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RESEARCH ARTICLE

Cerebrovascular Control in Health and Disease: From Modeling to Translational Research

Regional dynamic cerebral autoregulation in acute poikilocapnic hypoxia

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Abstract

Dynamic cerebral autoregulation (dCA) of the posterior circulation has been shown to be more pressure-passive compared with the anterior circulation, possibly due to a lower basal vascular tone. In hypoxia, vascular tone and dCA are typically reduced; however, evidence using volumetric assessment is limited to the anterior circulation. We hypothesized that the posterior circulation would have an exacerbated reduction in dCA than the anterior circulation in acute hypoxia. Twenty participants (14 males, 6 females) were exposed to 120 min of normoxia and acute poikilocapnic hypoxia (12.5% fraction of inspired oxygen). dCA was assessed as the rate of regulation (RoR) of vascular conductance to thigh cuff-induced acute hypotension, in the internal carotid artery (ICA) and vertebral artery (VA) by duplex ultrasound, and the middle cerebral artery (MCA) and posterior cerebral artery (PCA) by transcranial Doppler ultrasound, representing anterior (ICA and MCA) and posterior (VA and PCA) circulations. Linear mixed model analysis revealed that ICA RoR [−0.06 (0.22) s^{-1}, $P = 0.279$] and VA RoR [−0.05 (0.21) s^{-1}, $P = 0.343$] were comparable in normoxia and hypoxia. MCA RoR ($P = 0.995$) and PCA RoR ($P = 0.895$) were also comparable between conditions. In males only, hypoxia reduced VA RoR [−0.15 (0.19) s^{-1}, $P = 0.012$], but not ICA RoR [−0.07 (0.21) s^{-1}, $P = 0.264$]. In addition, hypoxia induced vasodilation of the ICA [+0.30 (0.32) mm, $P = 0.009$] but not the VA [+0.08 (0.33) mm, $P = 0.398$] in males. In conclusion, volumetric dCA of the cerebral conduit arteries to acute hypotension in hypoxia was regionally different in males and may not be influenced by changes in vascular tone.

NEW & NOTEWORTHY We demonstrate that hypoxia causes regional dynamic cerebral autoregulation (dCA) in males, where volumetric dCA was reduced in the vertebral artery but not the internal carotid artery. In addition, immediately before the dCA assessment, the vertebral artery diameter was unchanged, whereas the internal carotid artery diameter was increased. In combination, these findings challenge the prevailing view that reductions in dCA in hypoxia are due to a reduction in vascular tone.

cerebral autoregulation; cerebrovascular; Doppler; hypoxia; regional

INTRODUCTION

Dynamic cerebral autoregulation (dCA) is an intrinsic mechanism that regulates cerebral blood flow to fluctuations in arterial blood pressure within a few seconds via changes in vascular tone (1–3). Arterial vascular tone is regulated by the vascular smooth muscle that lines the cerebral arterial circulation (4). The type, density, and distribution of receptors and channels present on the arterial vascular wall and their sensitivity to vasoactive agents are key mediators responsible for the regulation of vascular tone (5), and variability within these mechanisms between the anterior and posterior cerebral circulation may underpin the observed regional cerebral blood flow regulation during systemic physiological stress, such as orthostasis (6), hypoxia (7–10), hyperthermia (11, 12), and alterations in end-tidal carbon dioxide (9, 13). Moreover, distinctive sympathetic adrenoreceptor subtype distribution and parasympathetic innervation between the anterior and posterior cerebral conduit arteries have been identified (14) and may explain early reports of opposing vasoactive responses to norepinephrine between anterior and posterior bovine cerebral conduit arteries (15). Furthermore, a lower sensitivity to vasoactive agents, such as reactive oxygen species and nitric oxide bioavailability, has been reported in the posterior circulation compared with the anterior circulation (16–18).

These observed regional differences in cerebral blood flow regulation may be necessary to maintain a lower basal vascular tone in the posterior compared with the anterior circulation. Such differences may preferentially maintain

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blood flow to the posterior regions of the brain involved in systemic cardiorespiratory control, particularly during times of systemic physiological stress (6), and/or to meet the neurometabolic demand of the occipital lobes to visual stimulation since assessments are normally conducted with eyes open (19–21). The influence of vascular tone on dCA has been seldom studied in humans, perhaps due to the difficulty of manipulating and measuring vascular tone before and during the dCA assessment. However, using an elegant design, one study to examine the role of vessel tone demonstrated regional differences in dCA (6). Specifically, in response to an orthostatic-induced reduction in blood pressure caused by head-up tilt, cerebral blood flow reductions were attenuated in the vertebral artery (VA) compared with the internal carotid artery (ICA), which are the upstream conduit arteries supplying blood to the posterior and anterior circulations, respectively. This was attributed to an unchanged vascular tone in the VA that contrasted with the increased vascular tone of the ICA (6). Volumetric dCA was then assessed by the rapid thigh cuff method during the head-up tilt, and it was reported that compared with supine the VA had a greater reduction in blood flow and a slower rate of regulation (RoR) of vascular conductance to the abrupt reduction in blood pressure caused by the thigh cuff deflation than the ICA (6). It was proposed that a lower basal vascular tone of the VA is necessary to preferentially attenuate the orthostatic-induced reduction in cerebral blood flow to the posterior regions of the brain, but this is at the expense of a reduced dCA. Further evidence of a more pressure-passive disposition of the posterior compared with the anterior circulation to acute reductions in blood pressure is reported elsewhere (22–25).

Exposure to acute hypoxia has been shown to reduce anterior dCA (26–34). This has been attributed to the reduction in vascular tone of the cerebrovasculature, which is a compensatory response in a low-oxygen environment to increase cerebral blood flow to maintain cerebral oxygen delivery (33, 35). Consequently, hypoxia is a suitable physiological stress to examine whether vascular tone and dynamic cerebral autoregulation are different in the posterior circulation compared with the anterior circulation. Recent recommendations (36) also suggest that single-site indices of cerebral hemodynamics (i.e., middle cerebral artery blood velocity) are not representative of global cerebral conduit function, and volumetric multisite measurements should be central to future investigations of dCA. Only a few studies have assessed anterior vascular tone and volumetric blood flow simultaneously during dCA in hypoxia, and none have assessed dCA in the posterior circulation (26–28). Establishing further evidence of a more pressure-passive nature of the posterior circulation compared with the anterior circulation may also help to explain the stronger association of the posterior than anterior circulation with pathophysiological symptoms and conditions, such as orthostatic (in)tolerance (37), acute mountain sickness (38, 39), and cerebral small vessel disease (40).

This study compared volumetric dCA of the anterior and posterior cerebral conduit arteries in a mixed cohort of males and females in normoxia and in acute poikilocapnic hypoxia. As previous research indicates the posterior circulation is more pressure-passive than the anterior circulation (6, 22, 41, 42), and the magnitude of hypoxia-induced vasodilation is similar between the anterior and posterior cerebral conduit arteries (7, 43), we hypothesized that the reduction in dCA to large abrupt reductions in blood pressure in acute hypoxia would be exacerbated in the posterior compared with the anterior circulation.

METHODS

Ethical Approval

Ethical approval for this study was obtained from the Ethics Committee of the School of Sport, Health, and Exercise Sciences at Bangor University (Ethics ID: P05-2021) and was conducted following the standards of the Declaration of Helsinki 2013, except for registration in a database, with written informed consent obtained from all participants.

Participants

Twenty young healthy participants were recruited for this study [14 males, 6 females, 25 (6) yr, 175.7 (8.5) cm, 71.1 (11.2) kg, body fat 15.8 (6.3) %, hemoglobin 14.4 (1.3) $g \cdot dL^{-1}$, hematocrit 43 (4) %, mean (standard deviation)]. Twenty participants were recruited to account for dropout, data loss, and to reflect the participant characteristics of previous studies involving exclusively male ($n = 12$) (27) or predominantly male (male: $n = 12$, female: $n = 1$) (28) cohorts, which reported reductions in ICA RoR in response to hypoxia. Participants were nonsmokers, free from cardiovascular, hematological, and neurological disease, not at an increased risk of COVID-19 as defined by the Welsh Government, and had not resided overnight at an altitude of >2,500 m within the last 6 mo. Females were included if they had a regular menstruating cycle or were taking an oral contraceptive pill that included inactive/placebo days. Participants with a regular menstrual cycle were tested during the onset of menses and the early follicular phase (*day 1–5*), and participants on the oral contraceptive pill were tested during their withdrawal bleed (44). Menstrual subphase identification was completed by a forward-counting self-report method (45). Before completing the experimental trials, participants were familiarized with the experimental procedures. On the day before each trial, participants refrained from consuming alcohol and undertaking exhaustive exercise. On the day of each trial, participants matched their diet and supplement intake and refrained from consuming caffeinated beverages.

Experimental Design

This study followed a repeated-measures, counterbalanced crossover design with each participant completing two experimental trials at the same time of day, separated by at least 48 h. Experimental trials consisted of a 120-min exposure to either normoxia (fraction of inspired oxygen [$F_{I_{O_2}}$] = 20.9%) or acute poikilocapnic hypoxia ($F_{I_{O_2}} = 12.5\%$) in a temperature [25.6 (1.1) °C] and humidity [29.0 (7.1) %] controlled environmental chamber (Hypoxico Inc., New York). A 120-min exposure to an $F_{I_{O_2}}$ of 12.5% was selected to achieve arterial desaturation (43) and relatively more stable ventilatory responses to hypoxia compared with shorter duration hypoxia (46, 47).

Experimental Measurements

Cardiorespiratory.

Peripheral arterial oxygen saturation was measured via pulse oximetry (Sp_{O_2}, Model 7500 Oximeter, Nonin Medical Inc., Minnesota). Beat-to-beat heart rate was measured with a Lead II electrocardiogram, and blood pressure was measured by finger photoplethysmography (Finometer MIDI, Finapres Medical Systems, The Netherlands). Measurements of systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP) were calculated from the finger arterial waveform and calibrated to the average of three automated brachial blood pressure measurements (Tango +, SunTech, Morrisville, NC). The partial pressure of end-tidal oxygen ($P_{ET_{O_2}}$) and partial pressure of end-tidal carbon dioxide ($P_{ET_{CO_2}}$) were recorded breath-by-breath by a gas analyzer (ML206, ADInstruments, Colorado, CO).

Extracranial arteries.

Blood flow of the ICA and VA was collected using duplex ultrasound with a 15-MHz linear transducer at 30 Hz (uSmart 3300, Terason, Burlington, MA). High-resolution images of vessel diameter were acquired using B-mode imaging, whereas pulse wave mode was used to simultaneously measure the Doppler velocity spectra. Care was taken to ensure the strongest Doppler velocity spectrum signal by positioning the Doppler gate in the center of the artery with a 60° angle of insonation and adjusting to fill the artery lumen as per recommended technical guidelines (48). The ICA was measured at least 1.0–1.5 cm distal to the carotid bifurcation, and the VA was measured between C3 and the subclavian artery.

Intracranial arteries.

Blood velocity of the middle cerebral artery (MCA) and posterior cerebral artery (PCA) was measured by transcranial Doppler ultrasound (TCD) using two 2-MHz probes placed over the left and right transtemporal windows and secured in place via an adjustable headpiece (PMD150, Spencer Technologies, Seattle, WA). Insonation of each artery was achieved using standardized procedures (49), with probe position, signal depth, and gain settings recorded to replicate the placement between sessions. All TCD measurements were collected by the same operator (A.T.F.). Pairs of MCA and ICA, and PCA and VA were measured on the same side of the participant as determined by the most reliable and reproducible signals.

In two separate day-to-day reproducibility studies completed by the same operator (A.T.F.), the coefficient of variation for duplex ultrasound ($n = 5$) measurements of blood flow, vessel diameter, and blood velocity of the ICA (4%, 1%, and 3%) and VA (8%, 1%, and 7%) and TCD ($n = 10$) blood velocity measurements of the MCA (3%) and PCA (3%) were comparable with recommended guidelines (48).

Experimental Procedures

Rapid thigh cuff deflation-induced hypotension.

dCA was assessed (elapsed time: 60 min) using the standardized rapid thigh cuff method that causes transient, abrupt hypotension (50). Participants were instrumented with bilateral thigh cuffs (CC17, Hokanson, Bellevue, WA) connected to a rapid deflator (E20 Rapid Cuff Inflator, Hokanson), seated comfortably in an upright position, and asked to rest for a 2-min baseline. The bilateral thigh cuffs were then inflated to 200 mmHg for 3 min. Participants were instructed to remain relaxed and were not given feedback regarding the elapsed time of thigh cuff occlusion. Immediately after the 3-min inflation, both thigh cuffs were rapidly deflated (<1 s), causing a transient fall in MAP, and participants were instructed to remain still for 1 min thereafter. Measurements of heart rate, MAP, Sp_{O_2}, $P_{ET_{O_2}}$, $P_{ET_{CO_2}}$, and blood velocity of the MCA and PCA were recorded continuously throughout each rapid thigh cuff deflation. Simultaneous ICA and VA measurements were recorded for 30 s pre and postdeflation. At least four thigh cuff deflations were completed per participant to enable a minimum of two recordings each of the ICA and VA. The coefficient of variation of the relative MAP reduction to the thigh cuff deflation in this study was 15% in normoxia and 18% in hypoxia.

Data Processing

Measurements of blood velocity of the MCA and PCA, heart rate, systolic and diastolic blood pressure, Sp_{O_2}, $P_{ET_{O_2}}$, and $P_{ET_{CO_2}}$ were all acquired continuously at 1 kHz using an analog-to-digital converter (PowerLab 16/30, ADInstruments) and interfaced on a computer in real time using LabChart software (Chart 8, ADInstruments). Real-time beat-to-beat MAP and time-averaged maximum velocity (TAMx) of the MCA or PCA were determined from each R-R interval. All duplex ultrasound data were captured and stored for subsequent offline analysis by an investigator blinded to the condition of the experimental trials. Concurrent measurements of vessel diameter and TAMx were acquired using an automated edge-detection tracking software (Brachial Analyzer, Vascular Research Tools 6, Medical Imaging Applications, Coralville, IA). Subsequently, blood flow was calculated using the following equation:

$$\text{Blood flow}\,(\text{mL}\cdot\text{min}^{-1}) = [\text{TAMx}\,(\text{cm}\cdot\text{s}^{-1})/2] \times \left[\pi \times \left(\text{mean vessel diameter}\,(\text{cm})/2\right)^2\right] \times 60$$

Following a conservative quality check, data and statistical analysis were completed on normoxia:hypoxia: 18:17 ICA (13:12 males, 5:5 females), 17:19 VA (12:13 males, 5:6 females), 19:19 MCA (13:13 males, 6:6 females), and 16:16 PCA (10:10 males, 6:6 females). The exclusions were due to a poor image or signal quality of the extra- and intracranial arteries.

Data Analysis

Cardiorespiratory.

Continuous beat-to-beat heart rate, systolic blood pressure, diastolic blood pressure, MAP, Sp_{O_2}, $P_{ET_{O_2}}$, and $P_{ET_{CO_2}}$ were calculated from a 2-min average before the rapid thigh cuff method.

Cerebrovascular.

In accordance with previous methods (51), dCA after rapid thigh cuff deflation was characterized by the following

metrics (Fig. 1): *1*) maximal reduction, *2*) time to counterregulation, and *3*) rate of regulation (RoR).

The absolute and relative maximum reduction following rapid thigh cuff deflation in MAP, blood flow, blood velocity, vessel diameter, and cerebrovascular conductance (CVC = blood flow/MAP) or index (CVCi = blood velocity/MAP) values were calculated as the difference from their respective predeflation mean that was defined as the 4 s immediately before thigh cuff release. The time taken from thigh cuff deflation to the nadir in MAP and CVC or CVCi was individually determined and defined as the time to first MAP nadir and time to CVC or CVCi counterregulation, respectively. RoR was calculated from CVC or CVCi. Post-thigh cuff deflation responses were normalized to their concomitant predeflation values. RoR was calculated using the following equation:

$$\text{RoR} = (\Delta\text{conductance}/\Delta\text{time})/\Delta\text{MAP}$$

where Δconductance/Δtime is the slope of the normalized CVC (or CVCi) regression line between time of CVC (or CVCi) counterregulation (i.e., the nadir) plus 2.5 s, and ΔMAP is the magnitude of the reduction in normalized MAP during thigh cuff release during the same 2.5-s phase.

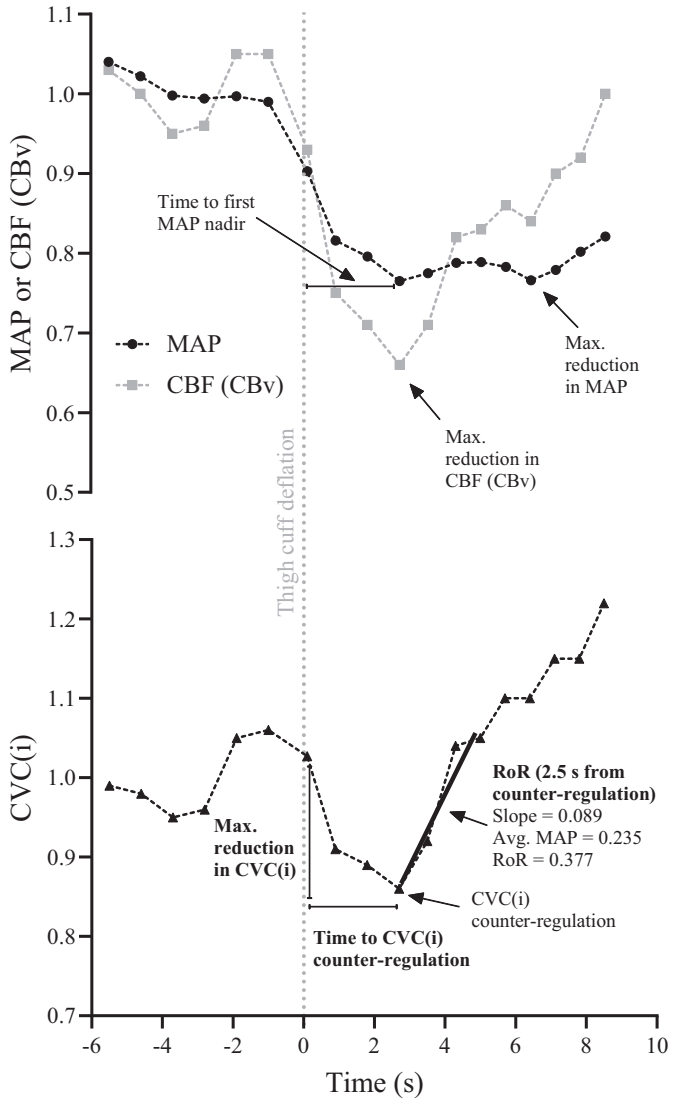

Figure 1. Representative illustration of the dynamic cerebral autoregulation metrics after rapid thigh cuff deflation-induced hypotension. Mean arterial pressure (MAP, circle), cerebral blood flow (CBF) or velocity (CBv, square), and cerebrovascular conductance (CVC) or index (CVCi, triangle) after rapid thigh cuff method assessment of dynamic cerebral autoregulation. Data were normalized relative to their respective means during the 4 s immediately before the thigh cuff release. In accordance with previous methods (51), dCA after rapid thigh cuff deflation was characterized as the following metrics *1*) maximal reduction, *2*) time to counterregulation, and *3*) rate of regulation (RoR).

Statistical Analysis

Statistical analysis was conducted using SPSS Statistics v27 (IBM Corp., Armonk, NY), and figures were created in GraphPad Prism (GraphPad Prism 9, San Diego, CA). Cardiorespiratory, cerebrovascular, and dCA metrics before and following the rapid thigh cuff method were analyzed by a linear mixed model with condition (normoxia and hypoxia) as the primary fixed effect of interest and participant as a random effect. Secondary additional fixed effects of interest of region (anterior and posterior) or $P_{ET_{CO_2}}$ were also investigated in the model. Raw data are mean (standard deviation), unless otherwise stated, and statistical significance was set at $P < 0.05$. Bonferroni-corrected multiple pairwise comparisons were conducted when significant main or interaction effects were detected. Values from linear mixed model pairwise comparison analysis are reported as estimated marginal means and an estimated standard deviation (43, 52).

RESULTS

Cardiorespiratory Response in Normoxia and Hypoxia before Thigh Cuff Deflation-Induced Hypotension

Compared with normoxia, acute poikilocapnic hypoxia reduced Sp_{O_2} [estimated marginal means (estimated standard deviation), −14.6 (3.7) %, main effect of condition, $P <$ 0.001, Table 1], $P_{ET_{O_2}}$ [−57.0 (4.8) mmHg, $P < 0.001$], $P_{ET_{CO_2}}$ [−2.7 (3.6) mmHg, $P = 0.004$], diastolic blood pressure [−5.1 (8.6) mmHg, $P = 0.014$], and MAP [−4.5 (7.4) mmHg, $P =$ 0.013] and increased heart rate [+7.0 (7.6) beats/min, $P =$ 0.001].

Regional Hemodynamics and Dynamic Cerebral Autoregulation in Normoxia and Hypoxia

Blood flow and blood velocity of the extracranial and intracranial arteries were unchanged to hypoxia (all $P >$ 0.05, Table 1). Hypoxia increased ICA vessel diameter (i.e., reduced vascular tone; $P = 0.002$) but did not significantly increase VA vessel diameter ($P = 0.076$) before thigh cuff deflation-induced hypotension (Table 1).

The rapid thigh cuff deflation caused a comparable time to the first MAP nadir and absolute maximum reduction in MAP in normoxia and hypoxia (both $P > 0.05$, Table 2). Due to lower pre thigh cuff deflation MAP in hypoxia than normoxia (Table 1), the relative maximum reduction in MAP was greater in hypoxia than normoxia (main effect of condition, $P = 0.048$). The relative maximum reduction to the thigh cuff-induced hypotension in blood velocity, vessel diameter, and blood flow of the extracranial (ICA and VA) arteries and blood velocity of the intracranial (MCA and

Table 1. *Cardiorespiratory and cerebrovascular responses before the rapid thigh cuff method in normoxia and hypoxia*

	Condition		*P* Value
	Normoxia	Hypoxia	Condition
Cardiorespiratory			
Sp_{O_2}, %	96.8 (1.0)	82.1 (3.7)	**<0.001**
Heart rate, beats/min	66.0 (8.2)	73.0 (10.4)	**0.001**
Systolic blood pressure, mmHg	117.1 (11.4)	113.8 (12.6)	0.076
Diastolic blood pressure, mmHg	73.3 (8.2)	68.2 (10.8)	**0.014**
Mean arterial pressure, mmHg	87.9 (8.1)	83.4 (10.3)	**0.013**
$P_{ET_{O_2}}$, mmHg	106.0 (4.4)	49.0 (3.9)	**<0.001**
$P_{ET_{CO_2}}$, mmHg	37.9 (3.4)	35.3 (2.8)	**0.004**
Extracranial blood flow, mL. min^{-1}			
Internal carotid artery	260.2 (58.8)	289.5 (68.3)	0.129
Vertebral artery	107.0 (33.3)	115.1 (54.3)	0.357
Extracranial vessel diameter, mm			
Internal carotid artery	5.03 (0.70)	5.41 (0.61)	**0.002**
Vertebral artery	3.69 (0.51)	3.87 (0.52)	0.075
Extracranial blood velocity, $cm \cdot s^{-1}$			
Internal carotid artery	45.0 (9.7)	42.2 (8.1)	0.279
Vertebral artery	32.8 (6.7)	31.9 (7.5)	0.450
Intracranial blood velocity, $cm \cdot s^{-1}$			
Middle cerebral artery	54.3 (13.3)	56.1 (13.6)	0.338
Posterior cerebral artery	43.4 (9.8)	45.3 (10.5)	0.355

Data were analyzed by linear mixed model analysis. The primary outcome of interest for these cardiorespiratory and cerebrovascular variables was the effect of condition (normoxia and acute poikilocapnic hypoxia). $P_{ET_{CO_2}}$, partial pressure of end-tidal carbon dioxide; $P_{ET_{O_2}}$, partial pressure of end-tidal oxygen; Sp_{O_2}, peripheral arterial oxygen saturation. Bolded values indicate statistical significance (i.e., $P < 0.05$). Data ($n = 20$ participants) are raw means (standard deviation).

PCA) arteries was comparable in normoxia and hypoxia (all $P > 0.05$, Table 2). ICA RoR [−0.06 (0.22) s^{-1}, $P = 0.279$] and VA RoR [−0.05 (0.21) s^{-1}, $P = 0.343$], maximal reduction in CVC or CVCi and time to CVC or CVCi counterregulation for the extracranial arteries, and all metrics of dCA for the intracranial arteries were comparable in normoxia and hypoxia (all $P > 0.05$, Fig. 2 and Table 3).

Table 2. *Hemodynamic responses to the rapid thigh cuff deflation-induced hypotension in normoxia and hypoxia*

	Condition		*P* Value
	Normoxia	Hypoxia	Condition
Mean arterial pressure (MAP)			
Time to MAP first nadir, s	4.5 (1.0)	4.5 (0.9)	0.846
Max. ΔMAP, mmHg	−21.3 (6.0)	−22.6 (2.8)	0.383
Max. ΔMAP, %	−23.3 (6.3)	−26.2 (3.7)	**0.048**
Extracranial max. Δblood flow, %			
Internal carotid artery	−33.9 (8.2)	−32.2 (9.4)	0.426
Vertebral artery	−34.3 (8.6)	−33.2 (8.2)	0.423
Extracranial max. Δvessel diameter, %			
Internal carotid artery	−6.3 (2.7)	−7.7 (3.1)	0.089
Vertebral artery	−7.2 (3.9)	−7.9 (4.9)	0.804
Extracranial max. Δblood velocity, %			
Internal carotid artery	−26.5 (7.3)	−22.9 (8.7)	0.096
Vertebral artery	−26.6 (8.2)	−24.4 (6.2)	0.226
Intracranial max. Δblood velocity, %			
Middle cerebral artery	−26.6 (6.2)	−25.8 (5.5)	0.429
Posterior cerebral artery	−26.2 (4.3)	−24.9 (6.0)	0.452

Data were analyzed by linear mixed model analysis. The primary outcome of interest for mean arterial pressure and cerebrovascular variables was the effect of condition (normoxia and acute poikilocapnic hypoxia). Bolded values indicate statistical significance (i.e., $P < 0.05$). Data ($n = 20$ participants) are raw means (standard deviation).

In males only, compared with normoxia, VA RoR was reduced in hypoxia [−0.15 (0.19) s^{-1}, $P = 0.012$, Fig. 3*C*], whereas ICA RoR was maintained [−0.07 (0.21) s^{-1}, $P = 0.264$, Fig. 3*A*]. In males, MCA RoR [+0.00 (0.07) s^{-1}, $P = 0.979$] and PCA RoR [+0.01 (0.15) s^{-1}, $P = 0.841$] were unchanged by acute hypoxia. In males, as in the mixed cohort, immediately before the thigh cuff deflation, hypoxia increased ICA diameter [+0.30 (0.32) mm, main effect of condition, $P = 0.009$, Fig. 3*B*] but did not increase VA vessel diameter [+0.08 (0.33) mm, $P = 0.398$, Fig. 3*D*]. Adding region or $P_{ET_{CO_2}}$ to the analysis did not change the statistical outcome for any cerebrovascular or dCA parameter in the mixed or male-only cohorts.

DISCUSSION

This study investigated volumetric dCA of the anterior and posterior cerebral conduit arteries in normoxia and acute poikilocapnic hypoxia. The three novel findings of this study are *1*) in a mixed cohort of males and females, the dCA of the intracranial and extracranial cerebral conduit arteries was regionally comparable during normoxia and acute poikilocapnic hypoxia, and *2*) in males only, hypoxia reduced dCA of the posterior extracranial artery, indicated by a reduction in VA RoR. In contrast, dCA of the ICA was similar in normoxia and hypoxia in males, and *3*) in males, we observed that immediately before the dCA assessment, hypoxia caused vasodilation (reduced vascular tone) of the ICA, but not the VA, which suggests an alternative mechanism to hypoxia-induced reduction in conduit artery vascular tone is responsible for the regional dCA responses observed in this study.

The absence of a reduction in anterior circulation dCA to acute hypoxia in the present study was unexpected, as the duration and severity of hypoxia and hypoxia-induced hypocapnia were comparable with the three previous studies to report reductions in volumetric RoR of the ICA in hypoxia (26–28). Moreover, as hypocapnia has been shown to attenuate dCA during acute hypoxia (33), we incorporated $P_{ET_{CO_2}}$ into the analyses, but this did not influence the study findings. One possible explanation for these contrasting reports of hypoxia on anterior dCA is posture differences between studies (53), since participants sat upright in the current study, contrasting the semirecumbent (26, 27) and supine (28) positions of previous studies. These posture differences may explain the differences in MAP observed between normoxia and hypoxia conditions in studies immediately before the thigh cuff test, where MAP was reduced in hypoxia compared with normoxia in the current study but elevated (26) or unchanged (27, 28) in hypoxia compared with normoxia in previous studies. A reduction in MAP before the thigh cuff test may cause an initial leftward shift along the autoregulatory curve (2), which may explain why we observed, in comparison with the previous literature (26–28), an exacerbated reduction in cerebral blood flow (−33% vs. max. −22%) for a comparable thigh cuff test reduction in MAP (−26% vs. max. −26%). Additional support for this explanation exists from research showing better dCA responses to the rapid thigh cuff test in supine compared with seated postures (53).

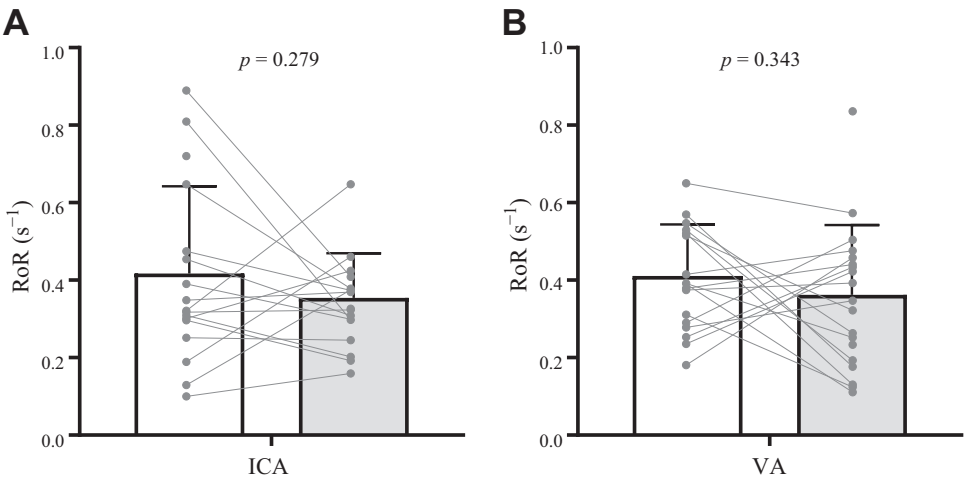

Figure 2. Rate of regulation following rapid thigh cuff deflation-induced hypotension in normoxia and hypoxia. Rate of regulation (RoR) of the internal carotid artery (ICA, *A*) and vertebral artery (VA, *B*) in normoxia (white bars, fraction of inspired oxygen [$F_{I_{O_2}}$] = 20.9%) and acute poikilocapnic hypoxia (gray bars, $F_{I_{O_2}}$ = 12.5%). Data (n = 20 participants) are raw means (standard deviation) and are presented with individual responses.

Another possible explanation for the contrasting reports of hypoxia on anterior dCA may relate to the thigh cuff stimulus and analysis. In the current study, a similar thigh cuff stimulus was achieved in normoxia and hypoxia (cerebral blood flow; −34% and −32%, respectively), whereas there were significant differences in previous studies (26–28). In addition, when RoR is calculated from a fixed period (i.e., 1–4 s), as was done in previous reports (26–28), neither MAP nor cerebral blood flow may have reached their nadir. Consequently, small or large deviations in maximal reduction in cerebral blood flow between conditions may cause a shortened or prolonged time to CVCi counterregulation and, in turn, a steeper or flatter RoR slope. Our study adopted the recently recommended analysis approach (51) that carefully accounts for these between-condition individual differences and provides a complete description of the autoregulatory response, and confidence that any change in RoR was not a consequence of a difference in stimulus intensity.

Table 3. *Dynamic cerebral autoregulation metrics after rapid thigh cuff deflation-induced hypotension of the extracranial and intracranial arteries in normoxia and hypoxia*

	Condition		*P* Value
	Normoxia	Hypoxia	Condition
Rate of regulation, s^{-1}			
Middle cerebral artery	0.20 (0.05)	0.20 (0.07)	0.995
Posterior cerebral artery	0.23 (0.08)	0.23 (0.13)	0.895
Maximal fall in CVCi, %			
Internal carotid artery	20.7 (8.3)	16.7 (11.8)	0.141
Vertebral artery	17.5 (11.0)	18.8 (8.7)	0.774
Middle cerebral artery	10.6 (8.0)	7.9 (5.5)	0.107
Posterior cerebral artery	9.6 (6.0)	6.5 (6.2)	0.150
Time to CVCi counterregulation, s			
Internal carotid artery	1.39 (0.45)	1.26 (0.63)	0.477
Vertebral artery	1.16 (0.65)	1.09 (0.49)	0.589
Middle cerebral artery	1.28 (0.45)	1.21 (0.65)	0.631
Posterior cerebral artery	1.37 (0.58)	1.28 (0.69)	0.763

Data were analyzed by linear mixed model analysis. The primary outcome of interest for mean arterial pressure and cerebrovascular variables was the effect of condition (normoxia and acute poikilocapnic hypoxia). CVCi, vascular conductance or vascular conductance index for extracranial and intracranial arteries, respectively. Data (n = 20 participants) are raw means (standard deviation).

We report for the first time, using volumetric blood flow RoR methods, that dCA of the VA to hypoxia may be regionally different to the ICA in males. The prevailing explanation for reduced dCA in the VA compared with the ICA during systemic physiological stress is a lower basal vascular tone of the posterior circulation, which is beneficial to maintain basal blood flow to the cardiorespiratory control centers of the brain while under physiological stress (6). Proposed mechanisms for lower basal vascular tone in the posterior circulation include increased metabolic state of the visual cortices (19–21), less sympathetic innervation (14), and different sensitivities to vasoactive agents, such as reactive oxygen species and nitric oxide bioavailability (16–18). Although no previous studies have examined regional volumetric responses to hypoxia, the results of the current study align with observations by Sato et al. (6), who reported in a male-only cohort reduced VA RoR, but not ICA RoR, following the thigh cuff test superimposed on head-up tilt. Indeed, the studies report similar reductions in basal MAP (our study vs. Sato; −5 mmHg vs. −6 mmHg), VA cerebral blood flow (−33% vs. −32%), and VA RoR (−32% vs. −36%). This study provides further evidence of a greater cerebrovascular sensitivity in the posterior compared with the anterior circulation, particularly to conditions involving reduced physiological levels (i.e., the "hypo-" range), such as hypoxia (8), hypocapnia (9), and hypothermia (54).

We report acute hypoxia-induced vasodilation of the ICA but not VA (Fig. 3). Combined with the hypoxia-induced reduction in dCA of the VA but not the ICA in males, this study provides evidence that contrasts the prevailing hypothesis that a lower vascular tone is the mechanism that reduces dCA. This was originally formulated from investigations of dCA during hypercapnia (55). In contrast, the findings of this study suggest that the reduction of dCA by hypercapnia may relate to secondary hypertensive effects, causing the basal MAP position on the autoregulatory curve to shift rightward away from the autoregulatory plateau. Another possible explanation for the lack of an association between lowered vascular tone and reduced dCA in the

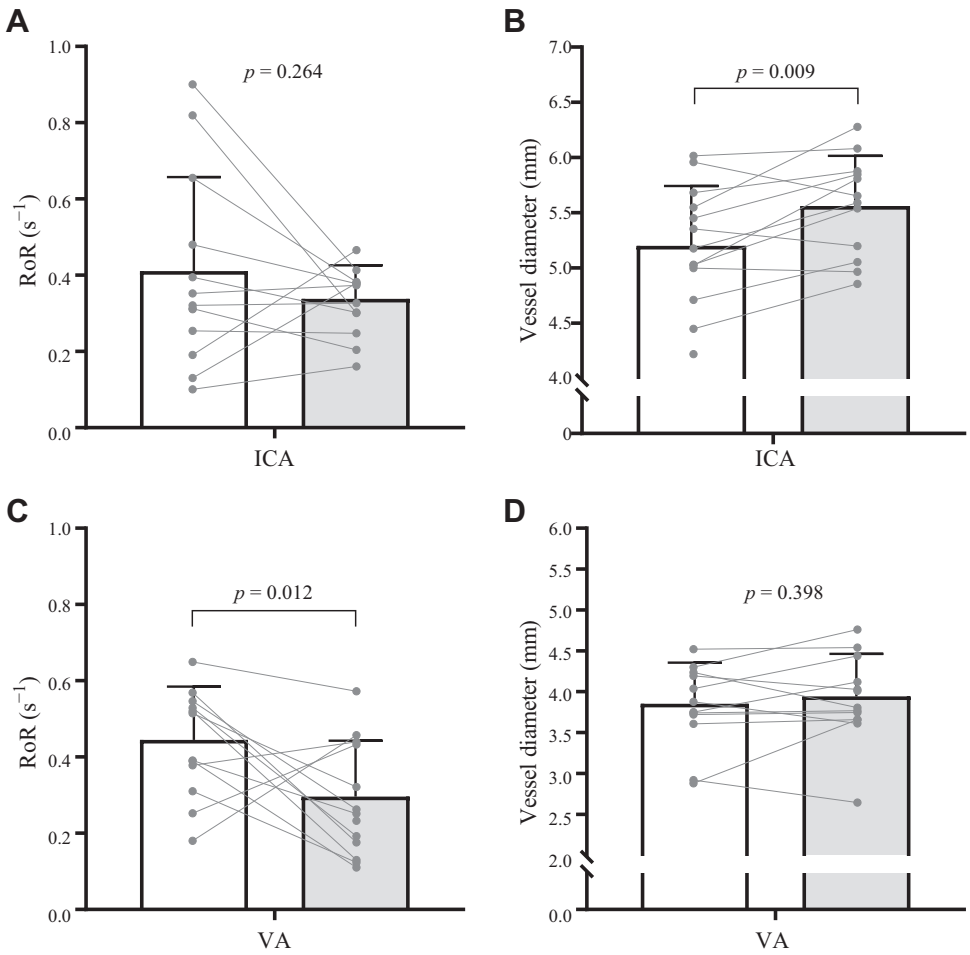

Figure 3. Rate of regulation after rapid thigh cuff deflation-induced hypotension and pre thigh cuff deflation vessel diameter in normoxia and hypoxia in males. Rate of regulation (RoR) and vessel diameter of the internal carotid artery (ICA, *A* and *B*) and vertebral artery (VA, *C* and *D*) in normoxia (white bars, fraction of inspired oxygen [$F_{I_{O_2}}$] = 20.9%) and acute poikilocapnic hypoxia (gray bars, $F_{I_{O_2}}$ = 12.5%) in males (n = 13 participants). Data are raw means (standard deviation) and are presented with individual responses.

extracranial arteries is that, although the large arteries contribute to vascular resistance (56), segmental differences in innervation and regulation of the vasculature suggest a large proportion of vasodilation-induced reductions in dCA occur in the microvasculature (14, 57, 58).

Methodological Considerations and Future Directions

In this study, we report intracranial dCA of MCA and PCA blood velocity was comparable in normoxia and hypoxia, which contrasts with the volumetric extracranial findings. Caution is needed when interpreting intracranial findings acquired by TCD, as they do not account for vessel diameter changes. TCD has previously been shown to underestimate dCA compared with duplex ultrasound (56), and the importance of capturing vessel diameter is highlighted herein as the regional dCA response was found only when RoR was derived from volumetric blood flow measurements obtained at the extracranial arteries. These findings align with recent recommendations (36) that dCA responses between different methods are not comparable and that volumetric measurements should be central to investigations of cerebrovascular regulation moving forward to have the most confidence in the physiological interpretation of cerebrovascular function.

Although there remains no gold standard measurement of dCA, and with evidence of a poor agreement between different metrics of dCA (59), we believe the dCA methods and analysis adopted in the current study strengthen the findings (Fig. 1). Duplex ultrasonography is the only method with a sufficient temporal resolution to examine dCA volumetrically to abrupt changes in blood pressure (<4 s), and the recommended analysis (51) accounts for between-condition individual differences, involves dCA metrics that assess the complete autoregulatory responses, and has revealed regional differences previously, including the relative maximal reduction in hemodynamics (25), the time to counterregulation (41), and RoR (6, 26–28). Moreover, the time to CVCi counterregulation (1.4 s maximum, Table 3) was within the time to first nadir in MAP (4.5 s on average, Table 2), so it is unlikely that our method for assessing dCA included any MAP-mediated counterregulation. We acknowledge emerging evidence indicating directional sensitivity in the cerebral pressure-flow relationship (60–66), and therefore, the present findings of regional differences in dCA to reductions in MAP shown here may not be present in scenarios where blood pressure is increased.

Our study highlights that including a mixed cohort may complicate the interpretation of dCA, particularly when hypotheses are generated from previous studies with almost entirely male samples (6, 26–28). Females in this study completed repeat assessments in a menstrual or nonactive pill phase associated with the lowest levels of estrogen and progesterone to reduce the variability of sex hormones,

which are known to influence cerebrovascular function (67–71). Our study provides some evidence to suggest that simplifying the variability between males and females to only differences in sex hormones is insufficient as an experimental control. Although other studies have not examined the influence of biological sex differences on volumetric dCA to acute hypotension in hypoxia, it is perhaps not surprising to observe potential sex-related dCA differences given the differences between males and females in resting cerebral perfusion (72–74) and blood pressure regulation (75). Future research is warranted to explore region-specific differences in dCA in females and to more fully elucidate the effect of sex on dCA in hypoxia.

Conclusions

In hypoxia, dCA to abrupt reductions in blood pressure was regionally different in males. Compared with normoxia, hypoxia reduced volumetrically determined dCA in the posterior circulation (i.e., VA RoR) but not the anterior circulation (i.e., ICA RoR). Hypoxia caused vasodilation of the ICA, but not the VA, suggesting alterations in vascular tone may not be responsible for the reduction in dCA of the VA observed in males in hypoxia. These findings provide further evidence of a more pressure-passive posterior cerebral circulation and support the need to consider multisite assessments in future cerebrovascular research.

DATA AVAILABILITY

The data that support the findings of this study are openly available in Figshare: https://doi.org/10.6084/m9.figshare.24032742.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.T.F., G.M.K.R., A.S., J.H.M., and S.J.O. conceived and designed research; A.T.F., M.E., and S.J.O. performed experiments; A.T.F. and S.J.O. analyzed data; A.T.F., M.E., M.H., G.M.K.R., A.S., J.H.M., and S.J.O. interpreted results of experiments; A.T.F. and S.J.O. prepared figures; A.T.F., M.E., M.H., G.M.K.R., A.S., J.H.M., and S.J.O. drafted manuscript; A.T.F., M.E., M.H., G.M.K.R., A.S., J.H.M., and S.J.O. edited and revised manuscript; A.T.F., M.E., M.H., G.M.K.R., A.S., J.H.M., and S.J.O. approved final version of manuscript.

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