Calibration and validation of TRUST MRI for the estimation of cerebral blood oxygenation

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INTRODUCTION: Recently, a T2-Relaxation-Under-Spin-Tagging (TRUST) MRI technique was developed to quantitatively estimate blood oxygenation (Y) via the measurement of pure blood T2 (1). This technique has shown great promise for normalization of fMRI signals (2) and for measurement of the cerebral metabolic rate of oxygen (CMRO2) (3), and has also been used in studies of cognitive aging (4) and multiple sclerosis (5). Methodological studies have also confirmed the sensitivity of this technique to physiologic procedures, e.g. TRUST-derived Y values increase with hypercapnia and hyperoxia, but decrease with caffeine uptake (1, 6). However, a human validation study has not been conducted for TRUST MRI. In addition, the calibration curve used to convert blood T2 to Y has not accounted for the effect of hematocrit (Hct), which could vary slightly across individuals. In the present study, we first used in vitro blood experiments to determine a 3-dimentional calibration plot for blood T2 as a function of both Y and Hct. Next, we used a human hypoxia challenge to control blood oxygenation and compared TRUST-derived arterial Y values to those measured with the gold-standard Pulse Oximeter (PulsOx). In using this procedure, we took advantage of the fact that, unlike venous oxygenation, the brain arterial oxygenation is identical to that in periphery and can be conveniently measured with non-invasive techniques such as PulsOx.

METHODS: *Calibration study:* Sample preparation was similar to that used in our previous studies (7,8). Briefly, bovine blood, which has MR properties similar to human blood, was circulated in a tube (to avoid precipitation) in a 3T magnet. The temperature was controlled using water bath and monitored with a fiber optic sensor. Oxygenation was controlled with a gas chamber and determined with a blood analyzer. Five Hct levels (controlled through mixing of plasma and blood cells) within the physiologic range (0.35-0.55) were studied. At each Hct level, four physiologically relevant oxygenation levels (40-100%) were investigated. Once the blood condition reached a stable state, the TRUST sequence was performed. TRUST MRI uses the spin labeling principle to separate flowing blood signals from static tissue, thereby obtaining pure blood signal (1). T2-weighting was then applied in the sequence with non-slice-selective preparation pulses (inter-echo spacing τ_{CPMG}=10ms). Mono-exponential fitting of the data yields the blood T2 value. For the case of blood sample, there is no need for subtraction, thus the control signal was used for fitting. To establish an analytical relationship between T2, Y and Hct, the blood T2 was fitted to a model described by Golay et al. (9), in which $1/T2=A+B*(1-Y)+C*(1-Y)^2$ and A, B and C are in turn functions of Hct (9). Note that, after characterization of this relationship between T2, Y and Hct, the knowledge of two parameters should allow estimation of the third, which was used in the validation study.

Validation study: Seven young, healthy subjects were studied on a 3T (Philips). TRUST MRI was performed to measure T2 of the arterial blood in major feeding arteries. A pseudo-continuous labeling scheme (10) was used with a labeling duration of 800ms and a short delay of 200ms. The use of these imaging parameters is expected to highlight arterial blood in major arteries before they enter small arteries or arterioles. Major arteries are preferred over smaller arteries, which are known to have a lower Hct, because our blood sampling and Hct measurement were conducted in the large vessels (described below). Other imaging parameters were: voxel size 3.75x3.75x10mm^3, TR=2695ms, four T2-weightings with the following effective TEs (associated with T2-preparation): 0ms, 40ms, 80ms and 160ms, with a τ_{CPMG}=10ms. TRUST MRI was first performed while the subject was breathing room-air. Then the breathing air was switched to 14% O2 (with balance N2) and a waiting period of 10 min was used to allow the arterial oxygenation to reach a new steady state before a second TRUST was performed. After the MRI scan was completed and the subject exited the scanner room, a blood sampling was conducted immediately on the basilic vein in the arm and the Hct was measured with a centrifuge.

RESULTS and DISCUSSION: *In vitro experiment* Fig. 1 illustrates the relationship between blood T2, Y and Hct. The symbols indicate the experimental data points and the mesh shows the model-fitted surface, which can be written as $1/T2=[-13.5+80.2*Hct-75.9*Hct^2]+[0.5*Hct+3.4*Hct^2]*(1-Y)+[247.4*Hct*(1-Hct)]*(1-Y)^2$. *Human experiment* Fig. 2 shows a representative control, labeled and difference image from the TRUST experiment (eTE=0ms). When breathing room-air, the arterial oxygenation as determined by PulsOx was Y_a=97.3±0.6% (mean±SD, N=7). Since Y_a is relative constant across subjects, the T2 is expected to be primarily dependent on Hct. Fig. 3a shows a scatter plot between blood T2 and Hct. Indeed, a significant correlation is observed (P=0.03). For comparison, Fig. 3b shows the in vitro results by fixing Y=97.3% in Fig. 1, demonstrating an excellent agreement between in vitro and in vivo data. During hypoxic breathing with 14% O2, Y_a measured with PulsOx was 84.0±3.6% (mean±SD, N=7), while Y_a derived from TRUST blood T2 and in vitro calibration plot was 83.7±3.6%. Furthermore, a significant correlation was observed between these two measures across subjects (P=0.05). The error between TRUST-derived and PulsOx-measured Y was 0.3±2.6%. An alternative approach to evaluate the data is to use PulsOx-derived Y_a and Hct to predict blood T2 from the calibration plot in Fig. 1, then compare it to the TRUST blood T2 values. The results are shown in Fig. 3c (red symbols: room-air data, black symbols: hypoxia data). A strong correlation is observed (P<0.001).

The present study establishes a comprehensive calibration plot that can be used to convert blood T2 to oxygenation on a Hct-specific manner. We have also used hypoxia as a non-invasive procedure to compare the TRUST-derived oxygenation to that measured with PulsOx. Although this study has primarily focused on the measurement and comparison of arterial oxygenation, the validation results are expected to be applicable for venous oxygenation measures as TRUST MRI can be used for both arterial and venous vessels in the brain (1,4,5,6). The venous oxygenation has a typical range of 50-75% (11) and within this range the slope between T2 and Y is greater (i.e. each unit of Y change will cause a large T2 change), rendering a higher sensitivity and potentially better accuracy for venous oxygenation measurement using TRUST MRI.

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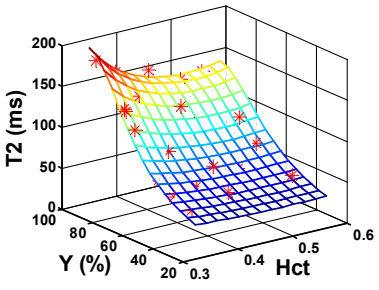

Fig. 1: In vitro data showing the dependence of blood T2 on oxygenation, Y, and hematocrit (Hct). 3T, τ_{CPMG}=10ms.

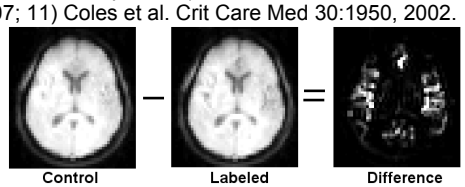

Fig. 2: TRUST MRI images. The subject was breathing room-air for this scan and only images for eTE=0ms are illustrated.

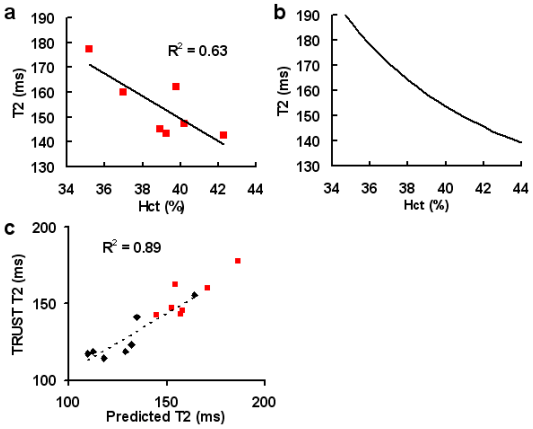

Fig. 3: In vivo TRUST data. (a) Scatter plot between Hct and in vivo T2 for fully oxygenated arterial blood (Y=97%). For comparison, in vitro results at this oxygenation level is shown in (b). (c) Relationship between TRUST-measured T2 and calibration-plot predicted T2 (using PulsOx Y and centrifuge Hct).