QUantitative Imaging of eXtraction of Oxygen and TIssue Consumption (QUIXOTIC) using velocity selective spin labeling

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INTRODUCTION: While oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$) are fundamental quantitative parameters in neuropathology and functional neuroactivation, a robust MRI-based OEF/$CMRO_2$ mapping technique has not been established. A key hurdle in OEF/$CMRO_2$ imaging is absolute quantification of venular oxygen saturation (Yv), which requires isolating signal exclusively from post-capillary venular (PCV) blood on a voxel-by-voxel basis. We propose and demonstrate a novel, voxel-wise method to isolate this signal using venous-targeted velocity selective spin-labeling. We subsequently estimate T_2 of isolated PCV blood, convert T_2 to Yv with a calibration curve, compute OEF from Yv, and estimate baseline $CMRO_2$ from OEF and an additional cerebral blood flow (CBF) measurement. This approach is dubbed QUantitative Imaging of eXtraction of Oxygen and TIssue Consumption (QUIXOTIC) MRI.

THEORY: QUIXOTIC MRI is adapted from velocity-selective arterial spin labeling [1], and uses nearly identical velocity selective (VS) modules to saturate blood spins above a given velocity. The pulse sequence (Fig 1) is played for both tag control acquisitions. The tag acquisition applies a user-defined cutoff velocity (V_C) for both VS Module I (VS1) and VS Module II (VS2), while the control uses V_C for VS1, but disables velocity selection for VS2 (i.e. moving spins are unaffected). Incorporated into VS2 is a T_2-preparation module [2], allowing acquisition at multiple echo times. An important feature of the sequence is an inversion pulse at TI_{INV}, which compensates for T_1 relaxation.

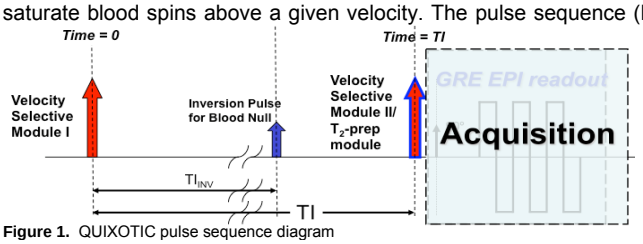

Figure 1. QUIXOTIC pulse sequence diagram

To introduce properties of this sequence, we first neglect T_1 relaxation and the TI_{INV} inversion pulse. At t=0, before VS1, all blood (arterial, venous, capillary) is relaxed. Strong velocity weighting (low V_C) is then applied during VS1 for both tag and control, selecting for slow moving spins in small arterioles, capillaries and small venules ($V < V_C$), but saturating faster moving spins in larger vessels ($V > V_C$). Notably, this large-vessel signal is eliminated on *both* sides of the circulation. After VS1, the inflow time (TI) allows the targeted blood to flow out of the small vessel compartments and accelerate into larger venular vasculature. VS2 is then applied at TI. This time, however, the tag and control acquisition experience different velocity weightings; the tag sees velocity selection at V_C, but the control experiences *no* velocity weighting. Spins that have accelerated above V_C during TI are saturated by the tag acquisition, but left unaltered in the control. As imaging starts immediately after VS2, subtraction of tag from control yields an image weighted to blood that has accelerated from below V_C, to above V_C during TI. Assuming unidirectional flow (arterial to capillary to venous), these spins are venous only. Other spins (static, CSF, non-venular blood) are eliminated via subtraction. If V_C and TI are chosen properly, signal from PCV blood is exclusively targeted.

Of course, T_1 relaxation complicates this idealized model. Spins saturated by VS1 at t = 0 experience recovery. Because velocity selection via VS2 occurs only for the tag and not control, spins from unwanted compartments will partially recover in the control, and fully saturate in the tag at TI. Without compensation, these unwanted spins will not subtract completely, and QUIXOTIC loses venous selectivity. We place an inversion pulse at TI_{INV} to null recovering blood at TI, so spins in this unwanted population are saturated in both control and tag at TI, leaving only desired PCV blood upon subtraction.

METHODS & RESULTS: Four healthy volunteers (2 M, 2 F, 21 to 27 years) were scanned at 3T (Siemens Tim Trio, 32-ch head coil) with QUIXOTIC MRI to image PCV blood (V_C = 2.4 cm/s, x-directed, TI_{INV}=400 ms assuming $T_{1,blood}$ = 1664 ms at 3T [3], TI = 722 ms, τ_{CPMG} of T_2-prep = 10 ms). A GRE-EPI readout (TE/TR = 12/3000 ms, 4 slices, 3.9x3.9x10 mm^3) was used for tag/control image acquisition. Eighty measurements were acquired. The raw data series were motion corrected and smoothed; pairwise subtraction was then performed. The subtraction series was averaged to produce mean PCV-weighted images. Here, mean PCV images at 8 effective TEs (ΔTE = 17.4 ms) were acquired (in principle only two are necessary). A double inversion recovery sequence yielded gray-matter-only (GM) images; these were used as GM ROI, from which venular blood signal intensity (SI) could be measured (with exclusion of an anterior region with signal-dropout artifacts, possibly due to gradient imperfections/eddy currents in VS). GM PCV-blood SI was plotted versus TE, and fit to measure T_2. High-quality fits were obtained for all subjects ($R^2 \geq 0.98$). Figs 2, 3 show representative images at four effective TEs, and a SI vs. TE with T_2 fit, respectively, for subject 1. Yv was calculated from the T_2/Y calibration curve (τ_{CPMG} = 10 ms, Hct = 0.44, 3T) [4,5]. Assuming fully oxygenated arterial blood (Ya = 1), OER was calculated (OER = 1-Yv) [6]. A separate two-minute PASL experiment (PICORE/QUIPSS2, TI_1=700 ms, TI_2 = 1600 ms, Tag = 150 mm) was performed to measure GM CBF and used to calculate GM $CMRO_2$ from OEF [6]. Results are in Table 1. Separately, the T_2-prep module was incorporated into the PASL sequence; experiments targeting arterial blood were performed as described in [4], with $T_{2,arterial}$ > 150 ms, indicating complete arterial oxygen saturation, supporting validity of the QUIXOTIC approach to measure oxygen saturation of deoxygenated venous blood.

DISCUSSION: Values reported for Yv and OEF agree with those acquired by other PET/MR studies, and fall within normal physiological range [4,6-11]. Prior GM $CMRO_2$ measurements are more scarce in the literature; those reported in PET studies [10,11] are lower than those reported here, perhaps due to substantially lower baseline CBF reported by PET imaging, thereby causing an underestimate in $CMRO_2$.

We have shown the feasibility of using QUIXOTIC MRI to isolate PCV blood signal and subsequently measure Yv, OEF, and $CMRO_2$. Advantages of this method are: 1) QUIXOTIC maps venous-only blood, with CSF, static tissue, and capillary/arterial blood eliminated; 2) QUIXOTIC analysis can be performed on a voxel-by-voxel basis, allowing creation of Yv, OER, and $CMRO_2$ maps; and 3) QUIXOTIC generates images every TR, making the technique amenable to functional imaging of Yv and OEF during block-design and event-related fMRI. One such study is described in [12]. To our knowledge, no currently available technique offers these three features. Future studies will explore optimal parameter settings (V_C,TI), employ a spin-echo EPI for rapidly acquiring multi-echo data, and focus on employing velocity selection in the control VS2 module to enable flexible "velocity bracketing;" i.e. targeting venous blood in a specific velocity range, offering better PCV targeting via elimination of blood in larger draining veins.

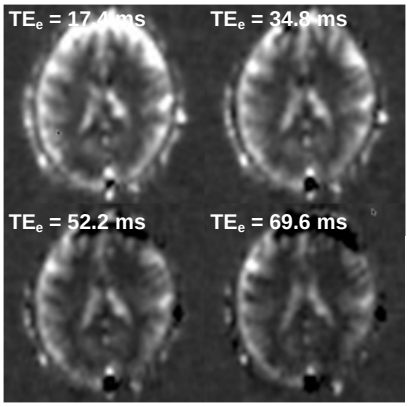

Figure 2. QUIXOTIC images from Subject 1

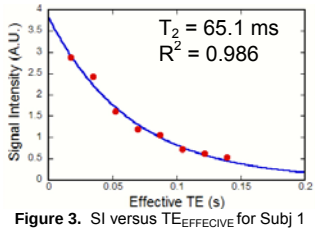

Figure 3. SI versus $TE_{EFFECIVE}$ for Subj 1

Subject	Sex	T_2, PCV(ms)	R^2 of T_2 fit	% SaO2, PCV	OEF	GM CBF (ml/100g/min)	GM $CMRO_2$ (μmol/g/min)
1	M	65.1	0.99	66.7	.333	49.7	1.49
2	M	56.7	0.98	62.0	.380	60.5	2.08
3	F	60.4	0.98	64.2	.358	65.7	2.12
4	F	58.6	0.99	63.1	.369	63.3	2.11
Mean/SD		**60.2 ± 3.6**	**0.985**	**64.0 ± 2.0**	**0.360 ± 0.020**	**59.8 ± 7.1**	**1.95 ± 0.30**

Table 1. Summary of results from VT-VSSL imaging

REFS: 1) Wong et al, MRM 55:1334-41 (2006), 2) Connolly et al, MRM 18: 28-38 (1991), 3) Lu et al, MRM 52: 679-682 (2004), 4) Lu et al, MRM 50:357-363 (2008), 5) van Zijl & Clingman, personal communication, 6) Oja et al, JCBFM 19:1289-1295 (1999), 7) Haacke et al HBM 5:341-346 (1997), 8) Golay et al MRM 46:282-291 (2001), 9) An & Lin JCBFM 20:1225-1236 (2000), 10) Leenders, J Neurooncol 22:269-273 (1994), 11) Madsen et al, JCBFM 15:485-91 (1995), 12) Bolar et al, submitted ISMRM 2009

ACKNOWLEDGEMENTS: NIH R01EB006847, NIH R01EB007942, NIH NCRR P41RR14075, HST Martinos Catalyst Fund, T Benner, T Reese