Quantitative estimation of cerebral oxygenation in micro-vessels

Harshan Ravi[1,2], Jinsoo Uh[3], Peiying Liu[1], Lisa C. Krishnamurthy[1,2], and Hanzhang Lu[1]

[1]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States,* [2]*Department of Bioengineering, University of Texas at Arlington, Arlington, Texas, United States,* [3]*Department of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, United States*

INTRODUCTION: Recently, there is a surging interest in the field to measure venous oxygenation (Y_v) of the brain, because quantitative information of Y_v can be combined with CBF to provide an estimation of cerebral metabolic rate of oxygen ($CMRO_2$), a key marker for tissue viability and brain function. One of the widely used approaches to estimate Y_v is to exploit the calibratable relationship between blood T_2 and oxygenation, by measuring blood T_2 and then converting the T_2 to oxygenation (1). The challenge is to isolate pure blood signal from the surrounding tissue signal. Spin labeling principle has been successfully used to achieve some of these goals. Our group has previously developed a T_2-Relaxation-Under-Spin-Tagging (TRUST) technique that spatially labels the venous blood and acquires image at a downstream location (2). We showed that TRUST MRI is able to reliably estimate Y_v in major veins such as sagittal sinus (3). More recent efforts by several groups (4-6) have extended the method to velocity-selective labeling schemes and have estimated oxygenation in veins with a flow velocity of 2 cm/s or above. However, estimation of oxygenation on the capillary/venule level, which presumably provides spatially more specific information, has not been reported. Here, we report a technique that isolates *microvascular* venous signal and provides an estimation of Y_v in these vessels. Intra-session reproducibility of the technique and response to caffeine challenge were also evaluated.

THEORY and PULSE SEQUENCE: A key component of this pulse sequence (Fig. 1a), dubbed microvascular TRUST or mTRUST, is to isolate post-arterial blood signal (e.g. capillaries, venules, and veins) from arterial blood, CSF, and tissue. Arterial vascular signal is suppressed by a slab-selective inversion RF pulse (denoted Arterial nulling In Fig. 1a) applied below the imaging slice in conjunction with an inversion time that nulls blood signal. CSF signal was suppressed by a slice-selective inversion pulse (denoted CSF nulling in Fig. 1a) applied on the imaging slice with a CSF-nulling TI. Tissue signal was separated from the post-arterial blood signal by taking advantage of their dramatically different apparent diffusion coefficients (ADC) (7). Note that the blood signal has an ADC approximately 20 times greater than tissue according to the random vessel-orientation theory described in the intravoxel-incoherent-motion (IVIM) model (7). Thus, the diffusion-related signal decay follows a biexponential function with a clear separation of fast components from slow components. In practice, one can use several moderate b values and their signal extrapolation to b=0, $\hat{S}_0$, will yield the tissue signal in the absence of any diffusion weighing (Fig. 1b). Computing the difference between $\hat{S}_0$ and the signal acquired without gradient, S_0, will result in a image with pure blood signal. Fig. 1b shows an example of experimental data using such a scheme. Once the post-arterial blood signal is isolated, its T_2 value can be measured by adding various numbers of T_2-preparation pulses (T_2-preparation in Fig. 1a) placed before the excitation pulse.

METHODS: *Experiments:* were conducted on a 3T (Philips) system. 8 healthy subjects were studied (5 males, 3 females, age 26±2 y). Imaging parameters for mTRUST were: TR=8000ms, TI_{CSF}=2356ms, $TI_{arterial}$=1126ms, single slice, thickness 5mm, voxel size 5x5mm^2, 4 b values (0, 100, 250, and 400 s/mm^2), 3 T_2-preparation effective TEs (eTE = 0, 40, 80ms) with τ_{CPMG}=10ms , 6 repetitions. The total duration for each scan was 12 min and 49 sec. To test the intra-session reproducibility of the measure, the scan was repeated once (without repositioning the subject). In a subset of 5 subjects, a second session was performed using caffeine challenge (ingestion of a 200mg tablet), which is known to cause a reduction in venous oxygenation (9). Thus, this allowed us to test the sensitivity of the technique in detecting oxygenation changes. Additionally, CBF was measured in these subjects using pCASL (10). *Data analysis:* As described earlier, the signals at b values of 100, 250, and 400s/mm^2 were extrapolated to b=0. The signal related to post-arterial cerebral blood volume (CBV) was then calculated as: $(S_0(eTE)-\hat{S}_0(eTE))/S_0(eTE=0)$. The calculation was performed for each eTE and the mono-exponential fitting of the signal as a function of eTE yields T2 of blood. Blood T2 was converted to blood oxygenation using a calibration plot established previously (8). For subjects in whom CBF data were available (N=5), a $CMRO_2$ index was computed as $CBF \times (Y_a - Y_v)$, where Y_a was assumed to be 99%.

RESULTS and DISCUSSION: Fig. 2a shows representative maps of post-arterial CBV at different eTE values. At eTE=0, the whole-slice-averaged CBV was 3.2±0.6 % (N=8), which is consistent with the expectation that post-arterial CBV is about 2/3 of the total CBV (~5%). With increasing eTE, the signal related to CBV became darker due to T_2 decay. Mono-exponential fitting of the CBV signal yielded a map of T_2, which was in turn converted to Y_v map (Fig. 2b). As expected, the Y_v map (Fig. 2b) showed less gray-white matter contrast (unlike CBF or CBV), as the oxygen extraction fraction is similar across tissue types. The whole-slice-averaged Y_v was found to be 81±9%. This oxygenation value is higher than those observed in large veins in the literature (2,5), but is consistent with the expectation that the signal detected by mTRUST contains considerable capillary blood, which has a higher oxygenation. ROI analyses were also performed for anterior/posterior halves of the slice, and a strong correlation (cc=0.91, p=0.0015) was observed. Reproducibility evaluations showed that Coefficient of Variation (CoV) between runs were 9±9% (N=8) and 9±6 % for CBV and Y_v, respectively.

Fig. 2c shows post-arterial CBV maps after caffeine ingestion. The group summary results are shown in Table 1. Ingestion of caffeine caused a significant reduction in both post-arterial CBV (p=0.004) and Y_v (p=0.031), consistent with its vasoconstriction effects (9). CBF as measured with ASL also revealed a reduction (p=0.034). The CMRO2 index, on the other hand, showed minimal change (p=0.5).

In summary, we presented a novel MR pulse sequence that is capable of measuring blood oxygenation in post-arterial vessels. In particular, this technique is sensitive to micro-vessels such as capillary and venules, thus complementing and extending the applicability of existing methods which mainly targets macroscopic veins with a flow velocity of 2 cm/s or above. The availability of a micro-vascular oxygenation technique may lay foundations for region-specific mapping of $CMRO_2$ in the future.

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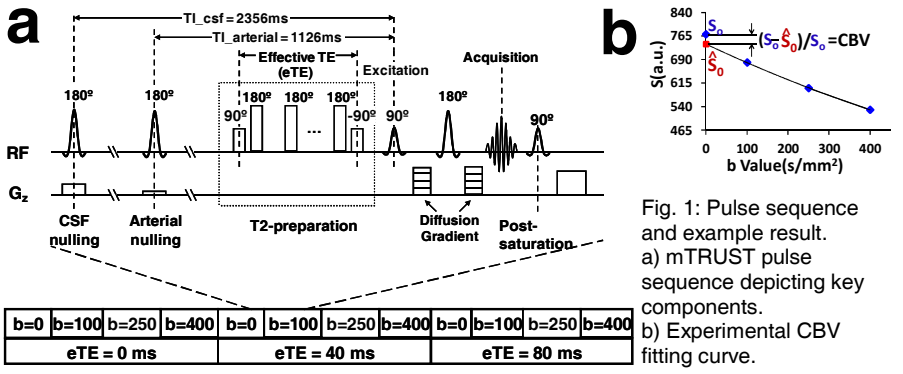

Fig. 1: Pulse sequence and example result. a) mTRUST pulse sequence depicting key components. b) Experimental CBV fitting curve.

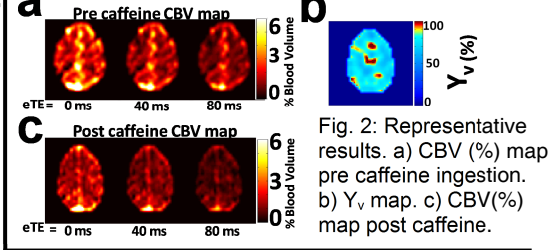

Fig. 2: Representative results. a) CBV (%) map pre caffeine ingestion. b) Y_v map. c) CBV(%) map post caffeine.

Table 1. Summary of caffeine study results.

	Post-arterial CBV(%)	Y_v(%)	CBF (ml/100g/min)	$CMRO_2$ Index
Before caffeine	3.2 ± 0.5	84 ± 2 %	67.9 ± 12.7	10.2 ± 1.5
After caffeine	2.5 ±0.6	78 ± 3 %	50.5 ± 3.4	10.6 ± 1.1
% change	22.2 %	7.0 %	25.7 %	3.9 %
p-value	0.004	0.031	0.034	0.505