Characterising the Origin of the Arterial Spin Labelling Signal in MRI using a Multi-Echo Acquisition Approach

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Introduction Arterial spin labelling (ASL) MRI [1] is increasingly being used to measure cerebral blood flow (CBF) non-invasively with good spatial and temporal resolution. However, it suffers from poor SNR and struggles to produce robust, reliable CBF estimates given the complexity of cerebral anatomy and the multifaceted nature of neuropathology. Understanding the complicated mechanisms underlying blood delivery and exchange will aid the development of an ASL CBF quantification model that can accurately characterize cerebral physiology. This will enable more reliable perfusion estimates over a broad range of flow values and will help reduce the potentially confounding effects of pathology. There is evidence that the transverse decay of brain tissue is bi-exponential due to a marked difference between the T2 of the intra- and extracellular compartments [2, 3]. However the transverse decay of the ASL perfusion weighted signal has not yet been interpreted in this way to estimate the location of the labelled blood water that has exchanged into the tissue. In this study we acquire multi-echo ASL data with vascular crusher gradients (VCGs) (to eliminate any intravascular contribution) to estimate the proportion of the ASL perfusion-weighted signal originating from the intracellular and extracellular tissue space. In addition we acquire equivalent measurements without VCGs to estimate the proportion of the ASL signal originating from the vascular compartment. By taking measurements over a range of post-labelling delays (PLDs) and tagging durations (τ) we can follow the dynamic changes in these parameters as blood is delivered to the brain. In this way, we provide a novel insight into the time-course of blood delivery and exchange within cerebral tissue.

Method 9 male Sprague Dawley rats (182-242g) were used in this study**.** MRI studies were performed using a 2.35T horizontal magnet interfaced to a Surrey Medical Imaging Systems (SMIS, UK) console. A volume transmitter coil (60mm length) and passively decoupled single loop surface coil receiver were used. A continuous arterial spin labelling (CASL) sequence [4] was implemented. The tagging pulse duration was varied over the range of values: 500, 750, 1000 and 3000ms in order to monitor the progression of labelled blood water within the cerebral vessels and tissue. After a PLD, single slice coronal images were acquired using a multi-echo spin echo half-Fourier EPI sequence to produce 4 images in a single shot. This was twice repeated, with different sequence timings to achieve a total of 12 echo times (29 to 176.6ms). A slice selective 90°-180° pulse combination was used to generate the first spin echo and subsequent echoes were generated using non-selective adiabatic BIR-4 pulses, to ensure efficient spin refocusing and accurate T2 measurements. The PLD was 50 ms, and was also extended for additional acquisitions at 300, 700 and 1200 ms after the 3 second labelling pulse to investigate the provenance of the ASL signal further downstream. The protocol was then repeated with the addition of monopolar diffusion gradients around the first 180° refocusing pulse in the slice select direction (b = 40 mm/s)^2. The entire set of interleaved acquisitions was repeated for a total of 30 averages at each echo time, τ /PLD combination, VCGs on and off, control and tag acquisition. Other acquisition parameters were: inter-experiment delay time = 4s; half-Fourier matrix size =36x64; FOV = 32mm x 32mm; slice thickness = 2mm. Phase cycling and spoiler gradients applied along the slice select axis (modulated as a function of echo number using the scheme recommended in [5]) were implemented for all the acquisitions. Images were first averaged in k-space and then reconstructed to 64 x 64 using the POCS algorithm [6].

Analysis*:* The mean signal within a cortical ROI was taken and the proportion of ASL signal from the intravascular (IV) compartment was estimated for each animal at each τ and PLD by calculating ΔM(VCGs-on)/ ΔM(VCGs-off) at the earliest echo time (29ms), assuming the VCGs crush the entire vascular signal [7]. Assuming the T2 values of the intracellular (IC) and extracellular (EC) compartments to be 53ms and 174ms respectively from previous measurements at the same field strength [2], the proportion of intracellular to extracellular ASL signal is estimated by fitting the ΔM(VCGs-on) observations to a bi-exponential model. The same analyses were performed on the control images which represent all the tissue in the ROI.

Results

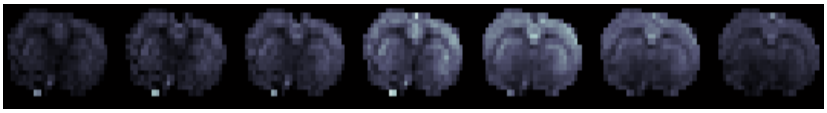

Figure 1 *Perfusion weighted images (n=30) acquired without VCGs at the first echo time (29ms) at the τ + PLD combinations below the respective images.*

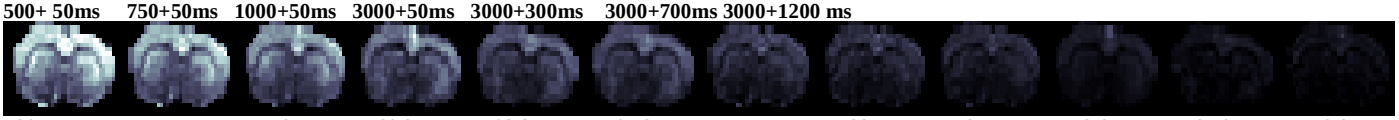

Figure 2 *Perfusion weighted images acquired at increasing echo times at τ =3000ms and PLD =300ms.*

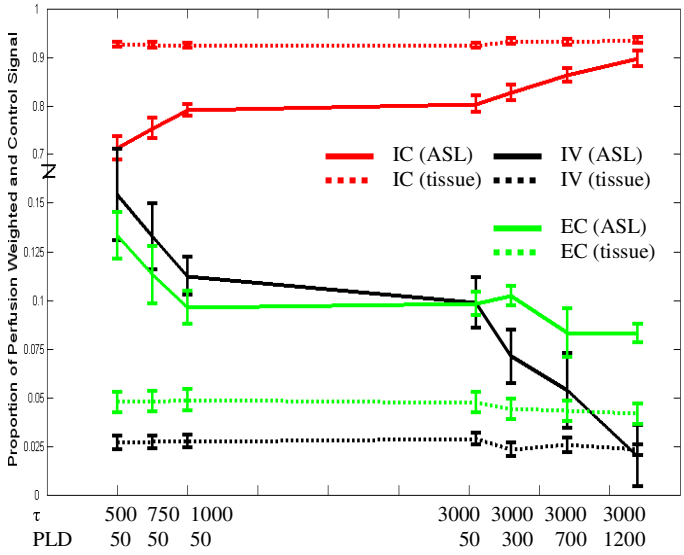

Figure 3. *The proportion of ASL signal originating from the vascular compartment (black line) and in the intracellular (red line) and extracellular (green line) tissue space at a range of τ and PLD combinations. The proportion of the control signal in the 3 different compartments is represented by a dotted line. For clarity the scale of the y-axis has been adjusted and is non-linear. Error bars denote the standard error of the estimates across the 9 experiments.*

Discussion. These are the first results to report the dynamic progression of labelled arterial blood from the intravascular space and in the intracellular and extracellular tissue spaces (see Figure 3). This provides a novel insight into the origin of the ASL signal as well as proof of principle of this approach for possible future applications in humans and in animal models of disease. Figure 2 suggests that even at short tagging durations (τ = 500ms), the majority of the ASL signal originates from the intracellular space. As τ increases to 1000ms, the source of the ASL signal shifts further into the intracellular space from the intravascular and extracellular compartments. The subsequent similarity of the estimates at τ = 1s and τ =3s suggests that a dynamic equilibrium between the three compartments is established by τ = 1s. As the PLD increases at τ =3000ms the ASL signal from the intravascular compartment seems to effectively shift into the intracellular space while the signal from the extracellular space appears relatively stable, perhaps acting as a "buffer" for the movement of labelled blood between the two compartments.

References [1]Detre *et.al* Magn Reson Med 1992; 23:37-45.[2] Haida *et al.*, JCBFM 1987 ;7: 552-556. [3] Matsumae M, Child's Nerv Sys. 2003 19(2) 91-5. [4] Alsop, Detre. JCBFM 1996; 16:1236-49 [5] Poon, Henkelman JMRI 1992; 2: 541-553. [6] Liang *et al* . Reviews of Magn Res Med 1992 4, 67-185. [7] Silva et al. Magn Reson Med 1997; 37:58-68.