Response to Letter Regarding Article, “Relative Contributions of Sympathetic, Cholinergic, and Myogenic Mechanisms to Cerebral Autoregulation”

We thank Dr. Shang for his interest in our study.2 We assessed cerebral autoregulation based on the relation between fluctuations in arterial pressure and those in middle cerebral artery blood flow before and after pharmacological blockade of 3 proposed mechanisms. The data suggested that α-adrenergic, cholinergic, and myogenic mechanisms collectively accounted for 62% of the relation between pressure and cerebral blood flow. However, implicit in our approach was the assumption that middle cerebral artery blood flow responses encompass the entirety of autoregulation across the cerebrovascular bed within the middle cerebral artery territory.

In his letter, Dr. Shang suggests that this assumption may be in error. In particular, he points out that regulation of the cerebral vasculature is segmental. First, there are fundamental differences in receptor expression (eg, a shift from α- to β-adrenergic receptors) and myogenic responses along the arterial tree. Second, pial arteries are primarily innervated by extrinsic (peripheral) nerve fibers, whereas parenchymal arteries are innervated by intrinsic (central) nerve fibers. And third, although both extrinsic and intrinsic fibers include noradrenergic and cholinergic projections, intrinsic ones also include GABAergic, dopaminergic, and serotonergic projections.3 Dr. Shang points out that given differences in control of pial versus parenchymal arteries, our approach may not account for the regulation of blood flow in parenchymal arteries and that this may underlie the remaining unexplained variance in the pressure–flow relation. Indeed, this is both a valid and an important point, and we completely agree with Dr. Shang. We focused on extrinsic neurogenic (as well as myogenic) mechanisms that have been previously shown to play an important role in shaping the pressure–flow relation in humans, but there is no doubt that a myriad of other mechanisms have intertwined roles in shaping cerebrovascular regulation.

Dr. Shang cites local metabolic factors among these mechanisms. The interaction between cerebral autoregulation (controlling global blood flow) and metabolic demand (controlling regional blood flow) may have significant implications for our understanding of cerebrovascular dysfunction and its clinical sequelae, and thus, warrants further consideration. The ability of the brain to meet local metabolic demand during cognitive tasks relies on both peripheral and central neurogenic control. Intrinsic innervation targets not only parenchymal arteries and arterioles but also astrocytes surrounding the parenchymal vessel walls as the arterioles penetrate deeper into the brain.4 This functional neurovascular unit of parenchymal arterioles, astrocytes, and nerve fibers modulates regional blood flow in response to local metabolic demand. However, the pial arteries operate as the main site of global flow control by offering the greatest resistance to flow. This suggests that regional blood flow in response to metabolic demand may not be increased effectively unless larger upstream pial vessels relax. Evidence indicates that under normal circumstances downstream functional hyperemia elicits vasodilation in upstream pial arteries via intramural vascular signaling, ensuring that pial and parenchymal vessels act in concert to meet metabolic demand.5 Thus, any impairment in extrinsic mechanisms that regulate pial arterial responses may affect metabolic responses, and vice versa. For example, some data suggest that neurovascular coupling may be impaired as a consequence of sustained hypertension,6 and given that hypertension is associated with peripheral sympathetic overactivity, reduced ability of pial vessels to dilate may partly underlie impaired neurovascular coupling. Our study explored just 1 component (autoregulation) of this integrated regulatory system, which may be, as Dr. Shang suggested, mostly reflective of regulation of blood flow in pial arteries. Clearly, more work is required to unravel the relative contributions of pial and parenchymal beds as well as global and local mechanisms (ie, autoregulation and neurovascular coupling) to overall cerebrovascular regulation.

Disclosures

None.

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References

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