Muscle metaboreflex and cerebral blood flow regulation in humans: implications for exercise with blood flow restriction

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NEW & NOTEWORTHY

Muscle metaboreflex activation increases cerebral blood flow but only when hyperventilation-mediated reductions in the partial pressure of end-tidal carbon dioxide are prevented. These findings may have implications for individuals practicing exercise training with blood flow restriction and patient populations in whom exaggerated muscle metaboreflex sensitivity has been identified.

INCREASES IN CEREBRAL BLOOD FLOW during exercise are associated with upsurges in brain activation and metabolism within regions such as the motor-sensory cortex and supplementary motor area (23). Several other interacting mechanisms also contribute to the cerebral circulatory response accompanying exercise, including chemical, hemodynamic, autoregulatory and neural factors (42). The stimulation of group III and IV skeletal muscle afferents has also been implicated in the cerebral blood flow responses to exercise, but this remains incompletely understood (19, 20, 27). Group III and IV skeletal muscle afferents are responsive to metabolic (muscle metaboreflex) and mechanical (muscle mechanoreflex) perturbation. Alongside central command (feedforward signals from higher brain centers) and the arterial and cardiopulmonary baroreceptors, group III and IV skeletal muscle afferents play a key role in mediating the cardiovascular adjustments to exercise (18). Early studies established two approaches for the assessment of the muscle metaboreflex (3, 4, 52). The first approach involved blood flow restriction (BFR) to the exercising muscles using proximally placed inflatable occlusion cuffs to create a mismatch between oxygen delivery and demand. This in turn evoked an accelerated accumulation of exercise-induced metabolites and enhanced activation of the metabolically sensitive skeletal muscle afferents. The second approach involved the complete circulatory arrest of the exercising skeletal muscle continued into the recovery period while the muscle is quiescent [i.e., postexercise ischemia (PEI)]. In this manner, metabolically sensitive skeletal muscle afferents may be activated in isolation by the trapping of exercise-induced metabolites within the muscle.

During the isolated activation of the muscle metaboreflex with PEI following handgrip, exercise-induced increases in middle cerebral artery (MCA) mean blood velocity (V̇m) are not sustained and MCAV̇m returns to baseline (28, 46). This is in conflict with reports that the use of local anesthesia to block sensory feedback from group III and IV skeletal muscle afferent fibers abolished the normal increase of MCAV̇m during static and dynamic handgrip (19, 20, 27). We recently observed that such contradictory reports may be attributable to muscle metaboreflex mediated increases in ventilation during PEI, which lead to a confounding reduction in the partial pressure of arterial carbon dioxide [PaCO2; indexed by the partial pressure of end-tidal carbon dioxide (PETCO2)] and a cerebral vasconstriction that prevents a muscle metaboreflex mediated increase in MCAV̇m. Indeed, the clamping of PETCO2 at baseline values during PEI following fatiguing static handgrip resulted in an elevation in MCAV̇m (13).

The aforementioned studies possess limitations with regards to the assessment of cerebral blood flow and mode of muscle metaboreflex activation that we seek to address in the present...
influence of the muscle metaboreflex activation on cerebral blood flow. To circumvent this issue, direct measures of internal carotid artery (ICA) diameter (d), velocity ($V_m$), and thus ICA blood flow ($ICAQ$) can be employed, but to date the contribution of skeletal muscle afferents to the ICAO responses to exercise remain unknown. Second, while the cerebral circulatory responses to muscle metaboreflex activation following exercise with PEI have been investigated, the responses to the enhanced muscle metaboreflex activation during exercise with BFR have not been considered. During PEI the muscle metaboreflex is activated in isolation from central command and skeletal muscle mechanoreflex (11, 16, 17). However, under clinical conditions such as peripheral vascular disease and chronic heart failure, where there is a hypoperfusion of the skeletal muscles, the muscle metaboreflex is not activated in isolation (7, 9, 24). Increasing metaboreflex signaling during exercise with BFR at the same time that central command and mechanoreflex are also activated would potentially provide a more realistic simulation of this paradigm. Furthermore, exercise with BFR is becoming an increasingly popular athletic training practice due to the potential for gains in muscle strength and endurance to occur without high-intensity training (54, 60). Spranger et al. (57) recently raised a “call for concern” regarding the practice of exercise with BFR on the basis of the exaggerated increases in blood pressure and the associated risk of cardiovascular and cerebrovascular insult. At present the effects of BFR exercise on cerebral blood flow are unknown.

Given this background, we sought to determine 1) the influence of the muscle metaboreflex activation on cerebral blood flow, 2) if changes in $PETCO_2$ are a key determinant of the cerebral blood flow response to muscle metaboreflex activation, and 3) whether the mode of muscle metaboreflex activation (i.e., during vs. following exercise) influences the corresponding cerebral blood flow response. To achieve this $MCAVm$ and $ICAQ$ were measured during exercise with BFR to enhance muscle metaboreflex activation and during isolated activation of the muscle metaboreflex with PEI. Trials were conducted where $PETCO_2$ was permitted to fluctuate spontaneously and where $PETCO_2$ was clamped at baseline values. We hypothesized that muscle metaboreflex activation would evoke an increase in $MCAVm$ and $ICAQ$ only when $PETCO_2$ was clamped at baseline.

**METHODS**

The study was approved by the Health, Safety and Ethics Committee of the School of Sport, Exercise and Rehabilitation Science at the University of Birmingham and was undertaken according to Declaration of Helsinki. Eleven male participants were recruited (age 25 ± 4 yr; height 180 ± 1 cm; weight 71 ± 7 kg; mean ± SD). After receiving a detailed verbal and written explanation of the experimental protocol, all participants signed the consent form. All participants were free of any cardiovascular, respiratory, neurological, renal, or metabolic diseases and were not using any prescription or over-the-counter medication. Abstinence of caffeine beverages, alcohol, or exercise was requested 24 h before experimental sessions. The room temperature was kept constant at 20–22°C, and external stimuli were kept to a minimum.

**Measurements**

Heart rate (HR) was monitored using lead II electrocardiogram and blood pressure was measured beat-to-beat from the middle finger of the right hand (Finometer Pro; Finapres Medical Systems, Amhlem, The Netherlands). Mean arterial pressure (MAP) was calculated offline by the integration of the arterial blood pressure waveform over a cardiac cycle. Resting blood pressure was verified by brachial arterial blood pressure measurement made from the left arm using an automated sphygmomanometer (Tango++; SunTech Medical). $MCAVm$ and $ICAQ$ were measured from the left side of the neck with duplex Doppler ultrasound (Logiq; GE Medical Systems) using a 10-MHz multifrequency linear-array transducer with a constant insonation angle of 60° relative to the skin. ICA measurements were performed 1 to 1.5 cm distal to the carotid bifurcation while the subject’s chin was slightly elevated. To measure the $ICAQ$, the brightness mode was used in a longitudinal section, the systolic and diastolic diameters were measured over 10 cardiac cycles, and the mean diameter was calculated as follows: mean diameter (cm) = \[
\frac{[\text{systolic diameter} \times 1/3] + [\text{diastolic diameter} \times 2/3]}{2}
\]. The Doppler velocity spectrum was analyzed using the pulsed wave mode and the time-averaged mean flow velocity obtained over 10 cardiac cycles. The internal carotid blood flow ($ICAQ$; ml/min) was calculated as $[MCAVm \times \pi \times (\text{diameter}/2)^2] \times 60$. ICA conductance ($ICAQ$; ml/min $\times$ mmHg$^{-1}$) was calculated as $ICAQ$/MAP.

$MCAVm$ was measured with a 2-MHz pulse wave transcranial Doppler ultrasound system (Doppler Box X; Compumedics, Singen, Germany). The MCA was insonated via the temporal window above the zygomatic arch on the left side of the head. After a satisfactory scan was found, the probe was fixed in place with a headband and ultrasonic gel. The MCA vascular conductance index ($MCAQ$/MAP) was calculated as $MCAVm$/$MAP$.

Participants wore a mouthpiece and nose-clip to permit breath-by-breath determination of min ventilation ($V_{\text{E}}$) via a turbine volume transducer (VMM400; Interface Associates, Aliso Viejo, CA). The end-tidal partial pressures of $O_2$ and $CO_2$ were determined using rapid response gas analyzers (Moxus Modular; AEI Technologies, Pittsburg, PA). Analog data were digitally converted at 1 kHz and stored on a PC for offline analysis (Powerlab and LabChart Pro; ADInstruments, Dunedin, New Zealand).

**Experimental Protocol**

An initial familiarization session was first conducted where the participants experienced all the experimental methods and protocols. The experimental protocol was subsequently conducted over two laboratory visits separated by 3–7 days with the order of protocol 1 and 2 (day 1 or 2) decided according to a coin toss. For each protocol, two trials were performed. In one trial, $PETCO_2$ fluctuated normally while subjects breathed medical grade air, and in another trial $PETCO_2$ was clamped at ~1 mmHg above the resting partial pressure. Trials were counterbalanced and separated by a minimum of 20 min. $PETCO_2$ clamping was undertaken using a dynamic end-tidal forcing system, which uses a prediction-correction system, whereby $PETCO_2$ is controlled at the desired level by altering the composition of the inspired gas on a breath-by-breath basis (50).

**Protocol 1: leg cycling with BFR.** After instrumentation participants sat quietly in a semirecumbent cycle ergometer and respiration was monitored for 10 min to determine the normal $PETCO_2$. Participants were then instructed to commence cycling exercise at 60 rpm. During the first ~3 to 5 min the workload was adjusted to reach a target HR of 120 beats/min after which ~10 min of steady-state cycling exercise was performed (Ex1). Following this period, bilateral thigh cuffs were inflated to 130 mmHg (Rapid Cuff Inflation System E20 AG101; Hokanson, Bellevue, WA) to partially restrict blood flow to exercising muscles and engage the muscle metaboreflex (BFR). The thigh cuffs were deflated after 3 min and a further 3 min of steady-state cycling exercise was performed under free-flow conditions (Ex2). ICA assessments were not carried out during Ex2.
perceived exertion (RPE) were obtained using the 1–10 Borg scale (12) at the end of the Ex1, BFR, and Ex2 periods. Mean HR, BP, respiratory, and MCA\textsubscript{Vm} data were obtained on a beat-to-beat basis and averages calculated at rest (3 min), Ex1 (last 1 min), BFR (last 1 min), and Ex2 (last 1 min). Ultrasound images for calculation of ICA\textsubscript{Q} were obtained during the last 1 min of rest, last 1 min of Ex1, and last 1 min of leg cycling with BFR. Measurements were then pooled to provide a mean value for each experimental phase.

Protocol 2: leg cycling with PEI. As described above, following a 10-min rest period during which the normal PET\textsubscript{CO\textsubscript{2}} was determined, participants undertook cycling exercise on a semirecumbent cycle ergometer (60 rpm). After a ∼3- to 5-min period during which the workload was adjusted to reach the target HR of 120 beats/min participants undertook steady-state cycling exercise for 10 min (Ex). Fifteen seconds before the end of the exercise, bilateral thigh cuffs were inflated to 300 mmHg to occlude the blood flow to the exercising muscles and remained inflated for 3 min to isolate the activation of the muscle metaboreflex (PEI). RPE was obtained after 5 min of steady-state cycling exercise. Mean HR, BP, respiratory, and MCA\textsubscript{Vm} data were obtained on a beat-to-beat basis and averages calculated at rest (3 min), Ex (last 1 min), and PEI (last 1 min). Ultrasound images for calculation of ICA\textsubscript{Q} were obtained during last 1 min of rest, last 1 min of Ex, and last 1 min of PEI. Measurements were then pooled to provide a mean value for each experimental phase.

Data and statistical analysis. Values are reported as means ± SE. Main effects of experimental phase (Rest, Ex, and PEI or Rest, Ex1, BFR, and Ex2), trial (control, PET\textsubscript{CO\textsubscript{2}} clamp) and interaction (phase × trial) were made using two-way repeated-measures ANOVA followed by Student-Newman-Keuls post hoc test. Between trial comparisons of exercise workload were made using Student t-tests. Statistical significance was set to $P < 0.05$. Analyses were conducted using SigmaPlot 12.5 (Systat Software, London, UK).

RESULTS

Leg Cycling with BFR

The exercise workload was not different between trials (control: $90 ± 9$ W and PET\textsubscript{CO\textsubscript{2}} clamp trial: $85 ± 9$ W, $P > 0.05$). In the control trial, PET\textsubscript{CO\textsubscript{2}} was slightly increased from rest during leg cycling (Ex1: $Δ2.2 ± 0.3$ mmHg, $P < 0.05$), decreased with BFR ($Δ−4.8 ± 0.9$ mmHg, $P < 0.05$), and returned to resting values upon the cessation of BFR (Ex2: $Δ0.8 ± 0.5$ mmHg, $P > 0.05$ vs. Rest; Fig. 1). By design, in the clamp trial PET\textsubscript{CO\textsubscript{2}} remained unchanged from the rest throughout all experimental phases. Leg cycling evoked similar increases in MCA\textsubscript{Vm} during the control and PET\textsubscript{CO\textsubscript{2}} clamp trials ($P < 0.05$, Rest vs. Ex1; Fig. 1). In the control trial, no change in MCA\textsubscript{Vm} was observed during exercise with BFR, whereas in the PET\textsubscript{CO\textsubscript{2}} clamp trial MCA\textsubscript{Vm} was increased ($P < 0.05$ vs. Rest, Ex1, and between conditions). In both trials, MCA\textsubscript{Vm} was not different during leg cycling before and after BFR ($P > 0.05$, Ex1 vs. Ex2). MCA\textsubscript{CVCi} was unchanged from rest during leg cycling ($P > 0.05$, Ex1 vs. Rest, Ex2 vs. Rest) but was decreased with BFR ($P < 0.05$ vs. Rest and Ex1; Table 1). The magnitude of this decrease was greater in the control trial than in the PET\textsubscript{CO\textsubscript{2}} clamp trial. ICA\textsubscript{Q} was unchanged from rest to leg cycling (Ex1) in both trials but was increased with BFR in the PET\textsubscript{CO\textsubscript{2}} clamp trial.

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*AJP-Heart Circ Physiol* • doi:10.1152/ajpheart.00894.2015 • www.ajpheart.org

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Fig. 1. Cardiorespiratory and cerebrovascular responses to leg cycling under free-flow conditions [exercise 1 and 2 (Ex1 and Ex2)] and with blood flow restriction (BFR). A: partial pressure of end-tidal carbon dioxide (PET\textsubscript{CO\textsubscript{2}}). B: middle cerebral artery blood velocity (MCA\textsubscript{Vm}). C: internal carotid artery blood flow (ICA\textsubscript{Q}). D: mean arterial pressure (MAP). Values are mean ± SE. *$P < 0.05$ vs. Rest; †$P < 0.05$ vs. Ex1; ‡$P < 0.05$ vs. control.
(P < 0.05 vs. Rest and between trials; Fig. 1), secondary to an increase in ICAM, ICAQ was unchanged throughout all experimental phases in both trials (Table 1). ICACVC was not different between trials and was similarly decreased from rest during leg cycling (P < 0.05, Rest vs. Ex1) and then further decreased during leg cycling with BFR (P < 0.05, Ex1 vs. Rest) in both trials.

HR was not different between the control and PETCO2 clamp trials at any experimental phase (Table 1). MAP was slightly higher in the PETCO2 clamp trial (Fig. 1). Leg cycling evoked increases in MAP and HR in both trials (P < 0.05, Ex1 vs. Rest), which were further increased during BFR (P < 0.05 vs. Ex1). During leg cycling following BFR, MAP and HR returned to values observed during leg cycling before BFR (P > 0.05, Ex1 vs. Ex2). RPE was not different between the control trial [Ex1: median, 4 (interquartile range, 4–5); BFR: 8 (7–8); and Ex2 5 (4–6); P < 0.05] and the PETCO2 clamp trial [Ex1: 4 (3–6); BFR: 8, (7–8); and Ex2: 5 (4–7); P < 0.05 by Wilcoxon signed-rank test].

**Leg Cycling with PEI**

Exercise workload was not different between trials (control: 89 ± 9 W and PETCO2 clamp trial: 89 ± 9 W, P > 0.05). In the control trial, PETCO2 was unchanged from rest during leg cycling and decreased with PEI (Δ−7 ± 1 mmHg, P < 0.05; Fig. 2), but by design, in the PETCO2, clamp trial it remained not different from rest throughout all experimental phases. In both the control and PETCO2 clamp trials, MCAVm increased from rest during leg cycling (P ≤ 0.05; Fig. 2). During PEI, in the control trial MCAVm was not different from rest (P > 0.05), whereas in the PETCO2 clamp trial MCAVm remained elevated (P < 0.05 vs. rest and between trials). In the control trial, MCAVCVC was not different from rest during leg cycling and was decreased from rest during PEI (P < 0.05 vs. Rest and between trials; Table 2). MCAVCVC was not different from rest throughout PETCO2 clamp trial (P > 0.05; Table 2). ICAQ was not different from rest during leg cycling in both control and PETCO2 clamp trials (P > 0.05; Fig. 2). However, during PEI, ICAQ was higher in the PETCO2 clamp trial than in the control trial (P < 0.05; Fig. 2). ICAQ was not different throughout all experimental phases in both trials (Table 2). ICACVC was greater in the PETCO2 clamp trial but decreased similarly from rest during leg cycling (P < 0.05 vs. Rest) in both trials. During PEI, ICACVC remained at levels sustained during exercise (P < 0.05 vs. Rest; P > 0.05 vs. Ex) in both trials. MAP and HR (Table 2; Fig. 2) were not different between the control and PETCO2 clamp trials at any experimental phase. Leg cycling evoked increases in MAP and HR in both trials (P < 0.05 vs. rest). In both trials, MAP was further increased with PEI from the level observed during leg cycling (P < 0.05 vs. Rest and Ex), whereas HR fell but remained above resting levels (P < 0.05 vs. Rest and Ex).

RPE were not different during leg cycling in the control [median, 5 (interquartile range, 4–7)] and the PETCO2 clamp trials [5 (4–6)] (Wilcoxon signed-rank test).

**DISCUSSION**

The major novel finding of this study is that the muscle metaboreflex failed to elevate either MCAVm or ICAQ, when engaged by leg cycling with BFR or isolated during PEI following leg cycling under control conditions. However, a significant reduction in PETCO2, secondary to an increase in V̇E, was induced by muscle metaboreflex activation with either BFR or PEI. Accordingly, when PETCO2 was clamped at resting tense.

**Table 1. Cardiorespiratory and cerebrovascular responses to leg cycling under free-flow conditions and with BFR**

<table>
<thead>
<tr>
<th>Value</th>
<th>Experimental Phase</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇E, l/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9 ± 1</td>
<td>35 ± 2*</td>
</tr>
<tr>
<td>PETCO2 clamp</td>
<td>11 ± 2</td>
<td>37 ± 3*</td>
</tr>
</tbody>
</table>
| MCAVCVCi, cm·s
| Control                      | 0.66 ± 0.06        | 0.65 ± 0.05 |
| PETCO2 clamp                 | 0.67 ± 0.06        | 0.63 ± 0.04 |
| ICACVCi, cm/s                | Control            | 28 ± 1      |
| PETCO2 clamp                 | 28 ± 1             | 29 ± 2*     |
| ICAd, cm                     | Control            | 0.46 ± 0.01 |
| PETCO2 clamp                 | 0.45 ± 0.01        | 0.45 ± 0.01 |
| ICAVm, cm/s                  | Control            | 3.3 ± 0.2   |
| PETCO2 clamp                 | 3.2 ± 0.2          | 2.9 ± 0.2   |
| SBP, mmHg                    | Control            | 117 ± 2     |
| PETCO2 clamp                 | 115 ± 3            | 153 ± 7     |
| DBP, mmHg                    | Control            | 67 ± 3      |
| PETCO2 clamp                 | 70 ± 2             | 72 ± 3      |
| HR, beats/min                | Control            | 64 ± 3      |
| PETCO2 clamp                 | 65 ± 3             | 121 ± 1     |

Values are means ± SE. Ex, exercise; BFR, blood flow restriction. V̇E, ventilation; PETCO2, partial pressure of end-tidal carbon dioxide; MCAVCVCi, middle cerebral artery conductance; ICAM, internal carotid artery mean velocity; ICAd, internal carotid artery diameter; ICACVCi, internal carotid artery conductance; SBP, systolic blood pressure; MAP, mean arterial pressure; HR, heart rate. *P < 0.05 vs. Rest; †P < 0.05 vs. Ex1; ‡P < 0.05 vs. control.
levels muscle metaboreflex-mediated increases in MCA\textsubscript{Vm} and ICA\textsubscript{Q} were revealed during both BFR and PEI. Thus, in accordance with our original hypothesis, these findings demonstrate that when hyperventilation-related decreases in PET\textsubscript{CO\textsubscript{2}} are prevented the muscle metaboreflex increases cerebral blood flow and this occurs irrespective of the mode of muscle metaboreflex activation.

A potential explanation why exercise with BFR, or indeed PEI, does not increase cerebral perfusion may be that the activation of metabolically sensitive skeletal muscle afferents evokes an increase in ventilation (5), which leads to a confounding reduction in PaCO\textsubscript{2} (indexed by PET\textsubscript{CO\textsubscript{2}}). The contribution of group III and IV skeletal muscle afferents to the control of breathing remains controversial, nevertheless in agreement with several previous reports we observed an increase in V\textsubscript{E} during muscle metaboreflex activation (1, 13, 15, 44) and a reduction in PET\textsubscript{CO\textsubscript{2}}. CO\textsubscript{2} is a powerful dilator of the cerebral vasculature (31) and decreases in PaCO\textsubscript{2} lead to cerebral vasoconstriction (2). In the present study, the clamping of PET\textsubscript{CO\textsubscript{2}} at resting levels unmasked a muscle metaboreflex-mediated increase in MCA\textsubscript{Vm} during leg cycling with BFR and during PEI following leg cycling. Furthermore, the degree of cerebral vasoconstriction (i.e., the magnitude of the reduction in MCA\textsubscript{CVC}) during PEI and exercise with BFR was attenuated in the PET\textsubscript{CO\textsubscript{2}} clamp trial, although a similar effect was not observed for ICA\textsubscript{CVC}. These observations are in concordance with our earlier report that PEI following fatiguing ischemic handgrip exercise only increases MCA\textsubscript{Vm} when PET\textsubscript{CO\textsubscript{2}} is clamped at resting levels (13). Such observations may help to explain why others have not shown MCA\textsubscript{Vm} to be elevated during PEI. Indeed, Jorgensen et al. (28) also reported that PaCO\textsubscript{2} was decreased below resting levels during PEI following cycling exercise. In agreement with Friedman et al. (19, 20) and Jorgensen et al. (29), who demonstrated that pharmacological blockade of sensory feedback from skeletal muscle afferents diminished the increase in cerebral perfusion during exercise, the results of the present study support a role for the muscle metaboreflex in the regulation of cerebral blood flow during exercise. This may be attributable to the pairing of local neuronal activation and perfusion (i.e., neural-vascular coupling), that is to say cerebral flow increases to increase O\textsubscript{2} delivery in accordance with increased metabolic. Studies employing advanced imaging techniques have shown that isolated metaboreflex stimulation (PEI) evokes increased activity in discrete brain regions (e.g., medial and lateral dorsal medulla, contralateral insula, and primary and secondary somatosensory cortex) (53). It is acknowledged that part of the cerebrovascular responses to PEI arises on account of the discomfort associated with this maneuver (35). In the present study we are not able to quantify the contribution of local discomfort to the cerebrovascular responses to PEI and BFR, but note that without the clamping of PET\textsubscript{CO\textsubscript{2}} at resting levels no changes in cerebral perfusion were observed. As such, the combination of PET\textsubscript{CO\textsubscript{2}} clamping and brain imaging modalities may provide additional insights into the effects of muscle metaboreflex activation on regional brain activation. The influence of exer-

![Fig. 2. Cardiorespiratory and cerebrovascular responses to leg cycling and postexercise ischemia (PEI). A: PET\textsubscript{CO\textsubscript{2}}. B: MCA\textsubscript{Vm}. C: ICA\textsubscript{Q}. D: MAP. Values are mean ± SE. *P < 0.05 vs. Rest; †*P < 0.05 vs. Ex; ‡*P < 0.05 vs. control.](http://ajpheart.physiology.org/).

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**AJP-Heart Circ Physiol** • doi:10.1152/ajpheart.00894.2015 • www.ajpheart.org

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**CEREBRAL BLOOD FLOW IN DYNAMIC EXERCISE**

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**Fig. 2.** Cardiorespiratory and cerebrovascular responses to leg cycling and postexercise ischemia (PEI). A: PETCO2. B: MCAVm. C: ICAQ. D: MAP. Values are mean ± SE. *P < 0.05 vs. Rest; †*P < 0.05 vs. Ex; ‡*P < 0.05 vs. control.
Exercise-induced increases of MAP on cerebral blood flow is somewhat controversial. The observation that during PEI, MCAVm remains at resting levels while MAP is elevated is part of the reason why the direct influence of blood pressure on the exercise-induced increase of cerebral perfusion has on occasion been discounted (26, 47, 55). However, when considering the effects of MAP on cerebral perfusion during exercise the potentially confounding effects of changes in PETCO2 should be considered. With PaCO2 controlled, MCAVm changes by ~0.8% per mmHg change in MAP within the so-called “autoregulatory range” (34). We observed that BFR evoked a 44-mmHg increase from rest in MAP and a 26% increase in MCAVm, while during PEI, MAP was elevated by 29 mmHg and MCAVm elevated by 17%. As such, increases in MAP may potentially confounding effects of changes in PETCO2 should be taken. As indicated above, this has applied relevance to those undertaking such practices to induce athletic enhancements but also patient populations in whom muscle metaboreflex activation on cerebral blood flow in humans. In addition to use of PEI to assess the effect of isolated skeletal muscle metaboreflex activation on cerebral blood flow, exercise with BFR was undertaken. As indicated above, this has applied relevance to those undertaking such practices to induce athletic enhancements but also patient populations in whom muscle metaboreflex activation may be heightened during exercise as a consequence of skeletal muscle underperfusion (e.g., chronic heart failure, peripheral vascular disease). Despite exercise with BFR and PEI evoking similar reductions from rest in PETCO2 (Δ−2.6 and Δ−5.0 mmHg for BFR and PEI, respectively), MCAVm was significantly elevated from rest during exercise with BFR such that it was similar to that observed during free-flow exercise, whereas MCAVm was not different from rest during PEI. Such findings may be explained by a greater elevations in cardiac output and the concomitant activation of central command during exercise with BFR compared with PEI (36). Nevertheless, independent of the mode of muscle metaboreflex activation, when muscle metaboreflex-mediated reductions in PETCO2 were prevented, increases in cerebral blood flow were observed.

Regular exercise with BFR (e.g., Kaatsu training) has been reported to enhance cardiorespiratory fitness (60) and skeletal muscle mass in healthy young and older individuals (32, 33, 63, 64) and patients (56). It is believed that exercise training with BFR exaggerates the normal accumulation of metabolites within the active skeletal muscle, thus promoting muscle...
growth and force-generating capacity without the need for high-intensity training (21, 22, 43, 62). In a recent article, Spranger et al. (57) raised a “call for concern” about this practice on the basis that it engages the muscle metaboreflex, which is known to powerfully increase sympathetic nerve activity to the heart and peripheral vasculature and can inhibit cardiac parasympathetic activity (18). As a consequence of these autonomic alterations, exercise with BFR evokes pronounced increases in peripheral vascular resistance, cardiac output, and blood pressure (59). This could be of particular concern to patients in whom exaggerated skeletal muscle afferent sensitivity has been identified (e.g., hypertension, chronic heart failure, chronic obstructive pulmonary disease, type 2 diabetes) (7, 9, 24, 25, 45) and could raise the risk of cardiovascular and cerebrovascular events (57). Indeed, in the present study of healthy individuals, exercise with BFR raised MAP by ~27 mmHg and heart rate by ~22 beats/min from levels established during a preceding period of leg cycling under free-flow conditions. However, despite such hemodynamic, alterations cerebral perfusion was unchanged during exercise with BFR, thus calling into question the contention that exercise with BFR may increase the risk of cerebrovascular injury as a consequence of a large local hyperemic response. In fact we observed that exercise with BFR evoked a lower than expected cerebral blood flow, on account of the coincident hyperventilation and hypocapnia linked cerebral vasoconstriction. During high intensity dynamic exercise, particularly when combined with hypoxia, a reduced cerebral oxygenation has been postulated as a fatigue mechanism (8, 40, 55). As such, in patients who exhibit exaggerated skeletal muscle afferent feedback and an excessive hyperventilatory response to exercise (e.g., chronic heart failure, congestive obstructive pulmonary disease) (7, 9, 58), the associated reduction in PaCO2 and cerebral vasoconstriction may precipitate exercise intolerance via a central mechanism (41, 48). Future studies utilizing arterial-internal jugular venous blood sampling are required, particularly in chronic disease populations, to better understand how cerebral metabolism (e.g., O2 delivery, cerebral metabolic rate for O2, fractional O2 extraction) is affected by the activation of skeletal muscle afferents while PETCO2 is clamped at baseline levels.

There are several limitations on the present study: PETCO2 was used as a surrogate for PaCO2, and although during exercise PETCO2 could have overestimated PaCO2 (49), there is a strong correlation between PETCO2 and PaCO2 across all levels of physiologic dead space (37). We used external thigh cuffs to decrease/occlude blood flow to the legs, and although no direct measures of the leg blood flow or local metabolite concentrations were possible, we observed marked increases in MAP during this manoeuvre indicative of muscle metaboreflex activation, which strongly suggest that reductions in blood flow were successfully induced. BFR may have increased in central command, which could have contributed to the increase of cerebral blood flow (6). Indeed, increases in RPE, historically related to central command (38, 39), were noted during leg cycling with BFR. Human studies are needed in which the cardiovasculard and cerebrovascular responses to the application of BFR during leg cycling are evaluated before and after pharmacological inhibition of feedback from group III and IV skeletal muscle afferents (e.g., intrathecal fentanyl) to test the contribution of central command to this manoeuvre. Automatic edge-tracking software was not used in the present study and this may be a limitation (61), although intraclass correlations between repeated rest and exercise measures made during a study visit were high (i.e., >0.8). Finally, we have only evaluated the effect of skeletal muscle afferent feedback with BFR during moderate cycling exercise, and care should be taken when directly extrapolating our findings to other exercise intensities and modalities. This is important in light of the concept that athletes may utilize BFR training to try to obtain a desirable training effects but at a lower exercise intensity (21, 22, 43, 62).

In conclusion, the findings of the present study indicate that only when hyperventilation-related decreases in PETCO2, are prevented does the activation of metabolically sensitive skeletal muscle afferent fibers evoke an increase in cerebral blood flow, irrespective of the mode of activation (i.e., during or following Ex).

ACKNOWLEDGMENTS

We appreciate the time and effort expended by the participants in this study. We also thank Joel Zvick and Prokopios Barmparigos for technical support.

GRANTS

This study was supported by Coordination for the Improvement of Higher Education Personnel (CAPES, Brazil) through the program Science without Borders and CNPq (456640/2014-2).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: E.P., G.M.B., and I.D.B. performed experiments; E.P. analyzed data; E.P., L.C.V., and J.P.F. interpreted results of experiments; E.P. prepared figures; E.P. drafted manuscript; E.P., G.M.B., I.D.B., A.C.L.N., L.C.V., and J.P.F. approved final version of manuscript; I.D.B., A.C.L.N., L.C.V., and J.P.F. edited and revised manuscript; J.P.F. conception and design of research.

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