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Two-photon microscopy measurement of cerebral metabolic rate of oxygen using periarteriolar oxygen concentration gradients

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Abstract:
Objective. The cerebral metabolic rate of oxygen ($CMRO_2$) is an essential parameter for evaluating brain function and pathophysiology. Measurements of $CMRO_2$ with high spatio-temporal resolution are critically important for understanding how the brain copes with metabolic and blood perfusion changes associated with various clinical conditions, such as stroke, periinfarct depolarizations, and various microvasculopathies (e.g., Alzheimer's disease, chronic hypertension). $CMRO_2$ measurements are also

important for understanding the physiological underpinnings of functional Magnetic Resonance Imaging signals. However, the currently available approaches for quantifying $CMRO_2$ rely on complex multimodal imaging and mathematical modeling. Here, we introduce a novel method that allows estimation of $CMRO_2$ based on a single measurement modality - two-photon phosphorescence lifetime microscopy (2PLM) imaging of the partial pressure of oxygen (PO_2) in cortical tissue.

Methods. We measured the baseline $CMRO_2$ in anesthetized rats, and modulated tissue PO_2 levels by manipulating the depth of anesthesia. $CMRO_2$ is estimated by fitting the changes of tissue PO_2 around cortical penetrating arterioles with the Krogh cylinder model of oxygen diffusion.

Results. Using this method, we obtained a mean baseline $CMRO_2$ of 1.71 ± 0.16 μmol cm^{-3} min^{-1}, within the error bounds of previously reported $CMRO_2$ under similar anesthesia in rats measured by MRI (2.5 ± 1.0 μmol cm^{-3} min^{-1}) [1]. To experimentally manipulate $CMRO_2$, we modulated the level of anesthesia by applying isoflurane (2%) on top of the ongoing alpha-chloralose anesthesia. Adding isoflurane resulted in the measured $CMRO_2$ decreased from 1.56 ± 0.07 μmol cm^{-3} min^{-1} (alpha-chloralose only) to 1.38 ± 0.07 μmol cm^{-3} min^{-1} (combined alpha-chloralose and isoflurane).

Conclusion. Our study demonstrates that we can estimate $CMRO_2$ using the Krogh cylinder model based on a single measurement modality - periarteriolar tissue PO_2 measurement by two-photon microscopy in a single plane perpendicular to the vessel axis. With this method, no measurements of blood flow are required for the $CMRO_2$ estimation. This method has a spatial resolution of approximately 200 μm and it may provide $CMRO_2$ measurements in individual cortical layers or within confined cortical regions such as in ischemic penumbra and the foci of functional activation.

[1] P. Hermán, H. K. F. Trübel, and F. Hyder, “A multiparametric assessment of oxygen efflux from the brain,” J. Cereb. Blood Flow Metab. 26(1), 79-91 (2005).

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