BOLD calibration with interleaved susceptometry-based oximetry

Zachary B Rodgers[1], Erin K Englund[2], Maria A Fernandez-Seara[3], and Felix W Wehrli[1]

[1]*Radiology, University of Pennsylvania, Philadelphia, PA, United States,* [2]*Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, United States,* [3]*Neuroimaging Laboratory, Center for Applied Medical Research, University of Navarra, Pamplona, Navarra, Spain*

Introduction. The relationship between blood-oxygen-level-dependent (BOLD) signal and brain oxygen metabolism reflects a complex interplay between multiple factors, including cerebral blood volume (CBV), venous oxygenation (Y_v), tissue properties such as blood vessel diameter, and field strength. This has motivated attempts to 'calibrate' the BOLD signal by solving the relationship between relative changes in BOLD signal and cerebral metabolic rate of oxygen consumption ($CMRO_2$), first described by Davis et al.[1] and shown in [Eq 1]. M is the BOLD calibration factor, representing the maximum possible BOLD signal change with full washout of deoxyhemoglobin, subscript (0) represents the baseline condition relative to stimulus condition (no subscript), □ is the Grubb constant, relating cerebral blood flow (CBF) and CBV, and □ is a B_0-dependent constant reflecting relative intra- and extra-vascular BOLD signal contributions. Calibration is accomplished by measuring BOLD and CBF changes in response to a whole-brain stimulus, often CO_2 or O_2 gas mixture breathing, and assuming specific changes in $CMRO_2$ or CBF to solve for M. *Here, we propose an improved approach to BOLD calibration based on direct quantification of whole-brain Y_v interleaved with the traditional BOLD and CBF measurements.*

Full Davis Model: $\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CMRO_2}{CMRO_{2|0}}\right)^{\beta}\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right)$ [Eq 1]

Davis Hypercapnia Model: $\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right)$ [Eq 2]

Chiarelli Hyperoxia Model: $\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{1-Y_V}{1-Y_{V|0}}\right)^{\beta}\right)$ [Eq 3]

Y_v-Based Model: $\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{1-Y_V}{1-Y_{V|0}}\right)^{\beta}\left(\frac{CBF}{CBF_0}\right)^{\alpha}\right)$ [Eq 4]

Theory. ***Current Models –*** Most BOLD calibration methods use hypercapnia (HC)[1], or more recently, hyperoxia (HO)[2], to induce BOLD signal changes. In the HC approach, CO_2 often is assumed to be isometabolic, allowing [Eq 1] to be simplified to [Eq 2]. This isometabolic assumption is a topic of debate[3], and the relatively strong dependence (large exponent) on noisy ASL data reduces the precision of M. In contrast, HO-based calibration involves measurement of BOLD signal and inference of Y_v based on end-tidal O_2 tension ($P_{ET}O_2$). By assuming HO causes no flow change, the calibration equation can be simplified to [Eq 3]. This model requires an assumed resting Y_v value, which although relatively uniform across the brain[4], varies between healthy subjects[5,6]. Additionally, $P_{ET}O_2$-based measurement of Y_v requires capnography, which may fail in patients with lung pathology. Finally, hyperoxia may cause a small reduction in flow and $CMRO_2$[7], which can be incorporated in the model[2] but must be assumed as the magnitude of flow change cannot be accurately measured with ASL. Recent approaches[8,9] have attempted to combine HC and HO for improved calibration, though this adds time and complexity to the protocol, yet eliminates few of the aforementioned assumptions. ***Y_v-Based Model –*** If whole-brain Y_v is measured alongside CBF and BOLD, a more general model can be applied ([Eq 4]). With this approach, the sole assumption is that in response to a stimulus, relative changes in Y_v are uniform across the brain, however no assumptions are placed on the flow/$CMRO_2$ changes (as these quantities are also measured). Thus, this approach can be used with any stimulus that provokes BOLD signal changes.

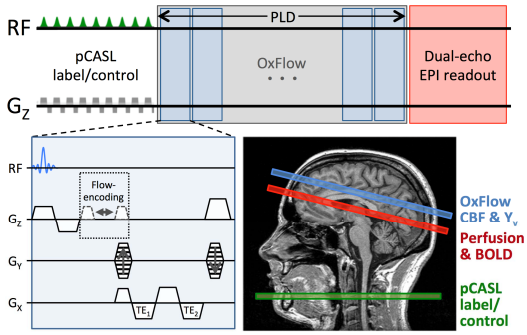

Figure 1. Pulse sequence diagram depicting OxFlow module interleaved within a standard pCASL sequence. Sequence parameters: pCASL: matrix=80×50 (reconstructed to 80×80), FOV=25×25 cm, slice thickness=5 mm, TR/TE_1/TE_2= 3750/ 8.1/52.9 ms. Label duration=1.8 s, PLD=1.8 s, Hanning window, average B_1=1.7 μT, pulse interval=1 ms, G_{max}/G_{avg}=9/1 mT/m. OxFlow: matrix=192×48 (BRISK reconstructed to 192×192), FOV=176×176 mm, slice thickness=5 mm, slice location = 2 cm distal, TR/TE_1/TE_2=17.5/7.2/13.85 ms, VENC=40 cm/s.

Methods. ***Pulse Sequence –*** Simultaneous measurement of BOLD-weighted signal, perfusion, and intravascular Y_v can be achieved by interleaving a velocity-encoded multi-echo GRE (OxFlow)[5,10] acquisition into the post-label delay (PLD) of a pCASL sequence (with dual-echo GRE-EPI readout), similar to the previously described PIVOT technique used in the leg[11] (**Figure 1**). The OxFlow interleave acquires data superior to the pCASL slice to ensure fidelity of the perfusion measurement. OxFlow additionally allows robust quantification of changes in global CBF, which can be used in HO where the flow changes are below the ASL detection sensitivity. ***In-Vivo Experiments –*** All imaging was performed at 3T. *Interleaved sequence assessment*: The impact of the presence and location of the OxFlow interleave on quantification of perfusion and T_2* was assessed by varying the OxFlow imaging location (□z = 20, 30, 60, 100 mm) relative to the EPI slice (which was kept constant). For each OxFlow location, slice-average perfusion and T_2* data were compared to data acquired without OxFlow. *Gas mixture breathing protocol:* MRI data were acquired in three healthy subjects throughout 5 minutes of room air (baseline) and 5 minutes breathing 5% CO_2 in room air (HC). Perfusion was quantified according to Alsop et al.[12] from the tag-control difference between the first EPI echo, while BOLD signal was measured from the average of tag and control images from the second EPI echo. From the OxFlow data, Y_v was quantified by generating phase maps between TE_1 and TE_2, and calculating the difference in phase accrual between blood and surrounding tissue using the infinite cylinder model[5,13]. M-maps were generated from [Eq 3] and [Eq 4] using α=0.18 & β=1.5[9]. In one subject, a Y_v-based M-map was also generated from 100% O_2 gas breathing.

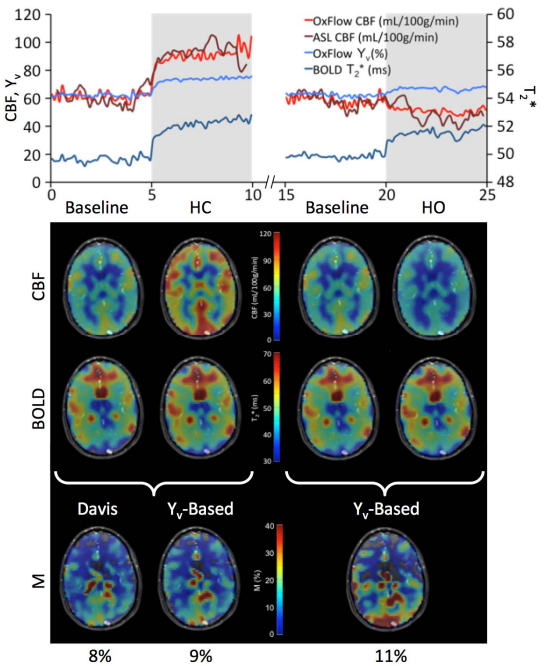

Figure 2. Average time courses and parametric maps for all measurements are shown for a single subject during 5 minutes HC (left) and 5 minutes HO (right). For HC, M maps are in agreement between the established Davis model and the proposed Y_v-based model. For HO, the Davis model fails due to the small flow change measured by ASL. However, using OxFlow-derived global CBF changes the Y_v-based model yields a plausible average M.

Results. ***Sequence Assessment –*** Average perfusion and T_2* were unbiased by the presence or location (up to 20 mm distal from the EPI) of the OxFlow interleave, suggesting that no substantial error is introduced by acquiring OxFlow data in the pCASL PLD. ***M Calculation (Figure 2) –*** Average grey-matter M for the three subjects who underwent hypercapnia was 8±1% using the Davis model, and 7±1% using the Y_v-based model. Both M-maps demonstrate plausible anatomic contrast. HO calibration (using OxFlow data for CBF) yielded a slightly higher M value using the Y_v-based model (M=11%). All reported M-values were normalized relative to a TE of 30 ms.[9]

Discussion and Conclusions. This work demonstrates the feasibility of calibrated BOLD with simultaneous quantification of BOLD, perfusion, and Y_v. The proposed model achieved M-values and maps similar to those of the Davis model, but without any assumptions on the $CMRO_2$ change associated with HC. Furthermore, the method achieved HO calibration without $P_{ET}O_2$ measurement and without assumptions on baseline OEF or flow/$CMRO_2$ changes. Although the pulse sequence as described is limited to a single slice, multi-slice or 3D implementation is possible by interleaving the OxFlow module outside the PLD, at a cost of reduced temporal efficiency. In applying the Y_v-based model to HC, it is also possible to assume uniform $CMRO_2$ changes (quantified from the OxFlow data) rather than uniform Y_v changes. This modification to the Y_v-based model relaxes the assumption of isometabolism required in the Davis HC model, but would be equally sensitive to noisy ASL-derived CBF values. Ongoing studies will investigate these various approaches and further assess the improvement in calibration afforded by the Y_v-based method compared to the Davis/Chiarelli models.

REFERENCES: [1] Davis et al., *PNAS* (1998); [2] Chiarelli et al., *NeuroImage* (2007); [3] Yablonskiy, *JCBFM* (2011); [4] Fox et al., *Science* (1998); [5] Jain et al., *JCBFM* (2010); [6] Lu et al., *JCBFM* (2008); [7] Xu et al., *JCBFM* (2012); [8] Bulte et al., *Neuroimage* (2012); [9] Gauthier and Hoge, *NeuroImage.* (2012); [10] Rodgers et al., *JCBFM* (2013); [11] Englund et al., *JCMR* (2013); [12] Alsop, et al., *MRM* (2014); [13] Fernandez-Seara, et al., *MRM* (2006); ***Grant Support:*** *An award from the AHA, NIH R21-HD069390, T32-EB000814.*