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Original Paper

Impact of transient hypotension on regional cerebral blood flow in humans

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Abstract

We examined the impact of progressive hypotension with and without hypocapnia on regional extracranial cerebral blood flow (CBF) and intracranial velocities. Participants underwent progressive lower-body negative pressure (LBNP) until pre-syncope to inflict hypotension. End-tidal carbon dioxide was clamped at baseline levels (isocapnic trial) or uncontrolled (poikilocapnic trial). Middle cerebral artery (MCA) and posterior cerebral artery (PCA) blood velocities (transcranial Doppler; TCD), heart rate, blood pressure and end-tidal carbon dioxide were obtained continuously. Measurements of internal carotid artery (ICA) and vertebral artery (VA) blood flow (ICA_{BF} and VA_{BF} respectively) were also obtained. Overall, blood pressure was reduced by ∼20% from baseline in both trials ($P < 0.001$). In the isocapnic trial, end-tidal carbon dioxide was successfully clamped at baseline with hypotension, whereas in the poikilocapnic trial it was reduced by 11.1 mmHg ($P < 0.001$) with hypotension. The decline in the ICA_{BF} with hypotension was comparable between trials (-139 ± 82 ml; ∼30%; $P < 0.0001$); however, the decline in the VA_{BF} was -28 ± 22 ml/min (∼21%) greater in the poikilocapnic trial compared with the isocapnic trial ($P = 0.002$). Regardless of trial, the blood flow reductions in ICA (-26 ± 14%) and VA (-27 ± 14%) were greater than the decline in MCA (-21 ± 15%) and PCA (-19 ± 10%) velocities respectively ($P \leqslant 0.01$). Significant reductions in the diameter of both the ICA (∼5%) and the VA (∼7%) contributed to the decline in cerebral perfusion with systemic hypotension, independent of hypocapnia. In summary, our findings indicate that blood flow in the VA, unlike the ICA, is sensitive to changes hypotension and hypocapnia. We show for the first time that the decline in global CBF with hypotension is influenced by arterial constriction in the ICA and VA. Additionally, our findings suggest TCD measures of blood flow velocity may modestly underestimate changes in CBF during hypotension with and without hypocapnia, particularly in the posterior circulation.

Key words: blood pressure, carbon dioxide, internal carotid artery blood flow, syncope, vertebral artery blood flow.

INTRODUCTION

The cerebral vasculature is highly sensitive to changes in arterial carbon dioxide ($PaCO_2$). In otherwise healthy humans, there is a ∼4–5% increase in cerebral blood flow (CBF) per mmHg increase in $PaCO_2$ above eupnic $PaCO_2$ and a 2–4% decrease in CBF below eupnic $PaCO_2$ [1,2]. These changes in CBF are historically believed to be governed principally by dilation or constriction of the pial arterioles [3]. However, earlier evidence indicates that the larger intra- and extra-cranial cerebral arteries may also constrict or dilate to a varying level of $PaCO_2$ as assessed via ultrasound [2] and high-strength MRI [4]. It is therefore reasonable to speculate that the entire cerebrovascular tree, rather than solely the pial vessels, change diameter in response to alterations in $PaCO_2$/pH, at least to some degree. On the other hand, although animal data indicate that both the internal carotid artery (ICA) and the vertebral artery (VA) may act as a first-line defence to aid the precise regulation of cerebral perfusion pressure [5,6], it is currently unknown whether the larger intra- and extra-cranial vessels dilate in response to hypotension in humans.

At rest, approximately 25–30% of global CBF is supplied posteriorly via the VA and the other 65–70% is supplied anteriorly via the ICA [7,8]. The VAs merge into the basilar artery which supplies CBF to regions of the brain with important and

Abbreviations: CBF, cerebral blood flow; HUT, head-up-tilt; ICA, internal carotid artery; ICA_{BF}, internal carotid artery blood flow; ICAv, internal carotid artery blood flow velocity; LBNP, lower-body negative pressure; MAP, mean arterial blood pressure; MCA, middle cerebral artery; MCAv, middle cerebral artery blood flow velocity; $PaCO_2$, arterial carbon dioxide; PCA, posterior cerebral artery; PCAv, posterior cerebral artery blood flow velocity; $P_{ET}CO_2$, end-tidal carbon dioxide; $P_{ET}O_2$, end-tidal oxygen; TCD, transcranial Doppler; VA, vertebral artery; VA_{BF}, vertebral artery blood flow; VAv, veterbal artery blood flow velocity.

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necessary homoeostatic function, such as the medulla oblongata, cerebellum, hypothalamus, thalamus and brainstem [9]. Regional differences in extracranial flow exist during hypocapnia as reflected in greater relative reductions in VA flow compared with the ICA [2]. Regional changes with hypotension are unclear. For example, Deegan et al. [10] reported no differences between velocities in the middle cerebral artery (MCA) and VA (MCAv and VAv respectively); and we recently observed no differences between the MCAv and posterior cerebral artery (PCA) velocities (PCAv) [11]. In contrast, Sato et al. [1] reported a differential blood flow response with normotensive orthostatic stress (2 min of head-up-tilt; HUT); a ∼9% decline in both ICA blood flow (ICA_{BF}; mediated by a decline in both ICA diameter and mean blood flow velocity) and MCAv, whereas VA flow (VA_{BF}) was preserved. The disparity between studies probably reflects: (1) variances in the degree of hypotension and resultant hypocapnia during HUT compared with pre-syncope; and (2) inconsistencies between insonated vessels (anterior compared with posterior circulation and extra- compared with intra-cranial) and measurements (blood velocity compared with blood flow). Additionally, it has been identified that during interventions involving perturbations in CBF, intracranial blood flow velocity (e.g. MCA, PCA) may not reflect true changes in blood flow because of changes in vessel tone [4].

We aimed to clearly delineate the impact of hypocapnia from progressive hypotension on volumetric regional extracranial CBF and compare changes in flow with changes in intracranial velocities. To achieve this, we monitored volumetric blood flow in the ICA and VA, as well as velocities in their distal intracranial arteries (MCA and PCA respectively) in humans during progressive non-pharmacological hypotension induced via lower-body negative pressure (LBNP) with and without hypocapnia. We examined the novel hypotheses that: (1) the decrease in blood flow in the ICA compared with the VA will be less with hypocapnic hypotension; (2) the regional CBF differences will be abolished during hypotension when hypocapnia is prevented; and (3) changes in MCAv and PCAv will be identical with changes in ICA velocity (ICAv) and VAv, but will underestimate the change in ICA_{BF} and VA_{BF} respectively.

MATERIALS AND METHODS

Ethical approval and screening

This study was approved by the Human Ethics Committee of the University of British Columbia and conformed to the standards set by the Declaration of Helsinki. All subjects provided written informed consent. Participants were non-smokers and free from disease. Experimental testing began after 12-h abstinence from alcohol, caffeine and strenuous exercise and at least a 4-h fast. Female participants were tested in the early follicular phase (day 1–7) of the menstrual cycle or during menstruation and the contraceptive withdrawal phase (day 2–7). All participants underwent a familiarization session of the experimental procedures and protocol on a separate day prior to their initial assessment.

Participants and study design

The present study is one main part of a two-part investigation. The adjacent report from this investigation, using the same experimental design, focused on the impact of hypocapnia on orthostatic tolerance and its relationship with brain arterial-venous oxygen differences [11]; there is no overlap of presented volumetric flow data and the related pre-defined 'a priori hypotheses' in the present paper are completely different from our other report. Twenty-four (12 males; 12 females) healthy participants with a mean ± S.D. age of 25 ± 4 years, body mass 69 ± 11 kg, height 178 ± 8 cm and body mass index 23.2 ± 3.3 kg/m^2 participated in the present study. The study design was a two-trial, randomized, counterbalanced experiment involving progressive LBNP until pre-syncope, with end-tidal carbon dioxide ($P_{ET}CO_2$) and oxygen ($P_{ET}O_2$) either clamped at baseline levels (isocapnic clamped condition) or uncontrolled (unclamped). Following instrumentation and $\geqslant$20 min of supine rest, participants engaged in a supine LBNP protocol consisting of 2 min increments of −20 mmHg until reaching −100 mmHg, at which point −100 mmHg was continued until the onset of pre-syncope. Following $\geqslant$1 h and 20 min of supine rest, participants underwent the LBNP again under the different condition. Pre-syncope was defined by a sustained drop in systolic blood pressure to $<$80 mmHg for more than 10 s or on participants' request due to one or more subjective pre-syncopal symptoms becoming intolerable (feelings of dizziness, nausea, faintness, visual disturbances, hearing disturbances and fatigue) [12].

Measurements

Beat-to-beat measurements of MCAv and PCAv were acquired using a 2-MHz pulsed transcranial Doppler (TCD) ultrasound system (Spencer Technologies), using methods described elsewhere [13]. Stroke volume (SV) and cardiac output (CO) were calculated from the finger photoplethysmography blood pressure waveform using the Modelflow method (BeatScope 1.0 software; TNO TPD; Biomedical Instruments) [14]. An estimate of global CBF was assessed by duplex ultrasound at baseline and throughout LBNP protocol. Continuous diameter and blood velocity recordings in the right VA and left ICA were obtained using a 10 MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (Terason 3000, Teratech). Two experienced sonographers conducted all measurements and measurements were made simultaneously. Measurement settings for each extracranial artery within each individual were standardized for all measurement sets. Table 1 highlights the low repeated measures variability, at rest, within trials and between experimental trials.

Custom-designed edge-detection and wall-tracking software, which is largely independent of investigator bias, was utilized for the analysis of ICA and VA diameter and blood flow velocity at 30 Hz [15,16]. Mean blood flow was determined as half the time averaged maximum velocity [17] multiplied by the cross-sectional lumen area [2,18]. Global CBF was estimated assuming symmetrical bilateral flow in the major triturating arteries of the brain as: global CBF = (ICA_{BF} + VA_{BF}) × 2 [2,18]. From synchronized measures, shear rate (an estimate of shear stress without the consideration of viscosity) was calculated as four

Table 1 Coefficient of variation (%) in measurements of MCAv, PCAv, ICAv and ICA diameter, VAv and VA diameter between resting measurements within both experimental trials and at rest between experimental trials

	Baseline 1 compared with Baseline 2*	Baseline Trial 1 compared with Baseline Trial 2†
MCAv (%)	2.5	3.9
PCAv (%)	2.7	6.8
ICAv (%)	6.4	10.3
ICA diameter (%)	0.9	1.4
VAv (%)	4.9	10.8
VA diameter (%)	1.2	2.3

*Within experimental trial.
†Between experimental trials.

times mean blood velocity per vessel diameter [19], representing the frictional stress applied by blood velocity against the lumen of the vessel.

Measurements and manipulation of $P_{ET}CO_2$ and $P_{ET}O_2$ was achieved as described in depth elsewhere [11,20]. Clamped $P_{ET}CO_2$ and $P_{ET}O_2$ levels were determined as the values measured during the last 5 min of baseline measurements. Baseline values represent a 1 min average prior to LBNP and pre-syncope values represents a 10 s average prior to the termination of the test protocol.

Statistical analysis

Data were analysed using SPSS (version 21) and expressed as means $\pm$ S.D. Statistical significance was defined as $P \leqslant 0.05$. A two-way repeated-measures ANOVA was used to explore the interaction between the experimental trial (poikilocapnic compared with isocapnic) and time point (baseline compared with hypotension). Additionally, a two-way repeated-measures ANOVA was used to explore the percentage change from baseline to hypotension in each experimental trial and two experimental variables (e.g. MCAv compared with ICAv). To further explore any significant interaction effects, paired Student's *t* tests were then employed, provided the data were normally distributed. A Pearson's correlation was used to explore relationships between select variables of interest. Bland–Altman analysis [21] was performed to examine the spread of differences between TCD and duplex ultrasound measures of ICA and VA flows for estimates of the percentage change in CBF.

RESULTS

Cardiorespiratory changes with hypotension and hypocapnia ($n = 24$)

Similar reductions in mean arterial blood pressure (MAP; ~20%) were evident under both experimental conditions. In the isocapnic trial, as designed, $P_{ET}CO_2$ was successfully maintained at baseline levels at pre-syncope (38.3 ± 2.7 compared with 38.5 ± 2.5 mmHg respectively; $P = 0.50$), whereas in the poikilocapnic trial $P_{ET}CO_2$ dropped from 37.2 ± 2.7 mmHg (baseline) to 26.3 ± 5.9 mmHg (hypotension) ($P < 0.001$). All other cardiovascular measurements were similar between trials [11] (results not shown).

Global cerebral blood flow effect of hypotension and hypocapnia

Due to the difficulty of gaining reliable images and blood flow velocity recording of the ICA and VA during hyperventilation (as developed throughout the hypotensive challenge), simultaneous measurements of the ICA and VA at the hypotensive end point in both trials were successfully obtained in nine out of the 24 participants. Therefore, global CBF data are based on nine individuals. Independent of the experimental condition, global CBF and ICA_{BF} decreased with hypotension by 177 ± 87 ml/min (−30%; $P < 0.0001$) and 139 ± 82 ml (−30%; $P < 0.0001$) respectively (Figure 1). However, reductions in VA_{BF} were 28 ± 22 ml/min (~−21%) greater in the poikilocapnic trial compared with the isocapnic trial ($P = 0.002$; Figure 1B). Independent of the experimental trial, ICA and VA diameter declined with hypotension [baseline compared with hypotension: ICA 0.49 ± 0.03 compared with 0.46 ± 0.02 (~−5%; $P = 0.002$); VA 0.38 ± 0.06 compared with 0.36 ± 0.06 (~−7%; $P = 0.001$ respectively; Figure 2)], no interaction between the trials was evident. Independent of the experimental trial, blood velocity in the ICA reduced from 41 ± 8 cm·s^{-1} at baseline to 31 ± 5 cm·s^{-1} with hypotension (~−24%, $P = 0.002$; Figure 2). Blood velocity in the VA was also reduced; however, an interaction between trials was evident and revealed that blood velocity in the VA was higher at pre-syncope in the isocapnic trial by 4 ± 3 cm·s^{-1} ($P = 0.001$); therefore, the decline in VAv was 22 ± 16% greater in the poikilocapnic trial than in the isocapnic trial ($P = 0.003$).

Independent of the experimental trial, mean shear rate in the ICA was reduced from 343 ± 81 l/s at baseline to 271 ± 47 l/s with hypotension (~−21%; $P = 0.01$; Figure 2). In contrast, compared with baseline (217 ± 59 l/s), VA mean shear was significantly reduced with hypotension (-163 ± 56 l/s; −25%; $P = 0.02$), whereas in the isocapnic trial VA mean shear did not significantly decrease with hypotension (−5%). As a result, VA mean shear with hypotension was 44 ± 36 l/s (27%; $P = 0.01$) greater in the poikilocapnic trial.

Comparison between vessels

Out of the 24 recruited individuals, sufficient simultaneous ultrasound images and blood flow velocity recordings in the ICA and MCA, VA and PCA at the hypotensive end point were obtained in 15 and 16 individuals respectively. Irrespective of the experimental trial, the relative decline in velocity in both the ICA and the MCA (-26 ± 14% compared with -20 ± 7%; $P = 0.15$) and VA and PCA (-19 ± 17% compared with -19 ± 10%; $P = 0.97$) were comparable with hypotension. However, the relative decline in ICA_{BF} (-26 ± 14%) and VA_{BF} (-27 ± 14%) with hypotension was larger than the declines in MCAv (-21 ± 15%) and PCAv (-19 ± 10%) respectively ($P \leqslant 0.01$; Figure 3).

Relationships between selected variables

In the isocapnic trial only, a moderate inverse relationship was evident between the absolute decline in MAP with the relative declines in MCAv ($r = 0.53$; $P = 0.04$), PCAv ($r = 0.47$; $P = 0.06$),

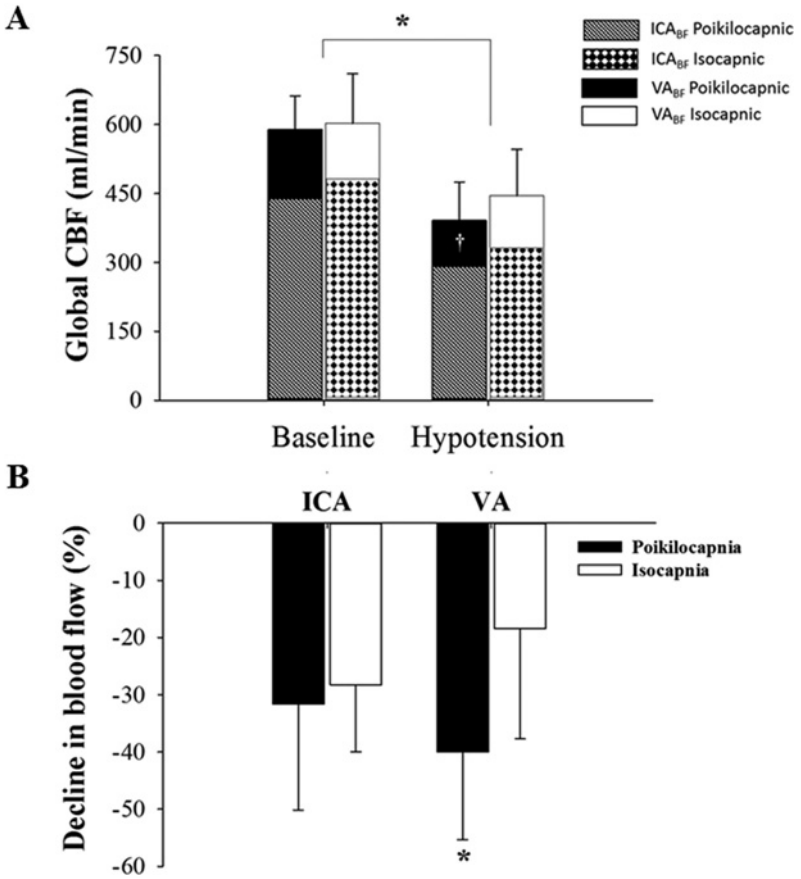

Figure 1 Decline in extracranial blood flow with hypotension

(**A**) Changes in estimated global CBF and the related contribution from blood flow in the ICA and VA under poikilocapnic and isocapnic experimental conditions. *Global CBF, ICA_{BF} and VA_{BF} blood flow at hypotension significantly different from baseline under both poikilocapnic and isocapnic experimental conditions ($P \leqslant 0.002$). †Significant interaction, VA_{BF} with hypotension under the poikilocapnic conditions was significantly less than under the isocapnic conditions ($P = 0.02$). (**B**) Percentage change in simultaneous blood flow from baseline to hypotension in the ICA and VA during the poikilocapnic and isocapnic trail. *Compared with the isocapnic trial, blood flow in the VA was greater in the poikilocapnic trial ($P = 0.004$). Data are means $\pm$ S.D.; $n = 9$.

VAv ($r = 0.50$; $P = 0.05$) and VA_{BF} ($r = 0.53$; $P = 0.04$). However, these relationships were not evident during the poikilocapnic trial. In the poikilocapnic trial, moderate inverse relationships were evident between the absolute decline in $P_{ET}CO_2$ with the relative declines in MCAv ($r = 0.67$; $P = 0.006$), PCAv ($r = 0.88$; $P < 0.001$), VAv ($r = 0.62$; $P = 0.01$), VA_{BF} ($r = 0.65$; $P = 0.007$); these relationships were not evident in the isocapnic trial.

There was a strong linear association between the percentage change in VA_{BF} and PCAv for the estimates of CBF in the poikilocapnic trial ($r = 0.67$, $P = 0.005$; Figure 4A). In the isocapnic trial there was a moderate linear association between the percentage change in VA_{BF} and PCAv for the estimates of CBF ($r = 0.47$, $P = 0.07$; Figure 4A). Bland–Altman analyses revealed a bias effect of -10% in the poikilocapnic and -8% in the isocapnic trial (Figure 4B); during hypotension, PCAv underestimated VA_{BF} by an average of 9% during hypotension with and without hypocapnia. There was a lack of association between the percentage change in ICA_{BF} and MCAv for the estimates of CBF in the poikilocapnic trial ($r = 0.04$, $P = 0.88$) and isocapnic trial ($r = 0.09$, $P = 0.75$; Figure 5A). Bland–Altman analysis revealed a bias of -2% in the poikilocapnic and -10% in the isocapnic trial; during hypotension, MCAv underestimates ICA_{BF} by -2% in the presence of hypocapnia and this underestimation is more pronounced (-10%) during a normocapnic clamp (Figure 5B).

DISCUSSION

The novel findings of this investigation are the following. (1) The decline in ICA_{BF} and VA_{BF} with hypotension was comparable in the presence of hypocapnia (poikilocapnic trial). Additionally, when compared with the poikilocapnic trial, the decline in VA_{BF} was significantly less (-21%) when hypocapnia was prevented in the isocapnic trial. (2) Independent of hypocapnia, a decline in both ICA and VA diameter contribute to the decline in cerebral perfusion with systemic hypotension. (3) Also independent of hypocapnia, the hypotensive decline in ICA_{BF} and VA_{BF} was

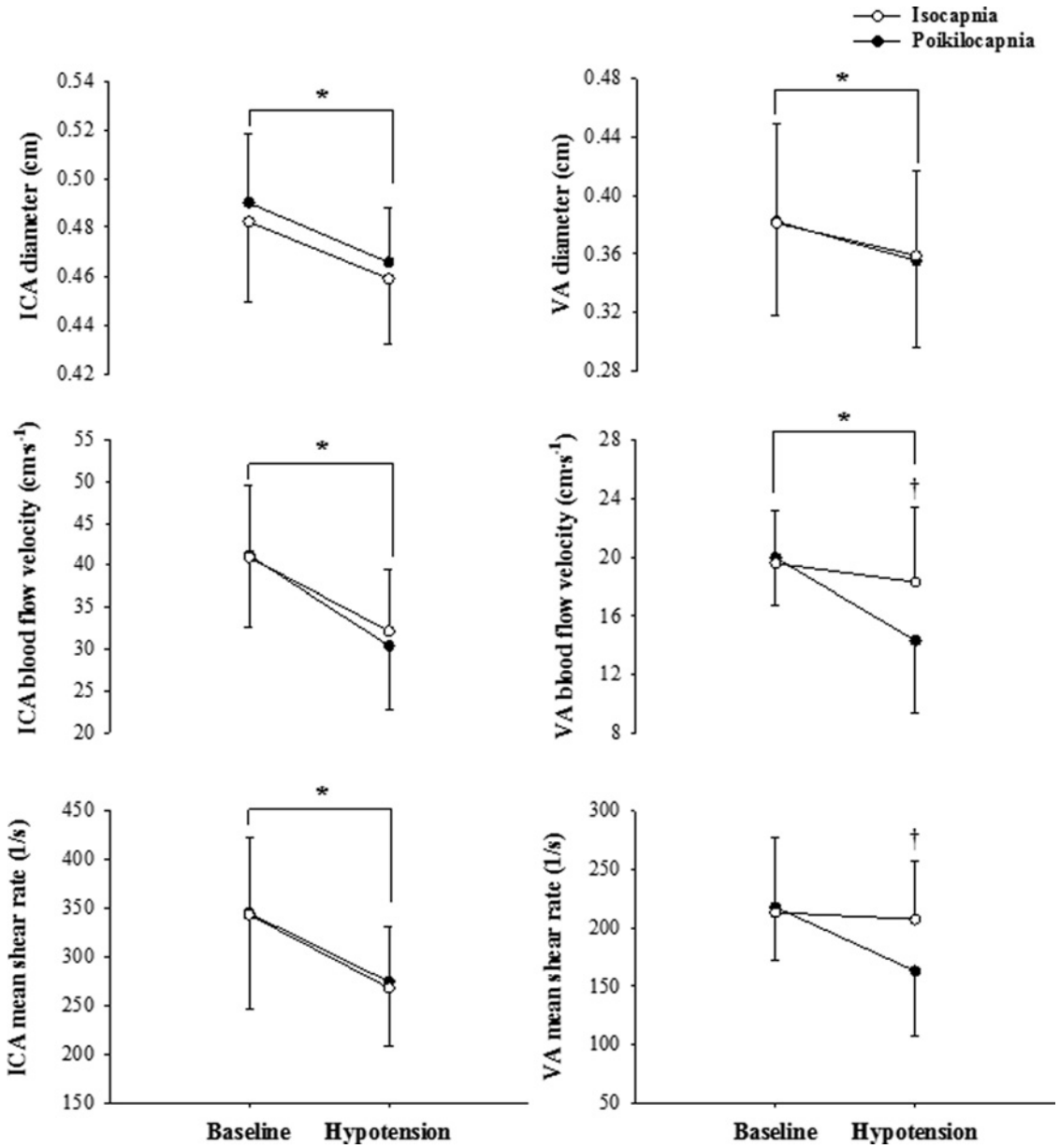

Figure 2 **Diameter, blood flow velocity and mean shear rate in the ICA and VA at baseline and hypotension ($n = 9$) during the poikilocapnic and isocapnic trail**

*Hypotension significantly different from baseline in both experimental trials ($P \leqslant 0.03$). †Blood velocity and shear rate in the VA is significantly higher in the poikilocapnic trial at hypotension than in the isocapnic trial ($P = 0.001$). Data are means ± S.D.

consistently larger than the decline in MCAv and PCAv respectively. Collectively these findings indicate that VA_{BF}, unlike ICA_{BF}, is sensitive to changes in hypotension and hypocapnia. (4) TCD measures of blood flow velocity underestimate changes in CBF during hypotension.

Regional distribution of global CBF during hypotension

Overall, global estimates of CBF in the present study decreased by 30% with hypotension (~20% decline in MAP) induced by orthostatic stress. However, in contrast with our hypothesis and the findings by Sato et al. [1] the decline in ICA_{BF} (~28%) and VA_{BF} (~30%) with hypotension was comparable in the presence of hypocapnia. Sato et al. [1] report a ~8% decline in global CBF following ~2 min of HUT (based on $n = 6$) and associated this cerebral hypoperfusion to a fall in ICA_{BF} (~−9%), as VA_{BF} was maintained near supine baseline levels. The discrepancy in VA_{BF} response between the current study and Sato et al. [1] is potentially due to: (1) a more severe and longer orthostatic stress used in the present study thereby inducing a greater degree of

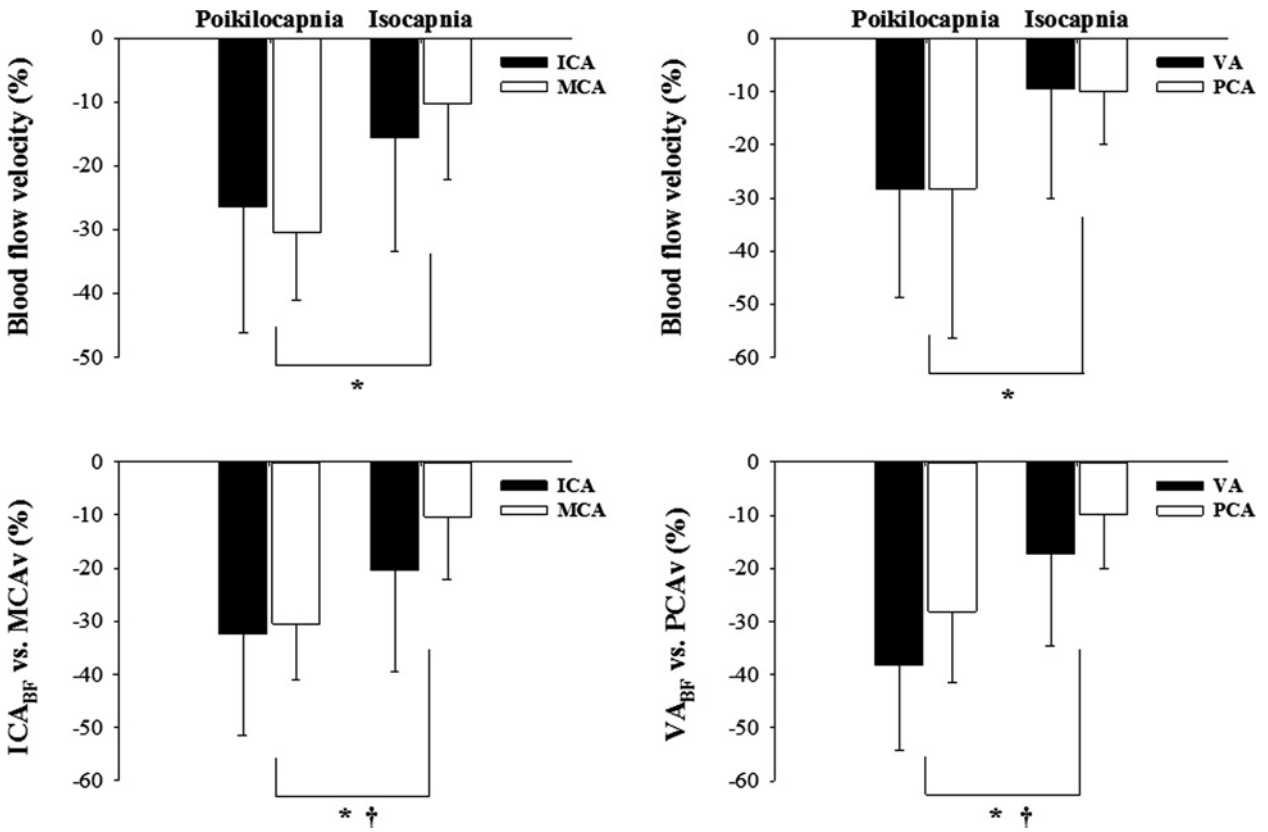

Figure 3 Percentage change from baseline to the hypotension end point in blood flow velocity and blood flow in the ICA and MCA ($n = 15$), VA and PCA ($n = 16$) in the poikilocapnic and isocapnic trials

*Independent of the blood vessel, the percentage change in blood flow and blood velocity was less in the isocapnic trial ($P \leqslant 0.001$). †Independent of the experimental trial, the decline in blood flow was greater than blood velocity ($P = 0.01$). Data are means ± S.D.

hypotension (decline in MAP: 7% compared with 20%); (2) a greater level of hypocapnia [−11 mmHg compared with −2.3 mmHg in Sato et al. [1]]; and, lastly, (3) manual compared with automated wall-tracking software of vessel diameter (the latter which reduces experimental bias) [15].

In contrast with our hypothesis, a differential blood flow response in the VA was evident with hypotension when hypocapnia was prevented. Moreover, this differential blood flow response was not evident in the ICA. For the same degree of hypotension and VA vasoconstriction, the decline in VA_{BF} was 39% in the poikilocapnic trial compared with 17% in the isocapnic trial. Unlike in the isocapnic trail, the development of hypocapnia in the poikilocapnic trial was significantly correlated with the decline in VA_{BF} (−2.3% per mmHg decline in $P_{ET}CO_2$); thus, the 11 mmHg decline in $P_{ET}CO_2$ may account for 25% of the 39% decline in VA_{BF}. As expected this significant correlation with hypocapnia was neither evident in the VA in the isocapnic trial, nor evident in the ICA under either experimental conditions. These findings are consistent with Willie et al. [2] who reported that CO_2 in the hypocapnic range is greater in the VA than the ICA. We extend these findings and show for the first time that the sensitivity of the VA to hypocapnia is still present in the presence of hypotension. This finding is particularly noteworthy given the evidence in animals showing that systemic hypotension leads to marked reductions in the CBF reactivity to both hyper- and hypocapnia [22]. Currently, the mechanism(s) and the reason(s) for the VA_{BF} being more sensitive to hypocapnia than the ICA_{BF} are unknown. Nevertheless, given that the VA_{BF} contributes ∼25–30% of total CBF, in addition to the fact that VA_{BF} is distributed among important posterior regions of the brain responsibility for homoeostatic functions (medulla oblongata, cerebellum, hypothalamus, thalamus and brainstem [9]), the heightened sensitivity of VA_{BF} to hypocapnia might be a protective mechanisms to detect early changes in posterior blood flow in an attempt to maintain consciousness.

The smaller decline in VA_{BF} with hypotension in the isocapnic trial is attributed to a higher VAv (∼4 cm·s^{-1}; +28%) as the VA diameter was identical between conditions. Therefore, the higher blood velocity could not have resulted from an increased vasoconstriction of the VA despite the greater shear rate stimulus (Figure 3). This finding potentially supports the notion that an increase in sympathetic outflow in response to arterial hypotension might have constrained arterial dilation in the VA in the isocapnic trial (see below). The heightened VAv in the isocapnic trial is probably a product of dilation of the posterior pial arterioles in response to the systemic hypotension in attempt to drive an increase in CBF to the posterior regions of the brain. Yet, despite this effort to increase posterior CBF, the development

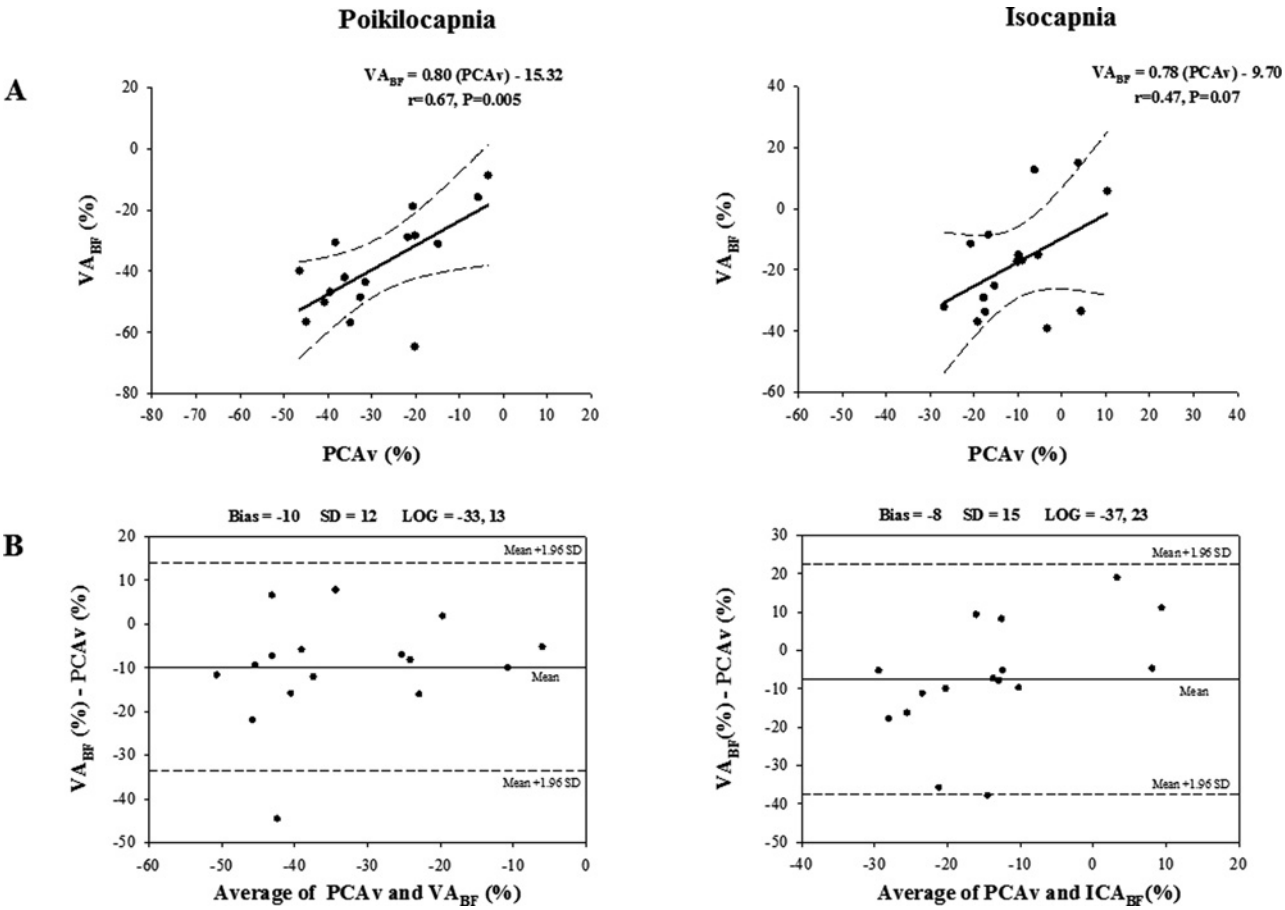

Figure 4 Bland–Altman and scatter plots comparing VA_{BF} and PCAv for the measure of percentage change in CBF during hypotension in a normocapnia (poikilocapnic trial) and hypocapnic condition (isocapnic trial; $n = 15$)

(**A**) Scatter plot with the regression line (continuous line) and 95% confidence intervals (dashed lines) for percentage change in CBF. (**B**) Bland–Altman plot of percentage change in CBF. Results show that during hypotension, PCAv underestimates VA_{BF} by −8% in the presence of hypocapnia and −9% without hypocapnia ($n = 16$).

of systemic hypotension and potentially arterial constriction in the VA appeared to outcompete the pial blood flow demand as posterior CBF was ultimately still reduced.

In the isocapnic trial, the decline in MAP was significantly correlated with the decline in VA_{BF} (−0.77% per mmHg in MAP), with declining MAP possibly accounting for ∼14% out of the 17% fall in VA_{BF}. Interestingly, this correlation was not evident in the poikilocapnic trial, suggesting that the development of hypocapnia masks the contribution of peripheral hypotension on the decline in VA_{BF}. The decline in ICA_{BF} was surprisingly not correlated with the development of arterial hypotension or hypocapnia under either experimental conditions, suggesting that the ICA may not be as sensitive to pressure changes as the VA and potentially in the presence of hypotension the ICA's reactivity to hypocapnia may be minimized.

Evidence of constriction of extracranial vessels during hypotension

Sato and co-workers [1] reported a significant ∼4% decline in ICA diameter with HUT and an unchanged VA diameter. They speculated that the between-vessel difference in diameter change with orthostatic stress is potentially due to a difference in their mechanical properties in response to hydrostatic pressure change from supine to HUT, autonomic innervation and reactivity to CO_2 [1]. However, in the present study and independent of the experimental trial, a significant decline in both ICA (−5%) and VA (−7%) diameter was observed with hypotension, suggesting that changes in hydrostatic pressure and the development of hypocapnia are not responsible for the observed constriction in the ICA or VA with hypotension. Based on the concept of cerebral auto-regulation, peripheral hypotension and consequent decline in CBF should result in vasodilation of the cerebral vessels in attempt to counter a declining CBF [23,24]; however, the present study indicates that the extracranial vessels constrict, rather than dilate, to reductions in MAP. Interestingly, the decline in ICA and VA diameter was not correlated with the decline in MAP, $P_{ET}CO_2$ or shear rate, suggesting that other factors are influencing the decline in ICA and VA diameter. Arterial hypotension induced by supine LBNP indeed leads to marked elevations in muscle sympathetic nerve activity [25]; therefore, given that the

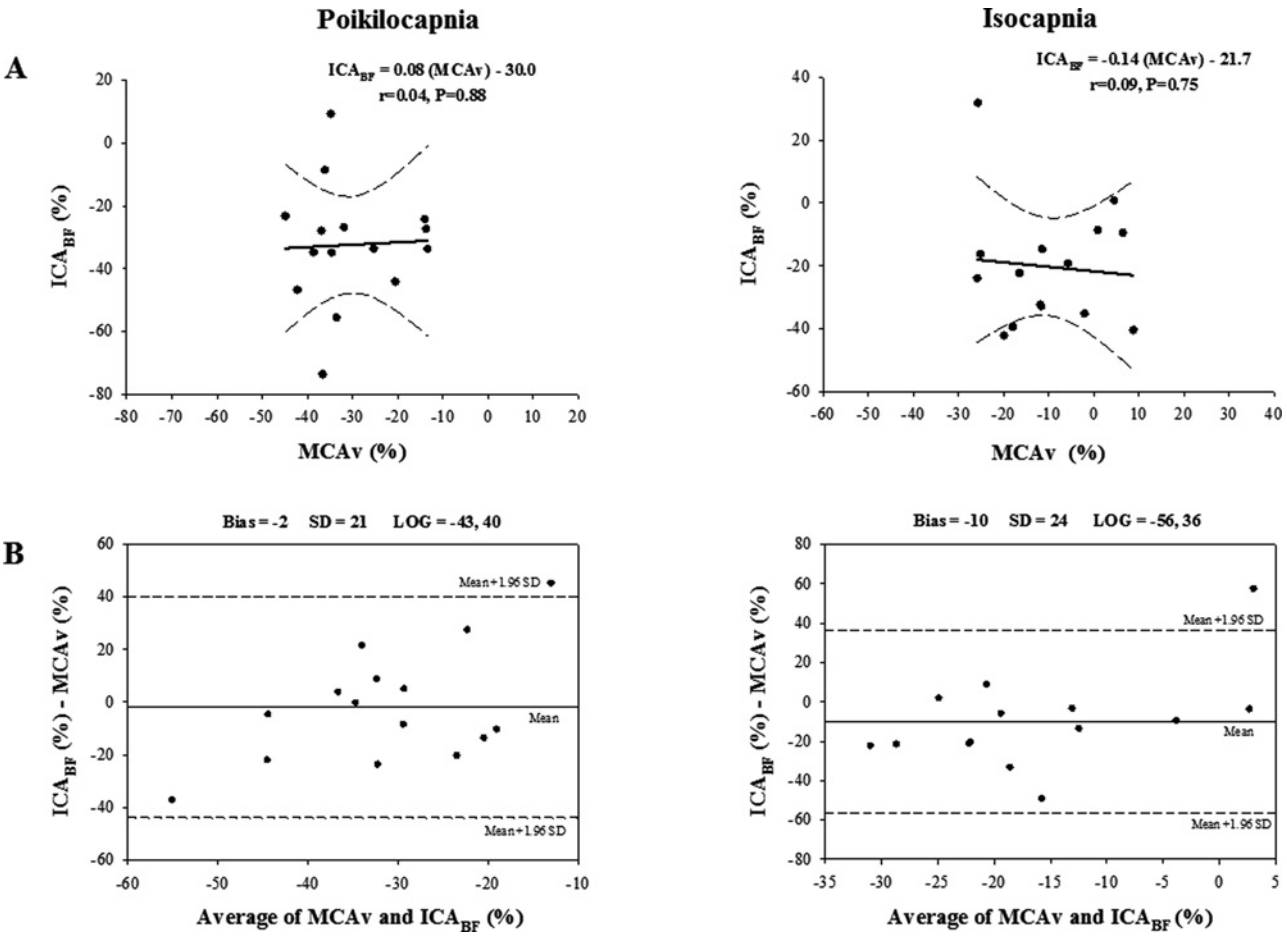

Figure 5 Bland–Altman and scatter plots comparing ICA_{BF} and MCAv for the measure of percentage change in the CBF during hypotension under both normocapnic (poikilocapnic trial) and hypocapnic conditions (isocapnic trial; $n = 15$)

(**A**) Scatter plot with the regression line (continuous line) and 95% confidence intervals (dashed lines) for percentage change in CBF. (**B**) Bland–Altman plot of percentage change in CBF. Results show that during hypotension, MCAv underestimates ICA_{BF} by −2% in the presence of hypocapnia and this underestimation is more pronounced (−10%) during a normocapnic clamp ($n = 15$).

ICA and VA blood vessels are well innervated with perivascular nerve bundles [26–28], it is plausible that vasoconstriction from elevated sympathetic activity at pre-syncope inhibits dilation of the larger extracranial cerebral vessels. Nevertheless, regardless of the mechanisms, the present study is the first to show that a decline in ICA and VA diameter contribute to the reductions in cerebral perfusion with hypotension. It remains to be explored whether these results are generalizable to patients with orthostatic pathologies, sometimes also associated with sympatho-excitation (e.g. postural orthostatic tachycardia syndromes).

Use of via transcranial Doppler to reflect flow during hypotension

In agreement with our hypothesis, independent of hypocapnia, the relative decline in MCAv and PCAv with hypotension was comparable with the relative decline in ICAv and VAv respectively. In contrast, because of extracranial arterial constriction, the relative decline in ICA_{BF} ($-26 \pm 14\%$) and VA_{BF} ($-27 \pm 14\%$) with hypotension was greater than in the MCAv ($-21 \pm 15\%$) and PCAv ($-19 \pm 10\%$) respectively. Bland–Altman analyses indicated that the measure of blood velocity via TCD systematically underestimates flow. Underestimation of PCAv of VA_{BF} was consistent between trials (poikilocapnic compared with isocapnic: 8–9%), whereas the MCAv underestimation of ICA_{BF} was not as consistent between trials (∼−2% compared with −10%). The greater underestimation of ICA_{BF} in the isocapnic trial may potentially be due to the fact that, unlike the ICA, the MCA became more sensitive to the development of hypotension in this trial, suggesting regional difference in the regulation of intracranial and extracranial blood vessels may potentially exist (specifically in the blood vessels supplying anterior CBF, i.e. ICA compared with MCA). Overall, given that the TCD underestimate of extracranial blood flow is relative small and the fact that the decline in extra- and intra-cranial blood velocity patterns are comparable, at least in healthy humans, we support (albeit with caveats) the use of TCD as an estimation of flow during conditions with hypotension and hypocapnia. Now these findings have been established in otherwise health humans; however, these

results may different in clinical cases of autonomic dysfunction is an important future question.

Limitations

All ICA and VA ultrasound measures were performed on the left and right side respectively of our participants. Although there is no evidence for bilateral differences in blood flow in the right and left ICA, the blood flow in the right VA has been reported to be ∼10–20% lower when compared with the left VA [7,29]. It is unknown, however, whether this bilateral difference is present during hypotension or hypocapnia. Therefore, although our conclusions remain, the findings in the present study probably underestimated rather than overestimated the changes in total blood flow in the VA. Global CBF in the present study was estimated based on blood flow in the ICA and VA as determined via ultrasound and therefore not an absolute direct measure of global CBF. TCD measures of intracranial blood velocities are a reliable index of changes in CBF provided that the diameter of the vessel in question does not change. Although recent reports using high-strength MRI has shown that the MCA does constrict with marked hypocapnia (−13 mmHg $P_{ET}CO_2$) [4], it is unknown whether this constriction also occurs in the PCA. However, given that the change in the MCAv and PCAv was comparable, it is possible that the PCAv also constricts in response to hypocapnia.

As highlighted, TCD measures of intracranial blood velocity underestimates extracranial blood flow, particularly in the posterior circulation. Given that the underestimate is relative small and the fact that the decline in extra- and intra-cranial blood velocity patterns are comparable, at least in healthy humans, we support (albeit with caveats) the use of TCD as an estimation of flow during conditions with hypotension and hypocapnia. Now these findings have been established in otherwise healthy humans, however, these results may different in clinical cases of autonomic dysfunction is an important future question.

Conclusion

Our findings indicate that the VA_{BF}, unlike the ICA_{BF}, is sensitive to changes hypotension and hypocapnia. The present study shows for the first time that the decline in global CBF with hypotension is influenced by arterial constriction in the ICA and VA. Additionally, our findings suggest TCD measures of blood flow velocity may modestly underestimate changes in CBF during hypotension with and without hypocapnia, particularly in the posterior circulation.

CLINICAL PERSPECTIVES

- Syncope is associated with hypotension and hypocapnia and currently it is unknown how the extra-cranial (ICA and VA) arteries response to hypotension and the influence of hypocapnia.
- Independent of hypocapnia, a decline in both ICA and VA diameter contributed to the decline in cerebral perfusion with systemic hypotension. The decline in VA_{BF} was greater when hypocapnia is present, this was no apparent in the ICA.
- Arterial constriction in response to hypotension has implications for the control of cerebral perfusion during pathological states, including syncope, hypertension and stroke.

AUTHOR CONTRIBUTION

Nia Lewis conceptualized and designed the experiments, collected, analysed and interpreted data, drafted the article and revised it critically for important intellectual content. Kurt Smith collected data and revised article critically for important intellectual content. Anthony Bain conceptualized and designed the experiments, collected, analysed and interpreted the data, drafted the article and revised it critically for important intellectual content. Kevin Wildfong performed data collection and revised the article critically for important intellectual content. Tianne Numan performed data collection, analysis and revised article critically for important intellectual content. Philip Ainslie conceptualized and designed the experiments, collected, analysed and interpreted data, drafted the article and revised it critically for important intellectual content.

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