Cerebral Blood Volume: Measurement and Change

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INTRODUCTION

An increasingly popular fMRI technique (1,2,3,4,5) uses injected blood pool contrast agents, which persist for several hours in the circulation. Appropriate concentrations of such contrast agents can provide larger activation-related changes than BOLD in MR image intensity, and it is claimed (4) that these CBV changes are better localized to the site of neuronal activity. The recent MRI technique, VASO, developed by Van Zijl and co-workers (6), also provides a measure of CBV changes but without contrast agent, since an inversion pulse is used, with an inversion time that nulls and thus labels blood signal. Comparable studies of CBV have also been performed using optical techniques (7). Here the easily observable changes in optical absorption depending on haemoglobin oxygenation, can be quantified in terms of haemoglobin concentrations (e.g. 8). The optical measure of CBV is taken as the sum of oxy- and deoxyhaemoglobin.

For each of these methods, the time course of activation-related changes in the CBV measure has been compared with the corresponding BOLD time course (1), and the well-known BOLD post-stimulus undershoot has been plausibly explained in terms of a delayed return of venous CBV levels to normal after activation (1,9). However, the concept of cerebral blood volume itself has received very little analysis, although there is a lack of detailed agreement between results (e.g. 8,10) from the three methods outlined above. In order to understand this discrepancy a deeper look is required at what the term can mean—blood plasma volume, total volume of intravascular blood, or volume of haemoglobin. Because MRI contrast agents do not easily penetrate red cells or the blood-brain barrier, such methods measure the first of these (CBVp). The VASO method measures all proton spins in rapid exchange with blood, and thus appears to indicate total blood volume (CBVt). Optical methods clearly measure only haemoglobin volume (CBVh), proportional to red cell volume. However, it is well known (11,12,13) that red cell density in blood, or haematocrit, can vary considerably as it passes through the capillary bed—some capillaries are occasionally even devoid of red cells, while during activation tightly stacked 'rouleaux' of red cells must squeeze their way through. Thus these three methods may show differing time courses during activation. If, for instance, capillaries did not dilate during activation, one should expect a decrease in plasma volume CBVp in the capillary bed as the haematocrit and CBVh rise, while CBVt remains constant. The experimental fact that all three CBV measures increase, even when larger vessels are excluded, implies that capillaries must expand, as confirmed by microscopic studies (12,13). These indicate increases in capillary diameter of 5-10%. Several workers using blood pool contrast agents argue that the dominating increase in CBV is at the capillary level, an idea supported by the apparent improvement in localization of activity (2,4). If surface veins expanded considerably it would be easy to observe in such studies. While large fractional changes in lumen diameter of arteries and arterioles occur during activation (10), the outside diameter of these vessels will change little, due to the conservation of mass of their smooth muscle walls.

This overall increase in CBV, and expansion of capillaries, presents a further considerable conceptual difficulty. The Monro-Kellie Doctrine describes the principles that guide normal intracranial pressure homeostasis. The cranium is a rigid, bony structure unable to accommodate a large increase in volume. The intracranial compartments—brain tissue, CBF and blood--occupy a fixed space and an increase in one compartment can only occur at the expense of another (14,15). The spinal canal provides only a limited extra space with slightly greater compliance to displaced CSF. Current research findings allow estimation of the blood volume changes relating (for example) to a full-field complex visual stimulation. Typically, this will activate perhaps one tenth of the cortex, say 70 ml of grey matter. The resting state blood volume in this activated tissue is about 3 ml, which might increase to about 4 ml during activation. An increase in CBV of 1 ml must then somehow be accommodated. Studies in brain trauma cases (16) of pressure-volume index (PVI), using injections of CSF-substitute into the brain cavity of patients while measuring consequent increases of intracerebral pressure (ICP), show that a bolus of only 1 ml causes a sustained large rise of ICP of some 15%. In itself, by decreasing the arteriovenous pressure difference, this would decrease CBF. To counteract this, in normal brain, an autoregulatory cerebrovascular response would be stimulated, dilation of arteries and arterioles (16). If brain activation could be considered as equivalent to such a bolus injection, and such a response is provoked, the result would be a further increase in CBV—a positive feedback loop unlikely to be operative in normal brain function. Thus such a model for the effects of activation-related changes in CBV is improbable. The question is, what might constitute a more realistic picture?

PROPOSAL

We propose that most of the activation-related increase in CBV comes about by exchange of water between the capillaries and the endothelial cells surrounding them. The important fact is that capillaries are very leaky to water molecules. Most of the water entering the capillary bed is extracted into the tissue (e.g. 17), demonstrating that the endothelium/capillary lumen membranes are highly porous. Regional cerebral blood flow increases by means of increased arteriolar diameter, which increases intra-capillary pressure. This, and the small additional pressure from red cell membranes as they pass, pushes outwards the delicate membrane separating the capillary lumen from the endothelium, decreasing resistance to blood flow and red cell movement, while water molecules simply exchange sides of the membrane. The important point is that there is no bulk volume change, simply a repositioning of the capillary membrane. This mechanism is consistent with the observed changes in capillary diameter, since endothelial cells typically have a thickness of about 5-10% of the lumen diameter. Note that optical data (10) shows very little change in CBVh in veins.

PREDICTIONS AND CONCLUSIONS

One way to evaluate this proposal is to test its predictions. a) If most of the CBV changes occur in the capillary bed, measurements of CBVp, CBVt or CBVh should all show good focal localization to neuronal activity sites. This is already borne out by the work of Harel et al (2) and Vanzetta et al (18,19). b) Because the process of recovery of exchanged water by endothelial cells across the membrane is driven only by osmotic gradients, it is likely to be slow, with a time constant similar to that of the water residue function measured in PET. Thus the capillary membrane itself would form the 'windkessel' of delayed compliance posited by Mandeville et al. This predicts, among other things, that the post-stimulus BOLD fMRI undershoot should be observable in capillary bed voxels, originating there and moving later to the surface draining vasculature—consistent with the recent findings of Yacoub et al (20). c) Measurements of intracranial pressure in animal models should show little change even with widespread cortical activation. This prediction remains to be investigated, although effects of hypercapnia on intracranial pressure have been studied (21), showing an increase of mean ICP only for deep hypercapnia. To allow a full range of brain activations without causing autoregulatory compromise of required local CBF changes, a mechanism is needed that enables local changes in microvascular diameter without entailing global changes in intracranial pressure. Exchange of water between capillary lumen and surrounding endothelial cells could provide such a mechanism.

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