Reply to Willie

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TO THE EDITOR: We are grateful to Dr. Willie (6) for his letter, which is a welcome contribution to the debate on the complex interaction between cerebrovascular regulatory mechanisms, namely neurovascular coupling (NVC), cerebral autoregulation (CA), and CO2 vasoreactivity (CO2-VR). A relatively large number of independent studies have confirmed that cerebral blood flow (or velocity) reaches zero for values of arterial blood pressure (BP) significantly greater than zero, which defines the critical closing pressure (CrCP) (2). The corresponding inverse slope of the instantaneous pressure-flow relationship has been termed the resistance-area product (RAP) (2). CrCP is considered to play a major role in controlling cerebral blood flow (CBF) (2). One issue raised by Dr. Willie is the extent to which it is possible to identify the main determinants of CrCP and RAP and what role they play in the interaction between NVC, CA, and CO2-VR. The effects of PaCO2 on CBF may be explained by changes in CrCP (2). The influence of metabolic pathways on CrCP is reinforced by studies of NVC (2–4). However, neural activation usually induces simultaneous changes in BP and PaCO2, activating CA and CO2-VR responses, which can then confound the NVC response. To clarify these issues, we have proposed the use of subcomponent analysis (4) and dynamic multivariate modeling (3). The former identifies the separate contributions of BP, CrCP, and RAP to CBF changes. With this method, a strong association was found between concomitant changes in BP and RAP, ascribed to myogenic mechanisms, and between CrCP and the NVC response, assumed to reflect metabolic pathways (4). Although hypocapnia-induced depression of CA led to NVC impairment via insufficient changes in CrCP (1), in acute stroke it was the RAP response that was altered (5). These results suggest that hypercapnia should not be considered a general model for CA impairment because it seems to affect only its metabolic component. Whether the attenuated NVC response in hypercapnia (1) could be due to an attenuated BP increase cannot be completely ruled out by our study. However, it would depend on a causal link between BP and CrCP, something that hitherto has not been described. Furthermore, even if the BP increase was attenuated in the hypercapnic condition, its contribution was not significantly different compared with normocapnia.

Dr. Willie also mentions multivariate dynamic modeling (3). This is a much more computationally intensive technique to quantify the influences of BP, PaCO2, and neural activation, separating the contributions of CrCP and RAP. The influence of BP was confirmed to be effected through changes in RAP (3). However, RAP was also influenced by neural activation and could then also reflect metabolic pathways. Therefore, to address Dr. Willie’s second question, we do not encourage generalizing RAP and CrCP as selective indicators of myogenic and metabolic cerebrovascular regulation, and we have only made such broad associations in the context of each individual study. We strongly advocate further research, including animal studies, to identify the role of CrCP and RAP in different physiological conditions.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

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