A Technical Perspective for Understanding Quantitative Arterial Spin-labeling MR Imaging using Q2TIPS

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We illustrate the fundamental theoretical principles of arterial spin-labeling (ASL) magnetic resonance imaging (MRI) and show a system that employs the second version of quantitative imaging of perfusion using a single subtraction (Q2TIPS) to quantify cerebral blood flow (CBF). We also discuss the effects of the parameters used in Q2TIPS on CBF values as measured with ASL-MRI.

Keywords: ASL, cerebral blood flow, perfusion, Q2TIPS, review

Introduction

Arterial spin labeling (ASL) is a magnetic resonance (MR) imaging technique that can be used to acquire brain perfusion images noninvasively without the use of contrast media.1 Clinical MR imaging using 3-tesla equipment has brought ASL-MRI into the spotlight because the increased magnetic field offers longer blood T1 values as well as improved signal-to-noise ratios (SNR).2 In general, ASL-MRI first applies an inversion pulse to the cervical area that labels the arterial blood that flows through the cervical area. Brain images (labeled images) are acquired after this labeled blood perfuses into the brain tissue. Control images of the same region are acquired similarly without labeling. Finally, perfusion images are acquired by subtracting the labeled from the control images. In fact, ASL-MRI uses electromagnetically labeled arterial blood as an intrinsic tracer, which avoids the administration of extrinsic tracers, such as contrast media or radioisotopes.1

ASL-MRI can be broadly divided into 2 types according to the spin-labeling technique used—pulsed ASL (PASL)3–9 and continuous ASL (CASL).1,10–14 PASL consists of the single application of an inversion pulse over a relatively wide area (approximately 10-cm slice thickness) and labeling of all the arterial blood in that area at once, whereas CASL comprises the repeated application of the pulse over a small area (approximately one to 2-cm slice thickness) and continuous labeling of the arterial blood that flows into that area.

Edelman’s group proposed the first PASL technique, echo planar imaging and signal targeting with alternating radiofrequency (EPISTAR),4 which applies the inversion pulse to the area proximal to the imaging slab in the labeling state or distal to the slab in the control state, respectively. Wong’s group5 described proximal inversion with control for off-resonance effects (PICORE), a derivative of EPISTAR in which a control image is acquired with no slab-selective gradient. Both EPISTAR and PICORE provide qualitative CBF maps, but quantitative imaging of perfusion using a single subtraction (QUIPPS) and its second version, QUIPPS II,6 as well as QUIPSS II with thin-slice TI1 (elapsed time from application of the inversion pulse until application of the saturation pulse begins) periodic saturation (Q2TIPS) can offer quantitative CBF maps by adding saturation pulses to the areas proximal to the imaging slab at a given time after the inversion pulse. Kwong and associates15 developed another PASL technique, flow-sensitive alternating inversion recovery (FAIR), in which labeling is applied using a nonselective inversion pulse to a wide area that includes the imaging slab as well as prox-
imal and distal areas outside the imaging slab, and the control is a slice-selective inversion applied to the imaging slice. Gunther and colleagues proposed inflow turbo-sampling EPI-FAIR (ITS-FAIR), adapting the Look-Locker technique to FAIR to acquire multiphase perfusion images at multiple timing points with an interval of a few hundred milliseconds and thereby delineate the temporal hemodynamics of the perfusion-related signal intensity. In recent years, the team of Peterson and Golay applied the Look-Locker technique to Q2TIPS and accomplished the model-free measurement of CBF with quantitative STAR labeling of arterial regions (QUASAR).

Detre’s group developed CASL, the origin of ASL-MRI, and Alsop and associates refined the technique by setting the delay time following continuous labeling to account more accurately for transit effects in quantitative CBF. To achieve multislice perfusion imaging by CASL without spatially dependent off-resonance effects, they developed the method to acquire control images by applying amplitude-modulated irradiation at an equal distance distal to the imaging slab. Pseudo-continuous ASL (pCASL), a technique in which an intermittent inversion pulse is applied at regular intervals, solved the problem of a highly specific absorbed fraction (SAR) in applying a continuous inversion pulse. Recently, 3-dimensional (3D) ASL has become available, which combines imaging technologies, such as the 3D-spiral FSE method, with quantitative STAR labeling of arterial regions.

PASL can measure absolute cerebral blood flow (CBF) relatively simply. Measurement of absolute CBF enables comparison between patients or facilities as well as sites within the brain or changes over time in the same patient. CASL has a high SNR, which is theoretically approximately 2.71 times (i.e., the same as Napier’s constant) that of PASL. However, measurement of absolute CBF ideally requires distribution images of T1 values (T1 maps) in addition to the perfusion images by CASL, and the acquisition of accurate T1 maps requires the addition of another imaging sequence.

Each different ASL-MRI technique has its own analytical equations to quantify absolute CBF, but the properties of these equations, with multiple specific parameters and various ways to express formulae, are generally difficult to understand. Furthermore, as authors alter those formulae, ASL-MRI techniques improve with each report. No handbook clearly summarizes these diverse ASL-MRI quantitative theories. Accordingly, ignorance of the prerequisites or limits in quantification of CBF might lead to pitfalls.

We herein explain the theoretical background of ASL-MRI using concrete illustrations, hold up Q2TIPS, a PASL method, as a straightforward example of a system for measuring CBF, and discuss current issues in CBF measurement by ASL-MRI.

**Basic Interpretation of ASL-MRI Methodology**

Nuclear magnetic resonance (NMR) imaging is created by the spinning motion of the hydrogen nucleus. Components of organisms consisting of a mixture of various hydrogen compounds can emit NMR signals, but it has been hypothesized that only NMR signals derived from the water molecule, or H2O, indicate blood flow when blood flow is being measured in organisms with a clinical MR imaging unit. We have created a basic schema (Fig. 1) for understanding PASL that takes the above into consideration. This diagram shows one blood vessel passing through one block of brain tissue. Water molecules are present inside and outside the blood vessel, and the magnetization vectors of each water molecule are shown with upward-pointing arrows. The labeling slab, the space where spin labeling is conducted, is positioned under this brain tissue (Fig. 1A); an inversion pulse is applied over the entire slab (Fig. 1B), which also causes inversion of the magnetization vectors of the water molecules inside the blood vessel in that site; the water molecules containing the inverted vectors flow into the brain tissue with blood flow (Fig. 1C); the water molecules of these inverted vectors are distributed throughout the brain tissue; and labeled images are taken (Fig. 1D). Though these labeled images are already perfusion-weighted, they also contain brain parenchymal signals, so control images are taken in the same way without application of an inversion pulse (Fig. 1E). In theory, subtracting the labeled images from these control images should eliminate signals of brain tissue, so images created reflect only the distribution of blood flow (Fig. 1F).

**Quantitative Equation of Cerebral Blood Flow by Q2TIPS**

A common solution has been clearly indicated for the quantification of CBF with ASL-MRI based on the theory proposed by Buxton’s group, and the PASL imaging sequences presented by Wong’s team, QUIPPSII and Q2TIPS, have enabled the creation of useful and highly precise CBF map im-

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The commercial version of Q2TIPS was placed on the market after the group validation study by Detre’s group, and PASL is becoming commonly used worldwide. Here, we provide a general explanation to allow the reader to understand the basic techniques involved in PASL. The following is an equation for CBF measurement by Q2TIPS based on a single-compartment kinetic model proposed by Wong’s team:

\[ CBF = \frac{\text{Labeled images} - \text{Control images}}{\text{Inversion pulse time}} \]

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**Fig. 1.** Schemata for explaining the fundamental principles of arterial spin-labeling magnetic resonance imaging (ASL-MRI). (A) One blood vessel passes through one block of brain tissue; upward-pointing arrows show the magnetization vectors of water molecules inside and outside the blood vessel. The labeling slab, the space where spin-labeling is conducted, is positioned under this brain tissue. (B) When the inversion pulse is applied to the entire labeling slab, the magnetization vectors of the water molecules within the blood vessel are also inverted. (C) After that, water molecules containing the inverted vectors flow into the brain tissue with blood. (D) Finally, these inverted vector water molecules are distributed in brain tissue. Labeled images are taken after waiting for this to happen. (E) Control images to which the inversion pulse has not been applied are taken with the same timing. (F) Theoretically, brain tissue signals should be eliminated by subtracting labeled images from these control images, creating perfusion images that reflect only the distribution of blood flow.
Here, $\Delta M$ is the difference in magnetization between the presence and absence of spin labeling in the magnetization of one gram of brain tissue; this actually equates with the signal intensity when the labeled image is subtracted from the control image. The labeling efficiency is $\alpha$ (%), $M_{0B}$ is the magnetization of one mL of arterial blood in a static magnetic field, and $f$ is CBF. This is measured in several ways as we will describe later. The units used in Equation (Eq.) [1] are mL/g brain tissue/s rather than mL/100 g brain tissue/min. $T_{1B}$ is the $T_1$ value of arterial blood. $q$ is a correction factor that explains the $T_1$ prolonged effect caused by spin exchange between blood and brain tissue and the effect of blood flowing out from brain tissue through veins. $\tau$ is the time elapsed for enough labeled arterial blood to fill the brain tissue and show no further improvements in SNR after application of the inversion pulse. $\Delta t$ represents arterial transit time (ATT), the prolonged time for labeled blood to first arrive at the imaging area after application of inversion pulse. $T_{11}$ is the elapsed time from application of inversion pulse until initiation of saturation pulse. $T_{12}$ is the elapsed time from initiation of inversion pulse in labeled area to collection of image data in imaging area.

$$\Delta M(T_{12}) = 2\alpha M_{0B} \cdot f \cdot e^{-T_{12}/T_{1B}} \cdot q$$

$(T_{11} < \tau$ and $T_{11} + \Delta t < T_{12} < \tau + \Delta t)$. [1]

The table below defines the parameters used in the equation:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Unit</th>
<th>Assumed value used in Q2TIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f$</td>
<td>cerebral blood flow</td>
<td>mL/g brain tissue/s</td>
<td>—</td>
</tr>
<tr>
<td>$\Delta M$</td>
<td>longitudinal magnetization difference of one g of brain tissue between presence and absence of spin labeling</td>
<td>/g brain tissue</td>
<td>—</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>labeling efficiency</td>
<td>%</td>
<td>95</td>
</tr>
<tr>
<td>$M_{0B}$</td>
<td>equilibrium longitudinal magnetization of one mL of arterial blood</td>
<td>/mL arterial blood</td>
<td>—</td>
</tr>
<tr>
<td>$M_0$</td>
<td>equilibrium longitudinal magnetization of one g of brain tissue</td>
<td>/g brain tissue</td>
<td>—</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>brain-blood partition coefficient for water</td>
<td>(g water/g brain tissue) / (mL water/mL blood)</td>
<td>0.9</td>
</tr>
<tr>
<td>$T_{1B}$</td>
<td>$T_1$ value of arterial blood</td>
<td>s</td>
<td>1.5 (3-tesla MRI)</td>
</tr>
<tr>
<td>$T_1'$</td>
<td>$T_1$ value of brain tissue</td>
<td>s</td>
<td>—</td>
</tr>
<tr>
<td>$q$</td>
<td>correction factor for $T_1$ prolonged effect caused by spin exchange between blood and brain tissue and effect of blood flowing out from brain tissue through veins</td>
<td>(no unit)</td>
<td>1</td>
</tr>
<tr>
<td>$\tau$</td>
<td>the time elapsed for enough labeled arterial blood to fill the brain tissue and show no further improvements in SNR after application of the inversion pulse</td>
<td>s</td>
<td>—</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>arterial transit time, the prolonged time for labeled blood to arrive at the imaging area after application of inversion pulse</td>
<td>s</td>
<td>—</td>
</tr>
<tr>
<td>$T_{11}$</td>
<td>elapsed time from application of inversion pulse until initiation of saturation pulse</td>
<td>s</td>
<td>0.7</td>
</tr>
<tr>
<td>$T_{12}$</td>
<td>elapsed time from initiation of inversion pulse in labeled area to collection of image data in imaging area</td>
<td>s</td>
<td>1.8</td>
</tr>
<tr>
<td>$f_{\text{min}}$</td>
<td>minimum flow rate that can be detected by Q2TIPS with a given $T_{12}$</td>
<td>mL/g brain tissue/s</td>
<td>0.0033 (= 20 mL/100 g brain tissue/min)</td>
</tr>
<tr>
<td>$f_{\text{peak}}$</td>
<td>maximum flow rate that can be detected by Q2TIPS with a given $T_{12}$</td>
<td>mL/g brain tissue/s</td>
<td>0.0150 (= 90 mL/100 g brain tissue/min)</td>
</tr>
</tbody>
</table>
A more detailed version of the schema just outlined will be used to explain this equation for quantification (Fig. 2). The block of brain tissue is one $g$; the magnetization of one mL of arterial blood within the blood vessel is $M_{0B}$; and inside the blood vessel, arterial blood flows at blood flow volume $f$ (mL/g/s) (Fig. 2A). Next, the time at which the inversion pulse is applied to the entire labeling slab is set as elapsed time 0 ($s$) (Fig. 2B). After that, after elapsed time $T_{1B}$ ($s$), the saturation pulse is applied to the labeling slab (Fig. 2C). (Though continuous saturation pulses are actually applied to a relatively thin slice on the distal side of the labeling pulse, the figure shows the pulse being applied to the entire area for convenience.) Accordingly, only the arterial blood that flows out from the labeling slab in the period from elapsed time 0 to $T_{1B}$ ($s$) remains spin labeling, but spin labeling is deleted from the rest by the saturation pulse. Because arterial blood flows at blood flow volume $f$ (mL/g/s) into one $g$ of the block of brain tissue, the total amount of labeled blood after $T_{1B}$ ($s$) is $f$·$T_{1B}$ (mL). Furthermore, after labeled blood is inverted at elapsed time 0 ($s$), the longitudinal magnetization of the labeled blood is relaxed according to $T_{1}$ (B). Therefore, after elapsed time of $T_{1B}$ ($s$), the magnetization per one mL is expressed as $M_{0B}(1 - 2αe^{-T_{1B}/T_{1}})$ under $α$ (%) of the labeling efficiency. Furthermore, after waiting until this labeled blood reaches and perfuses the brain tissue, and after $T_{2}$ ($s$) has passed, labeled images are taken. Here, the overall volume of magnetization of all labeled blood is $M_{0B}(1 - 2αe^{-T_{1B}/T_{1}})$·$f$·$T_{1B}$ (Fig. 2D). Control images taken without application of an inversion pulse are taken at the same time (Fig. 2E). At this time, the overall volume of magnetization of unlabeled arterial blood is $M_{0B}$·$f$·$T_{1B}$. The measured signal difference, $ΔM(T_{1})$, is acquired by subtracting labeled images from control images. Therefore, subtraction of $M_{0B}(1 - 2αe^{-T_{1B}/T_{1}})$·$f$·$T_{1B}$ from $M_{0B}$·$f$·$T_{1B}$ produces $2αM_{0B}$·$f$·$T_{1B}$·$e^{-T_{1B}/T_{1}}$ (Fig. 2F). However, because of the $T_{1}$-prolonged effect caused by spin exchange between blood and brain tissue and the fact that blood flows out from brain tissue to veins, the measured signal difference, $ΔM(T_{2})$, is actually lower than $2αM_{0B}$·$f$·$T_{1B}$·$e^{-T_{1B}/T_{1}}$. The correction factor, $q$, is included to correct this (according to the literature, $q$ is 0.85 to 1.0). Thus, Eq. [1] is completed.

However, in practice, $q$ is not a simple constant value. Buxton and associates showed the following equation that we will later describe in detail19:

$$q = \frac{e^{k·T_{1B}}(e^{-k·T_{1}+ΔT} - e^{-k·T_{1}})}{k·T_{1}}$$

and $k = \frac{1}{T_{1B}} - \frac{1}{T_{1}}$, where $\frac{1}{T_{1}} = \frac{1}{T_{1}} + \frac{f}{λ}$. [2]

**Arterial Blood Magnetization: $M_{0B}$**

In theory, arterial blood magnetization, $M_{0B}$, is measured as the signal intensity of one mL of arterial blood calculated from images ($M_{0}$ images) taken with a sequence under the same conditions as those for control images after enough time elapses for the full relaxation of the magnetization of the arterial blood under a static magnetic field. However, in reality, the accurate measurement of $M_{0B}$ is difficult because the arterial blood does not come to a standstill or pool in any tissue structures within living organisms. Therefore, $M_{0B}$ is calculated from a number of alternative measured values.

Wong’s team used the magnetization of venous blood inside the superior sagittal sinus instead of arterial blood4,8 based on the hypothesis that the water content of venous and arterial blood are almost equal. However, it is actually difficult to set a region of interest (ROI) in the superior sagittal sinus and make accurate measurements because $M_{0}$ images have low resolution. Therefore, the signal intensity values of venous blood and white matter are first measured on proton-density-weighted (PD) images. Because the ratio, $R$, of both signal values is almost identical to that of proton density, the ratios of $M_{0B}$ and white matter magnetization, $M_{0WM}$, measured with $M_{0}$ images are equal. Therefore,

$$M_{0B} = R \cdot M_{0WM}. \tag{3}$$

Wong and colleagues used the EPI method to acquire $M_{0}$ images.6,8 With this method, repetition time (TR) is $\infty$, effective echo time (TE) is $TE_{eff}$, blood signal intensity is $S_{0B}$, the $T_{2}^{*}$ value of blood is $T_{2}^{*}_{B}$, white matter signal intensity is $S_{WM}$, and the $T_{2}^{*}$ value of white matter is $T_{2}^{*}_{WM}$. Therefore, Eq. [3] is expressed as:

$$\frac{S_{0B}}{e^{-TE_{eff}/T_{2}^{*}_{B}}} = R \cdot \frac{S_{WM}}{e^{-TE_{eff}/T_{2}^{*}_{WM}}} \leftrightarrow \frac{S_{0B}}{R \cdot S_{WM}} = e^{(T_{2}^{*}_{WM} - T_{2}^{*}_{B})TE_{eff}}. \tag{4}$$

Therefore, $S_{0B}$ is calculated by measuring the signal intensity of the white matter on the PD image, that of the venous blood in the superior sagittal sinus on the PD image, and that of the white matter on the $M_{0}$ image. $ΔM(T_{2})$ is actually measured as the difference in signal intensity, $ΔS(T_{2})$, between control images and labeled images, which are acquired using EPI with the same TE. Therefore, one can apply
Fig. 2. Schemata for explaining the quantification of blood flow by the second version of quantitative imaging of perfusion using a single subtraction (Q2TIPS). (A) The magnetization of one mL of intravascular arterial blood is assumed as $M_{0B}$ (no unit). Intravascular arterial blood is hypothesized as flowing at a blood flow volume of $f (mL/g/s)$ into one g of brain tissue. (B) Time elapsed for application of the inversion pulse to the entire slab is set at 0. (C) After the elapsed time of $T_{11}$ s, the saturation pulse is applied. The volume of labeled blood that was not applied with the saturation pulse is $f \cdot T_{11}$ (mL). Furthermore, as labeled blood is defused with $T_{1B}$, the $T_1$ value of arterial blood, the magnetization per one mL after elapsed time of $T_{11}$ s is expressed as $M_{0B}(1-2ae^{-T_{11}/T_{1B}})$ under $\alpha$ (%) of the labeling efficiency. (D) Labeled images are taken after elapsed time of $T_{12}$ s. At this time, the total volume of the magnetization of labeled blood is $M_{0B}(1-2ae^{-T_{11}/T_{1B}})$. (E) Next, control images to which the inversion pulse has not been applied are taken at the same time. At this time, the total volume of the magnetization of unlabeled arterial blood is $M_{0B} \cdot f \cdot T_{11}$. For the actual signal difference $\Delta M(T_{12})$ acquired by subtracting labeled images from control images, $2\alpha M_{0B} \cdot f \cdot T_{12} \cdot e^{-T_{12}/T_{1B}}$ is acquired by subtracting $M_{0B}(1-2ae^{-T_{11}/T_{1B}}) \cdot f \cdot T_{11}$ from $M_{0B} \cdot f \cdot T_{11}$. 

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\[ \lambda = \frac{\text{tissue water content}}{\text{blood water content}} = \frac{M_0}{M_{OB}} \implies M_0 = \frac{M_B}{\lambda}. \quad [5] \]

In addition, \( M_{OB} \) in this equation has been calculated pixel by pixel from the signal intensity of brain tissue acquired from \( M_0 \) images subdivided by \( \lambda \) as a constant value, 0.9 (mL/g), based on the assumption that \( \lambda \) remains unchanged at all sites in the brain. This enables automatic creation of CBF maps and serves as the foundation for the current commercially available version of Q2TIPS.

**Brain-blood Partition Coefficient for Water: \( \lambda \)**

The commercial version of Q2TIPS uses the value 0.9 (mL/g) theoretically for the brain-blood partition coefficient for water, \( \lambda \). However, the brain-blood partition coefficient for water varies with hematocrit, brain topography, age, and pathological changes. Herscovitch and associates proposed that the water content of blood, \( C_{bl} \) (g/mL blood), was calculated with hematocrit, \( Hct \) (%), as:

\[ C_{bl} = 0.948 - 0.223 \times Hct. \quad [6] \]

They used 77 (g/100 g brain tissue) of the water content of the whole brain, so 0.9 (mL/g) of the brain-blood partition coefficient for water is assumed to be less than under 42% of the \( Hct \). An error occurs +1.7% (overestimation) to −0.9% (underestimation) in normal \( Hct \) range of 35 to 45% at \( T_2 = 1.8 \) (s) and \( T_{1B} = 1.5 \) (s).

Other values for the partition coefficient for water are: 0.82 (white matter), 0.98 (gray matter), 0.99 (cerebral cortex), 0.88 (thalamus), 0.95 (caudate nucleus), 0.83 (centrum semiovale), and 0.89 (corpus callosum). The partition coefficient for water in neonates is estimated as 1.10 (mL/g) because neonates have 45 to 65% of the normal range in \( Hct \) and 89 (g/100 g) of the water content of the entire brain. On the other hand, the partition coefficient in edematous centrum semiovale amounts to 0.96 (mL/g). Such variation might rather be considered to estimate the distribution of perfusion.

**T\(_1\) Value of Arterial Blood: \( T_{1B} \)**

A fixed \( T_1 \) value of arterial blood, \( T_{1B} \), is generally used for CBF measurement by ASL-MRI because the true \( T_1 \) value of arterial blood is similarly difficult to measure for the same reason \( M_{OB} \) measurement is difficult. In practice, \( T_{1B} \) is typically assumed to be about 1.5 to 1.7 (s) on a 3T MR imaging unit. On the other hand, Lu and colleagues proposed the relationship between \( T_{1B} \) and \( Hct \) as:

\[ I/T_{1B} = (0.52 \pm 0.15) \times Hct + (0.38 \pm 0.06). \quad [7] \]

This leads to an estimated 1.664 ± 0.014 (s) of \( T_{1B} \) at a typical human \( Hct \) of 42%. Equation [7] suggests that the normal \( Hct \) range of 35 to 45% causes an overestimation of 10 to 21% if it is used instead of a fixed \( T_{1B} \) of 1.5 (s), and the combination of Eqs. [5], [6], and [7] causes an overestimation of 9 to 23% in Eq. [1] at \( T_2 = 1.8 \) (s). Variations of \( T_{1B} \) might assume more importance as the resolution of perfusion imaging by ASL-MRI improves in the future.

**Correction Factor: \( q \)**

The model with \( q = 1 \) becomes identical to the single compartment model without consideration of the \( T_1 \) value of brain tissue, \( T_{1}' \), and venous outflow, where the labeled spin retains microvasculature and would not enter the tissue compartment. However, as time elapses after the spins reach the capillary system in the brain tissue, the labeled spins move into the tissue compartment, where they follow \( T_{1}' \) rather than the arterial relaxation time, \( T_{1B} \). The correction factor, \( q \), compensates for such consideration (See Appendix). Additionally, Buxton’s theory ignores the effect of blood flowing out from brain tissue through the veins. This effect rarely becomes significant because in practice, on an MR imaging unit of 3T or less, \( T_2 \) is usually set within a few seconds to gain SNR. However, it might rather be assumed if a longer \( T_{1B} \) is adopted.

**Arterial Transit Time: \( \Delta t \)**

\( \Delta t \), the biggest challenge in the accurate measurement of cerebral blood flow by ASL-MRI, is reported from 0.42 to 0.73 (s) in healthy subjects and can easily be affected by such factors as age, brain topography, cerebral blood flow value, and the structural property of ASL application. Transit time longer by approximately 0.1 (s) has been reported in...
the elderly.\textsuperscript{30} Measured delays were typically 1.0 to 1.3 (s) at the occipital pole, compared to 0.5 to 0.8 (s) in the parietal lobes.\textsuperscript{5} Wong’s group determined experimentally that this delay ranges from about 0.5 to 1.5 (s) for a physical gap of one to 3 cm between the labeling slab and imaging slab. Longer transit times were estimated in the region of hypoperfusion in patients with occlusive carotid artery disease,\textsuperscript{31} whereas high-grade brain tumor had a short arterial transit time.\textsuperscript{32} 

\( \Delta t \) is determined as the smallest \( T1_2 \) when \( \Delta M(T1_2) \) becomes more than zero. In practice, accurate measurement of \( \Delta t \) requires several perfusion images with several different \( T1_2 \) values, which extends scan time. A recent study using a Look-Locker method, however, achieved measurement within a reasonable imaging time.\textsuperscript{33} Application of ASL-MRI might equip such \( \Delta t \) correction technique before long.

**Errors due to Fixed Parameters of \( T1_i \) and \( T1_2 \)**

Equation [1] only works when, as this report states, parameters \( T1_i \) and \( T1_2 \) are \( T1_i < \tau \) and \( T1_i + \Delta t < T1_2 < \tau + \Delta t \). Under other conditions, \( f \) is represented with the following equations:

\[
\begin{align*}
\Delta M(T1_2) &= 0 \quad (T1_2 < \Delta t) \\
\Delta M(T1_2) &= 2\alpha M_0 / \lambda \cdot f \cdot T1_i \cdot e^{-T1_2/T1B} \quad (\Delta t < T1_2 < T1_i + \Delta t) \\
\Delta M(T1_2) &= 2\alpha M_0 / \lambda \cdot f \cdot T1_i \cdot e^{-T1_2/T1B} \cdot q \quad (T1_i < \tau, \ T1_i + \Delta t < T1_2 < \tau + \Delta t) \\
\Delta M(T1_2) &= 2\alpha M_0 / \lambda \cdot f \cdot \tau \cdot e^{-T1_2/T1B} \cdot q \quad (T1_i > \tau, \ \tau + \Delta t < T1_2) \\
\end{align*}
\]

where

\[
q = \frac{e^{k-T1_2} (e^{-k-T1_2} - e^{-k-T1_2}}{k \cdot (T1_2 - \Delta t)} (\Delta t < T1_2 < T1_i + \Delta t) \\
q = \frac{e^{k-T1_2} (e^{-k-T1_2} - e^{-k(T1_2+\Delta t)}}{k \cdot T1_i} (T1_i + \Delta t < T1_2 < \tau + \Delta t) \\
q = \frac{e^{k-T1_2} (e^{-k-T1_2} - e^{-k(t+\Delta t)}}{k \cdot \tau} (\tau + \Delta t < T1_2).
\]

Equation [10] represents the state after applying the labeling pulse before the flow of labeled blood into the brain tissue; Eq. [11], the state after applying the labeling pulse in the middle of the flow of labeled blood into the brain tissue; Eq. [12] (or [1]), the state after labeled blood finishes flow into the brain tissue; and Eq. [13], the state when prolongation of \( T1_i \) means that all labeled blood volume finally flows into the brain tissue and further \( T1_i \) prolongation will cause no increased signal difference \( \Delta M(T1_2) \), with \( \tau \) representing maximum \( T1_i \).\textsuperscript{8} In other words, \( \tau \) is the square bolus of duration for labeled spin flowing in the brain tissue. However, the commercial version of Q2TIPS\textsuperscript{20} uses the following equation for the calculation of CBF no matter the subject’s condition:

\[
\Delta M(T1_2) = 2\alpha M_0 / \lambda \cdot f \cdot T1_i \cdot e^{-T1_2/T1B}. \quad [14]
\]

It also uses assumed values of \( \lambda = 0.9 \) (mL/g), \( \alpha = 0.95 \), and \( T1B = 1.5 \) (s) on a 3T MR imaging unit and \( T1B = 1.2 \) (s) on a 1.5T unit, an acquired M0 image, and 80 pairs of control and labeled images. Compared with Eq. [1], \( q \) is set to one. Equations [10] to [13] reflect changes when \( T1_2 \) gradually increases from zero under the fixed condition of blood flow volume \( f \). Furthermore, in standard clinical practice, settings of \( T1_i \) and \( T1_2 \) are not altered for the individual patient. Under these conditions, CBF values measured with ASL-MRI could differ from true CBF values by reduced blood flow or reduced blood flow velocity caused by such pathological conditions as cerebral infarction or cerebrovascular stenosis. Thus far, this issue has been attributed to \( \Delta t \) using Eq. [11]. However, \( \Delta t \) is subject to cerebral blood flow values as mentioned above, and it might be difficult to understand the difference between true CBF values and CBF values measured with ASL-MRI in Eqs. [10] to [13], which contain both \( \Delta t \) and \( f \). In this section, the imaging phantom is assumed to be a single, well-mixed compartment with intra- and extravascular water in perfect communication with penetration of a single tube, similar to the model shown in Fig. 1. Labeled water enters and leaves with perfusion rate \( f \). These conditions are specifically expressed in the following ways:

\[
\begin{align*}
&f' = 0 \quad (0 < f < f_{min}) \quad [A] \\
&f' = \frac{T1_2}{T1i} \cdot (f - f_{min}) \quad \left(f_{min} < f < \frac{T1_2}{T12 - T1i} \cdot f_{min}\right) \quad [B]
\end{align*}
\]
\[ f' = f \left( \frac{TI2}{TI2 - TI1} \cdot f_{\text{min}} < f < f_{\text{peak}} \right) \quad \text{[C]} \]

\[ f' = f_{\text{peak}} \quad (f_{\text{peak}} < f) \quad \text{[D]} \]

Here, \( f' \) expresses the flow rate measured with ASL-MRI, and \( f \) signifies the true flow rate. In Eq. [A], \( f_{\text{min}} \) is the minimum flow rate that can be detected from the difference in signal, \( \Delta M(TI2) \), between control images and labeled images with a given \( TI2 \). Therefore, it follows that \( f' \) cannot be detected with ASL-MRI and remains 0 so long as \( f \) does not reach \( f_{\text{min}} \). Moreover, when set as \( v_{\text{ia}} \), the internal volume of the path in the tube through which labeled blood flows until reaching the imaging slab, the equation \( v_{\text{ia}} = f_{\text{min}} \cdot TI2 \), is established. In Eq. [B], even if the true flow rate increases more than \( f_{\text{min}} \), \( f' \) is underestimated more than \( f \) because \( f' \) is calculated using Eq. [12], though Eq. [11] should normally be used. Therefore, it follows that:

\[ 2\alpha M_{0B} \cdot f' \cdot TI1 \cdot e^{-TI2/TI1} = 2\alpha M_{0B} \cdot f \cdot (TI2 - \Delta t) \cdot e^{-TI2/TI1} \leftrightarrow f' = \frac{TI2 - \Delta t}{TI2} \cdot f. \quad \text{[15]} \]

At the same time, when \( f \) increases, \( \Delta t \) grows shorter. However, labeled blood follows the same path. Therefore:

\[ v_{\text{ia}} = TI2 \cdot f_{\text{min}} = \Delta t \cdot f \leftrightarrow \Delta t = \frac{f_{\text{min}}}{f} \cdot TI2. \quad \text{[16]} \]

Substituting this creates Eq. [B]. When \( f \) increases further, Eq. [12] is finally valid for \( f' \). Therefore, in Eq. [C], \( f' = f \), is true. The condition for this is a state of \( \frac{TI2}{TI2 - TI1} \cdot f_{\text{min}} < f \). This state is explained when \( f \) is substituted for \( f' \) in Eq. [B]. Furthermore, when \( \Delta M(TI2) \) eventually stops changing even with increases in \( f, f' \) becomes fixed at a specific flow rate of \( f_{\text{peak}} \). This is expressed with Eq. [D]. This is because labeled water volume in the labeling slab has reached its maximum. Figure 3 demonstrates a graph showing the relationship between \( f \) and \( f' \) using Eqs. [A] to [D] with fixed \( TI1 \) of 0.7 (s) and fixed \( TI2 \) of 1.8 (s). The value of \( f_{\text{min}} \) was assumed as 0.0033 mL/g/s (= 20 mL/100 g/min) and that of \( f_{\text{peak}} \), as 0.015 mL/g/s (= 90 mL/100 g/min). Previously, we conducted a phantom experiment using Q2TIPS, in which we created a phantom of water flow using a pump and compared water flow, \( f' \), measured with ASL-MRI and true water flow, \( f \), under \( TI1 \) and \( TI2 \) fixed, and measured variable rates of the water flowing through the phantom. Though measurement units differed due to demands of the phantom structure, switching \( f \) and \( f' \) in a graph of results creates similar results to those shown in Fig. 3. In addition, the relationship between true value of cerebral blood flow (CBF) and the CBF value measured with arterial spin labeling (ASL) with \( TI1 \) and \( TI2 \) fixed. In this graph, \( f' \) is the CBF value measured with ASL, \( f \) is the true CBF value, \( TI1 \) is 0.7 s, \( TI2 \) is 1.8 s, \( f_{\text{min}} \) is 20 mL/100 g/min and \( f_{\text{peak}} \) is 90 mL/100 g/min. Equation [A] shows that the true CBF value cannot be detected with ASL because it is low and \( f' \) is zero. Equation [B] shows that \( f' \) can be measured with ASL when \( f \) increases, but it is lower than the true value of blood flow. However, when \( f \) increases further, Eq. [C], \( f' = f \), applies. When \( \Delta M(TI2) \) eventually stops changing even with increases in \( f, f' \) becomes fixed at a specific blood flow value of \( f_{\text{peak}} \). This is Eq. [D].

Fig. 3. A virtual graph showing the relationship between the true value of cerebral blood flow (CBF) and the CBF value measured with arterial spin labeling (ASL) with \( TI1 \) and \( TI2 \) fixed. In this graph, \( f' \) is the CBF value measured with ASL, \( f \) is the true CBF value, \( TI1 \) is 0.7 s, \( TI2 \) is 1.8 s, \( f_{\text{min}} \) is 20 mL/100 g/min and \( f_{\text{peak}} \) is 90 mL/100 g/min. Equation [A] shows that the true CBF value cannot be detected with ASL because it is low and \( f' \) is zero. Equation [B] shows that \( f' \) can be measured with ASL when \( f \) increases, but it is lower than the true value of blood flow. However, when \( f \) increases further, Eq. [C], \( f' = f \), applies. When \( \Delta M(TI2) \) eventually stops changing even with increases in \( f, f' \) becomes fixed at a specific blood flow value of \( f_{\text{peak}} \). This is Eq. [D].

**Conclusions**

Though equations for quantitative CBF by ASL-MRI are quite difficult to understand, physical mathematics and schematic explanations can be helpful. Assumptions aid understanding of the optimized conditions and serious exceptions. It is important to see through to the truth of miscellaneous phenomen-
ena knowing that we are dealing with a complex system in which events do not necessarily go ideally.

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Appendix

Extended comment for correction factor, $q$ (Fig. 4)

Though the labeled blood in the artery decays with the $T_1$ value of the arterial blood, $T_{1A}$, it will decay with the $T_1$ value of the brain tissue, $T_{1B}$, after reaching the site of capillary exchange. Buxton’s theory assumes that the spin exchange takes place just after the elapsed time of $\Delta t$ (s) when the labeled blood first arrives at the imaging area after application of the inversion pulse. The micro-volume of arterial blood, $f \cdot dt$ (mL), flowing into the exchange site has the magnetization of $M_{0B}(1-2ae^{-\Delta t/T_{1B}})$ at the elapsed time of $\Delta t$ (s) and thereafter decays according to $M_{0B}(1-2ae^{-\Delta t/T_{1B}+\Delta t/T_{1B}+\Delta t/T_{1B}}) = M_{0B}(1-2ae^{-\Delta t/T_{1B}})$ (Fig. 4A). Therefore, it has the magnetization of $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$ at the elapsed time of $\Delta t + dt$ (s) (Fig. 4B). The micro-volume of arterial blood, $f \cdot dt$ (mL), has the magnetization of $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$ at the elapsed time of $\Delta t + dt$ (s) and decays according to $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$. Accordingly, it has the magnetization of $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$ at the elapsed time of $\Delta t + 2 \times dt$ (s) (Fig. 4C). After the elapsed time of $\Delta t + 2 \times dt$ (s), the inflowing of the labeled blood is finished. At the elapsed time of $T_{1B}$ when the labeled images are taken, the overall volume of the magnetization of all labeled blood is: $\int_{\Delta t}^{\Delta t+T_{1B}} M_{0B} \cdot (1 - 2ae^{-kT_{1B}/T_{1B}}) dt$ (Fig. 4D).

Based on the indefinite integral $\int e^{-A_k} dx = -e^{-A_k} / A + C$, it follows that:

![Fig. 4. Schemata for explaining the correction factor, $q$. (A) The spin-exchange starts just after elapsed time of $\Delta t$ (s) when the labeled blood first arrives at the imaging area. The micro-volume of arterial blood $f \cdot dt$ (mL) flowing into the exchange site has the magnetization of $M_{0B}(1-2ae^{-\Delta t/T_{1B}})$ and thereafter decays according to $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$. (B) It has the magnetization of $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$ at elapsed time of $\Delta t + dt$ (s). (C) The magnetization of the next micro-volume of arterial blood $f \cdot dt$ (mL) is $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$ at $\Delta t + dt$ (s) and becomes $M_{0B}(1-2ae^{-\Delta t/(T_{1B}+\Delta t+T_{1B}+\Delta t/T_{1B})})$ at $\Delta t + 2 \times dt$ (s) (D) At elapsed time of $T_{1B}$ (s), the total volume of the magnetization of all labeled blood amounts to: $\int_{\Delta t}^{\Delta t+T_{1B}} M_{0B}(1 - 2ae^{-kT_{1B}/T_{1B}}) dt$.](image-url)
\[
\int_{\Delta t}^{\Delta t + T_{1B}} f \cdot M_{0B} \cdot (1 - 2ae^{-kt-T_{1B}/T_1}) dt = f \cdot M_{0B} \cdot \left[ t - \left( \frac{-2ae^{-kt-T_{1B}/T_1}}{k} \right) \right]_{\Delta t}^{\Delta t + T_{1B}}
\]

\[
= f \cdot M_{0B} \cdot \left( T_{1B} - \frac{k \cdot T_{1B}}{k \cdot T_{1B}} \cdot \left( e^{-k \cdot T_{1B}} - e^{-k(T_{1B} + \Delta t)} \right) \right)
\]

When \( M_{0B} f \cdot T_{1B} \) is subtracted from Eq. [8], Eqs. [1] and [2] are acquired. In addition, \( q \) can be modified as:

\[
q = e^{k \cdot T_{1B}} \left( e^{-k \cdot T_{1B}} - e^{-k(T_{1B} + \Delta t)} \right) / k \cdot T_{1B}
\]

\[
q \text{ approaches one as } T_{1B} \text{ approaches } T_{1}' \text{ based on } \lim_{x \to 0} e^x = 1 \text{ and } \lim_{x \to 0} (e^x - 1) / x = 1.
\]

References

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