ISMRM Perfusion Workshop Invited Paper

Quantifying CBF With Arterial Spin Labeling

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The basic principles of measuring cerebral blood flow (CBF) using arterial spin labeling (ASL) are reviewed. The measurement is modeled by treating the ASL method as a magnetic resonance imaging (MRI) version of a microsphere study, rather than a diffusible tracer study. This approach, particularly when applied to pulsed ASL (PASL) experiments, clarifies that absolute calibration of CBF primarily depends on global properties of blood, rather than local tissue properties such as the water partition coefficient or relaxation time. However, transit delays from the tagging region to the image voxel are a potential problem in all standard ASL methods. The key to quantitative CBF measurements that compensate for this systematic error is to create a well-defined bolus of tagged blood and to ensure that all of the bolus has been delivered to an imaging voxel at the time of measurement. Two practical technical factors considered here are 1) producing a tagged bolus with a well-defined temporal width and 2) accounting for reduction in magnitude of the tagged magnetization due to relaxation. The ASL approach has the potential to provide a robust estimation of CBF, although the timing of water exchange into tissue and the effects of pulsatile flow require further investigation.

Key Words: cerebral blood flow; arterial spin labeling; magnetic resonance imaging; kinetic modeling; water exchange
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MEASURING CEREBRAL BLOOD FLOW

CEREBRAL BLOOD FLOW (CBF) IS THE volume of arterial blood (mL) delivered to 100 g of tissue per minute, and a typical human CBF is $f = 60$ mL/100 g-minute. In imaging applications, localization is in terms of an imaging voxel, so it is easier to define CBF in terms of a volume of tissue. Because the density of brain is near 1 g/mL, the typical human CBF value is 0.6 mL/mL-minute or 0.01 mL/mL-second. Note that when referenced to tissue volume, the dimensions of f are simply inverse time, the dimensions of a rate constant. This dimensionality highlights the primary role CBF plays in determining the delivery of metabolic substrates and the clearance of metabolic products: the rate of delivery to the tissue of any substrate is simply fC_a, where C_a is the arterial concentration of the substrate. Note that this definition emphasizes the delivery of arterial blood to the tissue element and has no fixed relationship with either the amount of blood present in the tissue volume (the cerebral blood volume (CBV)) or the motion of blood within the tissue element (blood velocity). For this reason, the most robust approaches to quantifying CBF are based on measuring the delivery of an agent carried in arterial blood.

The Microsphere Method

The classic gold standard for such measurements is microspheres, which are labeled particles that are too big to fit through the capillaries. After arterial injection, the microspheres are delivered to each tissue element in proportion to the local CBF and remain trapped there for subsequent counting. Mathematically, if the bolus of microspheres is described by $C_a(t)$, the arterial concentration of microspheres over time expressed in moles/mL blood, then the number of microspheres Q (moles/mL tissue) delivered to 1 mL of tissue by time T is

$$Q(T) = f \cdot \int_0^T C_a(t)\,dt. \qquad (1)$$

After the bolus has been delivered (i.e., $C_a(t)$ has returned to zero), the total number of microspheres delivered is simply f multiplied by the integral of $C_a(t)$. Because of this relationship, the measured value of Q for each tissue element can be interpreted as a quantitative index of blood flow, lacking only a global scaling factor, the integral of $C_a(t)$, to convert moles of microspheres into absolute blood flow units.

The ASL Method

Microsphere studies are highly invasive, requiring arterial injection and subsequent arterial sampling to measure $C_a(t)$, and tissue sampling after the bolus to measure $Q(T)$. Arterial spin labeling (ASL) techniques accomplish the same goal as microsphere studies by manipulating — in a noninvasive way — the magneti-

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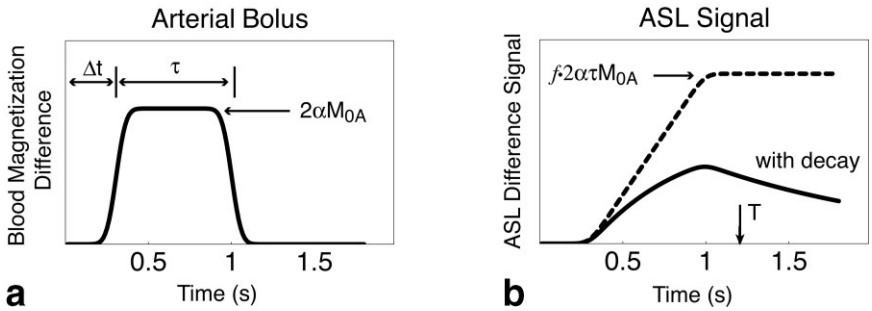

Figure 1. Idealized kinetics of the ASL signal for a pulsed experiment to measure cerebral perfusion. The ASL signal is the difference of two images acquired with and without prior inversion of the arterial magnetization, and is modeled in terms of a labeled bolus of magnetization delivered to each tissue element in proportion to local CBF (f). **a:** Time profile of the idealized arterial bolus of magnetization as it arrives at a local tissue element. The temporal features of the bolus are characterized by a duration τ and a transit delay Δt such that spins tagged at $t = 0$ do not begin to appear in the tissue element until $t = \Delta t$. The width of the bolus, τ, is equal to the duration of the RF continuous inversion pulse in a CASL experiment, or TI_1 in a PASL-QUIPSS II experiment, or unknown in a FAIR experiment. The rounded shape of the bolus profile as it arrives at the tissue element is meant to illustrate the broadening of the initial rectangular pulse during transit from the tagging region. **b:** Time profiles of the ASL magnetization difference in the cerebral tissue element as the arterial bolus arrives. The dashed curve shows the ideal case with no relaxation or clearance of the delivered magnetization, to emphasize the similarity of ASL to a classical microsphere experiment. If the image acquisition is delayed by a sufficient time T relative to the initial inversion RF pulse, all of the magnetized label will have been delivered to the tissue, and the magnitude of the ASL signal is simply local perfusion f multiplied by the area under the arterial bolus. The solid curve shows the actual ASL signal, including the decay of the labeled magnetization due to T_1 relaxation and possibly venous clearance of the tagged spins.

zation of the arterial blood before it reaches the slice of interest (see Buxton (1) for a general review). In a typical ASL experiment the arterial blood is tagged by inverting the magnetization, and after a delay this tagged blood arrives at the image plane and an image is acquired. A control measurement is then made without tagging the arterial blood. If the tag and control images are carefully adjusted so that the signal from the static spins is the same in both cases, then the difference signal will be proportional to the amount of arterial blood delivered, and thus will be proportional to CBF. Specifically, the local ASL difference signal (ΔS) measures how much of the original arterial magnetization created by the inversion pulse has been delivered to the voxel and survives to the time of measurement. In effect, we can think of the magnetization difference (control minus tag) carried into the voxel as an agent delivered by CBF and apply the same kinetic modeling arguments used for microspheres (1,2).

The key for understanding ASL quantification is in how we define the appropriate scaling factor, the equivalent of the integral of $C_a(t)$, taking account of the bolus shape (intrinsic width and transit delays) and relaxation of the inverted magnetization. If a voxel full of labeled blood could be examined immediately following the inversion pulse, the magnetization difference (control minus tag) would be $2\alpha M_{0A}$, where M_{0A} is the equilibrium magnetization of arterial blood and α is the inversion efficiency ($\alpha = 1$ for a perfect inversion). This defines the initial amplitude of the bolus, before relaxation has had any effect. In the ideal case with no relaxation, the magnetization difference of the arterial blood arriving at a particular voxel can be characterized by a transit delay Δt and an intrinsic duration τ, illustrated as a smoothed rectangular bolus in Fig. 1a. If the measurement time T is sufficiently late to allow all of the bolus to arrive, the total magnetization delivered to a local region of the tissue is $f(2\tau\alpha M_{0A})$ (Fig. 1b), analogous to Eq. [1], with the term in parentheses playing the role of the integral of $C_a(t)$.

QUANTITATIVE ASL

In order to quantify CBF measured with ASL, one must 1) produce an accurate control measurement, 2) create a well-defined tagged bolus and wait sufficiently long for that bolus to be delivered, and 3) account for relaxation (and possible clearance) of the magnetization tag (Fig. 1b). The first step, creating a good control experiment, has motivated a large body of work focused on technique development and was reviewed in the initial invited presentations in the ISMRM workshop on perfusion magnetic resonance imaging (MRI) (see other papers in this issue). The second and third steps are discussed next.

Creating a Well-Defined Bolus

The second step, creating a tagged bolus that is well defined in time and space, is critical because the parameters Δt and τ are potentially local rather than global parameters, making the delivered bolus nonuniform across the brain. The transit delay Δt, the time required for the leading edge of the bolus to travel from the edge of the tagging region to the image voxel, clearly depends on the location of that voxel. The duration τ of the bolus is a global parameter in a continuous ASL (CASL) experiment, determined by the duration of the long applied radio frequency (RF) tagging pulse that continuously inverts the magnetization of blood moving through the tagging plane. In a pulsed ASL (PASL) experiment, however, the tag is applied in space rather than in time by tagging a volume of tissue below the image plane. The duration of the tag is then determined

by the volume of tagged blood in the tagging band and how fast that volume clears from the tagging band, which will depend on the geometry and blood velocity of the large arteries, the spatial extent of the tagging, and ultimately the size of the RF coil. With the QUIPSS II modification of PASL, a saturation pulse is applied to the tagging band at a time TI_1 after the initial inversion pulse in both the tag and control experiments (3). This snips off the end of the tagged bolus, creating a well-defined bolus at the tagging band with a width of $\tau = TI_1$. Note that for this scheme to work, the intrinsic duration of the bolus, determined by the RF coil and the tagging geometry, must be greater than TI_1.

With a well-defined bolus, the effects of variable transit delays are minimized by waiting for a sufficiently long time to allow all of the bolus to reach each voxel. In PASL with QUIPSS II the image is collected at TI_2, and, as long as $TI_2 - TI_1 > \Delta t$, all of the bolus will be delivered. For CASL, a similar effect is achieved by inserting a delay after the end of the RF tagging pulse and before data collection (4). If this delay is longer than Δt, then again all of the bolus is delivered. Because the early versions of CASL (5) and PASL (e.g., FAIR (6) and EPISTAR (7)) did not account for these effects, they provide only qualitative indices of CBF.

Accounting for Loss of the Tag

The final necessary correction is to account for the loss of the tagged magnetization during the experiment. The label in an ASL experiment is longitudinal magnetization carried by arterial blood. This magnetization will disappear by longitudinal relaxation (T_1) during the experiment, and conceivably some of the blood water carrying this magnetization will clear in venous flow. As a first approximation, we assume that the tagged magnetization remains in blood for the entire experiment, so that the appropriate T_1 is T_{1A}, the relaxation time of arterial blood. We also assume that none of the tagged spins clear by venous flow. With these assumptions, the PASL signal difference measured at time T is

$$\Delta S(T) = f \cdot 2\alpha M_{0A} \tau e^{-T/T_{1A}} \quad (2)$$

For a PASL-QUIPSS II experiment, the timing parameters are $\tau = TI_1$ and $T = TI_2$.

DISCUSSION

The Primary Importance of the Global Properties of Blood

An important point to note about Eq. [2] is that the ASL signal depends on local CBF (f), but the other parameters are global parameters of blood (M_{0A} and T_{1A}). This means that the PASL-QUIPSS II signal itself is a quantitative reflection of local CBF, with a global calibration factor that depends only on the properties of arterial blood. In fact, if we define ΔS_A as the signal difference at the time of measurement of a voxel filled with tagged blood, then

$$\Delta S_A = 2\alpha M_{0A} e^{-T/T_{1A}} \quad (3a)$$

and

$$\Delta S = f \cdot \tau \Delta S_A. \quad (3b)$$

The key for quantifying PASL-QUIPPS II is then an accurate determination of the corresponding signal of a voxel filled with arterial blood. In practice, this calculation must also take into account the fact that the longitudinal magnetization modeled in these equations is not directly measured. Instead, this magnetization is tipped over to create a measurable transverse magnetization, but this will decay with the T_2* appropriate to the environment of the spin at the measurement time T. In other words, spins that have exchanged into the tissue will decay with the T_2* of tissue, while those still in the blood decay with the T_2* of blood. For this reason, a short TE is desirable to minimize these uncertainties due to T_2*.

The Single-Compartment Model Is a Poor Approximation for ASL Experiments

The ASL approach is analogous to the positron emission tomography (PET) approach using water labeled with ^{15}O. With ASL the agent also is labeled water, and the relaxation of the magnetization plays the role of radioactive decay of the ^{15}O. Much of the original mathematical modeling of ASL experiments was taken directly from earlier models developed for PET studies (2,5), in particular the single-compartment PET model for the kinetics of the tracer. However, there is a key difference between the PET and ASL experiments that makes the single-compartment model inappropriate for ASL: the time scale for a PET study is on the order of 1 minute, while the time scale for an ASL experiment is on the order of 1 second, which is too short for the assumption of a well-mixed compartment. For this reason, the question of when tagged spins exchange with the extravascular space has little effect on modeling the PET experiment but a large effect on modeling the ASL experiment.

The single-compartment ASL model replaces the T_1 of blood in Eq. [2] with the T_1 of tissue, equivalent to assuming that water of blood instantaneously exchanges into tissue as soon as it enters the voxel volume. In addition, the apparent spin density of blood (M_{0A}) is replaced by M_0/λ, where M_0 is the spin density of the local tissue element and λ is the local water partition coefficient. The single-compartment model is then

$$\Delta S = f \cdot 2\alpha \frac{M_0}{\lambda} \tau e^{-T/T_1}. \quad (4)$$

As argued above, this model does not adequately account for the decay of the tag because it assumes instantaneous exchange (8). The introduction of local parameters M_0 and λ is technically correct, provided that λ is defined specifically as M_0/M_{0A}, although this is not precisely the classical definition of λ used in PET. However, this model has created a great deal of confusion in the field because it suggests that the ASL signal depends on a number of local parameters in addition to

flow (M_0, λ, and T_1) and hides the central role played by the global properties of blood. In short, microspheres offer a better conceptual model for describing the ASL experiment than the single-compartment PET model, despite the apparent similarities between PET and ASL methods.

Current Issues for Quantifying CBF

ASL techniques potentially provide a highly robust approach for measuring CBF (9) and show good agreement with true microsphere measurements (10). However, several effects could make Eq. [2] inaccurate and require further experimental work. Because CASL involves longer-duration tagging experiments, these effects are likely to be a more significant source of error with CASL than PASL. Some questions that deserve further investigation are:

1. Is the decay of the tag accurately modeled by the T_1 of blood? The T_1 of blood and tissue are different, so properly accounting for decay requires knowledge of how much time the tagged spins have spent in the intravascular and extravascular spaces by the measurement time. Tagged water in blood enters the voxel in a small artery and must pass down the vascular tree before reaching the capillary bed and exchanging with the larger pool of tissue water. If the time of exchange is about 1 second after entering the voxel (11), then for a PASL experiment most of the longitudinal relaxation occurs while the spin is still in blood.
2. Does any of the tagged blood escape in venous flow? For a CBF of 0.01 mL/mL-second and CBV of 4%, the mean transit time through the vascular bed of a voxel is 4 seconds, compared to a typical $T_{1A} < 1.5$ seconds in a PASL experiment. In addition, most of the water of arterial blood is extracted from the capillary, greatly increasing its lifetime in the voxel. So for a PASL experiment we would expect little or no clearance by venous flow, but this may be a more significant effect for CASL experiments (8).
3. How does the flow velocity profile (including pulsatile flow) affect quantification of CBF? The idealized bolus profile in Fig. 1a in reality is broadened by nonplug flow, and variable because of pulsatile flow in the arteries. The effect on quantifying CBF is still being explored (12).
4. Does large vessel signal contaminate the flow measurement? If the delay before imaging is too short, some of the tagged spins may still be in the larger arterial vessels. If these spins are destined for a more distal capillary bed, they should not be counted as perfusing the voxel in which they are located at the time of measurement. If $TI_2 - TI_1$ is sufficiently long, this should not be a significant problem. Small amounts of diffusion weighting can also be added to diminish the vascular signal (11), although this has the effect of lengthening the apparent transit delay: the tagged blood does not become visible until it has moved sufficiently far down the vascular tree so that the diffusion weighting does not destroy the blood signal.

CONCLUSIONS

In summary, the ASL experiment can be interpreted more clearly as an MRI version of a microsphere blood flow measurement, rather than a diffusible tracer experiment, despite the fact that water is a classic diffusible tracer. A particular strength of the technique is that the ASL difference signal is proportional to local CBF, with a calibration factor that depends primarily on global properties of blood. The ASL approach has the potential to provide a robust estimation of CBF, although the timing of water exchange into tissue and the effects of pulsatile flow require further investigation.

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