ISMRM Perfusion Workshop Invited Paper

Quantifying CBF With Pulsed ASL: Technical and Pulse Sequence Factors

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We summarize here current methods for the quantification of CBF using pulsed arterial spin labeling (ASL) methods. Several technical issues related to CBF quantitation are described briefly, including transit delay, signal from larger arteries, radio frequency (RF) slice profiles, magnetization transfer, tagging efficiency, and tagging geometry. Many pulsed tagging schemes have been devised, which differ in the type of tag or control pulses, and which have various advantages and disadvantages for quantitation. Several other modifications are also available that can be implemented as modules in an ASL pulse sequence, such as varying the wash-in time to estimate the transit delay. Velocity-selective ASL (VS-ASL) uses a new type of pulse labeling in which inflowing arterial spins are tagged based on their velocity rather than their spatial location. In principle, this technique may allow ASL measurement of cerebral blood flow (CBF) that is insensitive to transit delays.

Key Words: magnetic resonance imaging (MRI); perfusion; cerebral blood flow; arterial spin labeling (ASL); arterial tagging; transit delay
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IN PULSED arterial spin labeling (ASL) (1–3), a single radio frequency (RF) pulse or a train of RF pulses is applied to modify (or tag) the longitudinal magnetization of arterial blood proximal to the tissues of interest. The RF pulse or train of pulses must be short in duration compared to the T_1 of blood. After a period of time TI after the initiation of the RF tagging pulse, an image (the tag image) is acquired of the region of interest (ROI), which represents a mixture of the preexisting magnetization in the ROI and the magnetization of the tagged blood that has flowed into the ROI. In typical implementations, a second image (the control image) is acquired without modulation of the magnetization of inflowing arterial blood. The difference between tag and control images reflects the amount of tagged blood that has flowed into the ROI during the time interval TI and is closely related to cerebral blood flow (CBF).

A simplified expression for the signal difference ΔS between tag and control images in pulsed ASL is given by

$$\Delta S = 2\alpha M_{0B}\tau CBF e^{-T_1/T_{1B}}, \quad (1)$$

where α is the tagging efficiency, M_{0B} is the MRI signal from a voxel full of arterial blood, τ is the temporal width of the bolus of blood that reaches the ROI, and T_{1B} is the T_1 of blood. In this expression, $2\alpha M_{0B}$ is the initial magnetization difference between tagged and control blood, the product τ *CBF* is the amount of tagged blood that flows into the ROI, and the exponential factor reflects T_1 relaxation of the tag.

A feature of ASL that distinguishes it from other tracer techniques is the short lifetime of the tracer. The T_1 of blood is approximately 1300 msec at 1.5 T and is the time constant for the decay of the tag. This sets the required time scale for the ASL experiment and determines many of the important properties of ASL. The ASL experiment is a race between the decay of the tag and the delivery of tagged blood to the ROI.

QUANTITATION ISSUES

Several potential sources of systematic errors can affect the quantitation of CBF and are summarized here. Many of the pulsed ASL techniques listed in the next section are aimed at reducing one or more of these sources of error.

Transit Delay

In all pulsed and continuous ASL techniques other than velocity-selective ASL (VS-ASL) (see below), the tagging process involves a spatially selective RF pulse or pulse train that tags blood proximal to the ROI. Because of imperfections in the spatial selectivity of the tag pulses, it is necessary to provide a spatial gap between the distal edge of the tagging slab or plane and the ROI. This spatial gap results in a transit delay (Δt) between the application of the tag and the delivery of tagged blood to the ROI, during which the tagged blood traverses this gap. For a gap of 1 cm, the measured Δt in a normal subject is shown in Fig. 1 and is in the range 300 to 1000 msec (4). Thus, the longest-duration bolus

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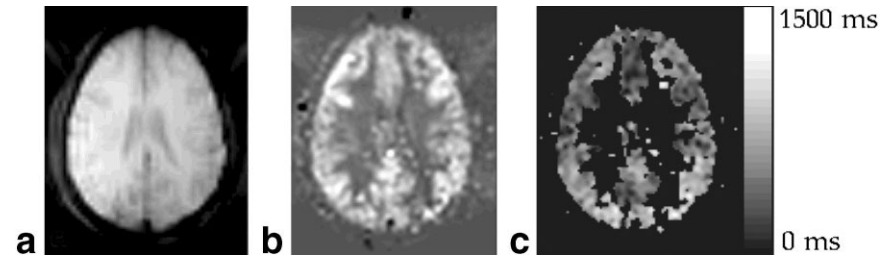

Figure 1. Images calculated from pulsed ASL data acquired at a series of values of TI. **a:** Control (unsubtracted) image. **b:** Calculated CBF map. **c:** Calculated map of Δt. The CBF and Δt were fit to the data acquired at multiple TI as in Buxton et al (21). Acquisition parameters: field of view (FOV) = 24 cm, slice thickness = 8 mm, single-shot EPI at 64^2 resolution, TR = 2000 msec, TE = 25 msec, FAIR tagging with TI = (600, 850, 1100, 1350, 1600) msec, 10-mm gap between tag and imaging slice, 200 repetitions per TI point, for a scan time of 34 minutes. (Reprinted from Wong EC, Buxton RB, Frank LR. Implementation of quantitative perfusion imaging techniques for functional brain mapping using pulsed arterial spin labeling. NMR Biomed 1997;10:237–249, with permission of John Wiley & Sons, Ltd.)

that can be delivered to the ROI (τ in Eq. [1]) is given by the difference ($TI - \Delta t$), where Δt is a local and unknown quantity and can be a large fraction of TI. Because Δt and TI are on the same order, the errors associated with transit delay effects can be on the order of 100%. In order to quantify CBF using ASL, it is necessary to measure, minimize, or provide insensitivity to Δt.

Intravascular Signal in Proximal Arteries

At the time of image acquisition, some of the tagged blood may be located in arteries or arterioles, rather than the target tissue. This can result in ASL images that reflect both perfusion of the imaged voxel and blood destined for more distal tissues. Diffusion or flow-weighting gradients can reduce this artifact, but these pulses can also diphase signals in small arteries that are destined to perfuse local tissues. In general, it is better to create a tagged bolus of well-defined temporal width and allow time for the bolus to be fully delivered to target tissues (5,6).

Slice Profile Effects

The RF pulses or pulse trains used for tagging have imperfect slice profiles and can contaminate the magnetization in the ROI. These effects can be on the order of a few percent of the static tissue magnetization, which is the same order as the ASL signal. Pulsed ASL techniques typically use hyperbolic secant (sech) or similar adiabatic pulses for efficient inversion that is relatively insensitive to both B_1 inhomogeneity and resonance offsets. Modified sech pulses such as frequency-offset-corrected inversion (FOCI) pulses (7) and variable-rate-selective excitation (VERSE) transformed sech pulses (8) have been introduced specifically to improve tagging slice profiles for ASL.

Table 1
Basic Tagging Techniques

Technique	Tag	Control	Key aspects	Advantages	Disadvantages
EPISTAR (12)	Slab-selective proximal inversion	Slab-selective distal inversion	Negative ASL signal from spins inflowing from distal side	Bolus width controllable	Sensitive to Slab profile
FAIR (13)	Global inversion	Slice-selective inversion	Bolus size limited only by RF coil	Better tag profile; positive ASL signal from either side of slice	Bolus width not controllable
PICORE (4)	Slab-selective proximal inversion	Off-resonance non-selective inversion	No signal from inflowing distal spins	No signal from inflowing distal spins	Need to know inflow direction
Modified EPISTAR (1)	Slab-selective proximal inversion	Slab-selective proximal double inversion	Good MT control	Good MT control	Higher RF power
TILT (14)	Slab-selective proximal inversion	Slab-selective proximal transparent pulse	Good MT control	Good MT control	Longer tagging pulse
FAIRER (15)	Global inversion	Slice-selective inversion	Gradient on during TI	Eliminates radiation damping	Bolus width not controllable

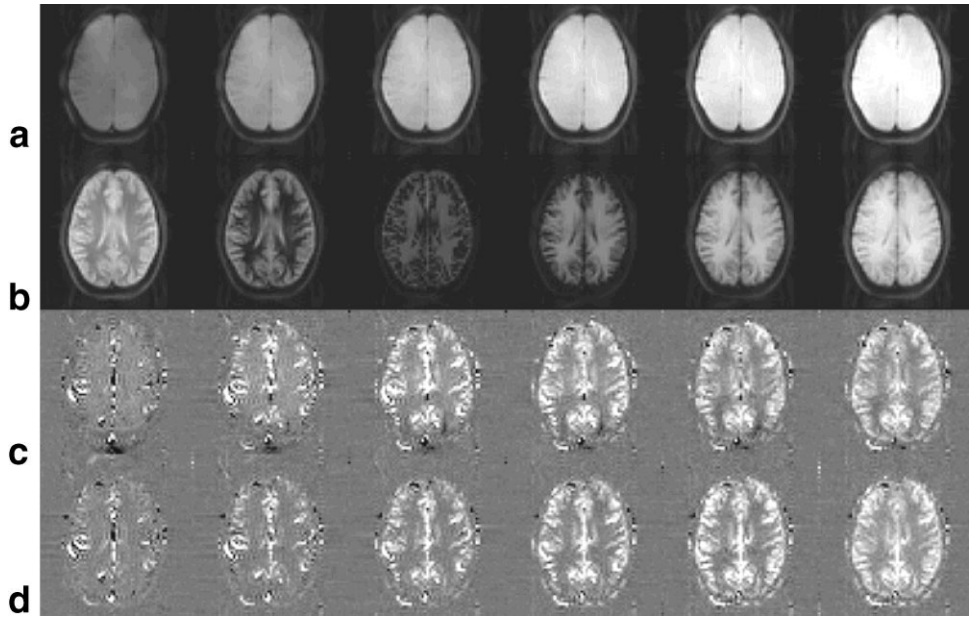

Figure 2. Source (raw) images (**a** and **b**) and ASL difference images (**c** and **d**) for two prototypical ASL methods at different times TI between the tagging RF pulse and the image acquisition. a: EPISTAR tag images. b: FAIR tag images. **c:** EPISTAR difference (control minus tag) ASL images. **d:** FAIR difference (control minus tag) ASL images. From left to right: TI = (200, 400, 600, 800, 1000, 1200) msec. Despite marked differences between EPISTAR and FAIR in raw image contrast (compare a and b), the ASL subtraction images are nearly identical (c and d). Other imaging parameters included field of view (FOV) = 24 cm, slice thickness = 8 mm; single-shot EPI at 64^2 resolution, TR = 2000 msec, TE = 25 msec, 100 repetitions per TI point, for a scan time of 200 seconds per image. (Reprinted from Wong EC, Buxton RB, Frank LR. Implementation of quantitative perfusion imaging techniques for functional brain mapping using pulsed arterial spin labeling. NMR Biomed 1997;10:237–249, with permission of John Wiley & Sons, Ltd.)

Magnetization Transfer

In addition to slice profile effects, the tag and control RF pulses can also modulate the magnetization in the imaging ROI through magnetization transfer effects. These can generate modulations of the static tissue magnetization that dominate the ASL signal in continuous ASL tagging methods, but are minimal in pulsed ASL.

Tagging Efficiency

In order to quantify perfusion, it is necessary to know the degree to which the tag and control RF pulses modulate the blood magnetization. The ideal tag pulse in typical pulsed ASL sequences inverts the inflowing blood, while the control pulse leaves the blood unperturbed, resulting in a blood magnetization difference of $2M_{0B}$ between tag and control ($\alpha = 1$). For most pulsed ASL techniques, the tagging efficiency α is greater than 0.95, and this is a relatively small source of error (9).

Tagging Geometry

The choice of tagging planes and regions depends on several anatomical and physiological factors, including the locations and flow directions of major arteries and

Table 2
Modular Features in Many ASL Sequences

Pulse sequence module	Description	Features
QUIPSS II (6)	Additional saturation pulse in the tagging region to directly control the temporal width of the tag.	This modification brings the bolus width τ under pulse sequence control and allows for quantitative pulsed ASL without acquiring data at multiple TI
Q2TIPS (16)	QUIPSS II with repeated thin saturation pulses rather than one thick saturation pulse	Better saturation profile than QUIPSS II
Multiple TI (17)	Repeat ASL experiment at various values of TI	Allows for fitting of data to inflow model to extract both CBF and Δt
In-Plane Presat (1)	Saturation of imaging region immediately before or after tag	Reduces contamination of imaging ROI by tag and control pulses
Diffusion weighting (18)	Diffusion/flow weighting gradients to reduce intravascular signal	Eliminates arterial signal at shorter TI, but complicates quantitation
Background Suppression (19, 20)	Nulling of static tissue signal at time of image acquisition	Reduces noise from fluctuations in static tissue signal

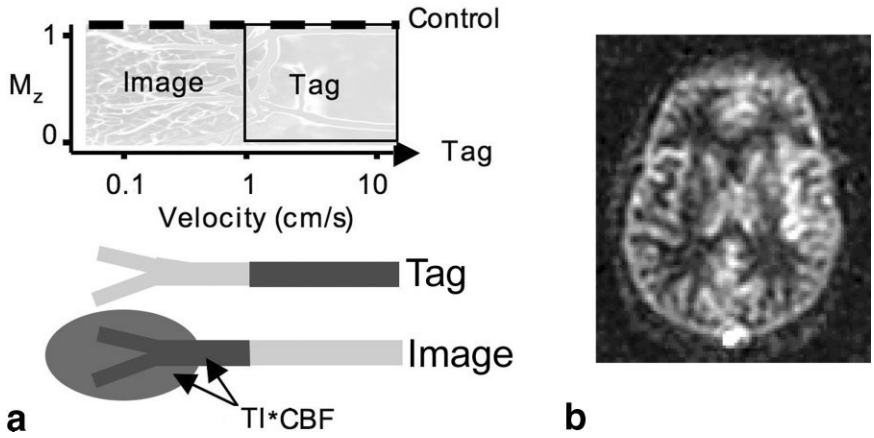

Figure 3. Schematics and image results for VS-ASL. **a:** Magnetization in the inflowing arterial blood (Tag) and brain tissue (Image) that occurs with VS-ASL. The RF pulses for tagging and imaging are designed to excite spins that are faster or slower than a critical velocity (V_c), respectively. A typical V_c of 1 cm/second is used to discriminate between inflowing arterial blood and static tissue. The plot above shows the velocity selectivity profile of ideal tag and control pulses. Shown shaded at the bottom is tagged blood upstream in the arterial tree immediately after the tag pulse (labeled Tag) and tagged blood downstream in smaller arteries and tissue at the time of image acquisition (labeled Image). The quantity of tagged blood that decelerates through the cutoff velocity during TI is given by TI times the local CBF. **b:** Difference ASL image (control minus tag) using VS-ASL. Imaging parameters: FOV = 24 cm, slice thickness = 8 mm, single-shot spiral at 64^2 resolution, TR = 2000 msec, TE = 3 msec, VS-ASL tagging with V_c = 2 cm/second, 100 repetitions, for a scan time of 200 seconds.

veins. The primary considerations are ensuring that a sufficient quantity of arterial blood is tagged to provide a large ASL signal, allowing for rapid refreshment of blood in the tagging region, minimizing interference between the tagging and imaging planes, and minimizing the tagging of venous blood.

TAGGING SCHEMES

The prototype pulsed ASL tagging schemes are EPISTAR (1) and FAIR (2,3), and there are several variants of these techniques tabulated in Table 1. EPISTAR and FAIR images are shown in Fig. 2. Note in this figure that despite very large differences in static tissue contrast between EPISTAR and FAIR, the ASL difference images are nearly identical.

In addition to the basic tagging techniques, there are several other pulse sequence modifications that can be added to the ASL pulse sequence as modules. These modular pulse sequence components and their features are shown in Table 2.

VS-ASL

VS-ASL is a newer form of pulsed ASL that tags blood based purely on flow velocity and not on spatial location (10,11). A velocity-selective tag pulse saturates or inverts blood above a cutoff velocity (V_c), as shown schematically in Fig. 3a. The plot of Mz vs. velocity shows the ideal velocity selectivity profiles of the tag pulse, which in this case saturates spins above 1 cm/second, and the control pulse is transparent (i.e., it does not affect the magnetization). The imaging process is velocity selective as well, acquiring data only from spins with velocity below V_c. In this manner, only spins that decelerated through the cutoff velocity during the inflow time TI will be observed, and the signal will be proportional to TI · CBF. Venous blood is automatically excluded, as it generally accelerates rather than decelerates. The primary theoretical advantage of VS-ASL is that it is inherently insensitive to transit delays, and thus may be the method of choice in pathologies such as stroke, where collateral or slow flow may otherwise result in long transit delays and grossly incorrect CBF measurements. A VS-ASL image is also shown in Fig. 3.

CONCLUSION

Quantitative and efficient measurement of CBF can be achieved using pulsed ASL. There are several basic tagging techniques that are more similar than different, with subtle differences shown in Table 1. Other modular components can be added to a pulsed ASL sequence to provide specific features. VS-ASL represents a new category of pulsed ASL that is promising for imaging of CBF in the presence of slow or collateral flow.

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