Regional changes in brain blood flow during severe passive hyperthermia: effects of PaCO\(_2\) and extracranial blood flow

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Bain AR, Smith KJ, Lewis NC, Foster GE, Wildfong KW, Willie CK, Hartley GL, Cheung SS, Ainslie PN. Regional changes in brain blood flow during severe passive hyperthermia: effects of PaCO\(_2\) and extracranial blood flow. J Appl Physiol 115: 653–659, 2013. First published July 3, 2013; doi:10.1152/japplphysiol.00394.2013.—We investigated (1) the regional distribution of cerebral blood flow (CBF), (2) the influence of end-tidal CO\(_2\) (PetCO\(_2\)) on CBF, and (3) the potential for an extracranial blood “steal” from the anterior brain region during passive hyperthermia. Nineteen (13 male) volunteers underwent supine passive heating until a steady-state esophageal temperature of 2°C above resting was established. Measurements were obtained (1) during normothermia (Normo), (2) during poikilothermic hyperthermia (Hyper), and (3) during hypercapnia with PetCO\(_2\) and end-tidal PO\(_2\) clamped to Normo levels (Hyper-clamp). Blood flow in the internal carotid (Q˙ICA), vertebral (Q˙VA), and external carotid (Q˙ECA) arteries (Duplex ultrasound), blood velocity of the middle cerebral (MCAv) and posterior cerebral (PCAv) arteries (transcranial Doppler), and cutaneous vascular conductance on the cheek (cheek CVC; Doppler velocimetry) were measured at each stage. During Hyper, PetCO\(_2\) was lowered by 7.0 ± 5.2 mmHg, resulting in a reduction in Q˙ICA (−18 ± 17%), Q˙VA (−31 ± 21%), MCAv (−22 ± 13%), and PCAv (−18 ± 10%) compared with Normo (P < 0.05). The reduction in Q˙VA was greater than that in Q˙ICA (P = 0.017), MCAv (P = 0.047), and PCAv (P = 0.034). Blood flow/velocity was completely restored in each intracranial vessel (ICA, VA, MCA, and PCA) during Hyper-clamp. Despite a ≈250% increase in Q˙ECA and a subsequent increase in cheek CVC during Hyper compared with Normo, reductions in Q˙ICA were unrelated to changes in Q˙ECA. These data provide three novel findings: (1) hyperthermia attenuates Q˙VA to a greater extent than Q˙ICA, (2) reductions in arterial PCO\(_2\) during hyperthermia are governed primarily by reductions in arterial PCO\(_2\) and extracranial blood flow, and (3) increased Q˙ECA is unlikely to compromise Q˙ICA during hyperthermia.

DURING PASSIVE HEATING, a 1°C rise in core body temperature elicits a 10–15% reduction in middle cerebral artery (MCA) blood velocity (MCAv) (6, 8, 14, 25), in turn increasing the risk of syncope (1, 5, 12, 26). The interplay of the underlying mechanisms responsible for reduced cerebral blood flow (CBF) during passive heat stress remains equivocal. For example, reductions in arterial PCO\(_2\) (Paco\(_2\)), consequent to a heat-induced metabolic hypercapnemic response, are responsible for the majority of the changes in CBF during heat stress in some (8, 14), but not all (6, 9), studies. In addition to this apparent discrepancy, an inherent limitation of all studies is the single use of MCAv measurements as a surrogate for global changes in CBF.

Recently, two studies using concurrent volumetric measurements reported that the anterior and posterior brain regions may have differential reactivity to changes in Paco\(_2\) (19, 24). Although not a universal finding (19), we have demonstrated that sensitivity to hypocapnia may be greater in the posterior region of the brain referred to as the posterior cerebral artery (PCA) during passive heat stress is often ascribed to the increased incidence of syncope (5–8). It is surprising that no studies have assessed regional differences during hyperthermia-induced changes in CBF.

During heavy aerobic exercise (i.e., 80% of maximum) and associated rises in body core temperature, Sato et al. (20) observed that blood flow in the ICA (Q˙ICA) was inversely proportional to increases in extracranial artery (ECA) blood flow (Q˙ECA). As the ICA supplies a large portion of the anterior brain and the ECA supplies superficial regions of the head (e.g., skin and cheek muscles), the authors speculated that hyperthermia might compromise blood flow to the anterior brain (independently of Paco\(_2\)) to increase blood supply to the cutaneous tissue of the forehead, face, and neck, a prerequisite for local thermoregulation. Interestingly, brain stem blood flow [index via blood flow in the VA (Q˙VA)] was increased proportionally throughout rising levels of exercise intensity (20). It remains to be examined if similar findings are observed during passive heat stress, i.e., is Q˙VA maintained despite reductions in Paco\(_2\) levels during non-exercise-induced hyperthermia? Moreover, is Q˙ECA elevated to optimize thermoregulation at the expense of reductions in Q˙ICA? The primary purpose of this study was to assess the regional distributions of CBF across the proximal vessels (ICA and VA) in conjunction with blood velocity in the distal vessels [MCA and posterior cerebral artery (PCA)] during severe passive heat stress. In doing so, we sought to partition the influence of Paco\(_2\) on regional CBF and examine whether a thermoregulatory prioritization compromises Q˙ICA through an ECA blood “steal” during severe passive hyperthermia. It was hypothesized that (1) hyperthermia-induced hyperventilation and related reductions in Paco\(_2\) would attenuate Q˙VA to a greater extent than Q˙ICA and (2) a hierarchy for thermoregulation would compro-

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mise $\dot{Q}_{\text{ICA}}$ via increases in $\dot{Q}_{\text{ECA}}$ and, subsequently, heat loss on the face and neck.

**METHODS**

**Participants**

After approval from the University of British Columbia Ethical Review Board and informed written consent, 19 volunteers [13 male, 6 female; 23 ± 2 yr of age, 177.5 ± 11.1 cm, 78.1 ± 15.1 kg body wt, and 24.7 ± 3.3 body mass index (means ± SD)] participated in one preliminary and one experimental session. During the preliminary session, an initial ultrasound screening was performed to ensure that reliable neck artery (ECA, ICA, and VA) images and intracranial artery (MCA and PCA) data could be attained. Each subject was familiarized with all other equipment and protocols during the preliminary session. All participants were non-heat-acclimated, did not smoke or take prescription drugs (other than contraceptives), and were free from cardiovascular or respiratory diseases.

**Experimental Protocol**

Participants arrived at the laboratory in the morning between 0700 and 1000 after eating a light breakfast. Exercise and caffeine were avoided for 24 h and alcohol for 48 h prior to testing. To control for possible thermoregulatory changes throughout the menstrual cycle, female participants were tested within the first 10 days following menstruation. Immediately upon arrival at the laboratory, urine specific gravity (model TS 400, Reichert Analytical Instruments, Depew, NY) was assessed to ensure adequate ($\pm 1.020$) hydration.

After instrumentation, subjects rested supine while normothermic (Normo) baseline measurements were acquired. Next, subjects were passively heated by circulation of 49°C water through a water-perfused suit (Med-Eng, Ottawa, ON, Canada) that covered the entire body except the hands, feet, and head. Temperature of the water in the suit was gradually lowered to ~44°C to stabilize the rise in esophageal temperature ($T_e$) as it approached 2.0°C above resting. After a steady-state $T_e$ of 2.0°C (or thermal tolerance) above baseline was established, measurements were taken while the subjects breathed spontaneously (Hyper) and then during end-tidal $PCO_2$ ($PET_{CO_2}$) and $PO_2$ ($PET_{O_2}$) clamping (Hyper-clamp) to eucapnic values established during Normo baseline (see Ventilation and end-tidal clamping).

**Measurements**

**Thermometry.** Core temperature was measured in the esophagus ($T_e$) by insertion of a pediatric thermocouple probe (Mon-a-therm general purpose temperature probe, Mallinckrodt Medical, St. Louis, MO) 40 cm past the nostril into the esophagus. Skin temperature was measured by placement of a copper-constantan thermocouple on the face and neck. Skin temperature was subsequently estimated as the weighted distribution of chest, 0.3% shoulder, 0.2% thigh, and 0.2% calf temperature (17).

**Hemodynamics.** Cerebral blood velocity of the MCA (MCAv) and PCA (PCAv) were measured using a 2-MHz pulsed transcranial Doppler ultrasound system (Spencer Technologies, Seattle, WA). A specialized headband fixation device (model M600 bilateral head frame, Spencer Technologies) was used to secure the probes in position throughout the trial. Standardized search techniques (23) were used to optimize signal quality and verify standardized vessel insonation. MCAv was measured through the temporal window, at a depth 1 cm distal to the MCA-anterior cerebral artery bifurcation. PCAv was insonated at the P1 segment through the temporal window on the contralateral side of the skull. The side of the skull for vessel insonation was determined by the strongest signal strength. Accordingly, all but four MCAv measurements were taken on the left side of the skull.

Neck blood flow in the ICA ($\dot{Q}_{\text{ICA}}$), VA ($\dot{Q}_{\text{VA}}$), and ECA ($\dot{Q}_{\text{ECA}}$) was measured using Doppler ultrasonography and a 10-MHz multi-frequency linear array probe attached to a high-resolution ultrasound machine (Terson 3000, Teratech, Burlington, MA). Approximately 1-min recordings of each vessel were obtained in a randomized order during each of the three conditions. Because of methodological constraints, all measurements were performed solely on the right side of the neck. The ICA was measured ≥2 cm from the carotid bifurcation. The ECA was measured ≥1.5 cm from the carotid bifurcation, or immediately before the first ECA branch. Measurements of the ICA and ECA were taken after there was no evidence of turbulent or retrograde flow as gauged from the flow velocity waveform (i.e., nonturbulent and anterograde velocity). The VA was measured between the transverse process of C4 and the subclavian artery. Care was taken to ensure that each artery was measured at exactly the same location within subjects. Average diameter and blood flow recordings were made from ≥15 cardiac cycles throughout stable recordings, with the insonation angle held constant at 60°. The sample volume was positioned in the center of the vessel and adjusted to cover the width of the vessel diameter. Test-retest reliability for baseline measures of $\dot{Q}_{\text{ICA}}$, $\dot{Q}_{\text{ECA}}$, and $\dot{Q}_{\text{VA}}$ are ~5%, 10%, and 11%, respectively. All neck blood flow images were directly stored as an AVI file for offline analysis. Artery diameter and flow were analyzed using customized-designed edge-detection and wall-tracking software, which is independent of investigator bias and has previously been comprehensively described (2, 27). From synchronized diameter and velocity data, blood flow (the product of lumen cross-sectional area and Doppler velocity) was calculated at 30 Hz. This semiautomated software results in significantly better reproducibility of diameter measurements than manual methods, reduces observer error and bias significantly, and possesses an intraobserver coefficient of variation of 6.7% (27).

**Beat-to-beat blood pressure** was measured by finger photoplethysmography (Finometer PRO, Finapress Medical Systems, Amsterdam, Netherlands) and normalized to manual cuff measurements of the brachial artery. Heart rate (HR) was obtained from the R-R intervals measured from a three-lead ECG. Online calculations of stroke volume were obtained using a three-element nonlinear arterial model of the arterial blood pressure waveform (Finometer) (22). Cardiac output (CO) was subsequently derived from the product of stroke volume and HR. Because of lack of clear validity of this approach to analyze awake volume and CO during heat stress, these metrics were used for descriptive purposes only and not as primary outcome variables.

**Cheek cutaneous vascular conductance (CVC)** was measured using laser-Doppler velocimetry (Periflux System 5000 main control unit and PF5010 LDPM operating unit, Perimed, Stockholm, Sweden) at the right upper cheek. The laser-Doppler flow probe (model PR 457 angled probe, Perimed) was taped to cleaned and shaved skin and, once secured, was not removed from its location until the end of the trial. The probe temperature was allowed to fluctuate spontaneously with skin temperature. Cheek CVC was subsequently derived from the ratio of perfusion units (arbitrary number) to mean arterial pressure (MAP).

**Ventilation and end-tidal clamping.** For measurement of $PET_{CO_2}$ and $PET_{O_2}$, the subjects breathed through a mouthpiece and two-way non rebreathing valve. Respirated gas pressures were sampled at the mouth by securing a calibrated online gas analyzer (model ML206, AD Instruments, Colorado Springs, CO) into the mouthpiece. Respiratory flow was measured at the mouth using a pneumotachograph (model HR 800L, HansRudolph, Shawnee, KS). $PET_{CO_2}$, $PET_{O_2}$, and inspiratory and expiratory tidal volume were determined for each breath online using specifically designed software (LabView, Austin, TX). $PET_{CO_2}$ and $PET_{O_2}$ were controlled by a portable end-tidal forcing system (AirForce, GE Foster, Vancouver, BC, Canada). This system uses independent gas solenoid valves for $O_2$, $CO_2$, and $N_2$ and controls the volume of each gas being delivered to the inspiratory reservoir through a mixing-and-humidification chamber. With use of feedback information regarding $PET_{CO_2}$, $PET_{O_2}$, and inspiratory and
Table 1. Absolute thermal, ventilator, hemodynamic, and cerebrovascular data for Norm, Hyper, and Hyper-clamp

<table>
<thead>
<tr>
<th></th>
<th>Normo</th>
<th>Hyper</th>
<th>Hyper-clamp</th>
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<tbody>
<tr>
<td><strong>Thermal</strong></td>
<td></td>
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<tr>
<td>$T_{es}$, °C</td>
<td>19</td>
<td>36.7 ± 0.3</td>
<td>38.7 ± 0.2*</td>
</tr>
<tr>
<td>$T_{sk}$, °C</td>
<td>19</td>
<td>33.4 ± 1.0</td>
<td>38.4 ± 0.9*</td>
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<tr>
<td><strong>Ventilatory</strong></td>
<td></td>
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<tr>
<td>$PET_{CO2}$, mmHg</td>
<td>19</td>
<td>40.1 ± 2.8</td>
<td>33.1 ± 6.2*</td>
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<tr>
<td>$Ve$, l/min</td>
<td>19</td>
<td>12.2 ± 1.8</td>
<td>18.2 ± 5.7*</td>
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<td><strong>Hemodynamics</strong></td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>19</td>
<td>66 ± 11</td>
<td>113 ± 19*</td>
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<tr>
<td>MAP, mmHg</td>
<td>19</td>
<td>82 ± 10</td>
<td>87 ± 1.9*</td>
</tr>
<tr>
<td>$CO$, l/min</td>
<td>19</td>
<td>6.5 ± 1.2</td>
<td>7.7 ± 1.9*</td>
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<td>$Q_{ECA}$, ml/min</td>
<td>14</td>
<td>157 ± 71</td>
<td>389 ± 159*</td>
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<tr>
<td>$Q_{ICA}$, ml/min</td>
<td>12</td>
<td>295 ± 51</td>
<td>237 ± 48*</td>
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<tr>
<td>$Q_{VA}$, ml/min</td>
<td>12</td>
<td>94 ± 35</td>
<td>65 ± 31*</td>
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<tr>
<td>$MCAv$, cm/s</td>
<td>15</td>
<td>68.8 ± 11.5</td>
<td>53.2 ± 10.3*</td>
</tr>
<tr>
<td>$PCAv$, cm/s</td>
<td>15</td>
<td>47.4 ± 4.6</td>
<td>38.7 ± 6.4*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, sample size. Normo, normothermia; Hyper, hyperthermia; Hyper-clamp, Hyper with end-tidal $PET_{CO2}$ ($PET_{CO2}$) clamp; $T_{es}$, esophageal temperature; $T_{sk}$, mean skin temperature; Ve, expired ventilation; HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; $Q_{ECA}$, flow in external carotid artery; $Q_{ICA}$, flow in internal carotid artery; $Q_{VA}$, flow in vertebral artery; $MCAv$, velocity in middle cerebral artery; $PCAv$, velocity in posterior cerebral artery. *Significantly different from Normo. †Significantly different from Hyper-clamp.

RESULTS

**Thermal and Ventilatory Data**

Absolute measures for $Tes$, $Tsk$, $PET_{CO2}$, and ventilation ($Ve$) across Normo, Hyper, and Hyper-clamp are presented in Table 1. There was a significant main effect of condition for $T_{es}$, $T_{sk}$, $PET_{CO2}$, and $Ve$ ($F = 313.75, 76.70, 19.94,$ and 24.33, respectively, all $P < 0.05$). $T_{es}$ and $T_{sk}$ were significantly elevated from Normo in both Hyper and Hyper-clamp conditions ($P < 0.05$). No differences were observed in $T_{es}$ or $T_{sk}$ between the hyperthermic conditions ($P > 0.05$). $PET_{CO2}$ was reduced by $7.0 \pm 5.2$ mmHg during Hyper compared with Normo ($P < 0.001$). $PET_{CO2}$, clamping during hyperthermia successfully restored $PET_{CO2}$ to baseline values (Table 1). Ventilation was significantly elevated from Normo to Hyper ($P = 0.007$) and further elevated following the Hyper-clamp from Hyper ($P = 0.028$).

**Cerebrovascular**

Figure 1 depicts the percent change from baseline in $Q_{VA}$, $Q_{ICA}$, $MCAv$, and $PCAv$ from Normo to Hyper. Table 1 shows absolute values during each condition. Despite the care taken during each scan, the increased ventilation associated with hyperthermia introduced difficulty in achieving reliable images in each subject. As such, to ensure reliability, scans were rejected from analysis if we observed a change in probe angle or location of artery insonation or if we were unable to achieve $\pm 15$ consecutive cardiac cycles. Therefore, despite 19 subjects having completed the entire study protocol, the sample size for the comparison of $Q_{VA}$ with $Q_{ICA}$, $Q_{ECA}$ with $Q_{ICA}$, and $Q_{ECA}$ with cheek CVC was reduced to 12, 10, and 12 subjects, respectively.

There was a significant main effect of condition for $Q_{ICA}$, $Q_{VA}$, $MCAv$, and $PCAv$ ($F = 5.33, 6.54, 19.47,$ and 28.86, respectively, all $P < 0.05$). Blood flow and velocity of all the insonated cerebral vessels were significantly reduced during Hyper compared with Normo (all $P < 0.05$). The percent reduction from Hyper to Normo was greater for $Q_{VA}$ than $Q_{ICA}$ ($-31 \pm 21\%$ vs. $-18 \pm 17\%$, $P = 0.017$). Conversely, no differences were found in percent reduction of $MCAv$ ($-22 \pm 13\%$) compared with $PCAv$ ($-18 \pm 10\%$) from Normo to Hyper ($P = 0.165$).

Figures 2 and 3 show the influence of Hyper-clamp on $Q_{ICA}$ and $Q_{VA}$ and on $MCAv$ and $PCAv$. $Q_{VA}$, $Q_{ICA}$, $MCAv$, and $PCAv$...
PCAv were elevated following Hyper-clamp compared with Hyper (all $P < 0.05$). Accordingly, during Hyper-clamp, $\dot{Q}_{VA}$ and $\dot{Q}_{ICA}$ were restored to $104 \pm 14\%$ and $98 \pm 18\%$ of Normo values, respectively. Meanwhile, MCAv and PCAv were restored to $94 \pm 9\%$ and $97 \pm 14\%$ of Normo values, respectively.

**Cheek CVC and $\dot{Q}_{ECA}$**

There was a significant main effect of condition for cheek CVC and $\dot{Q}_{ECA}$ ($F = 33.55$ and $79.60$, respectively, both $P < 0.05$). $\dot{Q}_{ECA}$ was significantly elevated during both Hyper and Hyper-clamp compared with Normo (Fig. 4; $P < 0.01$). Unlike the other insonated vessels, restoration of PaCO$_2$ resulted in no changes in $\dot{Q}_{ECA}$ (Fig. 4; $P > 0.05$) from Hyper to Hyper-clamp. As expected cheek CVC was elevated from Normo to Hyper ($P < 0.01$). No differences in cheek CVC were observed between Hyper ($815 \pm 599\%$ of baseline) and Hyper-clamp ($815 \pm 594\%$ of baseline) ($P > 0.05$), while elevations in cheek CVC were proportionally related to increases in $\dot{Q}_{ECA}$ from Normo to Hyper ($r = 0.67$, $P = 0.009$; Fig. 5). Figure 6 shows the positive relationship between increases in $\%\dot{Q}_{ECA}$ and reductions in $\%\dot{Q}_{ICA}$ from Normo to Hyper ($r = 0.53$, $P = 0.058$). When the one outlier ($-49\%$ change in $\dot{Q}_{ECA}$ and $139\%$ change in $\dot{Q}_{ICA}$) is removed, this relationship becomes stronger ($r = 0.72$, $P = 0.015$). These data indicate that reductions in $\dot{Q}_{ICA}$ are unlikely to be related to increases in $\dot{Q}_{ECA}$.

**Whole Body Hemodynamics**

Absolute measures for MAP, HR, and CO across Normo, Hyper, and Hyper-clamp are presented in Table 1. There was a significant main effect of condition for MAP, HR, and CO ($F = 4.80, 125.59$, and $16.80$, respectively, all $P < 0.05$). No differences were observed in MAP from Normo to Hyper ($P = 1.000$) or Hyper-clamp ($P = 0.813$). However, MAP was higher during Hyper-clamp than Hyper ($P = 0.021$). HR was elevated from Normo during Hyper ($P < 0.001$) and Hyper-clamp ($P < 0.001$) and increased slightly from Hyper to Hyper-clamp ($P = 0.079$). Similarly CO was significantly elevated from Normo during Hyper ($P = 0.003$) and Hyper-clamp ($P < 0.001$) but did not change from Hyper to Hyper-clamp ($P = 0.231$).

**DISCUSSION**

The primary aim of this study was to assess the regional distribution of CBF during severe passive hyperthermia. It was hypothesized that reductions in PaCO$_2$ would attenuate $\dot{Q}_{VA}$ to a greater extent than $\dot{Q}_{ICA}$, while a hierarchy for thermoregulation would further compromise $\dot{Q}_{ICA}$ via increases in $\dot{Q}_{ECA}$. There were three novel findings. 1) The relative reduction in blood flow during severe passive hyperthermia compared with normothermia was greater in the VA ($-31 \pm 21\%$) than the ICA ($-18 \pm 17\%$). 2) After PETCO$_2$ clamping, blood flow was completely restored to Normo levels in both the ICA and VA (Fig. 3). Moreover, PCAv and MCAv revealed nearly analogous reductions during Hyper ($-18\%$ and $-22\%$ of Normo, respectively) and were also comparably restored following Hyper-clamp ($-3\%$ and $-6\%$ of Normo, respectively; Fig. 2). 3) In contrast to our hypothesis and on the basis of correlational observations, it appears that increases in $\dot{Q}_{ECA}$ did not compromise $\dot{Q}_{ICA}$ (Fig. 6).

**Regional Changes of the Proximal and Distal Vessels**

The reduction in relative flow during hyperthermia was greater in the VA than ICA (Fig. 1). The implications of a greater relative reduction in posterior blood circulation remain speculative. However, cardiac strain and the risk of syncope are likely exacerbated when $\dot{Q}_{VA}$ is compromised, as the VA provides the primary blood supply to the cardiac, vasomotor, and respiratory control centers, i.e., the thalamus and medulla oblongata. It is well known that heat stress increases orthostatic
intolerance and the risk of syncope (5–8). Accordingly, reductions in posterior, rather than anterior, blood flow may better explain the increased risk of syncope during heat stress. Furthermore, although the well-reported lowering of CBF during hyperthermia occurs secondary to the hypocapnia, disproportional reductions in QVA might further expedite hyperthermia-induced hyperventilation by reducing the local thermal washout via blood flow in the hypothalamus (i.e., augmented hypothalamic temperature) (16). The mechanisms underlying this regional reduction in CBF are unclear. In addition, whether appropriate blood redistribution across the circle of Willis and communicating arteries maintains uniform blood flow across the posterior and anterior brain regions in the face of disparate QVA vs. QICA profiles also remains unknown.

Studies of the cerebral vasculature under heat stress have been limited to measurements of MCAv (4, 6, 9, 18, 25) and, to a lesser extent, PCAv (14). To our knowledge, this is the first study to assess volumetric blood flow in proximal cerebral vessels during passive severe hyperthermia. Given that the PCA is inevitably fed from the VA and the MCA is fed from the ICA, one might assume analogous changes in ICA/MCA and, similarly, in VA/PCA. However, the percent reduction in the VA compared with the PCA was ~13% greater from Normo to Hyper (Fig. 1, Table 1). Furthermore, disparate percent reductions during Hyper compared with Normo were found in the VA vs. ICA, but not in the PCA vs. MCA (Fig. 1). These findings are likely attributed to anatomic differences, measurement technique differences, or both. For example, the notion of uniform changes of the proximal vessels (ICA and VA) to the distal vessels (MCA and PCA) is contingent on a constant blood flow relationship between the communicating and additional arteries that network the vessels. Indeed, the vertebrobasilar system in particular has numerous branches (e.g., arterial branches to the cerebellum, medulla, and pons) before it forms the posterior circle of Willis and ramifies into the right and left posterior cerebral arteries (15). Although speculative, this may have apparent relevance during heat stress because of the increased metabolic demand of the thermoregulatory centers; that is, blood flow in the arterial branches that originate between the VA and PCA may be compromised to facilitate blood supply through the circle of Willis and PCA and, therefore, the hypothalamus. Indeed, this may explain the large discrepancy in PCAv compared with QVA. On the other hand, to assume synchronous changes in absolute flow, the measurements of MCAv and PCAv rely on a fixed vessel diameter. As such, it is usually presumed that diameter changes in the MCA and PCA are negligible. However, we recently showed that transcranial Doppler velocity measurements of the distal arteries underestimate cerebrovascular changes compared with volumetric-derived measurements of the proximal arteries during large reductions in PaCO2 (24). This, in concert with open craniotomy data that reveal a significant diameter change of up to 4% in the large cerebral arteries (i.e., MCA) and up to 29% in the smaller M2 segment of the MCA to changes in arterial CO2 (11), offers evidence to caution against the complete dismissal of diameter changes in sonicated MCA and PCA.

**Relationship Between QICA with QECA and cheek CVC**

On the basis of data from Sato et al. (20), we hypothesized that reductions in QICA would in part be influenced by increased QECA. In other words, cutaneous vasodilation in the head, face, and neck and consequent increases in QECA would...
steal $Q_{ICA}$, irrespective of changes in $P_{aCO_2}$. This hypothesis is potentially further supported by data that indicate increases in MCAv at rest and during exercise (13) following selective facial cooling with 4°C water misting (and, therefore, reduction in facial skin blood flow). However, we found that increases in $Q_{ECA}$ were not related to reductions in $Q_{ICA}$. In fact, $Q_{ECA}$ was positively correlated with $Q_{ICA}$ (Fig. 6). It therefore appears that blood flow in the common carotid artery is able to increase appropriately to maintain a high volume of blood to the face cutaneous circulation (a thermoregulatory prerequisite) while preserving $Q_{ICA}$. This is further evidenced by the finding of no changes in $Q_{ECA}$ or cheek CVC, despite restoration of $Q_{ICA}$ to baseline values during Hyper-clamp (Fig. 4). It remains unclear, however, whether similar responses (i.e., proportional increases in common carotid artery blood flow) persist during exercise. Nonetheless, these data lend insight into the work by Miyazawa et al. (13), who found that increases in MCAv following facial cooling during exercise and at rest were not explained by concomitant changes in face skin blood flow. Indeed, the increase in MCAv with selective facial cooling is likely best explained by the concomitant increases in MAP (~5 mmHg in Ref. 13), rather than an extracranial blood steal.

Effects of $P_{aCO_2}$ on CBF During Heat Stress

Clamping $P_{ETCO_2}$ to eucapnic levels during heat stress completely returned $Q_{ICA}$ and $Q_{VA}$ to Normo values (Fig. 3). Similarly, MCAv and PCAv were nearly completely returned to Normo values (94 ± 9% and 97 ± 14%, respectively; Fig. 2). These data indicate that changes in $P_{aCO_2}$ (referenced by $P_{ETCO_2}$) account for the majority, if not all, of the reductions in global CBF. Our MCAv and PCAv data following hyperthermic $P_{ETCO_2}$ restoration are in agreement with previous work by our laboratory (8, 14) but are not a universal finding. For example, some studies have reported that reductions in $P_{ETCO_2}$ account for only 38% (9) to 50% (6) of the drop in MCAv during heat stress of +1.6°C and +1.3°C, respectively. This discrepancy may likely be attributable to methodological differences, e.g., degree of hyperthermia, supine compared with upright body position (9), and protocol used for end-tidal clamping. The remaining drop in MCAv during heat stress in these studies (6, 9) was subsequently attributed to J) peripheral distribution of CO or 2) increased cerebrovascular constriction from increased sympathetic nerve activity (SNA). Evidence for the latter, however, is limited, as the role of SNA in the cerebral vasculature is typically ascribed to a protective mechanism against surges in perfusion pressure (7). Indeed, it is unknown whether increased SNA elicits a cerebral vasoconstriction that compromises CO distribution on the cerebral vasculature while supine.

Limitations

We are limited to the reliability of $P_{ETCO_2}$ for the estimation of $P_{aCO_2}$. However, we previously demonstrated that $P_{ETCO_2}$ accurately predicts direct measurements of $P_{aCO_2}$ throughout graded levels of hyper- and hypocapnia (24). Moreover, we (14, 18) and others (3) have shown that $P_{ETCO_2}$ is an accurate estimation of $P_{aCO_2}$ throughout incremental levels of hyperthermia. We are therefore confident that our $P_{ETCO_2}$ values correctly reflect $P_{aCO_2}$. Because all measurements of $Q_{ICA}$ and $Q_{VA}$ were limited to the right side, we cannot account for potential bilateral differences between the arteries. Indeed, Schoning et al. (21) found an average flow of 20% less in the right VA than the left VA. Regardless of potential differences in contralateral flows, it is unlikely that the reactivity to heat stress and $P_{aCO_2}$ differs between sides (unpublished observations). Therefore, the unilateral measurements of $Q_{VA}$ and $Q_{ICA}$ are likely to have negligible effects or influences on our main conclusions. Lastly, Ganio et al. (10) demonstrated that brachial auscultatory blood pressure (BP) and finger photoplethysmography do not appropriately track intra-arterial systolic BP during severe hyperthermia. Our BP data are limited to the reliability of the finger photoplethysmography and manual brachial cuff measurements. Given this limitation, it is possible that the between-subject variability of CBF during heat stress and particularly following $P_{ETCO_2}$ clamp (Figs. 2 and 3) may in part be due to unique changes in MAP that were not recognized by our measurement technique.

Conclusion and Implications

This study adds three novel findings to the growing body of literature on CBF during heat stress. 1) We have demonstrated that heat stress attenuates blood flow to a greater extent in the posterior than anterior brain region. 2) These data confirm the hierarchy of $P_{aCO_2}$ as the primary regulator of CBF during passive hyperthermia. 3) We provide initial evidence to refute the notion of an extracranial blood steal; i.e., an increased $Q_{ECA}$ and subsequent increased face cutaneous blood flow probably do not compromise $Q_{ICA}$. The implications of reductions in $Q_{VA}$ and, hence, brain stem blood flow as an important mechanism underlying syncope risk with heating warrant future research.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

A.R.B. and P.N.A. are responsible for conception and design of the research; A.R.B., K.J.S., N.C.L., K.W.W., and C.K.W. performed the exper-
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