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 \( f = 60 \text{ mL}/100 \text{ g-minute} \). 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-second. Note that when referenced to tissue volume, 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 \( f C_0 \), where \( C_0 \) 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 \( C_m(t) \), 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

\[
Q(T) = f \int_0^T C_m(t) \, dt. 
\]  

After the bolus has been delivered (i.e., \( C_m(t) \) has returned to zero), the total number of microspheres delivered is simply \( f \) multiplied by the integral of \( C_m(t) \). 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 \( C_m(t) \), 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 \( C_m(t) \), 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-
The key for understanding ASL quantification is in how we define the appropriate scaling factor, the equivalent of the integral of $C_d(t)$, 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 $\alpha$ 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 $\Delta t$ and an intrinsic duration $\tau$, 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 $f(2\alpha M_{0A})$ (Fig. 1b), analogous to Eq. [1], with the term in parentheses playing the role of the integral of $C_d(t)$.

### 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 $\Delta t$ and $\tau$ are potentially local rather than global parameters, making the delivered bolus nonuniform across the brain. The transit delay $\Delta t$, 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 $\tau$ 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 $T_{I1}$ 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 $\tau = T_{I1}$. 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 $T_{I1}$.

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 $T_{I2}$, and, as long as $T_{I2} - T_{I1} > \Delta t$, 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 $\Delta t$, 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

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

(2)

For a PASL-QUIPSS II experiment, the timing parameters are $\tau = T_{I1}$ and $T = T_{I2}$.

**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 $\Delta S_A$ as the signal difference at the time of measurement of a voxel filled with tagged blood, then

$$\Delta S_A = 2 \alpha M_{0A} e^{-T/T_{1A}}$$

(3a)

and

$$\Delta S = f \cdot \tau \Delta S_A.$$  

(3b)

The key for quantifying PASL-QUIPSS 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 $M_0/\lambda$, where $M_0$ is the spin density of the local tissue element and $\lambda$ is the local water partition coefficient. The single-compartment model is then

$$\Delta S = f \cdot 2 \alpha M_0 \lambda^{-1} e^{-T/T_1}.$$  

(4)

As argued above, this model does not adequately account for the decay of the tag because it assumes instantaneous exchange into tissue as soon as it enters the voxel volume. The introduction of local parameters $M_0$ and $\lambda$ is technically correct, provided that $\lambda$ is defined specifically as $M_0/M_{0A}$, although this is not precisely the classical definition of $\lambda$ 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 \((M_0, \lambda, \text{ and } T_1)\) 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. 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 blood, but this may be a more significant effect for CASL experiments (8).

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 blood, 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 \(T_{1c} = T_1\) 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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**REFERENCES**


