Brain Perfusion and Arterial Blood Flow Velocity During Prolonged Body Tilting

David Montero; Sven Rauber

BACKGROUND: It remains unknown whether brain perfusion is preserved and mirrored by middle cerebral blood flow velocity (MCA BFV) during prolonged changes in body posture. Herein, we examined the impact of sustained (180 min) 30° head-up (HUT) and head-down (HDT) tilt on brain perfusion, as determined by MCA BFV and blood flow in the extracranial arteries.

METHODS: In 10 healthy male subjects, arterial diameters, BFVs, and blood flows were determined in the left internal carotid (ICA) and vertebral (VA) arteries using duplex Doppler ultrasound in supine rest, and 5, 20, 60, 120, and 180 min following 30° HUT and HDT. MCA BFV was recorded throughout with transcranial Doppler ultrasound.

RESULTS: ICA as well as VA diameters and blood flows were unaltered during HUT. Likewise, brain blood flow and MCA BFV were preserved with HUT. In the HDT protocol, ICA and VA diameters were gradually increased, although ICA, VA, and brain blood flows were preserved. MCA BFV was progressively reduced during HDT. In addition, MCA BFV was positively associated with ICA BFV ($\beta = 0.9$) and negatively associated with ICA diameter ($\beta = -125.5$). MCA BFV was positively associated with brain blood flow during HUT ($\beta = 0.2$) but not HDT.

CONCLUSIONS: Brain perfusion is preserved whereas MCA BFV is progressively decreased and associated with extracranial arterial BFV during sustained 30° HDT. Therefore, MCA BFV may not be a surrogate of brain perfusion in conditions including prolonged HDT.

KEYWORDS: intrathoracic blood volume, brain blood flow, cerebral autoregulation, transcranial Doppler.

Montero D, Rauber S. *Brain perfusion and arterial blood flow velocity during prolonged body tilting.* Aerosp Med Hum Perform. 2016; 87(8):682–687.

Adequate brain perfusion depends upon the integrated control of cerebral perfusion pressure and cerebrovascular conductance, termed cerebral autoregulation (CA).[17] As a prominent organ, the brain is characterized by pronounced autoregulation, with myogenic, neurogenic, and metabolic mechanisms contributing to buffer changes in brain blood flow in response to alterations in cerebral perfusion pressure, which commonly approximates mean arterial pressure (MAP).[12,24] The defense of brain blood flow against changes in MAP is typically illustrated by shifts in body position.[4] Indeed, brain blood flow is preserved during acute 90° head-up (HUT) and head-down (HDT) tilt despite marked changes in MAP.[8] In contrast, relatively little is known about the impact of sustained changes in body position.

In humans, the most common noninvasive methodology to evaluate brain perfusion is transcranial Doppler ultrasound.[1,13] In brief, the mean blood flow velocity (BFV) of intracranial arteries, usually the middle cerebral artery (MCA), is assessed via real-time pulse Doppler. MCA BFV is reported as an index of brain blood flow, provided that the diameter of the MCA remains approximately constant. In this regard, it is known that the conductance of large intracranial vessels is sensitive to large alterations in cerebral perfusion pressure,[7,16] thus contributing to regulation of blood flow as well as to protecting downstream vessels. Nonetheless, MCA diameter may remain unchanged with acute orthostatic stress.[20] Moreover, MCA BFV is highly correlated with brain blood flow in conditions of varying MAP and cerebrovascular conductance.[3] However, no previous study has explored whether MCA BFV reflects brain perfusion during prolonged HUT and HDT. The aims of the present study

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This manuscript was received for review in December 2015. It was accepted for publication in April 2016.

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DOI: 10.3357/AMHP.4546.2016

were twofold: 1) to examine the impact of prolonged (180 min) 30° HUT and HDT on brain perfusion; and 2) to assess the association of MCA BFV with brain perfusion, as determined by means of duplex Doppler ultrasound in extracranial arteries, in healthy young individuals.

METHODS

Subjects

There were 10 healthy, recreationally active male subjects (age = 25.5 ± 2.1 yr, bodyweight = 74.8 ± 5.9 kg, height = 181.4 ± 4.3 cm) who volunteered for the study. As inclusion criteria, all subjects were normotensive [systolic blood pressure (SBP) <130 and diastolic blood pressure (DBP) <85 mmHg], medication free, and with no history of renal/cardiovascular diseases. The study was approved by the Ethical Commission of Zurich (KEK-ZH-Nr. 2015-0044) and conducted in accordance with the declaration of Helsinki. Prior to the start of the experiments, informed oral and written consents were obtained from all subjects.

Equipment

MAP, stroke volume (SV), and cardiac output (Q) were continuously measured using a Finometer PRO (Finapres Medical Systems, Amsterdam, Netherlands), with data exported into acquisition software (Labchart 7, AD Instruments, Oxford, United Kingdom). Systemic vascular resistance (SVR) was calculated as MAP/Q. In addition, the internal jugular vein (IJV) aspect ratio, a surrogate of central venous pressure, was determined at the level of the cricoid cartilage using the method described by Keller et al.[10] In brief, the left IJV was assessed by means of a 7-MHz linear array probe attached to a high-resolution ultrasound machine (Mindray M7, Mahwah, NJ). After obtaining an optimized IJV image, a 20-s B-mode cine loop was obtained and reviewed frame by frame to identify the largest cross-sectional area (during expiration) and vessel dimensions were recorded. The IJV height was divided by its width to obtain the aspect ratio. Central hemodynamics variables and IJV aspect ratio data were averaged at each time point (described below) over the last minute of steady state recording.

Arterial diameter and BFV were measured in a blinded manner by a single investigator at the left ICA and VA using duplex Doppler ultrasound (Mindray M7) with a 7.5-MHz linear array transducer. ICA values were achieved ~1.5 cm from the bifurcation of the common carotid artery. VA measurements were performed between the subclavian artery and the transverse process of the C3 vertebra. Mean systolic and diastolic diameters were averaged over at least five cardiac cycles to determine the mean artery diameter [mean artery diameter = (1/3 · systolic artery diameter) + (2/3 · diastolic artery diameter)]. Time-averaged mean BFV was acquired with the pulse wave mode over at least 10 cardiac cycles. The sample volume was adjusted to capture the entire vessel lumen while the angle of insonation was kept below 60°. Analysis of the ultrasound data was made offline using the recorded images.

Blood flow in each artery was calculated as:

$$\pi \cdot \left(\frac{mean\,diameter}{2} \right)^2 \cdot mean\,BFV \cdot 60$$

Left brain blood flow was calculated as the sum of the blood flow in the ICA and VA. Images were recorded and stored for offline analysis.

MCA mean BFV was continuously measured with transcranial Doppler ultrasonography (Doppler Box, DWL, Singen, Germany) using a 2-MHz probe fixed on the left temporal window using an adjustable headband. Signals were sampled at 1 kHz and recorded for offline analysis using an analog-to-digital converter and acquisition software (Labchart 7, AD Instruments). MCA BFV data were averaged at each time point (described below) over the last minute of steady state recording.

Procedure

Subjects were required to report to our laboratory on two occasions. All individuals avoided strenuous exercise, alcohol, and caffeine from 24 h prior to testing. Time of day of testing sessions was kept consistent for each subject with a minimum of

Table I. Central Hemodynamics at Baseline and During Head-Up (HUT) or Head-Down (HDT) 30° Tilt.

	TIME (min)							
	BASELINE	5	20	60	120	180	ANOVA	LINEAR TREND
30° HUT								
IJV aspect ratio	0.51 ± 0.12	0.32 ± 0.12	0.32 ± 0.09	0.25 ± 0.10	0.28 ± 0.12	0.28 ± 0.10	< 0.001	0.002
MAP (mmHg)	87.33 ± 5.04	90.05 ± 5.92	91.97 ± 8.63	96.56 ± 12.62	97.57 ± 7.45	96.71 ± 7.69	< 0.001	0.002
SV (ml)	115.12 ± 17.42	100.73 ± 17.70	99.72 ± 12.71	98.09 ± 15.39	97.15 ± 14.84	99.92 ± 19.71	< 0.001	0.019
Q (L · min^{-1})	6.55 ± 1.46	6.25 ± 1.17	6.27 ± 0.85	6.06 ± 0.71	6.28 ± 1.10	6.24 ± 1.20	NS (0.468)	NS (0.478)
SVR (mmHg · min · L^{-1})	13.94 ± 14.87	14.87 ± 2.98	14.85 ± 2.01	16.19 ± 3.00	15.91 ± 2.65	16.02 ± 3.15	0.034	0.048
30° HDT								
IJV aspect ratio	0.59 ± 0.17	0.76 ± 0.11	0.80 ± 0.09	0.83 ± 0.09	0.76 ± 0.07	0.78 ± 0.09	< 0.001	0.002
MAP (mmHg)	88.91 ± 13.98	90.70 ± 11.19	92.55 ± 10.99	103.73 ± 12.09	107.13 ± 14.42	109.76 ± 14.50	< 0.001	0.001
SV (ml)	97.42 ± 8.19	95.10 ± 8.19	92.99 ± 7.59	86.89 ± 9.09	87.41 ± 9.91	86.07 ± 11.30	< 0.001	0.005
Q (L · min^{-1})	5.75 ± 0.52	5.51 ± 0.71	5.49 ± 0.82	5.05 ± 0.66	5.09 ± 0.74	4.99 ± 0.65	0.001	0.008
SVR (mmHg · min · L^{-1})	15.52 ± 2.33	16.54 ± 1.76	17.10 ± 2.84	21.09 ± 5.40	21.45 ± 4.34	22.40 ± 4.61	< 0.001	0.002

Data are presented as mean ± SD.
HDT, head-down tilt; HUT, head-up tilt; IJV, internal jugular vein; MAP, mean arterial pressure; NS, not significant; Q, cardiac output; SV, stroke volume; SVR, systemic vascular restistance.

48 h and a maximum of 7 d between randomized HUT and HDT sessions. Following 30 min rest in the horizontal position, individuals were tilted to 30° (i.e., HUT) or −30° (i.e., HDT) for 180 min. A bicycle saddle was installed to hold their body weight throughout the HUT protocol. During the HDT protocol, individuals had their feet fastened into padding retainers integrated in the tilt table. The measures described above were assessed after 20 min of supine rest, and 5, 20, 60, 120, and 180 min following 30° HUT and HDT.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (SPSS, IBM, Armonk, NY). Data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with Levene's test. Repeated measures analysis of variance (ANOVA) was used to compare cardiovascular variables across time (six time points) in HUT and HDT protocols. In addition, linear mixed models were used to examine the association of MCA BFV with cardiovascular variables, including time as a factor. All data are reported as mean ± SD unless otherwise stated. A two-tailed *P*-value less than 0.05 was considered significant.

RESULTS

Central hemodynamic variables are presented in **Table I**. As expected, IJV aspect ratio was decreased [F (5, 4) = 8.0, $P <$ 0.001, P for linear trend = 0.002] and MAP increased [F (5, 4) = 5.7, $P < 0.001$, P for linear trend = 0.002] during HUT. Moreover, SV, but not Q, was decreased with HUT [F (5, 4) = 8.6, $P < 0.001$, P for linear trend = 0.019], while SVR was increased [F (5, 4) = 2.7, $P = 0.034$, P for linear trend = 0.048]. In the HDT protocol, IJV aspect ratio [F (5, 4) = 10.9, $P < 0.001$, P for linear trend = 0.002] and MAP [F (5, 4) = 14.3, $P < 0.001$, P for linear trend = 0.001] were increased. Conversely, SV [F (5, 4) = 8.5, $P < 0.001$, P for linear trend = 0.005] and Q [F (5, 4) = 5.5, $P = 0.001$, P for linear trend = 0.008] were decreased, whereas SVR was increased [F (5, 4) = 10.4, $P < 0.001$, P for linear trend = 0.002] during HDT.

ICA, VA, and MCA variables are illustrated in **Fig. 1**, **Fig. 2**, and **Fig. 3**. ICA and VA diameters, BFVs, and blood flows were unaltered with HUT. Accordingly, left brain blood flow was preserved during HUT. With HDT, both ICA diameter [F (5, 4) = 3.0, P = 0.021, P for linear trend = 0.020] and VA diameter [F (5, 4) = 5.5, P = 0.001, P for linear trend = 0.023] were increased. In addition, HDT induced a decrease in BFV in the VA [F (5, 4) = 3.8, P = 0.014, P for linear trend = 0.014]. A decrease in ICA BFV with HDT did not reach significance [F (5, 4) = 2.2, P = 0.066, P for linear trend = 0.128]. Blood flow was unchanged in both ICA and VA during HDT. Similarly, left brain blood flow was preserved in the HDT protocol. With respect to the MCA, MCA BFV was preserved during HUT. In contrast, MCA BFV was progressively decreased throughout HDT [F (5, 4) = 15.4, $P < 0.001$, P for linear trend < 0.001].

Table II shows the associations of MCA BFV with cardiovascular variables. Using data from HUT and HDT protocols, MCA BFV was positively associated with central hemodynamic variables such as MAP (β = 0.9; 95% CI = 0.7, 1.1; $P < 0.001$) and Q (β = 4.1; 95% CI = 0.4, 7.8; P = 0.028). In addition, MCA BFV was positively associated with ICA BFV (β = 0.9; 95% CI = 0.2, 1.6; P = 0.017) and negatively associated with ICA diameter (β = −125.5; 95% CI = −237.6, −13.4; P = 0.029). Furthermore,

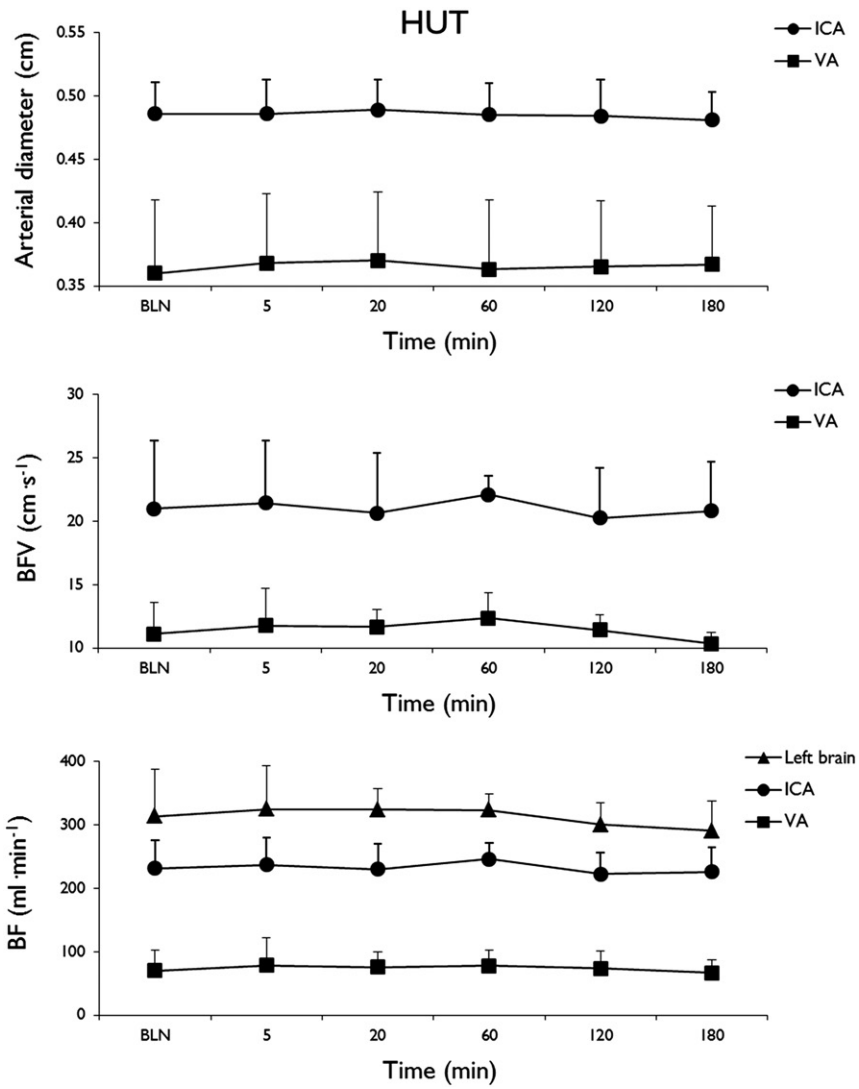

Fig. 1. Effects of 30° head-up tilt (HUT) on arterial diameter, blood flow velocity (BFV) and blood flow (BF). Data are expressed as mean ± SD. BLN, baseline; ICA, internal carotid artery; VA, vertebral artery.

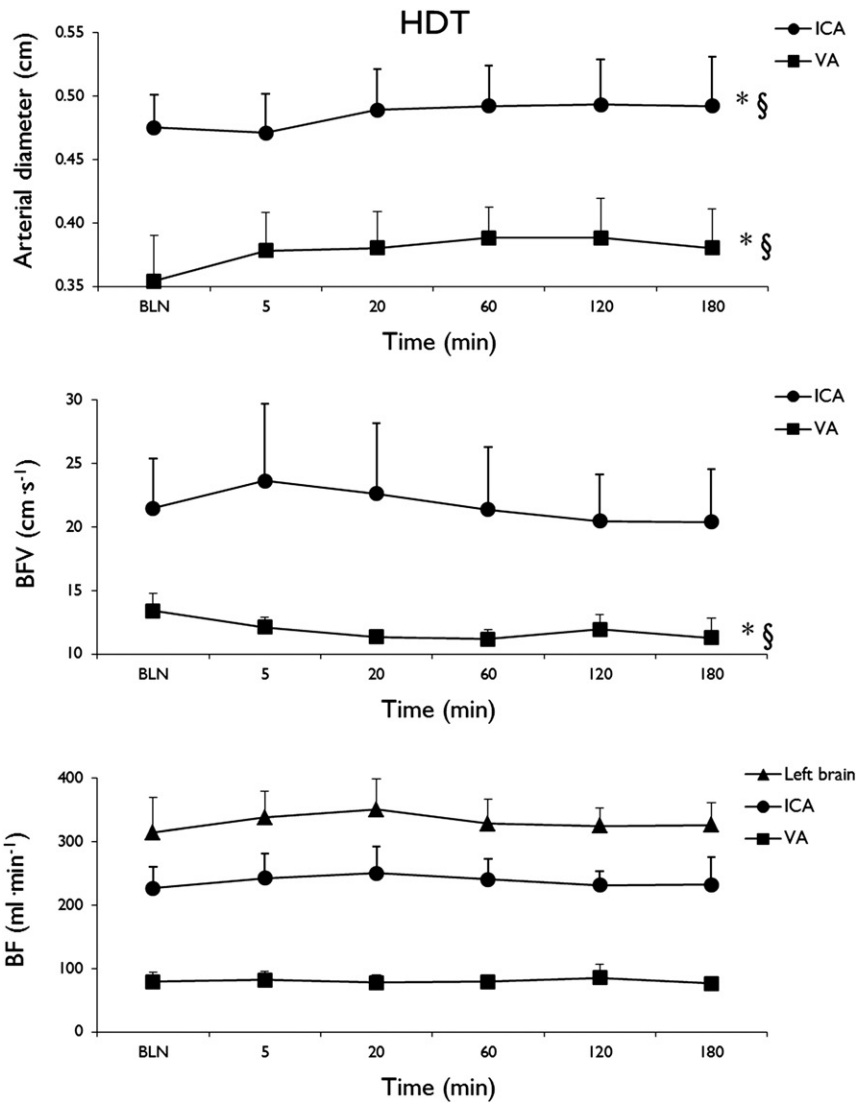

Fig. 2. Effects of 30° head-down tilt (HDT) on arterial diameter, blood flow velocity (BFV) and blood flow (BF). Data are expressed as mean ± SD *ANOVA main effect for time ($P < 0.05$); §linear trend ($P < 0.05$). BLN, baseline; ICA, internal carotid artery; VA, vertebral artery.

MCA BFV was positively associated with left brain blood flow ($\beta = 0.2$; 95% CI = 0.1, 0.3; $P = 0.007$) when only considering data from the HUT protocol.

DISCUSSION

We sought to determine whether brain perfusion is preserved and paralleled by MCA BFV during prolonged moderate HUT and HDT in healthy young individuals. The major novel findings of the present study are: 1) brain perfusion, as assessed by left ICA and VA blood flows, is preserved throughout 180 min of 30° HUT and HDT; 2) MCA BFV progressively decreases during HDT; and 3) MCA BFV is directly associated with ICA BFV and inversely with ICA diameter. These findings suggest that brain perfusion, but not MCA BFV, is maintained during sustained HUT and HDT despite increases in size of the extra- and plausibly intracranial large arteries with HDT, which likewise limits the use of MCA BFV as a surrogate of brain perfusion.

While the preservation of brain perfusion with acute changes in body position has been previously reported,[8] the impact of sustained changes in body position had not been yet explored. Our findings indicate that brain perfusion is maintained during prolonged 30° HUT and HDT, irrespective of gradual changes in MAP and central venous pressure. This concurs with the notion that CA successfully operates within relatively mild shifts in MAP (~25%).[14,21] Moreover, this study demonstrates that CA is effective in the presence of persistent high levels of venous congestion, as reflected by the unaltered brain perfusion against 8–9 mmHg central venous pressure estimated from the IJV aspect ratio during HDT.[10,18] Such findings are relevant to individuals exposed to altered effects of gravity for extended periods of time (e.g., aerospace professionals). As for the mechanisms, the myogenic response is activated by changes in MAP observed in the present study in healthy individuals.[22] Furthermore, a generalized increase in vascular resistance in noncerebral vessels, as denoted by the increase in SVR, may influence brain perfusion. Yet the relative contribution of local/systemic myogenic, autonomic, and metabolic factors to CA remains to be established.[5] Likewise, further studies are warranted to determine whether brain perfusion is preserved during prolonged HUT and HDT in high-risk populations such as elderly individuals and those with cardiovascular risk factors.

The vascular region in which CA primarily occurs has been the subject of controversy.[24] The observed increases in ICA and VA diameters during HDT suggest a passive role of extracranial arteries in CA. Similarly, the progressive decrease in MCA BFV in the presence of preserved brain blood flow suggests that MCA diameter was enlarged throughout HDT. The parallelism of increases in extra- and intracranial large arteries is denoted by the direct association of ICA BFV with MCA BFV. These findings support that large cerebral arteries (ICA, VA, MCA) do not actively participate in the regulation of brain perfusion in response to moderate increases in MAP, in line with previous human studies.[9,20] Greater augmentation of MAP (>25%), however, may prompt the myogenic response (i.e., constriction) in large cerebral arteries,[11] albeit brain perfusion may be maintained.[15] Taken together, the current study suggests that CA facing moderate and sustained alterations in MAP during HDT is primarily effected through a plausible increase in vascular resistance of smaller cerebral arteries and arterioles.

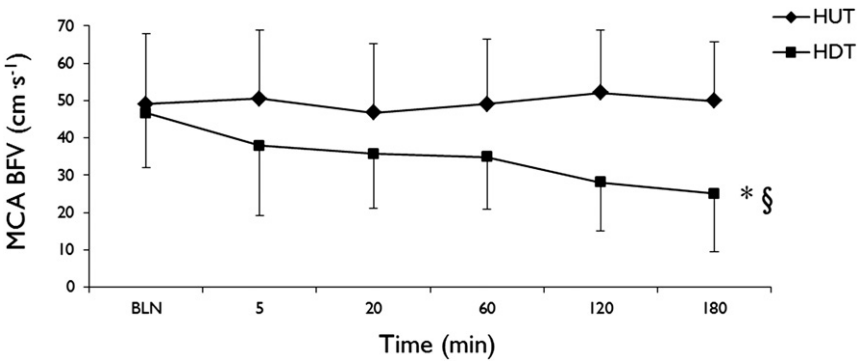

Fig. 3. Effects of 30° head-up tilt (HUT) and head-down tilt (HDT) on middle cerebral artery (MCA) blood flow velocity (BFV). Data are expressed as mean ± SD *ANOVA main effect for time ($P < 0.05$); [§]linear trend ($P < 0.05$). BLN, baseline.

Transcranial Doppler ultrasound has become a popular method to assess brain perfusion in human studies, given its accessibility, noninvasive nature, and high temporal resolution.[23] This approach quantifies BFV and assumes that cerebral artery diameter remains constant, which may be tenable under non-extreme conditions.[9,20] Indeed, in our study, the 11% increment in MAP during HUT did not alter ICA and VA diameters, brain blood flow, or MCA BFV. Moreover, MCA BFV was associated with brain blood flow during HUT, supporting the reliability of MCA BFV. Conversely, in the HDT protocol, the 23% increment in MAP was accompanied by the enlargement of ICA and VA diameters and a decrease in MCA BFV despite brain blood flow being unaltered. Therefore, this study disputes the reliability and validity of MCA BFV to determine brain perfusion in the setting of elevated MAP and congestion of cerebral vessels.

There are some limitations to this study that require comment. First, changes in body position may alter ventilation and thereby the partial pressure of arterial CO_2 (P_aCO_2), which in turn regulates cerebrovascular tone.[2] P_aCO_2 was not measured in our study. Nonetheless, there is evidence that the contribution of P_aCO_2 to the postural impact on brain perfusion is transient (2 min), therefore results of our study may not be determined by P_aCO_2. Second, we compared MCA BFV with extracranial artery measurements obtained by duplex Doppler ultrasound. The reliability of the latter methodology to assess brain perfusion is attested by its high correlation with gold-standard techniques such as positron emission tomography and magnetic resonance imaging.[6] However, we only assessed the ICA and VA on the left side, which could lead to a lower precision estimate of brain perfusion. Regardless, only slight differences between left and right VA blood flows and similar ICA blood flows are commonly reported in healthy adults.[19,25] Finally, no account was taken of cerebral volume and, thus, relative blood flow to cerebral mass.

Table II. Associations of MCA BFV with Cardiovascular Variables.

	β (95% CI)	*P*
MAP (mmHg)	0.9 (0.7, 1.1)	< 0.001
SV (ml)	−0.2 (−0.4, 0.01)	NS (0.147)
Q (L · min^{-1})	4.1 (0.4, 7.8)	0.028
SVR (mmHg · min · L^{-1})	0.4 (−0.6, 1.5)	NS (0.393)
ICA diameter (cm)	−125.5 (−237.6, −13.4)	0.029
ICA BFV (cm · s^{-1})	0.9 (0.2, 1.6)	0.017
ICA blood flow (ml · min^{-1})	0.0 (−0.0, 0.1)	NS (0.376)
VA diameter (cm)	−0.0 (−85.0, 85.0)	NS (0.999)
VA BFV (cm · s^{-1})	2.4 (−0.0, 4.9)	NS (0.051)
VA blood flow (ml · min^{-1})	0.0 (−0.2, 0.2)	NS (0.888)
Left brain blood flow (ml · min^{-1})	0.1 (−0.0, 0.2)	NS (0.129)

All analyses comprised data from HUT and HDT protocols and included time as a factor.
β, regression coefficient with MCA BFV (cm · s^{-1}) as outcome; BFV, blood flow velocity; HDT, head-down tilt; HUT, head-up tilt; IJV, internal jugular vein; MAP, mean arterial pressure; NS, not significant; Q, cardiac output; SV, stroke volume; VA, vertebral artery.

In summary, this study reveals that brain perfusion is maintained during prolonged 30° HUT and HDT despite changes in cerebral artery diameter in healthy young individuals. In addition, MCA BFV is linearly decreased with HDT, mimicking the response of upstream extracranial arteries. Therefore, MCA BFV may not be considered a proxy of brain perfusion during sustained HDT. Further research is needed to elucidate whether brain perfusion is preserved during prolonged moderate tilt in healthy elderly and individuals at risk of developing cardiovascular disease.

ACKNOWLEDGMENTS

The authors thank all study subjects for their willingness, time, and effort devoted to this study and all members of our research group for their excellent support.

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