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Regional redistribution of blood flow in the external and internal carotid arteries during acute hypotension

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Ogoh S, Lericollais R, Hirasawa A, Sakai S, Normand H, Bailey DM. Regional redistribution of blood flow in the external and internal carotid arteries during acute hypotension. *Am J Physiol Regul Integr Comp Physiol* 306: R747–R751, 2014. First published March 5, 2014; doi:10.1152/ajpregu.00535.2013.—The present study examined to what extent an acute bout of hypotension influences blood flow in the external carotid artery (ECA) and the corresponding implications for blood flow regulation in the internal carotid artery (ICA). Nine healthy male participants were subjected to an abrupt decrease in arterial pressure via the thigh-cuff inflation-deflation technique. Duplex ultrasound was employed to measure beat-to-beat ECA and ICA blood flow. Compared with the baseline normotensive control, acute hypotension resulted in a heterogeneous blood flow response. ICA blood flow initially decreased following cuff release and then returned quickly to baseline levels. In contrast, the reduction in ECA blood flow persisted for 30 s following cuff release. Thus, the contribution of common carotid artery blood flow to the ECA circulation decreased during acute hypotension ($-10 \pm 4\%$, $P < 0.001$). This finding suggests that a preserved reduction in ECA blood flow, as well as dynamic cerebral autoregulation likely prevent a further decrease in intracranial blood flow during acute hypotension. The peripheral vasculature of the ECA may, thus, be considered an important vascular bed for intracranial cerebral blood flow regulation.

arterial blood pressure; humans; arterial baroreflex; common carotid artery; skin blood flow

CEREBRAL AUTOREGULATION (CA) is a homeostatic mechanism that serves to maintain cerebral blood flow constant over a wide range of perfusion pressures (60 to 150 mmHg) and is subject to myogenic, neurogenic, and metabolic control (1, 12, 13, 20). 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 hypoperfusion/hyperperfusion (5).

Traditionally, CA has been investigated by assessing the dynamic relationship between spontaneous and/or stimulus-induced changes in arterial blood pressure (ABP) and middle cerebral artery blood velocity (MCA *V*) as measured by transcranial Doppler (1, 12, 13, 20). Notwithstanding technical limitations (14, 16), this method is based on the premise that MCA *V* is a reliable, albeit surrogate, measure of global cerebral blood flow, popularized, in part, by accessibility and ease of insonation. However, downstream of the MCA, blood is supplied to the head from both the vertebral and common carotid arteries, with the latter bifurcating into the external (ECA) and internal (ICA) carotid artery. The ECA supplies blood to the face, scalp, skull, and meninges, whereas the ICA supplies blood exclusively to the brain, where after entering the cranial cavity bilaterally, it divides into the anterior and middle cerebral arteries within the circle of Willis.

We have recently highlighted the heterogeneity of cerebral blood flow (CBF) with differential responses observed between the ICA, ECA, and vertebral arteries in response to thermal, exercise, and hypercapnic stress (15–17). Importantly, ~70% of global CBF is supplied by the intracranial arteries in these investigations. Importantly, the common carotid artery bifurcates into the ECA, which supplies blood to the face, anterior neck, and cranium wall. Therefore, it is possible that "downstream" alterations in extracranial ECA vascular tone may serve to regulate "upstream" MCA *V* and ICA blood flow. Indeed, during heavy dynamic exercise (16) and heat stress (15), the increased cardiac output was likely distributed to extracranial vascular beds with a reciprocal reduction in ICA blood flow. Collectively, these earlier observations suggest that vasodilation of the ECA not only serves to increase blood flow to the face and skin to optimize thermoregulation (10), but may equally prevent hyperperfusion and damage to the blood-brain barrier. Thus, it is conceivable that the ECA blood flow response to changes in ABP may be important mechanism underlying dynamic cerebral autoregulation. However, to what extent these regional differences in blood flow exist in response to acute hypotensive stress has not previously been examined.

In light of these findings, we hypothesized that an acute bout of hypotension would result in a more marked and prolonged reduction in ECA blood flow to support the recovery of ICA blood flow. To test our hypothesis, the relative distribution of common carotid artery blood flow to both ICA and ECA was evaluated using Doppler ultrasound during the thigh-cuff inflation-deflation technique (1).

MATERIALS AND METHODS

Participants

Nine healthy men aged 21 (mean) ± 1 (SD) yr with a body mass of 66 ± 11 kg volunteered for the present study. All subjects were free of any known cerebrovascular, cardiovascular, or pulmonary disorders and were not taking prescribed medication. Each subject provided written, informed consent as approved by the Institutional Review Boards of Faculty of Science Engineering, Toyo University (IRB no. 2010-R-06).

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Table 1. *Hemodynamic data*

	Trial 1 (for ECA Measure)		*Trial 2* (for ICA Measure)		*P* value		
	Control Baseline	Nadir of ABP	Control Baseline	Nadir of ABP	*Trial 1* vs. *2*	Base. vs. Nadir	Interaction
Time, s	0 ± 0	8.9 ± 2.8	0 ± 0	8.6 ± 1.8	$P = 0.607$	$P < 0.001$	$P = 0.607$
MAP, mmHg	91 ± 9	74 ± 8	94 ± 13	72 ± 10	$P = 0.907$	$P < 0.001$	$P = 0.182$
HR, bpm	63 ± 10	75 ± 7	65 ± 11	78 ± 8	$P = 0.204$	$P < 0.001$	$P = 0.721$
Mean MCA *V*, cm/s	53 ± 7	55 ± 13	51 ± 16	56 ± 17	$P = 0.972$	$P = 0.020$	$P = 0.334$
SkBF, AU	100 ± 0	69 ± 12	100 ± 0	74 ± 12	$P = 0.527$	$P < 0.001$	$P = 0.527$
Cerebral O_2Hb, AU	5.5 ± 10.1	3.5 ± 8.4	5.6 ± 8.2	2.1 ± 7.0	$P = 0.837$	$P = 0.005$	$P = 0.202$
Muscle O_2Hb, AU	6.0 ± 3.3	4.6 ± 3.6	5.7 ± 5.7	3.8 ± 5.3	$P = 0.672$	$P = 0.001$	$P = 0.211$

Values are expressed as means ± SD. ECA, external carotid artery; ICA, internal carotid artery; ABP, arterial blood pressure; MAP, mean arterial pressure; HR, heart rate; Mean MCA *V*, middle cerebral artery mean blood velocity; SkBF, skin blood flow; O_2Hb, oxyhemoglobin concentration; AU, arbitrary units.

Experimental Protocol

An abrupt decrease in ABP was induced by releasing bilateral thigh cuffs after 3 min of supra-systolic (220 mmHg) resting ischemia. Many previous studies have used this nonpharmacological technique to evaluate cerebral blood flow regulation, most notably during the assessment of dynamic CA (1). To minimize analytical and interinvestigator experimental error, all measurements were performed by the same investigator and single Doppler ultrasound machine. As a consequence, each subject performed this maneuver on four separate occasions (two repeat trials for ICA and ECA flow measurements in a balanced, single-blinded, randomized manner) on the same day. For the analysis, we selected one trial for each arterial site based on an equivalent ABP response during and following recovery from the hypotensive stimulus.

Measurements

Doppler ultrasound and finger photoplethysmography. Heart rate (HR) was monitored using a lead II electrocardiogram and beat-to-beat ABP using finger photoplethysmography (Finometer; Finapres Medical Systems BV, Amsterdam, The Netherlands). Blood flow velocity in the left middle cerebral artery (MCA *V*) was determined by transcranial Doppler ultrasonography (Multidop T; DWL, Sipplingen, Germany).

Duplex ultrasound. Blood flow measurements within the ICA and ECA (right arteries) were performed separately and in a randomized fashion (two trials for each artery) by a single investigator using one color-coded ultrasound system (Vivid-i; GE Healthcare, Tokyo, Japan) equipped with a 10-MHz linear transducer. Measurements were performed before and during cuff release for 1 min, as previously described in detail (15–17). In brief, ICA and ECA blood flow measurements were performed ~1.0–1.5 cm distal to the carotid bifurcation at each respective site, while the subject's chin was slightly elevated. The simultaneous measurement of MCA *V* does not interfere with these measures, given that the transcranial Doppler probe is located on the subject's temporal window, while the Duplex probe is located on the neck.

Near-infrared spectroscopy. Cerebral and muscle oxygenation were monitored simultaneously via multichannel near-infrared spectroscopy (NIRS; NIRO200; Hamamatsu Photonics, Hamamatsu, Japan). Two sets of NIRS probe holders were placed on the left side of the forehead above the supraorbital edge and brachioradial muscle of the left forearm, according to established techniques for the specific detection of (cerebral and muscle) oxyhemoglobin concentrations (O_2Hb). Skin blood flow was measured on the left forehead using laser-Doppler flowmetry (ALF21; Advance, Tokyo, Japan).

End-tidal partial pressure of carbon dioxide. Expired air was sampled breath-by-breath, and the end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) was measured via capnography (AE-310S; Minato Medical Science, Osaka, Japan).

Data Analysis

All data were sampled continuously at 1 kHz using an analog-to-digital converter interfaced with a computer for offline analysis. Absolute values for ICA and ECA blood flow, including vascular

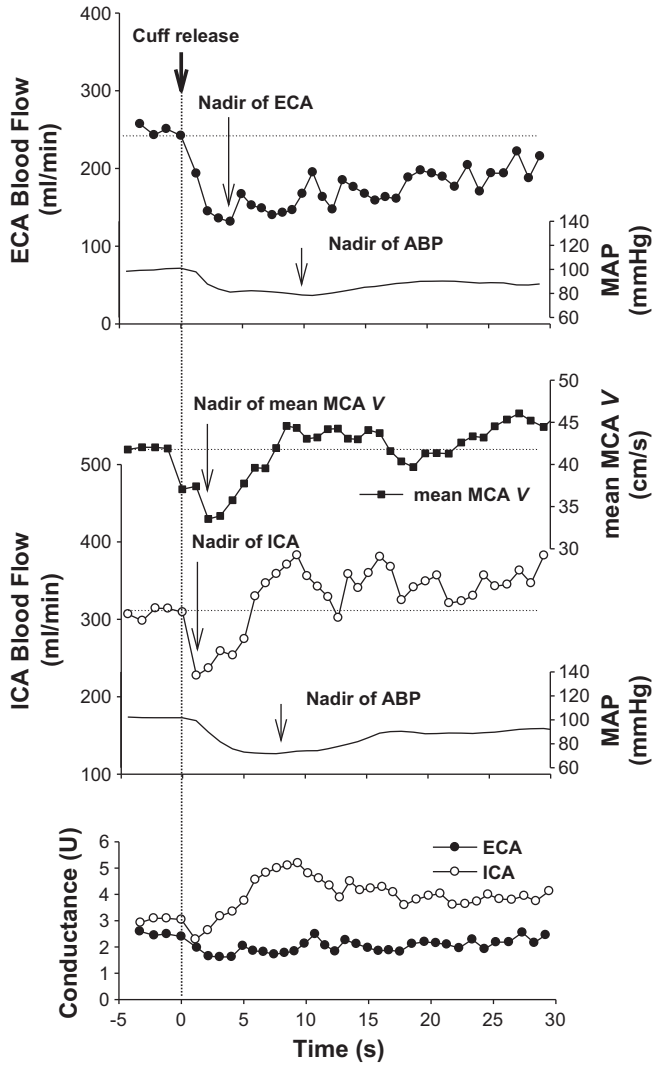

Fig. 1. Typical changes in external carotid artery (ECA; *top*), middle cerebral artery mean blood velocity (mean MCA *V*), internal carotid artery (ICA) blood flow (*middle*), and vascular conductance of both arteries (*bottom*) before and following cuff release (single subject).

conductance, were calculated as previously outlined (14, 16). Briefly, we employed the B-mode approach to identify mean vessel diameter in a longitudinal section, while the Doppler velocity spectrum was identified by pulsed wave mode (PW mode). Systolic and diastolic diameters were measured and beat-to-beat mean diameter was calculated as mean diameter = [(systolic diameter ×1⁄3)] + [(diastolic diameter ×2⁄3)]. Beat-to-beat mean blood flow velocity was calculated on the basis of velocity waveforms. Finally, blood flow was calculated as blood flow = mean blood flow velocity × cross-sectional area [π×(mean diameter/2)2] × 60. Common carotid artery (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 (×100%).

Statistical Analysis

Data were analyzed via a two-way repeated-measures ANOVA (trial × time) using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL). Following a significant interaction, post hoc Student-Newman-Keuls tests were employed to locate differences. Data are expressed as means ± SD, and significance for all two-tailed tests was established at $P < 0.05$.

RESULTS

Systemic Hemodynamic Responses

As anticipated, cuff release resulted in a marked reduction in ABP (10–32 mmHg), with the nadir occurring within 6–12 s (Table 1 and Fig. 1). We observed a corresponding increase in HR, while skin blood flow and cerebral and muscle oxyhemoglobin (NIRS signal) decreased significantly at the nadir of ABP. Mean MCA *V* decreased acutely after cuff release, before recovering to the baseline value at the nadir of ABP (Fig. 2). In contrast, we detected no changes in $P_{ET}CO_2$ following cuff release (control baseline vs. during cuff release: 43 ± 4 vs. 43 ± 4 mmHg; $P = 0.914$).

Regional Hemodynamic Responses

Acute hypotension resulted in a heterogeneous blood flow response as illustrated in Fig. 1. ICA blood flow decreased immediately and precipitously upon cuff release, and this was followed by rapid recovery to control baseline values prior to the nadir of ABP. The response kinetic was comparable to that observed for the mean MCA *V*. In contrast, while ECA blood flow decreased following cuff release, the recovery was far more prolonged (~30 s vs. control baseline; $P = 0.030$). Despite lower common carotid artery blood flow at the nadir of ABP, ICA blood flow recovered to baseline levels (Fig. 2).

DISCUSSION

The present study is the first to map regional differences in ICA and ECA perfusion during an acute hypotensive challenge. Our major finding was that during hypotension, ICA blood flow decreased and then rapidly recovered to control baseline levels, whereas, in contrast, the reduction in ECA blood flow was maintained throughout the recovery period. This finding suggests that the selective redistribution of blood flow from the ECA to support the recovery of ICA blood flow may reflect a neuroprotective mechanism that serves to optimize intracranial blood flow and oxygenation during acute hypotension. In this sense, the peripheral vasculature associated with the ECA may be an important and hitherto unrecognized site that contributes toward intracranial cerebral blood flow regulation.

In the present study, both ICA blood flow and mean MCA *V* decreased immediately following cuff release and returned quickly to control baseline values. In contrast, ECA blood flow decreased and remained depressed throughout the recovery period (Figs. 1 and 2). Accordingly, the contribution of the common carotid artery to ICA blood flow was better preserved during hypotension compared with ECA blood flow. Importantly, ICA blood flow returned to baseline control levels at the nadir of ABP following cuff release despite an incomplete recovery of common carotid artery blood flow (Fig. 2). These findings strongly suggest that the prolonged suppression of ECA blood flow rather than the increase in common carotid artery blood flow may help support the recovery of ICA blood flow, oxygenation, and substrate delivery from the physiological stress imposed by acute hypotension.

It is generally accepted that during normocapnia, changes in sympathetic tone appear to have limited effects on cerebral blood flow (11, 12). Previously, LeMarbre et al. (9) demonstrated that cerebral blood flow regulation was not altered by

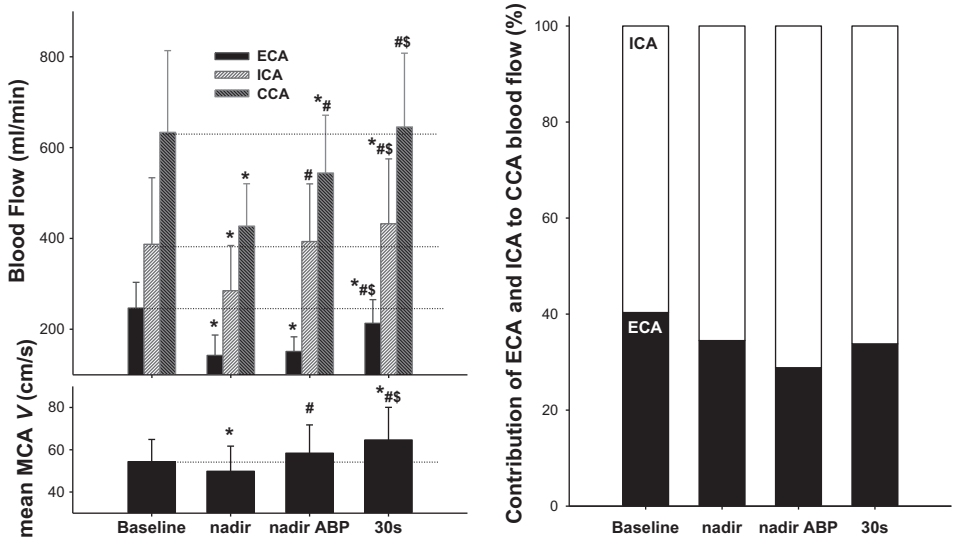

Fig. 2. *Left*: ECA, ICA, common carotid artery (CCA) blood flow, and mean MCA *V* before cuff release (baseline), and at the corresponding nadirs of both flow (nadir) and arterial blood pressure (nadir ABP), and finally 30 s following cuff release (30 s). *$P < 0.05$ vs. baseline; #$P < 0.05$ vs. nadir; \$$P < 0.05$ vs. nadir ABP. *Right*: regional contribution of ICA and ECA to CCA blood flow.

baroreflex-induced sympathetic activation using lower body negative pressure. Similarly, in the present study, changes in ICA blood flow were not likely affected during hypotension-induced sympathoexcitation via unloading of the arterial baroreflex.

In contrast, ECA is likely affected by sympathoexcitation. A previous study (8) using the neck chamber technique demonstrated that unloading or loading of the carotid baroreceptors altered cutaneous vascular conductance of the forearm, suggesting that the carotid baroreflex exhibits an efferent limb governing the cutaneous vasculature. In addition, postural changes that involve the transition from an upright to supine position have been shown to increase forehead cutaneous flow by 26% via loading of arterial and cardiopulmonary baroreceptors, as well as raising arterial pressure (4). Thus, it is possible that the facial cutaneous vasculature was also affected by acute hypotension induced sympathoexcitation via the baroreflex. Indeed, Sorensen et al. (18) indicated that norepinephrine infusion induced facial cutaneous vasoconstriction with no change in cerebral blood flow. These findings suggest that the prolonged suppression of ECA blood flow may be related to sympathoexcitation via unloading of the arterial baroreflex during acute hypotension. In contrast, the steady-state orthostatic stress (90° head-up tilt) failed to alter ECA (7). This finding suggests that dynamic arterial blood pressure changes via the arterial baroreflex rather than an unloading of cardiopulmonary baroreceptors likely affects the extracranial vasculature. Previous studies also suggested that large intracranial and extracranial cerebral vessels, such as the carotid or vertebral arteries, are a major site of resistance to blood flow in the cerebral circulation and contribute significantly to total cerebral vascular resistance (6). In support, Willie et al. (19) recently reported a trend for ICA diameter to change during changes in arterial P_{CO_2}, albeit not significantly. In the present study, arterial diameters generally decreased during acute hypotension, responses that were identical for both the ICA and ECA ($P = 0.763$). Thus, it is unlikely that the responses of large intracranial and extracranial cerebral vessels to acute hypotension can simply be attributed to different blood flow responses. However, our understanding of the precise mechanisms underlying the differential responses between ICA and ECA blood flow during hypotension remains to be established and are encouraged in follow-up studies.

Perspectives and Significance

Our findings revealed that during hypotension, ICA blood flow decreased followed by a rapid return to control baseline levels, whereas in contrast, the reduction in ECA blood flow persisted throughout. These findings indicate the selective preservation of ICA over ECA blood flow that likely serves to optimize CA (by maintaining adequate cerebral blood flow), thereby defending cerebral oxygenation and nutrient supply. In other words, dynamic ECA blood flow regulation affects intracranial cerebral blood flow. For example, systemic circulatory or autonomic dysfunction-induced attenuation in ECA regulation may exacerbate intracranial cerebral blood flow regulation. This has important clinical implications given that impaired CA is associated with poor clinical outcome, e.g., brain atrophy and cognitive dysfunction, following ischemic stroke and brain injury, and may also predispose to neurodegenerative disease (2, 3). Collectively, the present findings provide mechanistic insight into how impaired systemic circulatory and autonomic function can translate into regional brain disease.

In summary, the prolonged regional suppression of ECA blood flow appears to support the recovery of ICA blood flow during acute hypotension. The external cerebral vasculature may, therefore, prove an important vascular bed that contributes toward dynamic intracranial cerebral blood flow regulation.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: S.O. conception and design of research; S.O., R.L., A.H., and S.S. performed experiments; S.O. and A.H. analyzed data; S.O., A.H., and D.M.B. interpreted results of experiments; S.O. prepared figures; S.O. drafted manuscript; S.O., R.L., H.n., and D.M.B. edited and revised manuscript; S.O., R.L., A.H., S.S., H.n., and D.M.B. approved final version of manuscript.

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