On the regulation of the blood supply to the brain: old age concepts and new age ideas

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THE CRITICAL IMPORTANCE of cerebral blood flow (CBF) control was reported in 1890 in a landmark publication by Roy and Sherrington (15). Although the concept was not fully accepted until confirmed by more sophisticated methods of CBF assessment, these authors postulated that local changes in cerebral functional activity and perfusion are coupled. In this issue of the Journal of Applied Physiology, Brassard and colleagues (3) add valuable new insight into the fundamental mechanisms that regulate blood supply to the brain. At rest and during progressive elevations in exercise intensity, they examined the influence of acute phenylephrine-induced changes in blood pressure on transcranial Doppler (TCD)-determined middle cerebral artery (MCA) mean blood flow velocity ($V_{\text{mean}}$) and near-infrared spectroscopy (NIRS)-derived frontal lobe oxygenation ($\text{ScO}_2$). At rest, consistent with another recent report on this topic (7), mean arterial blood pressure (MAP) was increased by 20% and MCA $V_{\text{mean}}$ was increased by 10% at the highest doses of phenylephrine; at these time points, $\text{ScO}_2$ was reduced by 7%. However, with progressive increases in exercise intensity, the phenylephrine-induced changes in MCA $V_{\text{mean}}$ and $\text{ScO}_2$ were abolished. The authors concluded that phenylephrine leads to a differential influence on CBF and cortical oxygenation and that this effect is abolished by exercise-induced elevations in cerebral metabolic rate.

These new findings are important. Clinically, while a 7% reduction in cerebral oxygenation may seem small, a drop of 13% is associated with cerebral ischemia (1). Interestingly, a recent report showed a 14% decrease in $\text{ScO}_2$ with the utilization of phenylephrine in hypotensive patients undergoing elective surgery (13). Therefore, the clinical use of phenylephrine to correct for hypotension may actually have a negative impact on brain oxygenation. At a fundamental level, the findings of Brassard et al. (3) challenge us to reappraise basic assumptions related to human CBF control (Fig. 1) and invite new questions to be raised.

Is the Cerebrovascular System Under Adrenergic Control?

Both TCD and NIRS provide sufficient temporal resolution to assess the dynamic relationship between blood pressure and CBF. However, despite the widespread application of TCD and NIRS in human physiological research, the results of Brassard et al. (3) suggest that the information derived from these methods is not fully understood and, indeed, that common experimental interventions might alter their interpretation. For example, a bolus dose of the $\alpha_1$-adrenergic receptor agonist phenylephrine elicited reciprocal, rather than parallel, changes in MCA $V_{\text{mean}}$ and $\text{ScO}_2$, a finding consistent with recently reported data (7). Brassard et al. speculate that the reduction in $\text{ScO}_2$ and increase in MCA $V_{\text{mean}}$ may have been due to direct vasoconstrictive effects of phenylephrine on cerebral conduit and resistance vessels. Although this hypothesis is plausible, several aspects should be carefully considered.

Vasoconstriction of the MCA as a mechanism to explain a reduction in $\text{ScO}_2$ is possible, given that reductions in MCA caliber would lead to decreased CBF; however, this contrasts with human and animal studies that have reported negligible changes in CBF with intra-arterial injections of adrenergic agonists. Notably, rare conscious human recordings of internal carotid artery blood flow, using an electronic flowmeter, showed no flow changes for $\geq 20$ s after injection of norepinephrine (5), a finding indicative of absent adrenergic modulation of cerebral conduit vessel tone. If the MCA were also devoid of any significant adrenergic modulation, the rise in MCA $V_{\text{mean}}$ following phenylephrine injection observed by Brassard et al. (3) might be consistent with an increase in CBF, rather than a drug-induced decrease in vessel caliber. However, if we consider that MCA diameter remained unchanged and, therefore, that CBF was increased, what then accounts for the reduction in $\text{ScO}_2$ following phenylephrine injection?

Thus the findings of Brassard et al. (3) lead us to a controversial body of research suggesting that cerebral sympathetic activity is actively engaged in CBF control (16), but important knowledge deficits remain. For example, although changes in adrenergic activity may explain the reduction in $\text{ScO}_2$ following phenylephrine injection, whether these effects were due to the direct action of phenylephrine per se or, rather, changes that occurred secondary to the transient hypertension remains unknown. A direct effect of the drug cannot be excluded; however, evidence indicates that the intact blood-brain barrier prevents intravascular catecholamine release from binding to $\alpha_1$-adrenoreceptors of cerebral arterioles (6, 10, 12) and should, therefore, not be confused with vessel constriction due to perivascular release of endogenous catecholamines. Moreover, although the integrity of the blood-brain barrier can be compromised by raised intravascular pressure, which can lead to “leak through” of intravascular catecholamines, this mechanism is likely relevant only following sustained periods (hours) of extreme hypertension (i.e., MAP > 190 mmHg) (9). As recognized by Brassard et al. (3), an indirect effect could also account for their observations; whereas peripheral sympathetic nerve activity falls during acute hypertension (due to baroreflex-mediated inhibition), direct recordings in superior cervical ganglion of sheep indicate that the opposite occurs in the brain: cerebral sympathetic nerves are activated during...
acute hypertension, not hypotension (4). Thus, cerebral vessels may constrict due to an increase in perivascular sympathetic activity secondary to the phenylephrine-induced transient hypotension. This hypothesis is supported by recent studies showing that norepinephrine plasma kinetic measurements made with internal jugular venous sampling reflect extrinsic cerebrovascular sympathetic activity (11). However, in contrast, Bevan et al. (2) found that, compared with the middle meningeal and superficial temporal arteries, fresh human pial arteries received sparse adrenergic/sympathetic innervations and showed only marginal responsiveness to transmural nerve stimulation and topical norepinephrine. Therefore, the findings of Brassard et al. call for new research to determine if there is differential regulation of peripheral vs. cerebral sympathetic nerve activity in humans but, importantly, to explain how cerebral sympathetic activity contributes to CBF control, given the apparently low innervation density of human cerebral resistance vessels.

Is Cerebral Metabolism the Predominant Regulator of CBF?

The clear findings from Brassard et al. (3) show that exercise-induced elevations in cerebral metabolic rate abolished phenylephrine's differential influence on CBF and oxygenation at rest. Indeed, during functional activity or exercise, elevations in cerebral metabolism (i.e., neuronal demand) require increased CBF to deliver the oxygen required for aerobic metabolism of the brain. As summarized recently (14), these findings confirm that the vasodilatory effects of the exercise-induced increase in brain metabolism can override the effects of drug-induced changes in blood pressure/sympathetic nerve activity, as well as other factors such as hypocapnia. Thus, collective evidence supports cerebral metabolism as the predominant regulator of CBF.

In conclusion, the elegant findings of Brassard et al. (3) have allowed us to summarize the current knowledge and controversial areas about our understanding of CBF regulation. Future directions of research, ideally combining additional functional imaging with invasive procedures, have been proposed. Without improvement to our rudimentary understanding of the basic processes governing cerebrovascular physiology, the task of bettering our comprehension of cerebrovascular pathology and then developing novel therapeutic targets for future stroke treatment will be very difficult.

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