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Emerging views of how changes in blood pressure influence cerebral blood flow

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In addition to cerebral metabolism and autonomic control, cerebral blood flow (CBF) is principally regulated by the partial pressure of arterial carbon dioxide (P_{aCO_2}) and mean arterial pressure (MAP). The early understanding of the cerebrovascular pressure–flow relationship was 'pressure-passive'; this prevailing view indicates that a rise in MAP increases CBF and vice versa. Conversely, Lassen (1959) reviewed the CBF response across groups and clinical populations and suggested that CBF is stable across a relatively wide range of MAP (e.g. 60–150 mmHg), termed static cerebral autoregulation (CA); however, when considered within the same participants, the CBF *vs.* MAP relationship likely occurs over a much narrower range. Additionally, it has been shown that there is an interaction between CA and the sensitivity of CBF to changes in P_{aCO_2}. For example, a reduction in MAP (i.e. hypotension) effectively attenuates the cerebrovascular responsiveness to changes in P_{aCO_2} (Harper & Glass, 1965). The understanding of cerebrovascular regulation has been extended over the last 20 years with sophisticated models of MAP regulation in both animal and human studies. Together with various models of hypotension (e.g. pharmacological interventions, head-up tilt, lower-body negative pressure) and non-invasive measures of volumetric CBF (e.g. extra-cranial duplex ultrasound), recent research has provided new insights into the competing influences of MAP and P_{aCO_2} on the regulation of CBF.

In a recent issue of *The Journal of Physiology*, Olesen *et al.* (2018) evaluated the influence of hypotension via intravenous infusion of sodium nitroprusside (SNP) on regional CBF regulation in humans with an aimed 20% and 40% reduction in MAP, while keeping MAP ≥50 mmHg. In 19 healthy males (24 ± 4 years), regional CBF of the right internal carotid artery (ICA) and vertebral artery (VA) was assessed via duplex ultrasound together with transcranial Doppler (TCD) measures of right middle cerebral artery blood velocity (MCAv). Arterial catheterization was performed to measure arterial blood gases, metabolic substrates and cardiovascular variables. To account for the possible influence of hypocapnic cerebral vasoconstriction, Olesen *et al.* evaluated CO_2 reactivity for ICA and VA via hyperventilation at rest and have reported CBF with 'correction' for changes in P_{aCO_2} with hypotension (i.e. 2.8% reduction in CBF per mmHg reduction in P_{aCO_2}). The primary finding was that during SNP-induced reduction in MAP (and P_{aCO_2}), global CBF and VA blood flow were maintained via an increase in cerebrovascular conductance. In contrast, ICA blood flow was elevated at the moderate reduction in MAP but returned to the baseline value at the more severe level of hypotension. Following 'correction' for hypocapnia with progressive hypotension, global CBF and ICA blood flow were elevated; however, VA blood flow was unchanged. Overall, these results indicate a differential regional CBF regulation in the anterior (ICA) and posterior (VA) cerebral circulations during progressive hypotension; together these changes mediated the maintenance of global CBF. These novel findings merit further discussion with respect to: (1) the effectiveness of CA; (2) global and regional changes in CBF regulation during experimental models of hypotension; and (3) possible clinical implications.

Cerebral autoregulation and hypotension

Contrary to previous reports of a narrow CA range, Olesen *et al.* reported a relatively wide CA range during progressive hypotension (see Fig. 1). To extend these findings, we calculated the CA slope between the percentage change in cerebrovascular resistance (i.e. CVR = MAP/CBF) and relative reduction in MAP using the regression coefficient from three key studies to date. Notably, whereas Olesen *et al.* have shown stable CA across progressive hypotension using a pharmacological intervention, Sato *et al.* (2012) and Lewis *et al.* (2015) have reported a compromise in CA when hypotension was induced via head-up tilt with thigh cuff release and lower-body negative pressure (LBNP), respectively. Whereas the latter experimental models of hypotension evoke marked elevations in sympathetic nervous activity, the use of SNP seems to help facilitate CA via direct cerebral vasodilatation irrespective of modest increases in sympathetic activity. In other words, while all models of hypotension should theoretically result in some cerebral vasodilatation (i.e. CA), the use of SNP seems to cause additional dilatation (i.e. further facilitation of CA).

Global and regional changes in CBF regulation during experimental hypotension

Regulation of ICA and VA blood flow with alterations in P_{aCO_2} is also somewhat equivocal and may be related to the different physiological stresses elicited by different models of hypotension. Lewis and colleagues (2015) reported that independent of P_{aCO_2}, the reduction in global CBF with hypotension (i.e. 20% reduction in MAP) is influenced by *vasoconstriction* of both the ICA and VA. In contrast, in the study by Olesen *et al.* during poikilocapnic conditions (i.e. reduction in P_{aCO_2} from 41 to 39 mmHg), the 17% SNP-induced reduction in MAP evoked *vasodilatation* of both ICA and VA. Additionally, even at the highest rate of SNP infusion – provoking a 31% reduction in MAP – P_{aCO_2} was only lowered to 37 mmHg in the study by Olesen *et al.* compared to a marked reduction in P_{aCO_2} of 26 mmHg with a modest 20% decrease in MAP via LBNP by Lewis and colleagues (2015). The inconsistency between constriction *vs.* dilatation of the cerebral arteries is likely explained by differences in sympathetic activity and, therefore, differences in hyperventilatorily induced reductions in P_{aCO_2} evoked by LBNP and SNP.

Consistent with the Olesen *et al.* study, Sato and colleagues (2012) reported a preserved VA blood flow response to orthostatic stress (e.g. induced via 60° head-up tilt), indicating CBF regulation favouring the vertebro-basilar cerebral circulation

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supplying important cardiac, vasomotor and respiratory control centres. In contrast, Lewis *et al.* (2015) reported that VA and not ICA blood flow was sensitive to changes in hypotension and related hypocapnia. The relative reduction in regional VA blood flow by Lewis *et al.* (2015) was significantly correlated with the respective level of hypocapnia (i.e. 2.3% reduction in VA blood flow per mmHg reduction in P_{aCO_2}); these data indicate that VA reactivity to CO_2 is present during LBNP-induced hypotension. As recognized by Olesen *et al.* a future perspective will be to investigate the effect of SNP on CBF when P_{aCO_2} is maintained. Alternatively, the influence of systemic hypotension with and without SNP on CO_2 reactivity can also be explored.

Clinical relevance

Notably, SNP is an endothelium-independent relaxation agent that lowers MAP via systemic vasodilatation; however, SNP may also reduce CBF. This SNP-induced decrease in CBF may be related to arterial hypotension as well as an elevation in intra-cranial pressure (ICP), thereby reducing both MAP and cerebral perfusion pressure (CPP), respectively (i.e. CPP = MAP – ICP). Additionally, in some locations, SNP is used clinically to induce hypotensive anaesthesia to reduce surgical blood loss, and thus it is important whether SNP reduces the lower limit of CA or not. Notably, hypotension-induced hyperventilation and subsequent reduction in P_{aCO_2} may influence regional CBF regulation. As such, the contradictory reports of SNP on CBF may be related to reductions in P_{aCO_2} and thereby CBF. Additionally, irrespective of systemic hypotension, SNP may also directly influence both the extra- and intracranial cerebral arteries, thereby possibly contributing to and facilitating CA via additional cerebral vasodilatation. A future consideration for the current results from Olesen *et al.* would be to explore the effects of SNP on CBF regulation when MAP is maintained, perhaps with direct ICA administration of SNP utilizing carotid duplex ultrasound or magnetic resonance angiography assessment of CBF. This method would allow for cerebral vasodilatation via direct increased cerebral NO availability while controlling for the influence of systemic hypotension. Alternatively, the influence of SNP on CBF may be investigated in patients with neurological disease or traumatic brain injury who have been instrumented with a ventricular catheter for continuous ICP measurement. This assessment would further explain the effects of SNP on CBF regulation with the competing influence of a change in MAP.

Experimental considerations

Olesen *et al.* estimated changes in MCA diameter by assuming similar changes in blood flow for the ICA and MCA. With the observed decrease in MCAv with progressive infusion of SNP (by 14 ± 7% and 25 ± 10%, respectively), Olesen *et al.* estimated an increase in MCA diameter at both infusion rates (by 12 ± 7% and 18 ± 8%, respectively). Consistent with these results, Lewis *et al.* (2015) reported that independent of hypocapnia, the reduction in ICA and VA blood flow due to hypotension was consistently larger than the decrease in MCAv and PCAv, respectively; these data indicate that TCD measures of blood velocity underestimate changes in CBF during hypotension. Additionally, although the attempt to *post hoc* correct for P_{aCO_2} reductions holds merit, an improvement in the current study design would be to utilize an approach

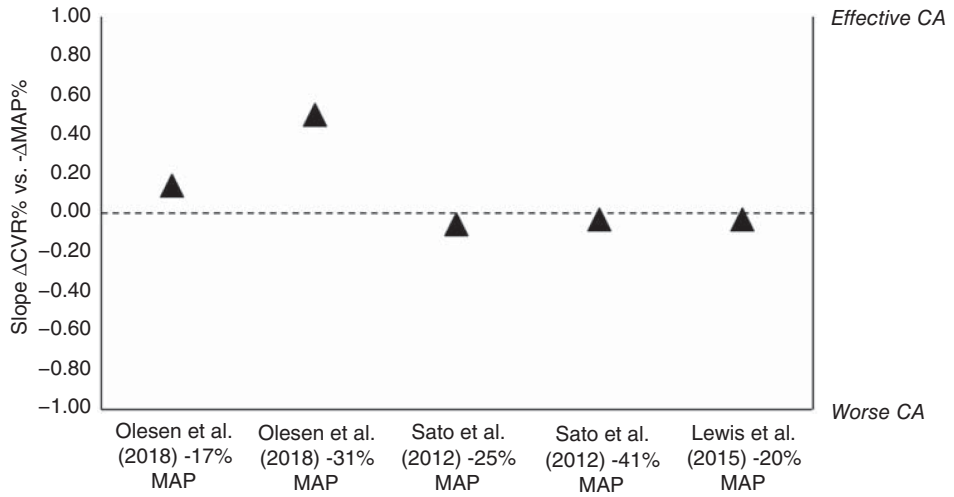

Figure 1. Summary of the key studies that have investigated cerebral blood flow changes during systemic hypotension
The slope of cerebral autoregulation (CA) is percentage change in cerebrovascular resistance (i.e. CVR = MAP/CBF; ΔCVR%) and mean arterial pressure relative to baseline values (−ΔMAP%) and is calculated via the regression coefficient from each of the estimated equations. These values are 'uncorrected' for changes in arterial CO_2 tension (P_{aCO_2}) in poikilocapnic conditions. A CA slope of 1 would correspond to complete CA (i.e. ΔCVR% = ΔMAP% for a constant CBF), and a value of 0 corresponds to no CA (i.e. ΔCBF% = ΔMAP% without any changes in CVR). The unexpected 7% increase in global CBF with modest hypotension (i.e. −17% MAP) is notable. As MAP was further reduced by −31%, the CA slope increased; these results indicate lower CVR for a given decrease in MAP. Lastly, the results by Sato *et al.* (2012) and Lewis *et al.* (2015) indicate less effective CA during the respective reductions in MAP.

to 'clamp' P_{aCO_2} directly independent of ventilation. Lastly, while pharmacologically induced hypotension elicits 'static CA' reported by Olesen *et al.*, the studies by Lewis *et al.* (2015) and Sato *et al.* (2012) reflect 'dynamic CA', thereby further adding to the experimental difficulties and interpretation of MAP control. Overall, Olesen *et al.* have offered valuable insights on cerebrovascular regulation during pharmacologically induced hypotension and have provided direction for many future follow-up studies.

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Additional information

Competing interests

None declared.

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