PERFUSION

Sue Francis susan.francis@nottingham.ac.uk
SPMMRC, University of Nottingham
University Park
Nottingham

Perfusion Measured by MRI Using a Diffusive Tracer

- Outline the basic principles of arterial spin labelling (ASL) and the key methods.
- Describe the issues in the extraction of physiological parameters from ASL data.

TARGET AUDIENCE: Physicists, radiologists, and clinicians

OBJECTIVES: To provide an outline of Arterial Spin Labelling (ASL), the challenges involved.

METHODS AND RESULTS:

Arterial Spin Labelling (ASL) is a non-invasive technique for the measurement of perfusion. Perfusion provides an estimate of the volume of blood that passes through the capillary bed per unit time to deliver nutrients to the tissue, typically expressed in units of ml $100g^{-1}$ min^{-1}. ASL was first introduced over 20 years ago [1], and since there has been a considerable research effort to develop ASL techniques and applications.

In ASL, endogenous arterial blood water is made a freely diffusible tracer by applying radiofrequency (RF) pulses to manipulate the magnetisation of the inflowing arterial blood. There are a number of ASL labelling strategies which are outlined below. For each strategy, a flow-sensitized image volume is formed from the difference of a 'label' and 'control' image volume. The 'label' image volume is acquired following inversion of the inflowing arterial blood signal. A post-label delay time (TI) is left between applying the 'label' and acquiring an image to allow the labelled arterial blood to traverse the capillaries and exchange with the tissue water. The 'label' condition causes off-resonant saturation of macromolecular spins in the tissue in the image volume, known as magnetisation transfer (MT). Therefore a 'control' image volume is also acquired for all ASL techniques such that the MT effects are matched to those of the 'label' condition. A perfusion weighted (PW) image volume then results from the subtraction of the 'label' image volume from the 'control' image volume (Figure 1).

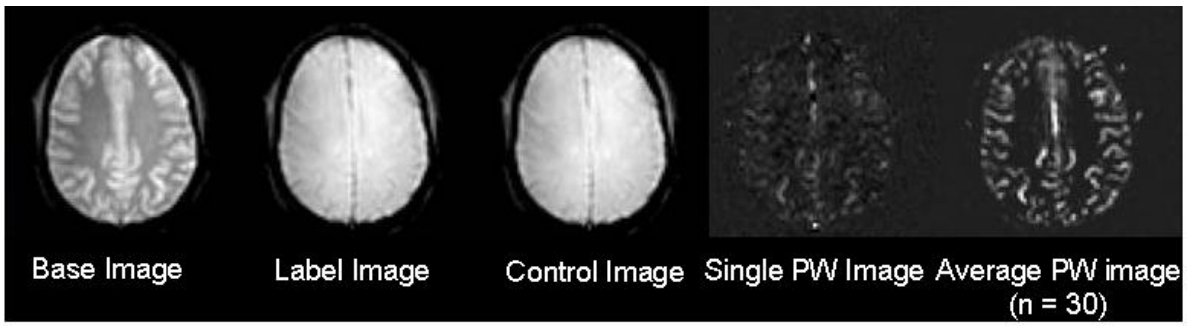

Figure 1: *Equilibrium base image (required for perfusion quantification), single 'label' and 'control' image and the corresponding single perfusion weighted (PW) image, and average PW image obtained from 30 averages. A single slice of a 20 slice image volume is shown.*

The perfusion weighted signal change is dependent on a number of parameters including the perfusion rate of the tissue, the longitudinal relaxation time (T_1) of blood and tissue, and the transit time (Δ) of the labelled blood to the tissue. ASL techniques benefit from increased magnetic field (B_0) as a result of both the increased signal-to-noise ratio (SNR), and also due to the lengthened T_1. Perfusion of grey matter is of the order of 70 ml/100g/min, giving a typical perfusion weighted signal change in grey matter of the brain of ~ 1 % of the equilibrium magnetisation at 3 Tesla, increasing to ~ 2 % at 7 Tesla [2]. Thus for sufficient SNR in the PW image a number of repetitions of 'label'-'control' pairs are acquired, subtracted and averaged (Figure 1).

The majority of ASL studies have been carried out in the brain, where the arterial blood supply is well defined. However, a number of studies have been carried out in other organs in the body, including the kidneys, heart, lung, eye and skeletal muscle. In particular there is an increasing number of studies using ASL to assess perfusion of the kidneys [3, 4]. In the kidneys perfusion is high (of the order of 300 ml/100g/min), and if breathing induced motion can be overcome this provides an alternative to gadolinium-based MRI contrast agents, which can lead to side-effects including Nephrogenic Systemic Fibrosis (NSF) in patients with renal disease.

ASL Labelling Methods

There are two distinct classes of ASL techniques: Pulsed ASL (PASL) and continuous ASL (as shown in Figure 2), with two distinct forms of continuous ASL, 1) CASL and 2) pseudo-continuous ASL (PCASL).

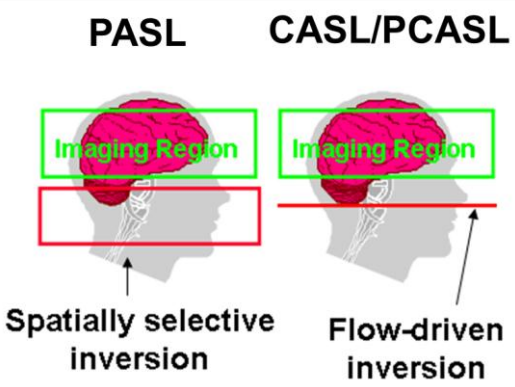

Figure 2: *Schematic diagram illustrating PASL and CASL strategies. PASL labels inflowing spins in a spatially selective slab. CASL/pCASL labels blood spins as they flow through a labelling plane.*

Pulsed ASL (PASL): In pulsed ASL, a large slab of arterial blood is labelled by a single spatially selective RF pulse, typically an adiabatic inversion pulse. The original PASL techniques include 'Echo Planar MR Imaging and Signal Targeting with Alternating Radio Frequency' (EPISTAR) [5] and flow alternating inversion recovery (FAIR) [6, 7]. In the original implementation of STAR the label was applied to inflowing blood in a 10 – 15 cm slab proximal to the image volume and the control distal to the image volume. However, to overcome MT effects for multi-slice image acquisition the STAR scheme was modified such that a nominal 360° flip angle is used for the adiabatic label and two 180° adiabatic pulses for the control to match magnetisation transfer effects [8]. FAIR uses a non-selective inversion slab for the label whilst the control condition comprises a selective inversion slab over the imaging volume. PASL techniques are easy to implement and have low SAR and so are widely used. Other PASL techniques include PICORE (proximal inversion with a control for off-resonance effects) [9], PULSAR (pulsed star labelling of arterial regions) [10], and DIPLOMA (double inversions with proximal labelling of both tag and control images) [11].

Continuous ASL (CASL): CASL uses flow driven adiabatic inversion where the inflowing blood is continuously labelled as it flows through a plane below the image volume using a 2 – 4 s low power continuous radiofrequency pulse while applying a magnetic field gradient in the flow direction. The inversion efficiency depends on the mean velocity of the blood, angulation of the vessels to the plane,

and the RF amplitude and gradient strength. Continuous labelling schemes maximize the signal difference between label and control, however this technique requires continuous RF transmit capabilities, and suffers from both increased SAR and magnetisation transfer effects.

Pseudo-continuous ASL (PCASL): PCASL [12] utilizes a train of discrete RF pulses spaced as close as possible, typically 1 ms, to mimic continuous tagging. There exist two versions of PCASL using balanced and unbalanced gradient waveforms in the 'label' and 'control' scans, with unbalanced PCASL being most standard. This uses a labelling pulse in which the slice-selective gradients are 10 mT/, with a mean gradient of 1 mT/m, and the RF pulses have a mean B_1 of 1.5 mT. For the pulses to remain in phase with the spins, the phase ϕ_n of the *n*th RF pulse should be $\phi_n = \gamma nGTZ$, where γ is the gyromagnetic ratio, *G* is the mean gradient, *T* is the RF pulse spacing, and *Z* is the distance from the isocentre of the gradients to the labelling plane [13]. A labelling duration of 1800 ms is typically used. For the control condition, the phase of every other RF pulse is shifted by π relative to the label condition, and the refocusing gradient lobes increased in amplitude such that the mean gradient is zero. PCASL has been shown to provide approximately a 50% increase of signal-to-noise ratio (SNR) compared with PASL and a higher labeling efficiency than CASL (80% vs. 68%).

Improving ASL stability

Since the PW difference signal is small it is important to suppress any signal changes which are not flow mediated. For example, an offset in the static tissue signal due to non-ideal inversion pulses can give rise to an artefactual PW signal. To overcome this pre-saturation and post-saturation slabs are typically applied to the imaging volume. In addition, physiological motion and head motion can dominate the signal change between label and control conditions. Background suppression [14] which employs additional inversion pulses in the labeling sequence can suppress the static tissue at the time of imaging while retaining the perfusion signal.

With all ASL techniques care must be taken to remove the signal from large vessels (arterial blood volume (CBV_a) when measuring the perfusion signal. This is typically performed by introducing vascular crushing gradients to dephase large vessel signal [15].

Accounting for transit time effects

In most ASL approaches, information on perfusion is assessed at a single time point (TI), and without information on the transit time (Δ) of the blood to the imaging plane. This can lead to errors in perfusion quantification.

Sequences such as QUIPSSII [16] and Q2-TIPS [17] have been developed to reduce the sensitivity to transit time effects in PASL schemes. In these techniques, a constant bolus duration is assured by applying an additional saturation slab to the trailing end of the label. However, this method has limitations in subjects/brain regions where the transit time is long.

An alternative is to collect ASL images at multiple inversion times after each labelling pulse, a technique known as quantitative STAR labelling of Arterial Regions (QUASAR)[18, 19] or Look-Locker EPI (LL-EPI)[20]. Information on the arterial and tissue transit time can be obtained from both non-vascular crushed and vascular crushed data sets improving the quantification of perfusion, and if vascular crushed data is subtracted from the non-vascular crushed data then arterial blood volume can also be estimated.

Territorial ASL

Selective or territorial arterial spin-labelling (TASL) has been introduced as the first non-invasive method to visualize the perfusion territories of the individual cerebral arteries [21], Figure 3. Several authors have demonstrated perfusion territory imaging based on the spatially selective application of CASL and PASL MR labeling vessels in the neck. Vessel-selective labelling ASL sequences have been developed to allow the selective labelling above the level of the circle of Willis [22].

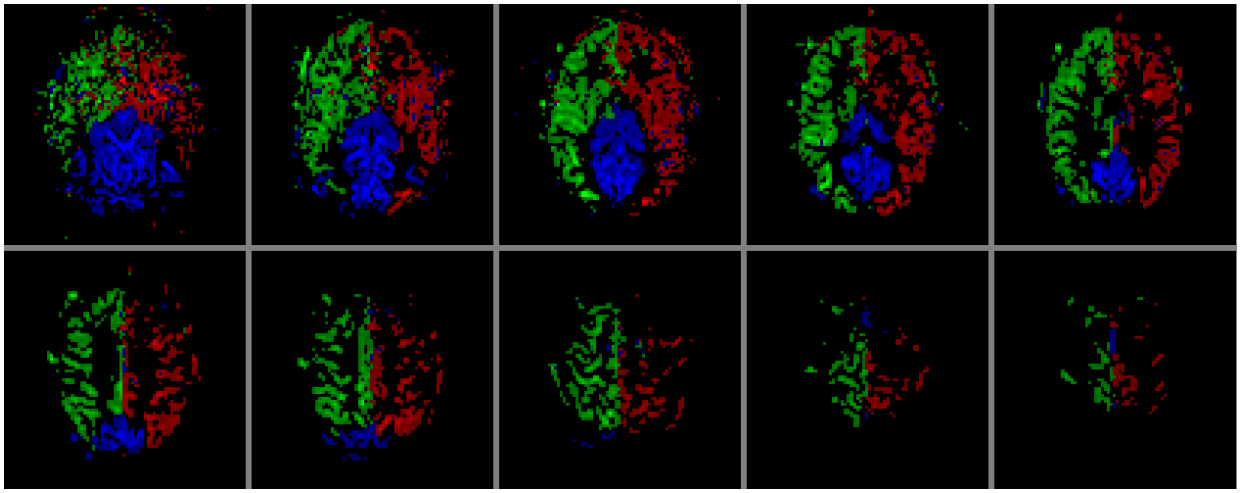

Figure 3: *Territorial ASL map illustrating the perfusion territories of the RICA in red, LICA in green and BA in blue.*

CONCLUSION: ASL provides a method for non-invasive assessment of perfusion in the brain as well as other organs, such as the kidneys and heart. For a review that provides a summary statement of recommended implementations of arterial spin labelling in the brain for clinical applications see [23].

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