

Heterogeneous Regulation of Brain Blood Flow during Low-Intensity Resistance Exercise

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ABSTRACT

HIRASAWA, A., K. SATO, M. YONEYA, T. SADAMOTO, D. M. BAILEY, and S. OGOH. Heterogeneous Regulation of Brain Blood Flow during Low-Intensity Resistance Exercise. *Med. Sci. Sports Exerc.*, Vol. 48, No. 9, pp. 1829–1834, 2016. **Purpose:** The present study was designed to explore to what extent low-intensity resistance exercise-induced acute hypertension influences intracranial cerebral perfusion. **Methods:** Twelve healthy participants performed one-legged static knee extension exercise at 30% maximal voluntary contraction for 2 min. Blood flow to the internal and external carotid arteries (ICA/ECA) were evaluated by duplex ultrasonography. **Results:** ICA blood flow increased and reached a plateau before stabilizing 60 s into exercise despite continued increases in cardiac output and arterial blood pressure. ICA conductance significantly decreased by $-14.4\% \pm 13.8\%$ at the end of exercise ($P < 0.01$), whereas in contrast, ECA blood flow ($P < 0.01$) and conductance were shown to increase ($P < 0.05$). **Conclusions:** The present findings demonstrate that low-intensity resistance exercise was associated with vasodilation of the ECA that was accompanied by vasoconstriction of the ICA. We propose that the heterogeneity and reciprocal regulation of intracranial cerebral blood flow reflect an adaptive neuroprotective mechanism that serves to protect the brain and associated vasculature against the structural damage associated with resistance exercise-induced hypertension. **Key Words:** ARTERIAL BLOOD PRESSURE, HYPERTENSION, SKIN BLOOD FLOW, HUMANS, DOPPLER ULTRASOUND

Cerebral autoregulation (CA) is a homeostatic mechanism that serves to maintain cerebral blood flow (CBF) constant over a wide range of perfusion pressures and is subject to myogenic, neurogenic, and metabolic control (17). Effective CA is important given the reliance of the human brain on oxygen and glucose to support the metabolic demands of neuronal activity and the need to protect brain tissue from the potentially damaging effects of hypo-/hyperperfusion.

It is well known that resistance exercise induces acute surges in arterial blood pressure (ABP). Indeed, heavy resistance exercise such as weight lifting has the potential to increase ABP supraphysiologically in excess of 480/350 mm Hg (10). The upper limit of CA is estimated to be 150 mm Hg (9), or

indeed lower (22,24), and dynamic CA has been shown to be unchanged during resistance exercise (14). Therefore, resistance exercise-induced acute hypertension should affect CBF directly by causing cerebral hyperperfusion. In support, it has been reported that heavy resistance exercise has the capacity to cause intracerebral bleeding subsequent to cerebral overperfusion (5,6,20). In contrast, Dickerman et al. (2) reported that middle cerebral artery (MCA) mean blood flow velocity was unchanged or even attenuated in elite power athletes during maximal weight lifting. Resistance exercise induces a large increase in sympathetic nerve activity with acute hypertension, and this may provide some protection against cerebral hyperperfusion. However, to what extent subtle, physiological increases in mean arterial pressure (MAP) during resistance exercise influence cerebral perfusion remains to be resolved.

The common carotid artery (CCA) divides into the external carotid artery (ECA), which supplies blood to the face, scalp, skull, and cranium wall, and the internal carotid artery (ICA), which supplies blood to the majority of the cerebral cortex. Recently, Ogoh et al. (13) reported the response of both ICA and ECA blood flows to acute hypotension after thigh cuff inflation–deflation. During acute hypotension, ICA blood flow was shown to initially decrease before quickly returning to baseline levels, whereas the reduction in ECA blood flow persisted. These findings suggest that preserved reduction in ECA blood flow likely prevents further decrease in

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intracranial blood flow during acute hypotension, highlighting its potential neuroprotective role in CBF regulation. In addition, our previous study has further demonstrated the different blood flow responses to dynamic exercise between these arteries, highlighting the heterogeneous nature of peripheral vasomotion (19). Exercise-induced differential perfusion may thus represent a neuroprotective mechanism that serves to prevent exercise-induced cerebral hyperperfusion and consequent blood–brain barrier disruption and complications potentially associated with vasogenic edema.

To what extent the arterial hypertension associated with heavy resistance (as opposed to dynamic aerobic or hypotensive exercise interventions) influences the spatial distribution of blood flow to the intracranial arterial bed remains unknown. In light of these observations, the present study was designed to explore to what extent subtle (i.e., physiological) resistance exercise-induced acute hypertension influences intracranial cerebral perfusion. Because the onset of low-intensity resistance exercise induces acute hypertension without any changes in core temperature and hyperventilation, this paradigm is free of potential contaminants that have equal capacity to influence CBF regulation. We hypothesized that low-intensity resistance exercise would be associated with reciprocal changes in ECA and ICA blood flow to reflect compensatory (ECA) vasodilation and (ICA) vasoconstriction that collectively serve to prevent intracranial cerebral overperfusion.

METHODS

Participants. Twelve healthy participants (four men and eight women) age 21 ± 2 yr (mean \pm SD), 165 ± 7 cm tall with a body mass of 58 ± 8 kg, volunteered for the study. All participants were free from any overt cardiovascular, pulmonary, metabolic, or neurological disease and were not taking any medication known to influence cerebral hemodynamic function. All experimental procedures and protocols conformed to the Declaration of Helsinki and were approved by the Ethics Committee of the Japan Women's College of Physical Education (no. 2014-13). Each participant provided written informed consent; after that, all potential risks and procedures were explained. Participants were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity including alcohol for at least 24 h before experimental sessions. All participants were familiarized with the equipment and procedures before any experimental session.

Experimental protocols. After arrival at the laboratory and after 30 min of seated rest, each participant performed two maximal static one-knee extensions of the right leg to determine their maximal voluntary contraction, taken as the highest (of the two) force generated. Exercise was performed at 30% maximal voluntary contraction for 2 min in a seated position with the knee joint angle set at 90° . During exercise, participants adjusted the achieved workload using visual feedback.

CBF. The right ECA and left ICA blood flow were measured simultaneously at baseline and during exercise by two separate trained investigators using two separate color-coded ultrasound systems (Vivid-i; GE Healthcare, Tokyo, Japan) equipped with 8-MHz linear transducers. ICA and ECA blood flow measurements were performed approximately 1.0 to 1.5 cm distal to the carotid bifurcation while the participant's chin was slightly elevated. In the present study, we measured the carotid blood flow instead of CBF. However, it has been established that changes in ICA/ECA blood flow or conductance are reliable indices of peripheral vasomotion within the ICA/ECA vascular beds,

For ICA and ECA blood flow measurements, we first used the brightness mode to measure the mean vessel diameter of each vessel in a longitudinal section, and the Doppler velocity spectrum was subsequently identified by the pulsed wave mode. Both systolic and diastolic diameters were measured, and the mean diameter (cm) was calculated in relation to the blood pressure curve: mean diameter = [(systolic diameter \times 1/3)] + [(diastolic diameter \times 2/3)]. The time-averaged mean flow velocity obtained in the pulsed wave mode was defined as the mean blood flow velocity ($\text{m}\cdot\text{s}^{-1}$). Blood flow velocity measurements were calculated as the average of approximately 10–20 cardiac cycles to eliminate the effects of respiration. When making blood flow velocity measurements, care was taken to ensure that the probe position was stable, that the insonation angle did not vary (approximately 60° in most cases), and that the sample volume was positioned in the center of the vessel and adjusted to cover the width of the vessel diameter. Finally, blood flow was calculated by multiplying the cross-sectional area [$\pi \times (\text{mean diameter}/2)^2$] by the mean blood flow velocity: blood flow = mean blood flow velocity \times area \times 60 ($\text{mL}\cdot\text{min}^{-1}$). In addition, the left MCA mean blood flow velocity (MCA V_{mean}) was measured using transcranial Doppler ultrasound (Multidop T; DWL, Sipplingen, Germany). A 2-MHz Doppler probe was adjusted over the temporal window of the left MCA until an optical signal was identified. The probe was then fixed and held in place using a headband strap.

Cardiorespiratory measures. HR was continuously monitored using a three-lead ECG (bedside monitor BMS-2400; Nihon Kohden, Japan). Systolic and diastolic blood pressure (SBP and DBP, respectively) and MAP were monitored continuously by finger photoplethysmography from the middle or index finger of the left hand (Finometer; Finapres Medical Systems BV, Amsterdam, The Netherlands). In addition, cardiac output (CO) was determined from the blood pressure waveform using Modelflow software, which incorporates gender, age, height, and weight (Beat Scope 1.1, Finapres Medical Systems BV); this method provides a reliable estimate of changes in stroke volume and CO during exercise in healthy young humans (21). Furthermore, relative changes in forehead skin blood flow (SkBF) were measured by laser Doppler flowmetry using an integrating flow probe (ALF21; Advance, Japan). Respiratory variables were sampled

breath by breath, and end-tidal partial pressure of CO₂ (P_{ET}CO₂) and ventilation (\dot{V}_E) were measured via capnography (AE-310S; Minato Medical Science, Osaka, Japan).

Data processing and statistics. With the exception of the Doppler and respiratory measurements, all data were sampled at 1 kHz using an analog-to-digital converter (PowerLab; ADInstruments, Milford, MA) interfaced with a computer for offline analysis. Doppler and respiratory variables during exercise were averaged at baseline and serially during exercise (30, 60, 90, and 120 s). The ratio of blood flow to MAP in each cerebral artery was used as an index of peripheral vascular conductance. To estimate the forehead cutaneous vascular conductance index, SkBF was divided by MAP. CCA blood flow was determined from the sum of ICA and ECA blood flow, and regional distribution was calculated as ECA or ICA blood flow/CCA blood flow ($\times 100\%$).

Statistical analysis. Data were analyzed using the Statistics Package for Social Scientists (IBM SPSS Statistics version 22.0). Distribution normality was confirmed using Shapiro–Wilk *W* tests. Differences between values at baseline and at each exercise time were evaluated by a one-factor repeated measures ANOVA followed by Tukey's HSD *post hoc* tests. ICA and ECA blood flow and cerebrovascular conductance index data were analyzed via a two-way repeated-measures ANOVA (site \times time) and Tukey's HSD test whenever an interaction effect was present. Data are expressed as mean \pm SD, and significance was established at $P < 0.05$ for all two-tailed tests.

RESULTS

Cardiorespiratory Responses

Resistance exercise was associated with progressive increases in HR, SBP, DBP, MAP, \dot{V}_E , P_{ET}CO₂, CO, forehead

SkBF, and the forehead vascular conductance index (Table 1, $P < 0.001$).

Cerebral Remodynamic Responses

Flow. MCA V_{mean} also increased during resistance exercise ($P < 0.001$) and reached a plateau before stabilizing 60 s into exercise (Fig. 1). Similarly, ICA blood flow increased from baseline ($P = 0.001$) before stabilizing at 60 s. There was a relationship between ICA and MCA V_{mean} ($r = 0.361$, $P = 0.0051$). In contrast, ECA blood flow progressively increased throughout exercise with the most marked changes observed between 60 and 120 s ($P < 0.001$). We also observed a relationship between increase in forehead SkBF and ECA blood flow ($r = 0.348$, $P < 0.01$). The diameters of both ICA and ECA were unchanged during resistance exercise; thus, changes in ICA and ECA blood flow were directly attributable to changes in the blood velocity.

Conductance. The MCA conductance index remained unchanged throughout the exercise ($P = 0.249$, Fig. 2), whereas ICA conductance decreased by $-14.4\% \pm 13.8\%$ at 120 s ($P < 0.01$). In contrast, ECA conductance increased to $20.0\% \pm 30.5\%$ at 120 s ($P < 0.05$).

Distribution. The distribution of CCA blood flow to ECA blood flow increased significantly (29% to 35% from baseline to 120 s, Fig. 3), whereas that to ICA blood flow decreased (71% to 65% from baseline to 120 s). In addition, CCA blood flow accounted for $8.7\% \pm 2.4\%$ of CO at baseline, but CO distribution to CCA blood flow significantly decreased during exercise ($7.2\% \pm 2.2\%$ at 30 s to $6.4\% \pm 1.9\%$ at 120 s, Fig. 4).

DISCUSSION

The present findings have provided additional novel insight into the differential regulation of intracranial CBF in

TABLE 1. Cardiorespiratory and cerebrovascular variables at baseline and during exercise.

	Baseline	30 s	60 s	90 s	120 s	<i>P</i>
Cardiorespiratory responses						
HR (bpm)	66 \pm 11	86 \pm 13**	88 \pm 12**	92 \pm 12**	96 \pm 13**	<0.001
SBP (mm Hg)	116 \pm 11	129 \pm 17**	139 \pm 14***	147 \pm 15**	150 \pm 16**	<0.001
DBP (mm Hg)	64 \pm 9	71 \pm 11**	79 \pm 9***	85 \pm 10***	87 \pm 10**	<0.001
MAP (mm Hg)	82 \pm 9	91 \pm 12**	99 \pm 10***	107 \pm 11***	109 \pm 12**	<0.001
\dot{V}_E (mL)	7.7 \pm 1.9	9.8 \pm 3.9	10.9 \pm 4.3*	13.9 \pm 6.2***	13.1 \pm 2.8**	<0.001
P _{ET} CO ₂ (mm Hg)	35.5 \pm 4.5	38.7 \pm 5.4	39.3 \pm 3.7*	40.1 \pm 5.1**	41.2 \pm 5.4**	<0.001
CO (%)	100 \pm 0	141 \pm 17**	154 \pm 18**	163 \pm 27**	172 \pm 31**	<0.001
Forehead SkBF (%)	100 \pm 0	150.4 \pm 41.8	162.7 \pm 60.6**	200.6 \pm 87.6**	215.8 \pm 84.1**	<0.001
Forehead CON index (%)	100 \pm 0	138.6 \pm 47.7*	134.0 \pm 47.3	153.5 \pm 62.0**	161.4 \pm 56.1**	<0.001
Cerebrovascular responses						
ICA blood flow (mL·min ⁻¹)	294 \pm 84	335 \pm 91*	349 \pm 95**	339 \pm 101*	336 \pm 111*	0.001
ICA D_{mean} (cm)	0.49 \pm 0.07	0.49 \pm 0.08	0.50 \pm 0.09	0.50 \pm 0.09	0.50 \pm 0.09	0.347
ICA V_{mean} (cm·s ⁻¹)	26.1 \pm 5.3	29.7 \pm 6.5**	30.3 \pm 6.7**	29.0 \pm 6.9*	28.4 \pm 7.2	0.001
ICA CON (mL·min ⁻¹ ·mm Hg ⁻¹)	3.64 \pm 1.13	3.79 \pm 1.24	3.53 \pm 0.97	3.18 \pm 0.91	3.08 \pm 1.00*	0.001
ECA blood flow (mL·min ⁻¹)	116 \pm 47	133 \pm 41	137 \pm 49	153 \pm 52**	173 \pm 46**	<0.001
ECA D_{mean} (cm)	0.37 \pm 0.05	0.38 \pm 0.06	0.38 \pm 0.06	0.38 \pm 0.06	0.38 \pm 0.06	0.086
ECA V_{mean} (cm·s ⁻¹)	17.6 \pm 4.4	19.9 \pm 4.5	20.7 \pm 6.2	22.5 \pm 7.0**	26.2 \pm 9.1**	<0.001
ECA CON (mL·min ⁻¹ ·mm Hg ⁻¹)	1.41 \pm 0.56	1.48 \pm 0.48	1.38 \pm 0.47	1.44 \pm 0.47	1.58 \pm 0.38	0.196
MCA V_{mean} (cm·s ⁻¹)	49.7 \pm 11.0	54.5 \pm 12.8	60.1 \pm 15.6**	62.9 \pm 16.8**	62.5 \pm 19.1**	<0.001
MCA CON index (cm·s ⁻¹ ·mm Hg ⁻¹)	0.61 \pm 0.13	0.61 \pm 0.14	0.60 \pm 0.13	0.59 \pm 0.12	0.57 \pm 0.13	0.249

Data are presented as mean \pm SD.

* $P < 0.05$ and ** $P < 0.01$ different from baseline. *** $P < 0.05$ and **** $P < 0.01$ different from previous time.

CON, conductance.

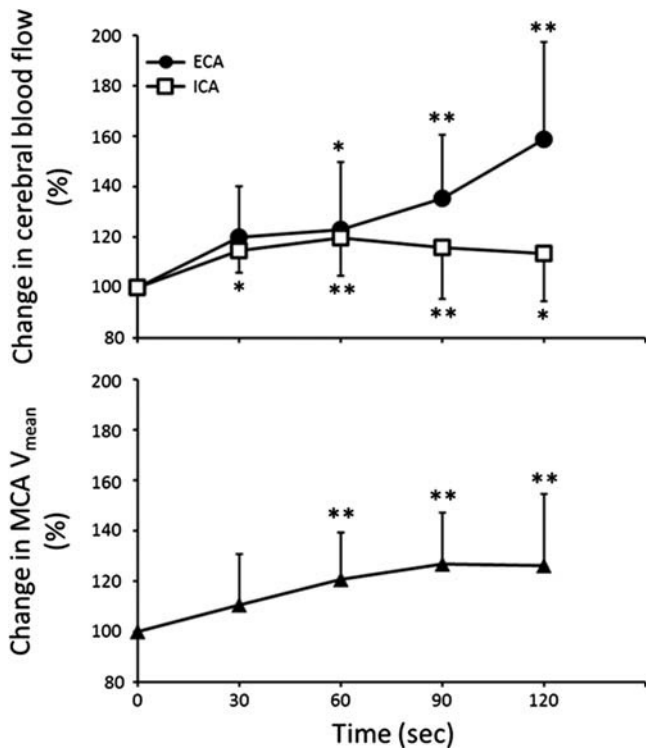


FIGURE 1—The percentage change in CBF (*upper panel*) and MCA V_{mean} (*lower panel*) from baseline throughout resistance exercise. Values are expressed as mean \pm SD. ** $P < 0.01$ and * $P < 0.05$ different from baseline.

response to resistance exercise-induced acute hypertension. Our primary finding was that low-intensity resistance exercise was associated with functional vasodilation at the ECA peripheral vascular bed, and this was opposed by vasoconstriction of the ICA. We propose that the heterogeneous nature of intracranial flow (“vascular steal” from ICA to ECA) may reflect an adaptive neuroprotective mechanism that serves to protect against cerebral hyperperfusion in the face of even subtle, physiological exercise-induced hypertension.

ECA blood flow and conductance were shown to progressively increase during exercise ($P < 0.01$ and $P < 0.05$, respectively), reflecting vasodilation at peripheral ECA vascular bed that opposed the peripheral vasoconstriction observed in the ICA. Furthermore, the distribution of CCA to ECA blood flow increased gradually, whereas the converse was true for the ICA. Because CCA bifurcates to ICA and ECA, this finding suggests that resistance exercise-induced hypertension is associated with ICA “steal” toward the ECA. The ECA mainly supplies blood flow to the face, anterior neck, and cranium wall and plays an important role in thermoregulation during heat stress and dynamic cycling exercise (4,19). Indeed, in the present study, the change in ECA blood flow was associated with increase in forehead SkBF ($r = 0.348$, $P < 0.01$). However, during short resistance exercise, body temperature rise and/or sweating are not observed (1). Therefore, in the exercise model of the present study, the increase in ECA blood flow or conductance is not associated with the thermoregulatory system, suggesting that

the larger blood flow distribution to ECA may not only serve to increase blood flow to the face and skin to optimize thermoregulation. We expected CA of the ECA to be less effective compared with other cerebral arteries (13), suggesting that ECA blood flow is potentially more receptive to changes in perfusion pressure compared with the ICA. Indeed, during acute hypotension via thigh cuff occlusion release, ICA conductance increased rapidly, whereas in contrast, ECA conductance remained unchanged (13).

Resistance exercise is associated with acute hypertension that can exceed the upper limits of CA (approximately 150 mm Hg) (10). However, the brain appears to be more able to buffer increases more effectively than decreases in perfusion pressure consistent with cerebral hysteresis (24). To what extent resistance exercise-induced hypertension influences MCA V_{mean} remains unresolved with increases or no changes reported in the literature (2,3). Similarly, we observed only minor increases in MCA V_{mean} and ICA blood flow in the present study. Although the ICA blood flow increased at the onset of exercise, it stabilized after 60 s despite marked increases in both CO and ABP. More importantly, ICA conductance gradually decreased during resistance exercise (Table 1 and Fig. 2, $P < 0.01$), reflecting cerebral vasoconstriction despite an increase in P_{ETCO_2} ($P < 0.001$).

Although speculative, the reduction in ICA conductance may have served to protect against the structural damage associated with cerebral hyperperfusion. The mechanism of the response of ICA vasculature to resistance exercise remains

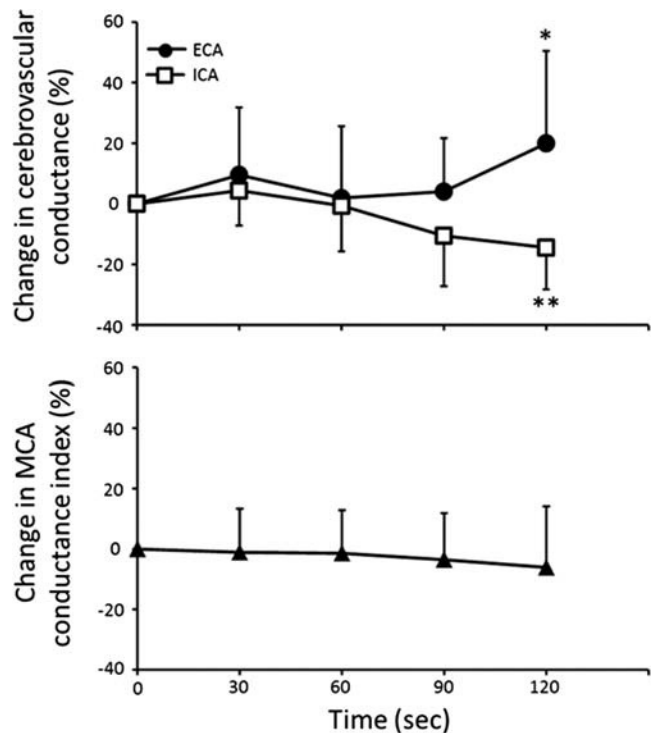


FIGURE 2—The percentage change in cerebrovascular conductance (*upper panel*) and MCA conductance index (*lower panel*) from baseline throughout resistance exercise. Values are expressed as mean \pm SD. ** $P < 0.01$ and * $P < 0.05$ different from baseline.

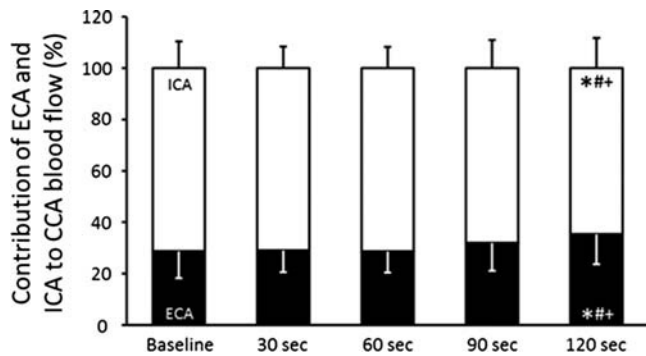


FIGURE 3—Regional contribution of ECA and ICA to CCA blood flow. * $P < 0.01$ different from baseline, # $P < 0.01$ different from 30 s, and + $P < 0.01$ different from 60 s.

unclear; however, several possible mechanisms of ICA vasoconstriction during resistance exercise could be considered. One possible mechanism is sympathetic nerve activation, because resistance exercise causes a large increase in sympathetic nerve activity (8). In humans, it remains controversial whether sympathetic nerve activity directly regulates the cerebral vasculature (23). However, in hypertensive patients, sympathetic stimulation decreased CBF (7,16,18). Therefore, in the present study, resistance exercise-induced activation of sympathetic nerve may have caused peripheral vasoconstriction of ICA. Alternatively and beyond the scope of the present study, the plateau in ICA blood flow may simply reflect a physical limitation of the vessels because of increased intracranial pressure. Increasing blood pressure will stretch the cerebral arteries to a point at which intracranial pressure will push back and not allow more flow, which would appear as a decrease in conductance in the case of rising blood pressure. The vessels fed by the ECA do not encounter this problem so they are free to stretch and allow conductance to increase. Further research is warranted to test this hypothesis, including the net exchange of molecular markers indicating that there was vasoconstriction in the skull and vasodilation outside of it.

We observed an inverse relationship between CO and global CBF during resistance exercise, which is opposite to that observed during dynamic cycling exercise highlighting the marked blood flow regulation that occurs as a function of

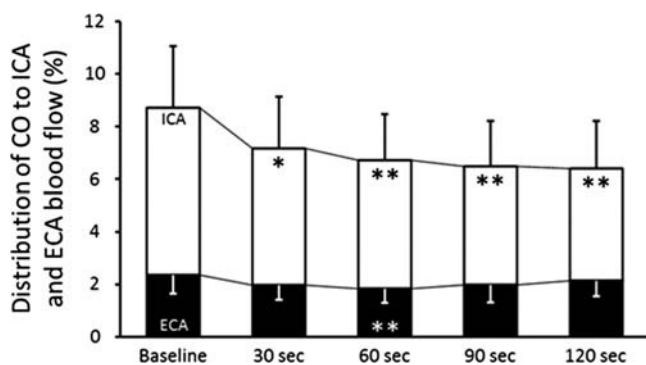


FIGURE 4—The change in the proportion of CO distributed to ICA and ECA blood flow at baseline and during resistance exercise. ** $P < 0.01$ and * $P < 0.05$ different from baseline.

exercise mode (12). The contribution of CO to ICA was shown to gradually decrease during exercise, whereas ECA blood flow was preserved highlighting subtle differences in blood flow regulation despite the fact these arteries emanate from a common vessel (CCA). ICA blood flow was likely regulated by change in ICA vascular bed itself given that it was independent from changes in CO and ABP. The decrease in the proportion of CO distributed to the head possibly reflects the increase in CO redistribution to exercising muscle via functional sympatholysis (11), and that O_2 supply to the brain as a function of metabolic demand is likely adequate.

There were several limitations to the present study. We were unable to measure ipsilateral blood flow in ICA and ECA because of the interference caused by the ultrasound beam. Blood flow was measured continually during resistance exercise. However, we excluded the period when participants swallowed saliva or moved with changes in the probe position and the insonation angle of the ultrasound beam. Also, it was not feasible to directly measure CCA blood flow at time points identical to the combined ICA/ECA measurements given the unavoidable technical limitations associated with Doppler ultrasound, notably insufficient space for insonation, and interference of Doppler beams from multiple probes. CCA flow was assessed at each time point by rapidly switching probes from the ICA to confirm whether the sum of contralateral ICA/ECA blood flows is indeed a reliable and reproducible estimate of directly measured CCA blood flow. We subsequently demonstrated that this was indeed the case with no differences observed between the direct vs. indirect measures ($P = 0.947$, $n = 12$, Fig. 5). This finding agrees with our previous studies using different interventions that have facilitated comparison of these measurements during steady-state perturbations (heat stress and dynamic exercise) (15,19). Thus, we are confident that the CCA data estimated by the sum of contralateral ICA/ECA flows was both reliable and reproducible.

Another limitation is that the resistance exercise protocol did not increase blood pressure to such an extent as that expected during weight lifting. Simultaneously, evaluation of blood flow in ipsilateral cerebral arteries is constrained by

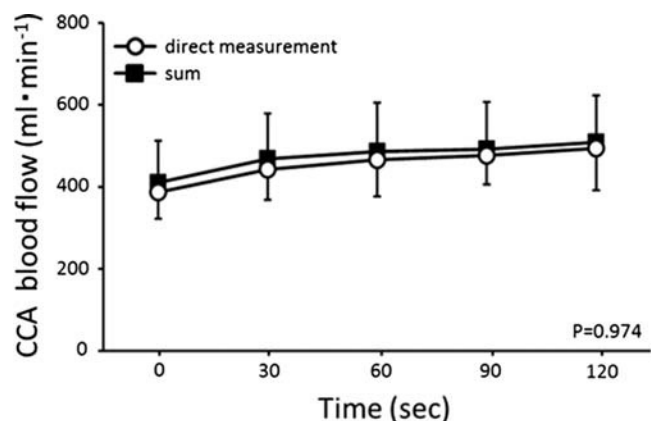


FIGURE 5—CCA blood flow measured directly and estimated by the sum of contralateral ICA/ECA flows during resistance exercise.

insufficient space at the neck and interference between Doppler beams from multiple probes. In addition, the probe position needs to be stable without any change in insonation angle for accurate Doppler measurement. Thus, the subjects need to avoid body and neck movement during resistance exercise. We thus chose to focus on short-duration, low-intensity exercise to avoid movement artifact and induce physiological (i.e., real world as opposed to supraphysiological) changes in MAP.

Perspectives. The present findings provide important mechanistic insight into the dynamic regulation of CBF. ECA blood flow appears to be more sensitive to changes in perfusion pressure compared with intracranial blood flow. The increase in ECA blood flow may prove an adaptive mechanism that serves to preserve intracranial CBF and oxygenation with cerebral vasoconstriction during acute hypertension. Functional heterogeneous changes in the ECA and ICA vasculatures, hitherto unexplored, may contribute toward understanding of the pathophysiology of neurodegenerative disease including sedentary aging.

In conclusion, the present findings demonstrate that low-intensity resistance exercise was associated with peripheral

vasodilation of the ECA vascular bed that was accompanied by peripheral vasoconstriction of the ICA vascular bed. We propose that the heterogeneity and reciprocal regulation of intracranial CBF reflects an adaptive neuroprotective mechanism that serves to protect the brain and associated vasculature against the structural damage associated with resistance exercise-induced hypertension.

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S. O. was responsible for the conception and design of research; A. H., K. S., M. Y., and S. O. performed the experiments; A. H. and S. O. analyzed the data; A. H., S. O., and D. M. B., interpreted the results of experiments; A. H. and S. O. prepared the figures; A. H. and S. O. drafted the manuscript; A. H., K. S., D. M. B., and S. O. edited and revised the manuscript; A. H., K. S., M. Y., T. S., D. M. B., and S. O. approved the final version of the manuscript.

No conflicts of interest, financial or otherwise, are declared by the authors. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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