Modeling the regulation of cerebral oxygen extraction by flow heterogeneity

S. N. Jespersen[1], M. Ashkanian[1], K. Mouridsen[1], and L. Ostergaard[1]
[1]Center for functionally integrative neuroscience, Aarhus University, Aarhus, Denmark

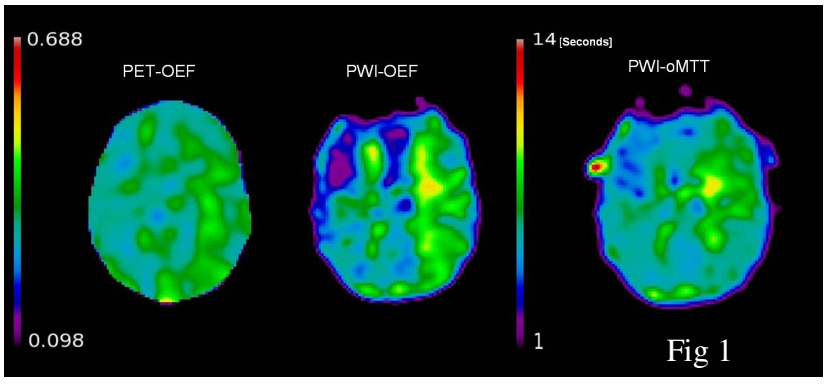
Introduction: The normal heterogeneity of blood flow velocities within the capillary bed has been speculated to constitute a reserve capacity, by which oxygen extraction fraction (OEF) can be increased by homogenization of microvascular flow velocities, even at constant CBF (1). A method by which capillary flow heterogeneity may be derived from dynamic suceptibility contrast MRI ('bolus tracking') experiments has been developed (2), and flow homogenization shown to be associated with high risk of subsequent infarction in acute ischemic stroke (3). Here we present a comprehensive framework for relating flow heterogeneity to deriving OEF from perfusion raw data, and present an initial validation of the approach by comparison to the 'gold standard' O-15 PET method.

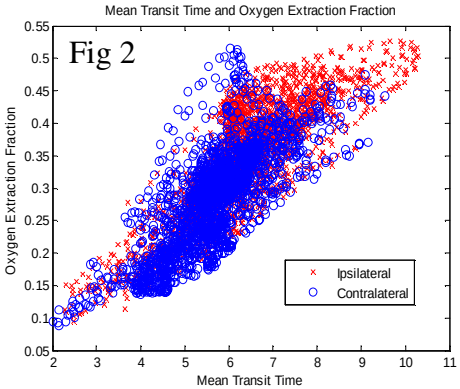
Theory: We developed a framework relating capillary geometry and blood flow to oxygen transport. In particular, we combined the properties of intravoxel flow distributions with an explicit hemodynamic model relating capillary transit time to oxygen extraction fraction. The relation between blood flow and capillary oxygen extraction is similar to earlier models (4,5,6), and includes cooperative oxygen binding to hemoglobin. It is characterized by a first-order rate constant k for unidirectional oxygen transport from capillaries to the site of the consumption. The distribution of transit times is parameterized by a gamma distribution, the parameters of which (α and β) were determined in a voxelwise fashion from a perfusion weighted image (see below). Averaging over the transit time distribution yielded a simple closed expression for OEF as a function of α and β in each voxel.

Methods: To test the theoretical model described above we calculated OEF maps in patients with occlusion of right carotid artery (n=3). All patients had experienced short time episodes of left sided hemiparesis and right sided amaurosis fugax (blindness). The subjects were scanned by positron emission tomography (PET), as the reference modality, followed by T2* Perfusion Weighted Imaging (PWI). We used [^{15}O]-labeled Oxygen and [^{15}O]-labeled H_2O scans to measure cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF). Oxygen extraction fraction maps were then generated by division of parametric maps of $CMRO_2$-and CBF-data. By transforming PET-images to the native space of MRI, we co-registered the resulting PET-OEF to the corresponding PWI-based OEF maps calculated by our model.

Results: In Fig 1 we demonstrate the striking similarity in contrast between the MR and PET images, despite being obtained from fundamentally different modalities. Also shown to the right is an image of mean transit time (MTT) calculated using circular SVD. Critically, the right posterior region in the MTT image appears normal, whereas both PET and MR OEF images demonstrate highly elevated OEF. To verify this point, MR OEF values are plotted against delay insensitive MTT in Fig 2. Clearly, knowledge of one parameter does not determine the other. Finally, we compared the value of the MR OEF of the ischemic side to the healthy. In all patients, a significant ($p<0.0001$) elevation in the ischemic side (0.385±0.140, 0.430±0.138 and 0.460±0.150) as compared to the healthy side (0.311±0.137, 0.331±0.147 and 0.427±0.136) was observed. This is in good agreement with known pathophysiological changes occurring as a result of ischemia. We also found a small regional variability in k, indicating a direct influence of physiological and pathophysiological factors on the basic physical properties of capillary oxygen transfer.

Conclusions: We have presented the basic ingredients of a framework allowing the determination of OEF from perfusion weighted MR data. The preliminary investigation presented here provides encouraging results for the method. A good agreement with PET was found, independence of the common MTT parameter established, and a significant increase in the value of the OEF in the ischemic hemisphere as compared to the healthy was detected. Elaborating the model to account for full diffusive dynamics with a nonvanishing oxygen tension in tissue, and further improving the determination of the blood flow distribution, are at the focus of our current efforts.





References: 1. Kuschinsky W, Paulson OB, *Cerebrovasc.Brain Metab.Rev.* **4**(3):261-86 (1992). 2. Østergaard L, Chesler D, Weisskoff RM, Sorensen AG, Rosen BR, *J Cereb Blood Flow Metab* **19**:690-9 (1999). 3. Østergaard L, A. Gregory Sorensen, David A. Chesler, Robert M. Weisskoff, Walter J. Koroshetz, Ona Wu, Carsten Gyldensted, and Bruce R. Rosen, *Stroke* **31**:1097-1103 (2000). 4. Crone C. *Acta Physiologica Scandivica* **58**: 292 – (1963) 5. Buxton RB. Frank LR *J Cereb Blood Flow Metab* **17**: 64 – 72 (1997). 6. Hayashi T., Watabe H., Kudomi N., Kim K.M., Enmi JI., Hayashida T., Iida H. *J Cereb Blood Flow Metab* **23**: 1314 – 1323 (2003).