Prospects for rapid $CMRO_2$ quantification with interleaved TRUST, susceptometry-based oximetry, and phase-contrast MRI

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INTRODUCTION: Cerebral metabolic rate of oxygen consumption ($CMRO_2$) is believed to be a more direct measure of neurometabolic function than traditional measures such as CBF or BOLD fMRI. While regionalization remains a major challenge, MR-based methods for whole-brain $CMRO_2$ quantification have the ability to robustly measure $CMRO_2$ at baseline[1,2], in response to physiologic stimuli[3-5], and in a variety of diseases[6,7]. MR-based global $CMRO_2$ quantification methods require measurement of total cerebral blood flow (tCBF), arterial oxygen saturation (Y_a), and venous oxygen saturation (Y_v), which are related by Fick's Equation: $CMRO_2$=tCBF(Y_a-Y_v). Quantification of Y_v poses the greatest technical challenge. Two well established methods for global Y_v quantification are susceptibility-based oximetry (SBO)[8,9] and T_2-Relaxation-Under-Spin-Tagging (TRUST)[10], which quantify intravascular blood susceptibility (X_b) or T_2, respectively, in the superior sagittal sinus (SSS), the largest draining vein of the brain. Recent work has shown that SBO in combination with phase-contrast (PC) CBF quantification (OxFlow) can yield $CMRO_2$ quantification with 3 s temporal resolution[5]. Such high temporal resolution is critical for studying dynamics of the neurovascular response in health and disease and offers a powerful tool for investigating BOLD signal models and calibration. Unfortunately, SBO is sensitive to vessel geometry and requires robust background phase removal. While TRUST has no such geometric limitations, it has inherently lower temporal resolution and requires separate tCBF measurement.

We propose a combined technique – TRUST-Ox – whereby inserting an OxFlow module within the T_1 recovery period of the TRUST sequence, we obviate the need for separate, non-simultaneous tCBF measurement, substantially improving TRUST temporal resolution for $CMRO_2$ quantification and allowing for direct comparison of SBO- and T_2-based Y_v quantification. Further temporal acceleration is achieved by using fewer tag-control image pairs for T_2 fitting.

METHODS: ***TRUST*** **–** The TRUST pulse sequence uses non-selective MLEV-4 CPMG T_2 preparation pulses of varying effective echo time (eTE) following either blood inversion with an adiabatic hyperbolic secant pulse (tag) or application of an equivalent off-resonance pulse without gradient (control). Control–tag subtraction of each eTE image pair isolates the venous blood signal, with slice-selective saturation improving static tissue nulling. T_2 is quantified by mono-exponential fitting of difference signals in the SSS vs. eTE, and Y_v then determined from a calibration curve. Sequence parameters: TR=3s, TI=1200ms, T_2-prep times=0,40,80,160ms, t_{CMPG}=10ms, TE_{EPI}=7ms (5/8th partial Fourier), matrix=64×40, resolution=3.4×3.4×5.0mm. ***OxFlow*** **–** A dual-echo GRE with phase-contrast (PC) flow encoding allows simultaneous acquisition of a field map for X_b quantification and a velocity map for flow determination. X_b (and thus Y_v) can be related to local field offset of the intravascular blood by modeling the vessel as a pseudo-infinite cylinder. Use of keyhole phase-encode reduction and SSS blood flow-based estimation of tCBF[5] allows $CMRO_2$ quantification in just 1420ms with OxFlow. Sequence parameters: TR/TE_1/TE_2=14.8/5.5/10.5ms, VENC=40cm/s, matrix=196×196, resolution=1×1×5mm. ***Combined Method (TRUST-Ox)*** **–** An OxFlow sequence module was inserted into each T_1 recovery period of the TRUST sequence 350ms following global saturation to capture the slice in steady state (**Figure 1**). ***Resting State Validation*** **–** Equivalent TRUST, TRUST-Ox, and OxFlow pulse sequences were run in series for 4 minutes each (10 repetitions TRUST/TRUST-Ox, 80 OxFlow) at baseline, repeated in three healthy volunteers. T_2 values were determined from the TRUST-Ox data using 4, 2 (0 and 80 ms), or 1 (80 ms only) eTE image pair. The 1 eTE image pair data used a single reference eTE=0 image pair for T_2 fitting. ***Apnea Paradigm*** **–** A TRUST-Ox sequence was applied in one healthy volunteer during a 1-minute breath hold, repeated with a 2 eTE and 1 eTE version of the sequence. Data was processed with sliding window reconstruction, producing T_2 values every 6 seconds (2 eTEs) or 3 seconds (1 eTE). All MRI experiments were completed at 3T with a 12-ch. head coil.

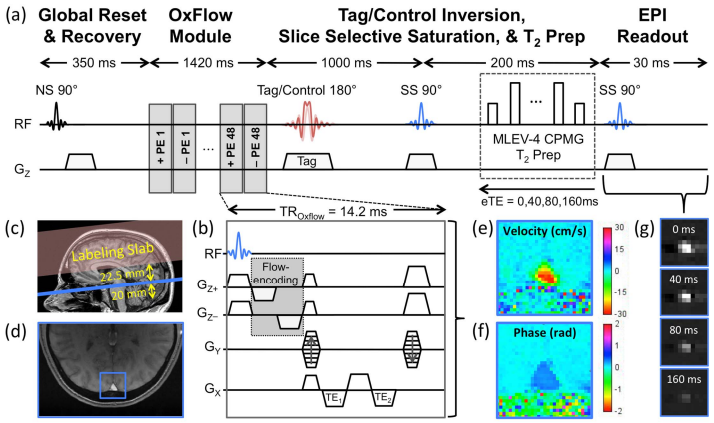

Figure 1: (a) TRUST-Ox pulse sequence with (b) OxFlow module highlighted; (c) relative locations of the labeling slab and imaging slice; (d) OxFlow derived magnitude image with ROI indicating corresponding (e) OxFlow velocity, (f) OxFlow phase, and (g) TRUST difference images.

RESULTS and DISCUSSION: Table 1 shows parameter values quantified from the baseline study. TRUST-Ox derived T_2 values using 4, 2, or 1 eTE(s) differ <2.0 %HbO_2 on average from those of standard TRUST, with only minimal reduction in precision with 2 and 1 eTE(s). SBO-based Y_v and tCBF from TRUST-Ox and OxFlow are also in excellent agreement, as are the simultaneously acquired TRUST-Ox T_2- and SBO-based Y_v values for each subject. The absence of bias introduced from combining the two sequences is not unexpected as the OxFlow module is run during both tag and control, so its effect on the EPI image is removed by control-tag subtraction, and it is itself unaffected by the TRUST measurement due to the global reset. There was little bias when using fewer eTEs, which is attributable to the fact that the 80 ms eTE most closely matches physiologic T_2 values (60-100 ms), and is thus most sensitive to T_2 changes. The 160 ms eTE has very low SNR, contributing little to the fitting and potentially introducing error. **Figure 2** shows Y_v and flow values derived from both the 2 and 1 eTE versions of TRUST-Ox pulse sequence applied during breath-hold. The excellent agreement between T_2- and SBO-based Y_v values suggests that it is possible to use a single 0 ms eTE reference image and dynamically acquire only 80 ms eTE image pairs. This is attributable to the fact that the 0 ms eTE images are unaffected by T_2 changes and minimally affected by Y_v driven T_1 variation (expected to be <0.5% in the physiologic venous blood T_1 range). While M_0 changes secondary to flow variation or movement could potentially affect the 0 ms eTE difference signal, eTE=0 ms signal values from the 2 eTE data set did not differ between baseline and apnea states (p=0.63). Furthermore, Y_v-T_2 and Y_v-SBO showed excellent agreement for both the 2 eTE and 1 eTE image pair data sets, further supporting the reduced eTE approach. These preliminary results suggest that a combined TRUST-Ox pulse sequence can quantify Y_v-T_2, Y_v-SBO, and tCBF simultaneously and without bias relative to the individual sequences, offering a promising approach to dynamic $CMRO_2$ quantification.

Table 1: Mean (SD) parameter values and group-averaged differences between TRUST-Ox and standard method.

Sequence	TRUST	TRUST-Ox					OxFlow	
Parameter	Y_v-T_2	Y_v-T_2	Y_v-T_2 (2 eTEs)	Y_v-T_2 (1 eTE)	Y_v-SBO	tCBF	Y_v-SBO	tCBF
Subject 1	63.8 (1.5)	64.1 (1.7)	64.1 (2.1)	64.5 (2.1)	65.4 (3.7)	45.0 (4.8)	69.0 (4.7)	46.8 (5.9)
Subject 2	62.1 (1.4)	60.5 (1.5)	60.4 (3.0)	60.8 (3.1)	61.2 (1.4)	42.9 (0.8)	61.9 (1.0)	42.9 (0.6)
Subject 3	67.0 (2.3)	69.7 (1.7)	70.3 (2.6)	69.3 (2.8)	72.8 (2.8)	51.7 (3.4)	71.4 (3.2)	47.1 (4.5)
Mean Absolute Diff.	---	1.5	1.8	1.4	1.9	2.1	---	---

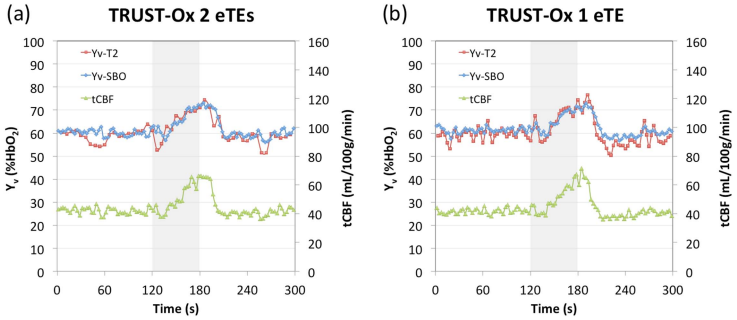

Figure 2: TRUST-Ox acquired parameter values in response to a 1-minute breath hold (indicated by grey box). The experiment was repeated with a 2 eTE (a) and 1 eTE (b) version of the sequence, providing 6 and 3 s temporal resolution for T_2-based Y_v quantification, respectively.

REFERENCES: [1] Jain, et al., *JCBFM* **30** (2010); [2] Xu, et al., *MRM* **62** (2009); [3] Jain, et al., *JCBFM* **31** (2011); [4] Xu, et al., *JCBFM* **32** (2012); [5] Rodgers, et al., *JCBFM* **33** (2013); [6] Lu, et al., *Cereb. Cortex* **21** (2011); [7] Ge, et al., *JCBFM* **31** (2011); [8] Haacke, et al., *Hum. Brain Mapp.* **5** (1997); [9] Fernandez-Seara, et al., *MRM* **55** (2006); [10] Lu, et al., *MRM* **60** (2008). Grant Support: **NIH R21-HD069390 / T32-EB000814.**