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Feature Article Commentary

Optically quantified cerebral blood flow

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In vivo imaging allows detailed studies of cerebral blood flow and brain metabolism in both normal and pathological states. Since the 1980s, several methods to measure tissue perfusion in the brain have been introduced. Magnetic resonance imaging (MRI) techniques such as blood oxygen level dependent MRI (BOLD MRI) (Sorensen *et al*, 1995) and arterial spin labeling (Buxton and Frank 1997) as well as micropositron emission tomography (Heiss *et al*, 1994) have enabled noninvasive chronic imaging of both regional blood flow changes and absolute perfusion in both humans and animal models. These methods, however, suffer from poor spatial resolution and are mainly useful when studying regional blood flow in the brain. Intrinsic optical imaging (Ts'o *et al*, 1990) enables higher spatial resolution mapping of changes in blood volume. Laser Doppler spectroscopy (Eyre *et al*, 1988) enables measurement of relative changes in blood flow speeds averaged over $\sim$1-mm^2 cortical areas, while laser speckle contrast imaging (Boas and Dunn, 2010) enables these relative blood flow changes to be imaged with a spatial resolution of $<100\,\mu$m. None of these optical techniques, however, can accurately resolve changes in flow in individual microvessels or determine the absolute perfusion of cortical tissue. When absolute speed measurement of individual vessels is required, two-photon excited fluorescence (2PEF) microscopy has been the tool of choice (Schaffer *et al*, 2006). It is, however, limited to measurement of flow speed in vessels that are oriented parallel to the imaging plane, and measurements need to be made one vessel at a time, which is a time-consuming process. Currently lacking is an imaging technique that enables absolute blood flow speed measurements in multiple individual vessels at once. In this issue of *JCBFM*, Srinivasan *et al* (2011) introduce the use of Doppler optical coherence tomography (DOCT) (Chen *et al*, 1997) to fill this gap.

Srinivasan *et al* demonstrated DOCT as a viable technique to quantify blood flow across many individual vessels simultaneously in the brain of live, anesthetized rodents. Doppler optical coherence tomography measures the Doppler shift of light scattered off from moving red blood cells to quantify flow speeds, with three-dimensional spatial resolution obtained from the use of coherence tomography to isolate the signal from a single axial location and laser scanning to map the two lateral dimensions. Using this tool, absolute blood flow velocity can be rapidly determined in blood vessels that contain an axial projection. In their article, Srinivasan *et al* demonstrated that DOCT measurements of flow speed and vessel cross-sectional area showed conservation of volumetric flow along non-branching and branching vascular segments, confirming the quantitative accuracy of the method. They further demonstrated that DOCT enables straightforward measurement of blood flow speed in penetrating arterioles and ascending venules (the vessels most difficult to characterize with 2PEF), with all these vessels being within an $\sim$1-mm^2 field of view measured in an $\sim$1-min-long scan (as opposed to 2PEF, which allows measurement of only one vessel every few minutes). To obtain a quantitative estimate of tissue perfusion, the authors summed the volumetric flow from all ascending venules in a patch of cortex and estimated the cortical volume that is served by these vessels. They found strong correlation between this DOCT measurement of tissue perfusion and the values obtained from a standard hydrogen clearance method (von Kummer *et al*, 1986). The DOCT measurements, however, consistently yielded higher values for tissue perfusion, likely reflecting depressed blood flow due to tissue damage from the electrode used for hydrogen clearance measurements. The DOCT technique was best suited to measurements in the top 150 μm of the brain and in larger blood vessels rather than in capillaries, and the technique is optimal for flow speeds between $\sim$0.5 and 10 mm/s with current DOCT systems. Overall, the approach of summing the volumetric flow measured by DOCT of all the ascending venules in a patch of cortex appears to provide a robust tool for minimally invasive measurements of absolute brain tissue perfusion with a spatial resolution that is not matched by previous methods, opening the door to studies of how blood flow is altered at the microvascular scale by physiological and pathophysiological events in the brain.

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