Measuring Bi-exponential Transverse Relaxation of the ASL signal at 9.4T to Estimate Arterial Oxygen Saturation and the Time of Exchange of Labelled Blood Water into Cortical Brain Tissue

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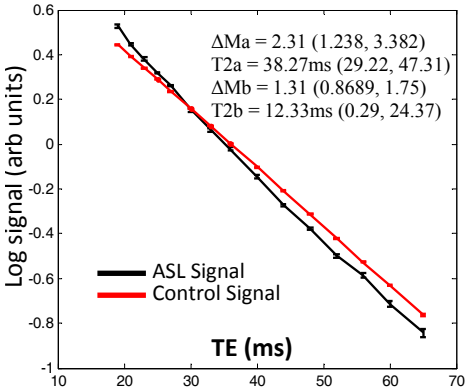
Introduction Flow sensitive alternating inversion recovery (FAIR) is a pulsed arterial spin labelling (PASL) technique in which pairs of images are acquired following global and slice-selective inversion pulses [Kwong *et al.,* 1992]. The time between labelling (inversion) and image acquisition is known as the inflow time (TI). During the inflow time, some of the labelled blood water exchanges into the tissue (extra-vascular [EV]) and some remains in the vessels (intra-vascular [IV]) [Kim and Kim., 2006]. Accurate measurement of the distribution of labelled blood water in the IV and EV space can be used to estimate tissue transit time (δ) which has direct implications for the accuracy of CBF quantification. This is particularly important in cerebral pathology where transit and exchange times may be significantly different in comparison to healthy tissue. In addition, accurate, non-invasive mapping of blood water exchange times may improve understanding of disease processes (e.g breakdown of the blood brain barrier) and allow the assessment of targeted therapies (e.g vascular disrupting agent). At 9.4 T there is a marked difference between the T2 of blood (with an oxygen saturation less than 100%) and EV brain tissue (e.g. T2 of blood with a 90% oxygen saturation =15ms, tissue T2 =38ms) [Lee *et al*., 1999]. In this study we measured the transverse decay of the ASL signal and fit the data to a bi-exponential model in order to estimate the exchange time of labelled blood water into cortical brain tissue.

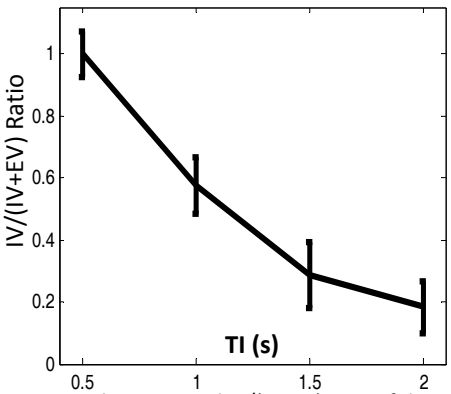
Methods In this investigation, two separate sets of experiments were performed: **part i)** Multiple average acquisitions at a single TI to precisely sample the transverse decay of labelled blood water and therefore to provide novel evidence for bi-exponential transverse relaxation through an unconstrained 4 parameter fit to the decay curve (n=8)**; part ii)** Sampling the transverse decay of the ASL signal over five inflow times to estimate tissue transit time and dynamic changes in blood oxygenation on the arterial side of the vasculature (n=9) . Imaging was performed on male Sprague Dawley rats under 100% medical air and 1.5-2% isoflurane using a 9.4T VNMRS horizontal bore scanner (Varian Inc., Palo Alto, CA). A 72mm inner diameter volume coil was used for RF transmission (Rapid Biomedical) and signal was received using a 4 channel array head coil (Rapid Biomedical). A single slice FAIR sequence with a two shot spin-echo EPI readout was implemented with the following parameters: Slice thickness= 2mm; TR =TI +1s; FOV = 35mm × 35mm; Matrix size = 64 × 64; Width of slice selective inversion = 8mm. Crusher gradients were applied along the slice select axis with a *b*-value of 5s/mm^2. Images were acquired at 15 echo times in a randomized order (19, 21, 36, 25, 48, 33, 65, 27, 30, 56, 23, 40, 60, 52, 44 ms). For **part i)** 50 averages at each echo time were acquired at a single TI of 1500ms (typical value used for a single TI FAIR measurements) (n=6). The protocol was repeated under 100% O_2 in two separate animals (40 averages at each echo time under medical air and Oxygen [n=3]). For **part ii)** 20 averages at each echo time were acquired at 5 TIs (500, 1000, 1500, 2000, 2500ms) [n=9]. In addition separate images at a single echo time (19ms) were acquired at short TIs (100, 200, 300, 400, 500ms) to precisely measure arterial transit time [δa] (required to estimate tissue transit time from the IV/EV ASL signal measurements). For **part i)** the mean ASL signal was taken within a cortical ROI and fitted to a bi-exponential decay model with no constraints or priors on the four fitted parameters [ΔM = ΔMa × exp(-TE/T2a) + ΔMb × exp(-TE/T2b)]. For **parts ii)** the "slow" decaying T2 component was fixed at the T2 of the control signal (a close approximation to the T2 of the EV tissue) based on the similarity of the two components observed in **part i).** Tissue transit time was calculated by incorporating the IV/(IV+EV) and δa estimates into the model described by [Alsop and Detre, 1996] and later adapted by [Wang *et al*., 2002] to incorporate variable bolus length. In this work we define the exchange time to be δ – δa.

Results

Part i) Figure A shows the mean cortical ASL and control signal (log scale) as a function of TE for six animals. The coefficient of determination (r square) was greater for a bi-exponential fit to the transverse decay of the ASL signal compared to a mono-exponential fit for each of the 6 rats. The mean "slow" T2component (±SEM) from fitting each of the 6 experiments separately was 36.5ms ± 2.5, closely matching the mean T2 of the control signal (38.1ms ± 0.2) providing evidence that this component represents labeled blood water that has exchanged into the EV space. The fast T2 component was 11.3ms ± 4.5 which corresponds to blood with an oxygen saturation of 85% in good agreement with [Vasquez *et al*., 2010; Wells *et al.,* 2009]. The mean "fast" T2 component was greater when the animal was breathing 100% O_2 in comparison to 100% medical air (33ms ± 3ms [oxygen saturation 97.5%] and 15ms ± 5ms [oxygen saturation 90%]) providing some validation of the sensitivity of this technique to estimate arterial blood oxygenation.



A: The mean log (signal) at increasing echo time over all 6 experiments for **part i).** The four fitted parameters from the bi-exponential fit to the mean curve are also reported



B: The estimated IV/(IV+EV) ratio of the ASL signal at increasing TI for **part ii)**.

Part ii) Figure B shows the estimated IV/(IV+EV) ratio of the ASL signal at increasing TI across the 9 rats and demonstrates gradual exchange of labeled blood water into the EV cortical tissue with increasing TI. Data at a TI of 2500ms are not reported due to the very low IV signal returning poor bi-exponential fits to the data (hard to differentiate from mono-exponential fits). The mean arterial transit time was 236ms ± 13ms. The mean exchange time (δ – δa) was 443ms ± 41ms.

Conclusion In this work we present a new method to estimate the time of exchange of labelled blood water into cortical EV brain tissue. By explicitly measuring the fast T2 component, the mean oxygen saturation of the labelled water in the vasculature can be estimated. This allows non-invasive estimation of the oxygen saturation of the blood in the arterial side of the micro-vessels and capillaries, which may improve the accuracy of future quantitative fMRI studies (where the arterial oxygen saturation is often assumed to be 100%). Our data indicates that blood water takes on average 443ms ± 41ms to exchange from the vascular space in the slice into the EV tissue. Based on this evidence, we would recommend setting the tissue transit time to equal δa + 443ms in the normal rat brain cortex for accurate CBF quantification using standard ASL models.

Alsop and Detre, JCBFM 16, 1236-1249; Kwong *et al*., Proc Natl Acad Sci 1992 89; 5675-5679; Kim T, Kim SG Magn Reson Med 55:1047–1057.2006. Lee *et al*., Magn Reson Med 42:919–928 (1999); Wells *et* al., J Cereb Blood Flow Metab. 2009;29(11):1836-45; Vazquez *et al*., Front Neuroenergetics. 2010 J18;2:11 Wang et al., Magn Reson Med 2002;48:242–254.