ETO_2} = 50 mmHg) with respiratory frequency and tidal volume volitionally matched to levels observed during normoxia (i.e., restricted breathing (RB)). Isocapnia was maintained in all conditions. Middle cerebral artery mean blood velocity (MCA V_{mean}), assessed by transcranial Doppler ultrasound, was increased during hypoxia (58 ± 12 cm/s, P = 0.04) and hypoxia + RB (61 ± 14 cm/s, $P < 0.001$) compared to normoxia (55 ± 11 cm/s), while it was unchanged during hyperpnoea (52 ± 13 cm/s, P = 0.08). MCA V_{mean} was not different between hypoxia and hypoxia + RB ($P > 0.05$). These findings suggest that the hypoxic ventilatory response does not increase cerebral perfusion, indexed using MCA V_{mean}, during moderate isocapnic acute hypoxia beyond that elicited by reduced oxygen saturation.

KEYWORDS
blood flow, brain, heart rate, ventilation

1 | INTRODUCTION

Hypoxia induces ventilatory, cardiovascular and cerebrovascular adjustments to defend against reductions in convective oxygen delivery to organs such as the heart, brain and kidneys (Guyenet, 2000, 2014; Marshall, 1994). Although the cardiorespiratory responses to acute hypoxia have been well described, partitioning the contribution of primary effects and secondary consequences is challenging, particularly in humans.

Isocapnic hypoxia increases internal carotid and vertebral artery blood flows (Ogoh et al., 2013), along with middle cerebral artery mean blood velocity (MCA V_{mean}) (Willie et al., 2012). It is possible

that, in addition to the local vasodilatory effect of hypoxaemia (Kety & Schmidt, 1948; Rocha et al., 2020), the increase in ventilation contributes to the cerebral hyperaemic responses to isocapnic hypoxia. Indeed, the breathing changes that occur in hypoxia lead to changes in ventilation efficiency, blood oxygenation, systemic and pulmonary pressure (Bilo et al., 2012) – all with the potential to increase cerebral blood flow (Willie et al., 2014). Furthermore, during isocapnic hypoxia the activation of brain regions accompanying heightened respiratory muscle activity and sensations of 'air hunger' may enhance brain blood flow. Indeed, descending inputs from sensorimotor higher brain centres (e.g., primary motor cortex, premotor area, supplementary area, insula cortex, anterior cingulate, cerebellum and amygdala) can influence the neural network located within the brainstem that controls respiratory rhythm and pattern (Colebatch et al., 1991; Guz, 1997; Pattinson et al., 2009a,b; Smith et al., 2013). Studies employing a variety of experimental manipulations (e.g., hypercapnia, mechanical ventilation, resistive loads) have identified the involvement of a complex network of brain regions in the sensation of dyspnoea (Evans et al., 2002; von Leupoldt & Dahme, 2005). However, when Ogoh et al. (2014) asked participants to wilfully restrain chemoreflex-mediated increases in ventilation during pokilocapnic hypoxia, rather than being attenuating, internal carotid artery blood flow and MCA V_{mean} were augmented relative to pokilocapnic hypoxia with unrestricted breathing. However, the partial pressure of end-tidal CO_2 (P_{ETCO_2}) was also higher during the restricted breathing condition, potentially confounding the results. It thus remains unclear whether ventilation independently modulates the cerebrovascular response to acute hypoxia.

Herein, we sought to isolate the contribution of hypoxia from the possible secondary effects of increased ventilation on MCA V_{mean} during acute normobaric isocapnic hypoxia. Four experimental conditions were conducted in which participants breathed spontaneously in normoxia (Normoxia); breathed spontaneously in hypoxia (Hypoxia); were exposed to normoxia with ventilation matched to that observed during Hypoxia (Hyperpnoea); and were exposed to hypoxia with ventilation matched to that observed during normoxia (hypoxia with restricted breathing, Hypoxia + RB). Isocapnia was ensured throughout to avoid potential confounding effects of changes in P_{ETCO_2}. This experimental approach enabled us to test the hypothesis that enhanced ventilation independently increases MCA V_{mean} during acute isocapnic hypoxia.

New Findings

- **What is the central question of this study?**
  Does the ventilatory response to moderate acute hypoxia increase cerebral perfusion independently of changes in arterial oxygen tension in humans?
- **What is the main finding and its importance?**
  The ventilatory response does not increase middle cerebral artery mean blood velocity during moderate isocapnic acute hypoxia beyond that elicited by reduced oxygen saturation.

2 | METHODS

2.1 | Ethical approval

The Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham (ERN_18-2066) approved the study protocol, which was performed according to the *Declaration of Helsinki*, except for registration in a database. Before starting the study, written informed consent was obtained from each participant after they had been provided with a detailed verbal and written overview of the experimental procedures.

2.2 | Participants

A total of 11 male volunteers (23 ± 3 years, 173 ± 7 cm, 73 ± 9 kg: mean ± SD) completed this study. Prior to inclusion they completed a screening (Medical Health Questionnaire) to ensure that they were healthy and not taking any prescription or over-the-counter medications. Instructions were provided to participants to refrain from alcohol, caffeine and heavy exercise for >24 h before the study.

2.3 | Experimental protocol

At an initial familiarisation session participants breathed through a mouthpiece for a 10-min period to establish normal breathing values. They were then familiarised to the Normoxia, Hypoxia, Hyperpnoea and Hypoxia + RB conditions (described below) for 15 min each.

At the start of the experimental session, participants again breathed through the mouthpiece for 10 min in order to establish normal values for P_{ETCO_2} and partial pressure of end-tidal oxygen (P_{ETO_2}). The four experimental conditions were then undertaken with P_{ETCO_2} and P_{ETO_2} controlled using a dynamic end-tidal forcing system to manipulate inspired (humidified) gases on a breath-by-breath basis (Robbins et al., 1982; Prodel et al., 2016). In all conditions, P_{ETCO_2} was held at baseline +1 mmHg. Conditions were: (1) Normoxia: participants breathed spontaneously at a normal rate and depth while inspiring a gas that controlled P_{ETO_2} at baseline levels to ensure there were no effects of isocapnia on P_{ETO_2}; (2) Hypoxia: participants breathed spontaneously while P_{ETO_2} was clamped at 50 mmHg; (3) Hyperpnoea: participants were instructed to increase their respiratory rate and depth to target values observed during Hypoxia, while P_{ETO_2} was maintained at baseline levels; and (4) Hypoxia + RB: participants were instructed to maintain their respiratory frequency (R_f) and tidal volume (V_T) at values observed during Normoxia, while P_{ETO_2} was clamped at 50 mmHg.

A 10-min recovery period was undertaken between conditions. Conditions 1 and 2 were always performed before conditions 3 and 4, since the target R_f and V_T in conditions 3 and 4 were based on values

obtained during conditions 1 and 2. However, a coin toss was used to randomize the order of conditions 1 and 2 (Normoxia and Hypoxia) and conditions 3 and 4 (Hyperpnoea and Hypoxia + RB). R_f was guided using a metronome, while V_T was guided using an oscilloscope. During conditions 1 and 2, participants were able to view a screen showing an innocuous documentary to shift their attention away from breathing.

2.4 | Experimental measures

All participants rested on a chair in an upright position throughout the study. Heart rate (HR) was monitored by electrocardiography (lead II, ECG) and beat-to-beat arterial blood pressure assessed using finger photoplethysmography (Finometer Pro; Finapres Medical Systems, Arnhem, the Netherlands). Stroke volume (SV) was derived from the finger blood pressure waveform using the Modelflow technique (FMS, Amsterdam, the Netherlands) (Bogert & van Lieshout, 2005). An automated sphygmomanometer (Tango+; SunTech Medical, Raleigh, NC, USA) was used to verify resting blood pressure measures. A mouthpiece and a nose-clip were worn by participants and the partial pressures of P_{ETCO_2} and P_{ETO_2} determined using a rapid response gas analysers (Moxus Modular; AEI Technologies, Pittsburg, PA, USA). Minute ventilation ($\dot{V}_E$), V_T and R_f were determined using a turbine volume transducer (VMM400; Interface Associates, Aliso Viejo, CA, USA). Finger pulse oximetry was used to establish O_2 saturation (S_{pO_2}) (Magna Medical 1400 Multi Parameter Monitor, Datex-Ohmeda Medical Equipment, Louisville, CO, USA). A 2-MHz pulsed Doppler ultrasound probe (Doppler Box X; Compumedics, Singen, Germany) was used to measure the right MCA V_{mean} through the temporal window (Willie et al. 2011). The probe was fixed using a modifiable head kit that locked the angle of insonation at the optimum position to ensure signal stability, and once the signal was acquired no further adjustments were made during the protocol.

2.5 | Data analysis

All measurements recorded were converted from analog to digital data at 1 kHz (PowerLab, 16/30; ADInstruments, Dunedin, New Zealand) and stored for offline analysis (LabChart Pro; ADInstruments). Respiratory data were extracted on a breath-by-breath basis, while cardiovascular and cerebrovascular data were extracted on a beat-by-beat basis. The last 5 min of each condition was used for analysis and averaged for data representation.

Mean arterial blood pressure (MAP) was calculated as:

$$\text{MAP} = \left(\frac{\text{Systolic Blood Pressure} - \text{Diastolic Blood Pressure}}{3}\right) + \text{Diastolic Blood Pressure}$$

Cardiac output (CO) was calculated as SV × HR and total peripheral resistance (TPR) calculated as MAP/CO. Cerebrovascular conductance index (CVCi) was calculated as MCA V_{mean}/MAP (Flück et al., 2017).

2.6 | Statistical analysis

A two-way repeated measures analysis of variance (ANOVA) was used to examine the main effects of oxygenation (hypoxia, normoxia), breathing (spontaneous, controlled) and their interaction (oxygenation × breathing). Significant interactions were explored *post hoc* using the Student–Newman–Keuls test. Statistical analysis was performed using SigmaPlot (version 14.0, Systat Software Inc., San Jose, CA, USA). Data are displayed as mean ± SD, unless otherwise indicated. Differences were considered significant if $P < 0.05$.

3 | RESULTS

P_{ETO_2}, P_{ETCO_2}, R_f, $\dot{V}_E$ and V_T were successfully controlled to the target values (Figure 1). By design, P_{ETO_2} was matched between Normoxia (101 ± 2 mmHg) and Hyperpnoea (100 ± 0.1 mmHg; $P = 0.92$) as well as between Hypoxia (53 ± 0.1 mmHg) and Hypoxia + RB (52 ± 0.3 mmHg; $P = 0.84$). S_{pO_2} was lower during hypoxic conditions (Hypoxia 87 ± 2%; Hypoxia + RB 85 ± 1%) than normoxic conditions (Normoxia 98 ± 1%; Hyperpnoea 98 ± 1%; $P < 0.001$), but no main effect of breathing (spontaneous vs. controlled; $P = 0.407$) or interaction (breathing × oxygenation; $P = 0.598$) was observed. P_{ETCO_2} was not different between all four conditions (38.7 ± 2.4, 39.0 ± 1.3, 38.8 ± 1.3 and 38.9 ± 1.3 mmHg for Normoxia, Hypoxia, Hyperventilation and Hypoxia + RB, respectively; $P = 0.34$). As expected, V_T and $\dot{V}_E$ were elevated in Hypoxia compared to Normoxia ($P = 0.01$ and $P < 0.001$, respectively), whereas, by design, there were no differences in V_T, R_f and $\dot{V}_E$ between the Normoxia and Hypoxia + RB, and between the Hypoxia and Hyperpnoea (all $P > 0.05$).

Compared to Normoxia, MCA V_{mean} was increased during Hypoxia ($P = 0.042$), unchanged during Hyperpnoea ($P = 0.08$) and increased during Hypoxia + RB ($P < 0.001$) (Figure 2). MCA V_{mean} was not different between Hypoxia and Hypoxia + RB ($P = 0.11$). CVCi was lower ($P = 0.026$; Figure 2), and MAP was higher ($P = 0.02$; Figure 3), while CO ($P = 0.15$) and HR ($P = 0.90$) were unchanged, during the controlled breathing conditions (Hyperpnoea, Hypoxia + RB) compared to the spontaneous breathing conditions (Normoxia, Hypoxia). CVCi ($P = 0.002$), CO ($P = 0.002$) and HR ($P < 0.001$) were higher during the hypoxic conditions (Hypoxia, Hypoxia + RB) than the normoxic conditions (Normoxia, Hyperpnoea).

4 | DISCUSSION

We sought to determine the contribution of the increased ventilation to cerebrovascular responses to acute normobaric isocapnic hypoxia in humans. Our major novel finding is that MCA V_{mean} was increased to the same extent by Hypoxia and Hypoxia + RB, and not increased

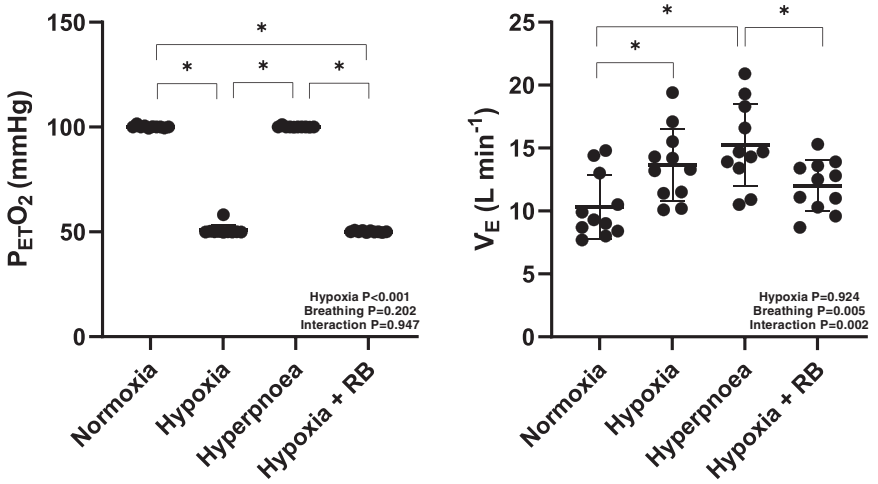
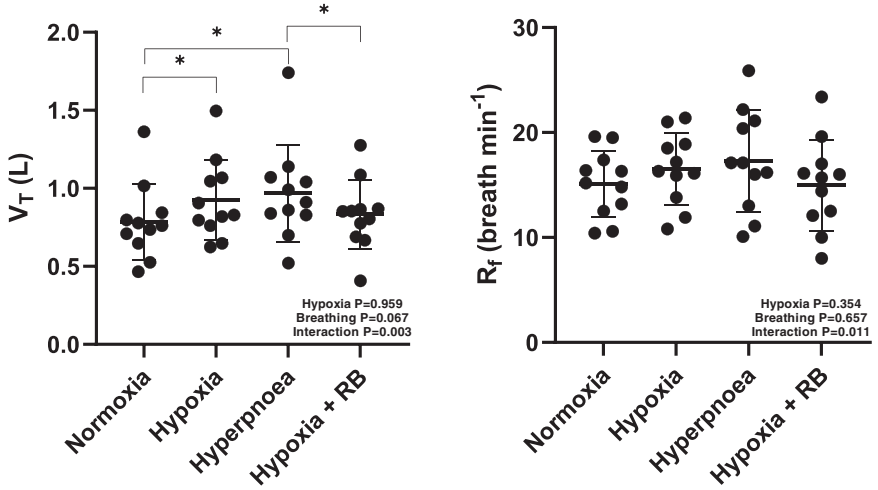


FIGURE 1 V_T, R_f, $\dot{V}_E$ and P_{ETO_2} during the Normoxia, Hypoxia, Hyperpnoea and Hypoxia + RB conditions. *$P < 0.05$. Horizontal bars show mean and SD



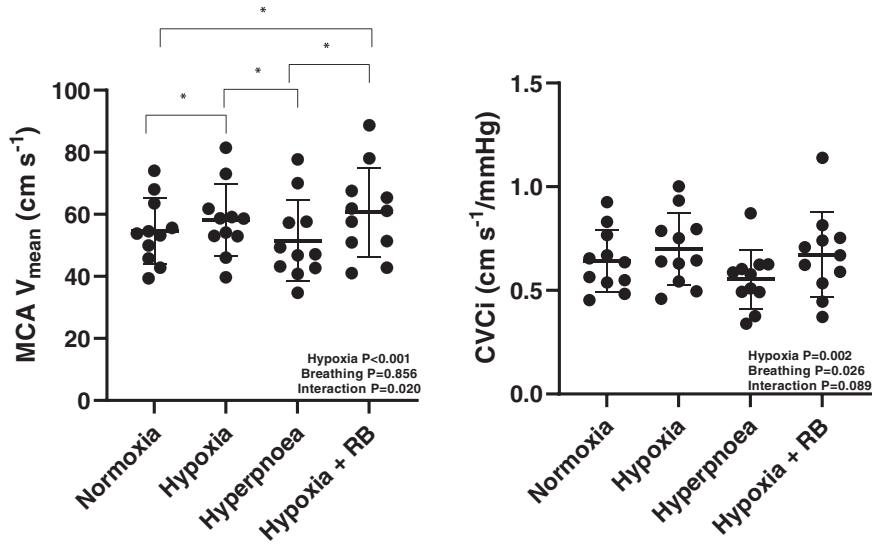


FIGURE 2 MCA V_{mean} and CVCi during the Normoxia, Hypoxia, Hyperpnoea and Hypoxia + RB conditions. *$P < 0.05$. Horizontal bars show mean and SD

by Hyperpnoea. These findings indicate that increases in ventilation do not independently influence the cerebrovascular response to acute normobaric hypoxia in humans.

Cerebral blood flow increases when P_{ETO_2} falls below ~58 mmHg and/or oxygen saturation (S_{pO_2}) falls below ~90% (Gupta et al., 1997). This response may be governed by local vasodilatory mechanisms (e.g. factors associated with the endothelium such as adenosine, nitric oxide and prostaglandins; Ainslie & Ogoh, 2010; Rocha et al., 2020). However, as a potential contribution from the secondary effects of an increase in ventilation might be possible we tested the hypothesis

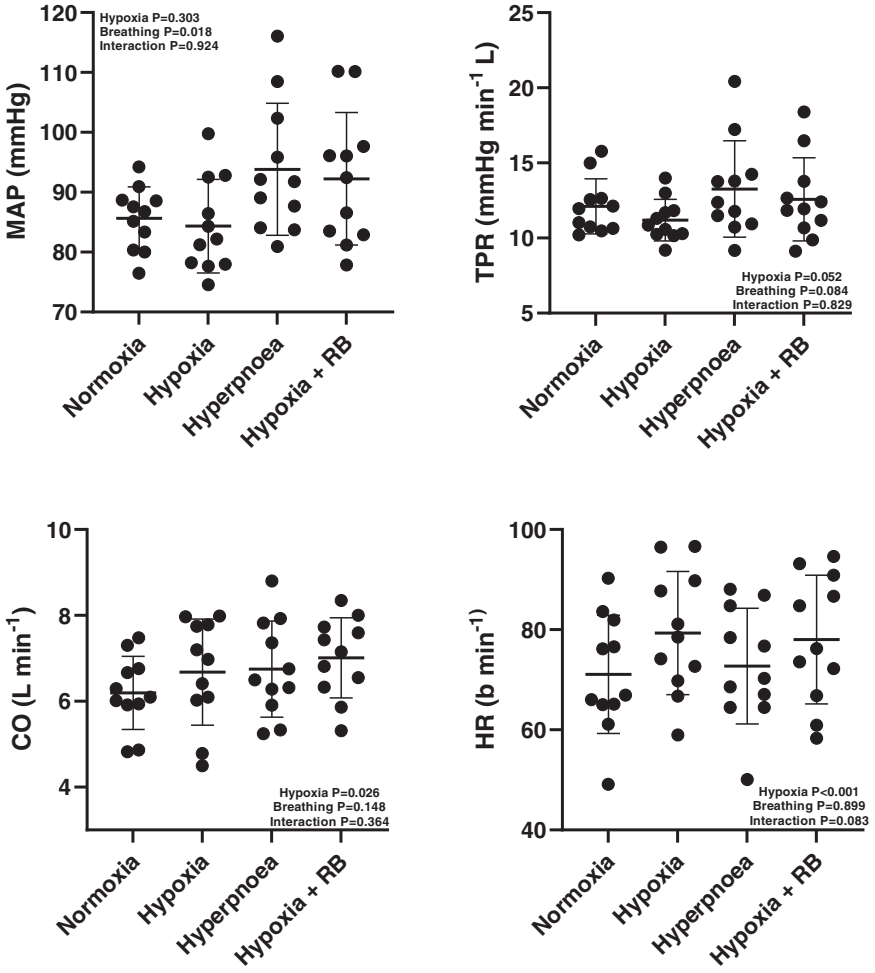


FIGURE 3 MAP, TPR, CO and HR during the Normoxia, Hypoxia, Hyperpnoea and Hypoxia + RB conditions. *$P < 0.05$. Horizontal bars show mean and SD

that enhanced ventilation independently increases MCA V_{mean} during acute isocapnic hypoxia. Contrary to this hypothesis, MCA V_{mean} did not increase during Hyperpnoea and the increases in MCA V_{mean} during Hypoxia and Hypoxia + RB were similar. Interestingly, when participants were asked to wilfully restrain increases in ventilation during poikilocapnic hypoxia, internal carotid artery and MCA V_{mean} increased to a greater extent than during poikilocapnic hypoxia with unrestricted breathing (Ogoh et al., 2014). However, P_{ETCO_2} was higher when ventilation was wilfully restricted, which could have explained the increased cerebral blood flow; therefore, to discern the effects of arterial CO_2 and ventilation, we matched ventilation during hypoxia to normoxia while controlling P_{ETCO_2}.

We observed that Hypoxia and Hypoxia + RB evoked similar increases in MCA V_{mean}. Previously, Bilo et al. (2012) demonstrated that 15 min of breathing at a reduced rate of 6 breaths/min while at high altitude (4559–5400 m) enhanced S_{pO_2} (+6–9%) and reduced pulmonary artery pressure (−4 mmHg). Such changes in systemic oxygenation and central haemodynamics might be expected to modify cerebral blood flow, although this was not measured by Bilo et al. (2012). In contrast to Bilo et al. (2012), in our Hypoxia and Hypoxia + RB conditionsP_{ETO_2} and S_{pO_2} were experimentally matched, allowing us to more precisely evaluate the distinct influence of breathing pattern on MCA V_{mean}. Similar to MCA V_{mean}, CVCi was increased in Hypoxia and Hypoxia + RB relative to the normoxic conditions (Normoxia, Hyperpnoea), suggesting that these hemodynamic changes were not secondary to changes in MAP. However, CVCi was lower and MAP was elevated during the breathing manipulation trials (Hyperpnoea and Hypoxia + RB vs. Normoxia and Hypoxia). A main effect of hypoxia on CO was observed (i.e., CO elevated in the Hypoxia and Hypoxia + RB trials relative to the Normoxia and Hyperpnoea trials) and a contribution to the elevated MCA V_{mean} in these conditions is possible.

Dyspnoea arises from the activation of multiple sensory afferent mechanisms (e.g. pulmonary vagal afferents, respiratory muscle mechanoreceptors) and its perception involves several cortical sites (von Leupoldt & Dahme, 2005). These mechanisms could be another pathway by which the ventilatory response could increase cerebral blood flow during hypoxia. Indeed, respiratory discomfort induced with loaded breathing increases blood flow in the right anterior insula, cerebellar vermis and medial pons (Peiffer et al., 2001), while active inspiration and expiration increases cortical blood flow in discrete regions when compared with a passive condition (i.e., mechanical ventilation) (Ramsay et al., 1993). Functional magnetic resonance imaging has been used to identify the central pattern of activation

induced by hypoxia (Critchley et al., 2015), but the extent to which this is explicitly related to changes in ventilation has not been explored. Herein, we observed increases in MCA V_{mean} during Hypoxia, but not during either Hypoxia + RB or Hyperpnoea, suggesting that changes in breathing rate and depth do not contribute. However, it is possible that neither the hypoxic stimulus nor the ventilatory response in our study evoked a sufficiently large activation of higher brain centres perfused by the middle cerebral artery.

4.1 | Methodological considerations

There are several methodological issues that should be considered. MCA V_{mean} was used to assess cerebral perfusion, and the relative strengths and weaknesses of this technique have been discussed (Ainslie & Hoiland, 2014; Willie et al., 2011). In brief, in the absence of MCA diameter measurements, we can only assume that the MCA V_{mean} data are representative of MCA flow. Given that acute hypoxia can cause cerebral vasodilatation (Wilson et al., 2011), it is possible that the magnitude of the increases in MCA V_{mean} underestimate the true increases in cerebral blood flow under these conditions. However, as this would presumably have affected the Hypoxia and Hypoxia + RB conditions equally, it is not likely that it could affect the findings of this study. Further studies are warranted using advanced brain imaging technologies (e.g., magnetic resonance imaging, arterial spin labelling). Finally, care should be taken when considering our findings gathered under conditions of acute normobaric hypoxia in the context of high altitude conditions of chronic hypobaric hypoxia (Coppel et al., 2015).

In conclusion, the results of this study indicate that during moderate isocapnic acute hypoxia the hypoxic ventilatory response does not increase cerebral perfusion beyond that elicited by reduced oxygen saturation.

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COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

All the experiments took place at the School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham. J.P.F. conceived and designed the research. S.E.A., R.T.J., C.B. and G.B. acquired the data. S.E.A. analysed the data. J.P.F., S.E.A., R.T.J. and C.S. interpreted the data. J.P.F. and S.E.A. drafted the work, and along with C.S., revised it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors quality for authorship, and all those whose qualify for authorship are listed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sultan E. AlSalahi https://orcid.org/0000-0001-7359-6528
Rehan T. Junejo https://orcid.org/0000-0002-0670-8339

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