INVITED COMMENTARY

Distinction Between Cerebral Blood Flow and Vascular Activity by PET Tracer Kinetic Analysis: Practical and Physiologic Considerations

Quantitative measurement of cerebral blood flow using PET dates back more than 20 y. The emergence of PET as a clinical experimental tool permitted 3-dimensional measurement of radioactivity within the brain and applications of tracer kinetic analyses to estimate quantitatively various physiologic parameters of the brain. The estimation of cerebral blood flow was one of the earliest and most extensively researched applications by pioneers of PET imaging. Early investigations of cerebral blood flow measurements commonly used Kety's (*1*) 1-compartment model, in which radioactive water was treated as a freely diffusible tracer between blood and brain. However, the diffusibility of water across the blood-brain barrier was questioned (*2–5*), and 2-compartment models including a vascular component subsequently were developed (*6,7*). Ohta et al. (*8*) from the Montreal Neurological Institute examined further influences of residual vascular activity in the estimation of cerebral blood flow and introduced a 2-compartment model that included an "apparent vascular distribution volume," the parameters of which could be estimated efficiently using a weighted integration method (*9*).

The study presented by Okazawa and Vafaee (*10*) used the 2-compartment model and reexamined influences of the vascular activity in the estimation of cerebral blood flow under basal conditions and visual stimulation using statistical parametric mapping. As has been reported (*8*), a conventional 1-compartment analysis resulted in overestimation (though not significant in this study) of true water clearance in brain regions with greater vascularity. The distribution of such overestimation is better appreciated in 3 dimensions by means of statistical parametric mapping (Fig. 4). The authors also confirmed the work of Koeppe et al. (*5*), which showed that eliminating initial dynamic frames in a 1-compartment autoradiographic approach could reduce overestimation inherent from vascular activity. However, even when optimal elimination of initial dynamic frames was conducted, there still remained overestimation of cerebral blood flow in comparison with estimation by the 2-compartment model (Table 1). These findings indicate that the use of the 2-compartment model in conjunction with dynamic PET imaging has an advantage in estimating absolute levels of cerebral blood flow with minimal influences from residual vascular activity because of the limited diffusion of water.

Cerebral blood flow and vascular distribution volume were also examined within brain regions where transient hemodynamic changes were evoked by sensory stimulation. The authors used visual stimulation delivered by a reversing checkerboard pattern. When comparing 1-compartment and 2-compartment models, 2 important observations emerged, as was shown previously with vibrotactile stimulation (*11*). First, increased neuronal activity in the occipital cortex was associated with increased cerebral blood flow and increased vascular distribution volume, which could be demonstrated by the 2-compartment model. Because the estimated vascular distribution volume by the 2-compartment model is reported to reflect radioactivity in the arteries, arterioles, and a small fraction of the capillary (*12*), this finding indicates the presence of arterial hyperemia at activation foci. This is an interesting contrast to functional MRI (fMRI), which detects blood oxygenation level dependent signals primarily arising from draining venules (and parenchyma, particularly with a high magnetic filed scanner) near activation foci (*13*). Second, peak locations of changes in cerebral blood flow and vascular distribution volume revealed by the 2-compartment model were not identical. The previous (*11*) and current study (*10*) showed differences of several millimeters between peak changes of cerebral blood flow and vascular distribution volume. The peak changes of vascular distribution volume were located closer to arterial vascular trees (*11*). The peak change detected by a conventional 1-compartment model resides between these 2 peaks. Similarly, the nonquantitative 1-compartment autoradiographic approach commonly used in brain activation studies suffers from a mixture of changes in blood flow and arterial vascular volume, which makes comparisons between PET and fMRI signal localization in relation to local neuro-

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nal activity even more difficult (*14*). The use of the 2-compartment model improves spatial accuracy in identifying regional cerebral blood flow changes that are associated with evoked local neuronal activity in brain activation studies.

Better quantification of cerebral blood flow and better localization of brain activation can be achieved by the proposed 2-compartment model. Should this technique routinely be used in cerebral blood flow measurements? For the purpose of better quantifying cerebral blood flow in certain brain disorders, such as strokes, the 2-compartment model minimizes potential overestimation of cerebral blood flow caused by vascular activities. This is advantageous if the primary goal of the investigation or clinical application is to measure quantitatively local cerebral blood flow. For brain activation studies, some practical and physiologic issues need to be addressed. One of the practical issues is the requirement of arterial blood sampling. Brain activation studies typically require repeat imaging with different types of stimulation or task paradigms. In addition to the somewhat invasive procedure of arterial catheter placement, the total amount of blood withdrawn during the study cannot be ignored. Although peripheral arterial sampling is nothing extraordinary to brain investigators who perform much more invasive and complex interventions to research subjects, frequent and repeat blood sampling introduces additional uncertainty and increases the potential for technical error.

One assumption of brain activation studies is the physiologic coupling between local neuronal activity and blood flow. However, absolute levels of cerebral blood flow can be modulated by factors independent of local neuronal activities. For example, the plasma carbon dioxide level is a significant factor that influences global and local cerebral blood flow (*15*). In this regard, an absolute level of cerebral blood flow is not a sensitive or specific marker of neuronal activity (*16*), and proper data normalization procedures can identify regional cerebral blood flow changes associated with neuronal activities sensitively and semiquantitatively (*17*,*18*). Attempts to measure absolute levels of cerebral blood flow changes quantitatively have been largely abandoned in brain activation studies for this reason. Another factor that can potentially bias cerebral blood flow measurement that is often overlooked in brain activation studies is the assumption of a physiologic "steady state" of neural activities and cerebral blood flow changes evoked by task or stimulation. For example, when constant repetitive nociceptive stimuli are given to subjects, neuronal activities within the brain gradually can change within a minute, partly because of spatial and temporal summation (*19*). Neuronal activities relating to attention, anxiety, tolerance, and fatigue during a single imaging session can potentially fluctuate and influence local neuronal activities and patterns of activities. These changes can be difficult to appreciate unless they are specifically investigated. Changes in neuronal activities during image acquisition were shown to bias significantly the final estimation of cerebral blood flow in a conventional autoradiographic approach (*20*).

In the kinetic models presented in this article, regional cerebral blood flow is assumed to be constant (Fig. 1). In addition, the dynamic imaging method requires longer image acquisition (3 min), compared with a generally shorter acquisition (1 min) for the nonquantitative autoradiographic method that is often used in conventional brain activation studies. The longer scan duration increases likelihood for violation of the physiologic steady state assumption. The magnitude of potential bias introduced by such violations can be estimated for the proposed 2-compartment model. This is an important tradeoff between physics (more imaging data, better accuracy) and physiology (long scan duration, more difficult to maintain physiologic steady state) in the optimization of imaging protocols.

Finally, it is interesting to note that statistical significance in the detection of brain activation was consistently greater with the 1-compartment model compared with the cerebral blood flow maps generated by the 2-compartment model (*10*,*11*). There are 2 probable reasons for this observation. First, the additive effects of increases in cerebral blood flow and vascular volume associated with neuronal excitation produce greater signals at activation foci, despite small blurring effects caused by mismatching of peaks. Second, the precision of parameter estimation generally improves when fewer parameters are estimated. Thus, increased signals and smaller variances at activation foci probably contribute to the greater statistical significance.

This result indicates that the widely used nonquantitative autoradiographic method with proper data normalization is a sensitive way to detect the presence of local neuronal activation evoked by task or stimulation, but with a small compromise in spatial accuracy. Advanced and complex image analysis improves our understanding of local brain physiology and the nature of signals measured by in vivo imaging, but it often comes back to the simplest form when the methodology matures for more general applications.

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