Arterial Spin Labeling

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Introduction

Among the various MRI methods measuring cerebral blood flow (CBF), Arterial Spin Labeling (ASL) is the only one that does not require injection of any exogenous contrast agent or tracer. Indeed, as suggested in the name of the technique, the measurement of perfusion is obtained by non-invasive labeling of arterial blood water spins (i.e. inversion or saturation) proximal to the tissue of interest. These labeled spins are then imaged at a later time point after exchange with the tissue magnetization (1). As such, it can be repeated over a time period of a few seconds or minutes, and has a wide range of applications in the brain, from basic neuroscience to applied clinical neurology, as well as for the assessment of organ homeostasis anywhere in the body.

In this lecture, the basic principles of ASL will be described, and the important parameters defining the different sequences will be explained. The main MRI acquisition strategies, together with their method of quantification will also be described, and finally, the potential problems and artifacts will be addressed.

Theory

i) Physiological Parameters measured by ASL

Frist, it is important to note that, unlike other perfusion measurements which make use of an exogenous intravascular contrast agent, arterial spin labeling is in principle unable to directly assess the entire blood volume, because it is extracted almost completely from the capillaries during the first pass through the vasculature (2). Indeed, for a measurement of CBV (or V) to be possible, one must be able to discriminate the tracer present in the blood from that in the extravascular tissue. As such, a few studies have looked into the possibility of measuring the extraction rate of labeled water spins into the tissue to get indirect access to V, but it is generally accepted that such ASL measurements lack the signal-to-noise ratio (SNR) to provide accurate estimates of this parameter (3).

ASL was developed mainly to measure CBF (or f). However, recent improvements in the methodology enabled the estimation of other important physiological parameters. One very important parameter for neurovascular diseases is related to the time of arrival of the blood to the tissue, named in the literature as bolus arrival time (BAT), or arterial transit time (ATT) (4,5). By measuring the signal at different time points after the labeling of the blood, it is possible to detect the first arrival of the blood in the tissue, defined as the BAT. It is interesting to note that this time is usually short because effort is made to label the blood as closely to the tissue of interest as possible. Note that the BAT is also directly dependent on the technique used to label the blood, and it therefore not generally comparable across studies.

Finally, it is also possible to measure the aBV, or blood present in the arteries before it exchanges with the tissue. Here as well, as long as the tracer stays within a certain compartment, it is possible to assign the signal measured to that particular compartment, and several methods have been proposed to measure aBV, either by continuous nulling of the exchanged signal (6) or by subtraction of the ASL signal present with and without crusher gradients to selectively destroy the arterial blood signal (5).

ii) Quantification and Modelling

The theoretical bases for quantifying the ASL signal comes from indicator dilution theory (7). This theory describes the kinetics of an injected tracer of a known concentration into a system. For the case of an open system, corresponding to the medical use of a freely-diffusible tracer such as a gas, the changes in the concentration of the tracer over time in the system will be equal to the flow multiplied by the difference in concentration between the input and output of the system:

$$\frac{dc_T(t)}{dt} = f\big(c_a(t) - c_v(t)\big) \qquad [1]$$

Where $c_T(t)$ is the measured concentration of the agent in the tissue, f is the blood flow, $c_a(t)$ is the arterial blood concentration of the tracer and $c_v(t)$ the venous blood concentration. If the tracer becomes well mixed within the organ, the measured tissue concentration is the same as the outflowing blood or venous blood concentration, corrected for the difference in densities of the agent in the organ vs. the blood. In the brain, this correction factor is called the blood:brain partition coefficient, and is written as λ: $c_T(t) = \lambda c_v(t)$. With this assumption, it is possible to find a simple solution to equation [1], which becomes:

$$\lambda c_v(t) = c_T(t) = f \cdot \int_0^t \big(c_a(\tau) - c_v(\tau)\big)\, d\tau \qquad [2]$$

or

$$f(t) = \frac{\lambda c_v(t)}{\int_0^t (c_a(\tau) - c_v(\tau))\, d\tau} \qquad [3]$$

This equation is sometimes referred to as the single compartment Kety equation, as it was used originally by Kety and Schmidt to measure perfusion of the whole brain using nitrous oxide (8). Looking at Eq. [2], one can directly see that the estimated flow will vary over time and will only reach a steady state value once the concentration in the tissue reaches a steady-state concentration. This method can easily be used in ASL, where labeled water can be assumed to act as a freely diffusible tracer.

However, in order to be able to use this theory for quantification of perfusion in practice, the basic equation needs to be slightly modified to account for the fact that a short-lived pulsed input function and not a continuous infusion is being used (7). Equation [2] becomes then:

$$c_T(t) = f \cdot \int_0^t c_a(\tau)\big(R(t-\tau)\big)\, d\tau = f \cdot c_a(\tau) \otimes R(t) \qquad [4]$$

With $\otimes$ representing the convolution symbol. As such, the measured tissue concentration $c_T(t)$ of tracer is equal to the flow f multiplied by the convolution of the arterial input function $c_a(t)$ by the tissue response function, also known as residue function, $R(t)$.

Based on this theory, Buxton et al. (9) proposed a simple model to estimate tissue perfusion, by rewriting equation [4] in MRI terms. This is known as the general kinetic model:

$$\Delta M = 2 \cdot \alpha \cdot M_{a,0} \cdot f \cdot \int_0^t c(t) \cdot r(t-\tau) \cdot m(t-\tau) d\tau \quad [5]$$

where $M_{a,0}$ is the equilibrium magnetization of blood, $c(t)$ is the delivery function, and the arterial input function (AIF) is equal to $c_a(t) = 2 \cdot \alpha \cdot M_{a,0} \cdot c(t)$. The residue function $r(t-\tau)$ describes the washout of labeled spins from a voxel, and $m(t-\tau)$ includes the longitudinal magnetization relaxation effects, not present in the original theory. To solve this equation, Buxton originally makes the general assumption of a "plug flow" or rectangular AIF (9). In addition, he discards any effect of dispersion and dilution of the bolus, and arrives at the following equations, known as the "standard kinetic model", which gives, for the case of Pulsed ASL:

$$c(t) = \begin{cases} 0, & < \tau_a \\ e^{-tR_{1a}}, & \tau_a \leq t < \tau_d \\ 0, & t \geq \tau_d \end{cases} \quad [6]$$

$$r(t) = e^{-\frac{ft}{\lambda}} \quad [7]$$

$$m(t) = e^{-tR_{1t}} \quad [8]$$

Solving Eq. [5] using Eq. [6-8] gives a step-wise defined equation:

$$\Delta M(t) = \begin{cases} 0, & < \tau_a \\ \frac{-2 \cdot \alpha \cdot M_{a,0} \cdot f}{\delta R} e^{-R_{1a} \cdot t} \left(1 - e^{-\delta R \cdot (t-\tau_a)}\right), & \tau_a \leq t < \tau_d \\ \frac{-2 \cdot \alpha \cdot M_{a,0} \cdot f}{\delta R} e^{-R_{1a} \cdot \tau_d} \left(1 - e^{-\delta R \cdot (t-\tau_a)}\right) e^{-R_{1app} \cdot (t-\tau_d)}, & t \geq \tau_d \end{cases} \quad [9]$$

where, $\delta R = R_{1a} - R_{1app}$ and $R_{1app} = R_{1t} + \frac{f}{\lambda}$, also called the apparent tissue relaxation rate. A similar set of equations can be obtained for continuous ASL experiments, with the only difference that $c(t)$ in Eq. [6] will then be constant for CASL, whereas it is subject to T_{1a} decay for PASL. As can be seen, various parameters such as the transit time τ_a, blood-tissue partition coefficient λ, $M_{a,0}$, R_{1a} and R_{1t} need to be estimated or measured in order to obtain quantitative CBF values. The difference between the models used to quantify most ASL sequences lies in the number of estimated vs. measured parameters.

Methods

The basic scheme used by ASL is the following (see Fig. 1). At the most general level, ASL is based on the consecutive (interleaved) acquisition of two MRI experiments (1). In the first experiment arterial water spins are labeled upstream from the tissue of interest by the combined application of field gradients and RF pulses. This labeling usually consists of an inversion of the arterial water magnetization. An image is then acquired after a suitable delay time, during which the RF-labeled arterial water spins have the time to travel to the tissue of interest, and to exchange there with the stationary spins located in the extravascular compartment. In the second experiment, a sham labeling is performed, to set the system in the same conditions as the first experiment, and a second image of the tissue of interest is acquired. Ideally, the only difference between the labeled acquisition and this "control" acquisition is that the latter has no manipulation of the arterial spins. Both labeling and control acquisitions are acquired after a time TI ("inversion time"). The difference between both images will provide a signal proportional to the exchanged water magnetization and therefore water delivered to the tissue at the time TI.

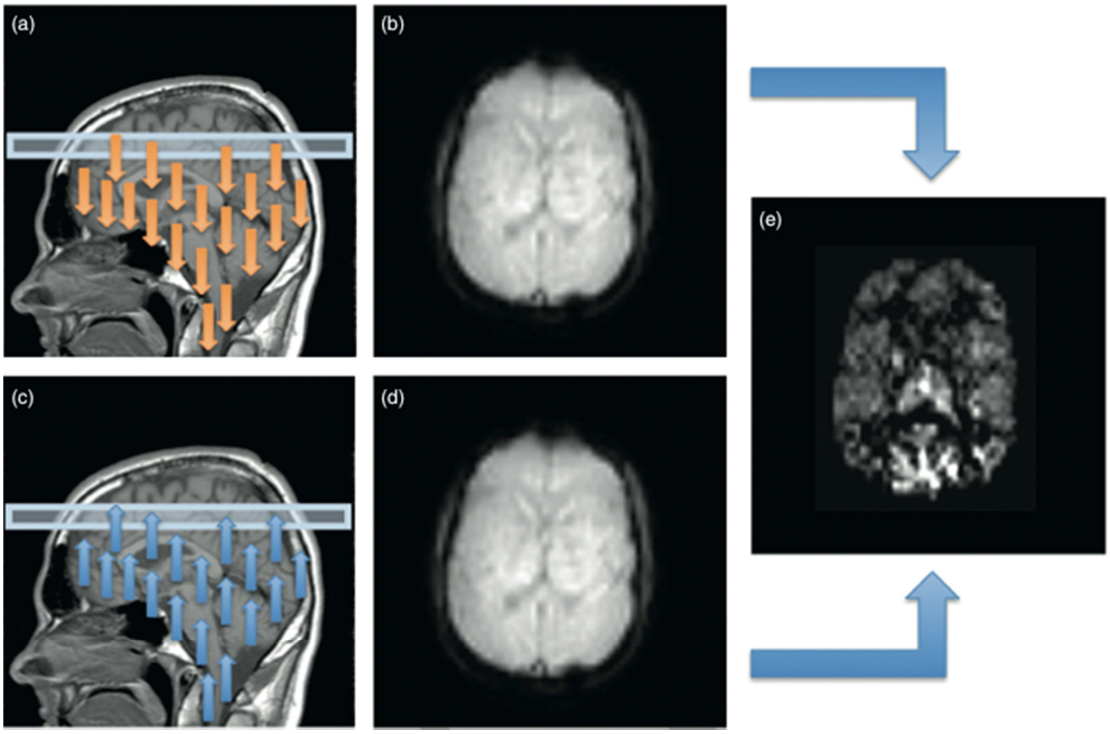

Fig. 1: Basic ASL principles. An image (b) is acquired after inversion of magnetization proximally (represented by inverted arrows in a), followed by a second image (d) acquired after a control experiment, in which the magnetization has been left unchanged (c). The subtraction of d – b gives the perfusion-weighted image (e).

Note that the labeling of the water spins will decrease due to longitudinal decay (T_{1blood}) during its transit to the tissue and through the capillary bed. This, combined with the fact that the blood volume in most organs is usually small – typically about 2-4% in the brain for example – makes ASL a signal-to-noise (SNR) limited technique, in particular in the white matter (10). As such, numerous ways of improving the SNR have been introduced, from new ways to

label the water spins, to advanced readout techniques providing the best possible SNR per unit time.

Generally numerous labeling and readout methods are possible. The most important ones are summarized in Fig. 2. Several review papers (e.g. 11) and book chapters (e.g. 12) list them in details, and we refer the reader to those for more information.

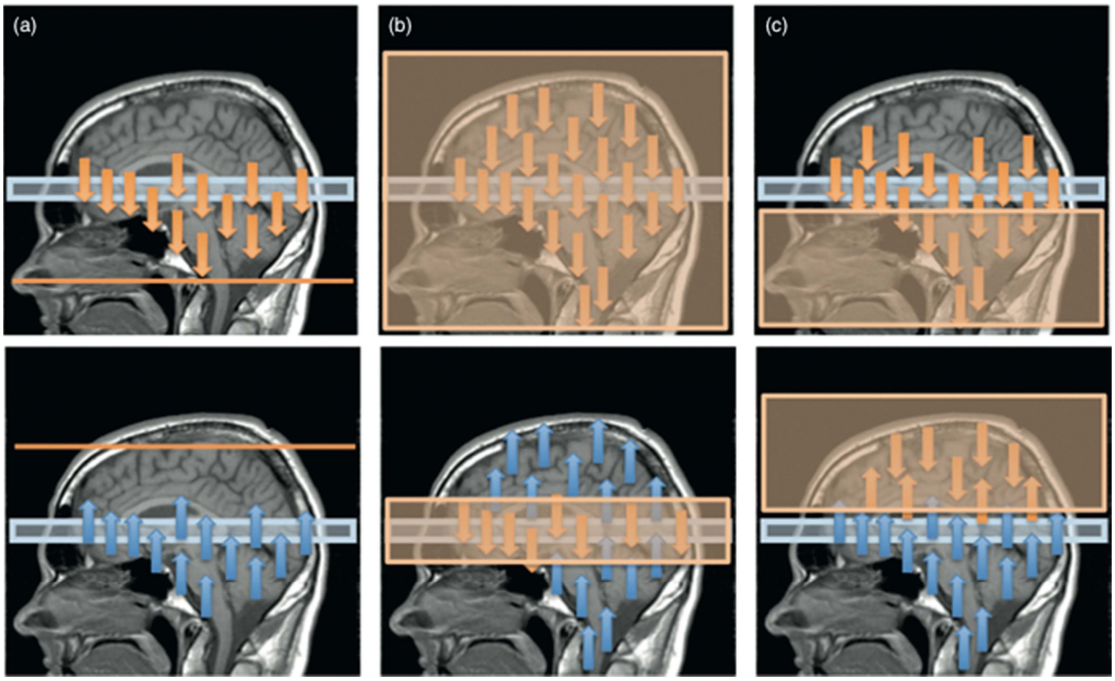

Fig. 2: Basic ASL schemes. (a) Original continuous ASL sequence, where the spins are inverted using a combination of gradient and RF pulse over a long period of time, resulting in a very well-defined narrow inversion region, usually placed at the cervico-medullar junction for labeling, and at equidistance on the other side for control. (b) The symmetrical pulsed ASL scheme (also known as FAIR sequence) in which labeling is achieved by the alternating application of a slice-selective and non-selective inversion-recovery sequence. (c) Asymmetrical pulsed ASL scheme, as originally presented in the EPISTAR sequence. The labeling is achieved by a slab-selective inversion pulse, placed proximally for labeling and distally for the control acquisition.

Problems and limitations

ASL's major problem is its intrinsic low SNR. In fact, the measured ΔM is often on the order of 1% or less, and subtraction errors are frequent, often caused by motion artifacts, especially in clinical studies of difficult patient populations. Many acquisition tricks can be used, such as background-suppression techniques. Such methods have been developed to cancel the background signal not related to perfusion. They usually achieve complete annihilation of the static signal over a wide range of T_1 values (particularly necessary for brain perfusion) using multiple inversion pulses (13).

Another problem in ASL is the remaining labeled signal in the vasculature, which is an especially important potential source of error at short inversion times, and when using multiple inversion times to fit the labeled bolus in PASL (14). One of the first solutions implemented was the use small diffusion gradients (diffusion b-value = 1-10 s/mm^2) to eliminate the remaining arterial signal (15). Also, for

non-vessel suppressed ASL images, the vascular signal is known as arterial transit artifact (ATA) and is indicative of slow flow in patients with cerebrovascular disease (16).
Finally, another potential source of problems for PASL techniques are the inversion pulses used, as poorly-defined slice profiles will result in reduced labeling efficiency, as well as possible contamination of the volume of interest by the labeling pulse. For this reason, very sharp labeling pulses are needed, and most modern implementations use adiabatic RF pulses of one sort or another (e.g. 17).

Conclusions and Outlook

ASL is far from being harmonized among vendors, and probably presents so far the widest variety among all modern pulse sequences. For this reason, it is just beginning to enter clinical use, and a considerable amount of work remains to be done to ensure that users will employ the right sequence for the right disease (94). In addition, very simplistic post-processing procedures are available so far for analyzing ASL data on the main manufacturers platforms, and a limited amount of products are available from research groups. The Oxford-based FSL package has a tool-box (http://www.fmrib.ox.ac.uk/), and other tools exist as well, but this scarcity, together with the variety of existing pulse sequences and models, has led most groups working on the subject to develop their own in-house software, which complicates the comparison of results from different groups in different diseases.
For this reason, a recent paper has been submitted, put together by a consortium of people including the Perfusion Study Group of the ISMRM and the EU-funded COST Action (BM1103) on 'ASL in Dementia', aiming at providing a set of specific recommendation to establish standard approach to be used in the clinic (18).

Note

This syllabus is a shorter version from reference (12). The reader will find in there many more details, in particular regarding implementations, labeling and readout schemes.

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