Accuracy of Pulsed Arterial Spin Labeling Magnetic Resonance Imaging in the Human Brain: Tag Width and Timing Effects
by
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ABSTRACT

Arterial spin labeling (ASL) is the only non-invasive magnetic resonance imaging (MRI) technique that allows absolute quantification of cerebral blood flow (CBF). It involves using radiofrequency pulses designed to invert the spins of water in arterial blood, effectively creating a magnetic bolus. This inverted blood can be considered an endogenous contrast agent; imaging as it traverses the vascular tree allows CBF measurements. Such types of experiments are especially useful for functional neuro-activation studies and in settings of neuropathology. Two flavors of ASL exist: continuous ASL and pulsed ASL. Pulsed ASL has the advantage of not requiring specialized imaging hardware, and can be performed using standard clinical scanners found in most hospitals.

Pulsed ASL techniques, however, may yield inaccurate perfusion values and diminished perfusion sensitivity if appropriate labeling parameters are not chosen, particularly during global challenges such as hypercapnia. In this study, the accuracy of QUIPSS II (Quantitative Imaging of Perfusion using a Single Subtraction - second version) ASL for measuring flow changes during a global flow perturbation (hypercapnia) was assessed. Multiple inversion time ASL experiments were performed to examine bolus delivery dynamics under conditions of normocapnia and hypercapnia and at variable inversion band thicknesses. Tag delivery (inflow) curves revealed that typical published parameter values can cause substantial perfusion error during global challenges and render perfusion increases nearly undetectable. Theoretical criteria for choosing optimal QUIPSS II ASL parameter values are explored, and a multiple inversion time method for empirical determination of tag characteristics presented. Single inversion time functional experiments were subsequently performed to show that by using larger inversion band thicknesses and optimized timing parameters, perfusion accuracy and sensitivity can be substantially improved. Activation maps from block design visual cortex activation experiments and normocapnia-hypercapnia experiments support this conclusion.

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1. Introduction

In recent years, numerous groups have demonstrated the use of arterial spin labeling (ASL) magnetic resonance imaging (MRI) to measure changes in cerebral blood flow (CBF) during cognitive and sensory tasks (1-5). ASL uses radiofrequency (RF) pulses to invert the magnetization of water protons in blood flowing through arteries feeding the brain. This creates a bolus of magnetically labeled blood, which subsequently serves as a freely diffusible endogenous tracer. In the seconds following this inversion, the tagged blood arrives in the brain via the arteries and capillaries and accumulates in parenchymal tissues. Echo-planar imaging (EPI) is then typically performed after a suitable delay (the inversion time, or TI) to acquire an image containing this flow-dependent component. A control image is also acquired by repeating the experiment in the absence of blood tagging. Perfusion can be calculated by dividing the flow-dependent signal component by the inversion time and normalizing by a magnetization calibration constant. Changes in CBF associated with focal neural activation have been well characterized, and the ASL technique experimentally and theoretically validated (6,7).

There have been few studies using ASL to quantify changes in CBF during global challenges such as hypercapnia (8-10), however, and previous theoretical work has suggested that particular care must be exercised to control tagging duration during such manipulations. Such studies are of considerable interest for studying the physics of BOLD (Blood Oxygen Level Dependent) signal formation and physiology of brain activation (11,12).

In the present study, a pulsed ASL (pASL) labeling geometry and timing scheme known as PICORE (Proximal Inversion of magnetization with a Control for Off-Resonance Effects) (13) was used. Tag duration was controlled by using a variant of QUIPSS II (Quantitative Imaging of
Perfusion using a Single Subtraction, second version) (14) called Q2tips (15). Q2tips uses thinslice TI\textsubscript{1} periodic saturation to prevent inflow of additional tagged blood after a preset delay.

PICORE is a commonly used pASL variant designed to minimize magnetization transfer effects, and QUIPSS II addresses one of the fundamental problems of pASL techniques: the transit delay (14). The transit delay confounds the perfusion calculation by causing a mismatch between the ASL bolus delivery time and inversion time. The QUIPSS II approach corrects for this error by applying saturation pulses at a predetermined time following the initial inversion, but before imaging commencement. Saturation effectively eliminates any tag remaining in the inversion band and allows the ASL bolus delivery time to be fixed by the user. As a result, absolute quantification becomes possible with just a single tag-pair acquisition, or single subtraction. In the QUIPSS II ASL scheme, two types of inversion times are considered; the time between the initial inversion and application of the saturation pulses is termed TI\textsubscript{1}, and the time between inversion and imaging slice excitation is called TI\textsubscript{2}. At time TI\textsubscript{2} imaging commences, and in a properly conducted QUIPSS II experiment, the total delivery time of tagged spins (\(\tau\)) is equivalent to TI\textsubscript{1}.

The PICORE-QUIPSS II approach has been used for CBF quantification, especially in functional activation studies (13,16,17). ASL parameter values, specifically inversion times and inversion band thickness (tag width), for normal subjects have been reported in the literature for flow quantification (18,19) and functional studies (17). We have found that in certain situations, use of these values can lead to underestimation in apparent perfusion changes and reduced functional sensitivity. In this study, we specifically investigate PICORE flow dynamics in normal subjects at 3T, during hypercapnia and normocapnia. In order to determine the suitability of ASL parameter values, we performed ASL imaging at multiple inversion times. This multi-TI
approach makes it possible to generate the full magnetic bolus inflow profile (also called delivery curve) over time. This profile includes the transit delay period (Δt), during which tagged blood crosses the physical gap between the inversion band and imaging slab, the delivery period (τ_{geometric}), during which tagged blood arrives at the imaging volume, and the clearance period, during which the ASL signal decreases (as a function of T1 decay), following passage of the trailing edge of the volume of tagged blood (20). QUIPSS II saturation in these multi-TI experiments was turned off as we were interested in the delivery of the entire geometrically defined tag, not one that was temporally defined by saturation. The delivery curves thus obtained can be used to determine whether saturation pulses in a QUIPSS II experiment would in fact control the tag duration – or, alternatively, show that the trailing edge of the tag would pass prior to the pulses, rendering them ineffectual.

While the multi-TI approach provides the entire bolus inflow curve (and hence a simple framework for absolute quantification), it requires a substantial increase in scan time, and so is rarely used in practical applications of ASL. Additionally, it is extremely difficult to utilize this method for block design fMRI activation studies. The more typically used single-TI (QUIPSS II) approach has the potential to generate a quantitative perfusion map with a single-tag pair acquisition, and can be done in a fraction of the time. Therefore, the ultimate goal is to design a single-TI experiment with parameters optimized to provide accurate perfusion measurements with optimal sensitivity based on dynamic parameters determined using the multi-TI approach.

Several types of PICORE experiments were performed in this study to investigate sources of perfusion error and identify ways to eliminate or minimize them, thereby improving ASL accuracy. Multi-TI inflow curves allowed us to determine appropriate ASL parameter values (specifically, TI1, TI2, and tag width) in situations of resting CBF and of a global flow
perturbation (a condition created by hypercapnia induction). We also explored the consequences of using larger tag widths on perfusion accuracy and sensitivity, especially since early ASL experiments in humans were conducted using RF transmit/receive coils, limiting the width of ASL tags to around 10 cm. Finally, we performed two sets of single-TI block design functional experiments, one using a normocapnia-hypercapnia paradigm and the other a visual cortex activation paradigm. Within each set, functional runs were performed with varying tag widths and/or timing parameters, and the resulting ASL perfusion activation maps were compared.
2. Methods

2.1 Data Acquisition

Imaging experiments were performed on nine healthy human subjects (5 male, 4 female) ranging in age from 23-30. Written informed consent was obtained from all volunteers. The local Institutional Review Board (IRB) approved the research protocol, and guidelines posed by the IRB were followed.

All MR imaging was performed on a Siemens Magnetom Trio 3.0 Tesla whole-body system (Siemens Medical Systems, Erlangen, Germany). The Siemens product multi-channel phased-array head coil was used as the receive coil, while the internal body coil served as the transmit coil. A custom PICORE pASL MRI sequence with available QUIPSS II thin-slice TI1 periodic saturation was used for all data acquisition (15). Adiabatic inversion was done using a 10 ms frequency offset corrected inversion (FOCI) RF pulse (bandwidth 2kHz). Other ASL specific parameters varied based on experiment type (see below).

For image acquisition, a single-shot, blipped gradient-echo planar imaging (EPI) sequence was employed at matrix size = 64x64, FOV = 225 mm, slice thickness = 5 mm, and interslice gap = 2.5 mm. Six axial slices were positioned parallel to the anterior commissure-posterior commissure (AC-PC) line, such that the inferior-most slice intersected the lateral ventricles. Such positioning gave coverage of cortical areas in frontal, parietal, and occipital lobes. Two minor modifications were made for the visual cortex activation experiments: 1) slices were positioned to intersect the visual areas of the occipital lobe and 2) interslice gap was reduced to 0 mm to allow contiguous slices. Automatic alignment protocols were used to ensure near-identical slice orientations between subjects (21). For all orientations, the inferiorly
positioned inversion slab covered the major supplying arteries to the brain (i.e., the internal carotid, vertebral, and basilar arteries).

Hypercapnia was induced by having the subject breathe a 7% CO₂/21% O₂/room air mixture through a breathing mask (Hudson RCI, Arlington Heights, Illinois), while in the MRI scanner. Two custom blenders were used to mix the gases; the control apparatus was accessible to the scanner operator in the control room and could be used to adjust gas flow rate and CO₂ concentration. Gas flow rate was set to 16 liters/min; CO₂ contribution could be adjusted between 0% and 10%, to create states of normocapnia and hypercapnia in the subject. The face mask was fit on the subject's face and the subject was instructed to breathe normally. As a safety precaution, the subject's oxygen saturation was monitored using a pulse oximeter (Invivo Research, Latham, New York).

Four sets of experiments were performed:

**Experiment Set I: Multi-TI ASL during normocapnia and hypercapnia**

ASL bolus delivery was examined in three volunteers, under conditions of normocapnia and hypercapnia, using the multi-TI approach described above. Multi-TI ASL involved acquiring tag and control pairs at various times after the initial inversion, by repetitively cycling through a range of TI₂ values until a desired number of averages were acquired. This inversion time cycling, or "TI stepping", allowed generation of the entire bolus inflow curve.QUIPSS II saturation pulses were not applied (i.e. the TI₁ parameter was not used). The ASL imaging parameters were as follows: TI₂ = 50 ms to 2000 ms, in increments of either 100 ms or 150 ms; tagging band width = 100 mm, TR = 3 sec; 330 - 480 measurements; and scan time = 16 min - 24 min.
Experiment Set II: Multi-TI ASL at variable tag widths

In the second experiment set, a multi-TI approach was taken to examine ASL bolus delivery as a function of inversion band thickness. Three studies were performed on each of three normal subjects, with respective inversion bands of 50 mm, 100 mm, and 200 mm. Other imaging parameters were identical to Experiment Set I.

Experiment Set III: Functional activation study using single-TI ASL at different tag widths: normocapnia versus hypercapnia

The third set of experiments used a standard ASL approach for fMRI (which employs a single, fixed TI) to perform a block-design normocapnia-hypercapnia experiment. With this approach QUIPSS II saturation was applied at a time TI1 after the initial inversion, and imaging commenced at a fixed TI2. The paradigm consisted of 2 minute epochs of the subject breathing room air, interleaved with 2 minute epochs of the subject breathing the CO2/O2/room air mixture, for a total duration of ten minutes (i.e. 3 epochs of room air and 2 epochs of air mixture total). The imaging parameters were as follows: TI1 = 700 ms, TI2 = 1400 ms, tagging band width = 100 mm or 200 mm, TR = 2 sec. TI1 and TI2 were chosen based on values suggested in (17-19). A single subject was scanned for this experiment set.

Experiment Set IV: Functional activation study using single-TI ASL with different tag width and timing parameters: visual cortex activation

Similar to experiment set III, a standard single-TI ASL approach was used to perform a visual cortex activation study. The visual stimulus consisted of one minute presentations of a
flashing radial checkerboard (with central fixation point), interleaved with one minute presentations of the fixation point alone, for a total of six minutes (i.e. three activation/inactivation cycles). The subject was instructed to gaze at the fixation point for the duration of the scan. Two scans per subject were performed with following imaging parameters: TI$_1$ = 700 ms (scan 1)/1000 ms (scan 2), TI$_2$ = 1400 ms, tagging band width = 100 mm (scan 1)/200 mm (scan 2), TR = 3 sec. For scan 1, TI$_1$ and TI$_2$ were chosen based on published values. For scan 2, TI$_1$ and TI$_2$ were chosen by analyzing bolus delivery curves generated in experiment set II. Two subjects were scanned for this experiment set.

2.2 Data Analysis

For all experiments, EPI images in the acquired series were first smoothed with a 6 mm FWHM 3D Gaussian kernel to improve the signal-to-noise ratio. A sequence of perfusion images was subsequently generated by pairwise subtraction of control images from tag images. It was not possible to motion correct data acquired using the TI-stepping sequence due to large intensity differences caused by the variable time offset of the PICORE imaging-slab presaturation pulses. Retrospective motion correction was applied, however, to the single-TI functional runs.

Data acquired from experiment sets I and II were analyzed first. An image sequence showing the mean tag delivery over time at each voxel was generated by averaging volumes at a given TI$_2$ and concatenating the averaged volumes into a new series. A region-of-interest (ROI) was then drawn in cortical gray matter (GM) and the average ROI voxel signal intensity (SI) plotted versus TI$_2$. To quantify absolute perfusion from this bolus inflow curve, the standard kinetic model (SKM) for quantitative ASL perfusion imaging (20) was applied. Perfusion
parameters were fit with a Levenberg-Marquardt least squares optimization method, as implemented in MATLAB (Mathworks, Natick, Massachusetts). Transit delay ($\Delta t$), delivery time ($\tau_{\text{geometric}}$), and CBF ($f_{\text{Multi-TI}}$) were reported for all subjects and all experiments.

Although a single-TI experiment was not explicitly performed for experiment sets I and II, a PICORE-QUIPSS II analysis using literature parameter values ($\text{TI}_1 = 700$ ms, $\text{TI}_2 = 1400$ ms, and tag width = 100 mm) was done by considering the averaged perfusion map at $\text{TI}_2 = 1400$. In this case, the difference signal is given by (14):

$$
\Delta M(\text{TI}_2) = 2M_{0A}f_{\text{SS}}\text{TI}_1 e^{-\text{TI}_2/\tau_{\text{in}}}
$$

where $T_{1B}$ is the $T_1$ of arterial blood and $M_{0A}$ is the magnetization calibration constant (defined below). Thus, in addition to CBF calculated using the SKM ($f_{\text{Multi-TI}}$), an analogous CBF calculated with a single-TI analysis ($f_{\text{Single-TI}}$) is also reported.

To compute absolute flow, in both multiple- and single-TI methodologies, it is necessary to calculate the equilibrium magnetization constant for arterial blood, $M_{0A}$, which is related to the signal intensity of a full voxel of relaxed arterial blood. However, because of the low spatial resolution of the EPI images, a voxel filled only with blood is difficult to find. An alternative method was therefore used to estimate the magnetization constant, based on an experimentally determined ratio ($R$) of the proton density of blood in the sagittal sinus to that of white matter ($R = 1.06$)(14). A single-shot EPI image was acquired ($\text{TR} = 2$ s), without any preceding ASL inversion or saturation pulses. From this image, the signal from white matter ($M_{0WM}$) was measured. The $M_{0A}$ was subsequently calculated using the following expression (14):

$$
M_{0A} = RM_{0WM}e^{\left(\frac{1}{T_{2WM}} - \frac{1}{T_{2b}}\right)T_E}
$$

where $T_{2wm}$ and $T_{2b}$ are transverse relaxation constants of white matter and arterial blood, respectively. Unique $M_{0A}$ values were calculated for each experiment, as the value is not
constant from subject to subject. Normalization of the subtraction maps with $M_{0A}$ allowed
generation of quantitative perfusion maps, with CBF in units of ml/ 100 mg of tissue/ min.

Functional analysis for experiment set III and IV (conventional functional ASL using a
single TI) was performed in NeuroLens software (R. Hoge, Montreal, Canada) by fitting a linear
signal model to the perfusion image time-series. The model consisted of a regressor representing
the block stimulus presentation, plus a third order polynomial representing drift terms.
Regressors were pre-convolved with an assumed hemodynamic response function described by
Glover et al. (22). Pre-whitening using a global AR1 parameter of 0.1 was performed, based on
estimation from the perfusion time-series in cortical GM. The modeled effect size was divided
by the root-mean-squared residual error for each voxel, effectively generating maps of t-statistic.
These t-statistic maps reveal significant increases in CBF. Functional sensitivity was assessed by
counting the number of activated voxels (NAV) across the volume; a voxel was considered
activated if its t-statistic was above the threshold corresponding to $p = 0.00001$ ($t = 4.81$).
3. Results

Figure 1 shows representative PICORE perfusion-weighted image maps acquired using a mutli-TI approach from a healthy subject breathing room air (Subject 4). TI2 values ranged from 150 ms to 1450 ms for a tag width of 100 mm. As TI2 increases, progressive enhancement is seen in cortical GM, indicating increased volume of tagged spins delivered. At later TI2’s, GM signal decreases as decay effects begin to dominate. In contrast, macro-vessels are bright initially, but quickly lose intensity due to early clearance by fast flowing blood.

Figure 2 depicts representative gray matter inflow profiles for each subject during conditions of normocapnia and hypercapnia. Figure 3 depicts representative gray matter inflow profiles for acquisitions using variable inversion band thicknesses of 50 mm, 100 mm, and 200 mm, all under normocapnic conditions. The standard kinetic model fit curve overlays figure data, and tables 1 and 2 summarize relevant ASL parameters for experiment sets I and II, respectively.

Figure 4 shows representative maps of the relative ASL signal at the three tag widths, to demonstrate the effect of inversion band thickness on perfusion SNR.

Figure 5 shows t-statistic activation maps from experiment set III (block design normocapnia-hypercapnia); figures 5a and 5b depict results acquired using a 100 mm tag and 200 mm tag, respectively. A clear increase in gray matter cortical perfusion is seen in (b), whereas it is largely undetectable in (a).

Figure 6 shows visual cortex t-statistic activation maps for subjects 8 and 9, thresholded to the t-value corresponding to p < 0.00001, and overlaid onto an original EPI image. Figures 6a,c show activation from acquisitions using TI1 = 700 ms, TI2 = 1400 ms, and tag width = 100 mm, whereas figures 6b,d show activation from acquisitions using TI1 = 1000 ms, TI2 = 1400 ms,
and tag width = 200 mm. Table 3 summarizes the NAV found in each functional run and provides the percentage change between scans 1 and 2.
4. Discussion

Absolute blood flow can be quantified by measuring the volume of blood delivered to an imaging voxel and dividing by the delivery time. In subtracted ASL perfusion maps, the signal intensity represents the volume of tagged spins delivered to the imaging slice following the labeling pulse. It follows that by dividing perfusion map voxel signal intensity by the tagged spin delivery time (\(\tau\)), a value proportional to voxel blood flow can be calculated. Accurate knowledge of \(\tau\) is therefore crucial for making a quantitative flow measurement.

PICORE pASL with QUIPSS II can be used for quantitative measurement of CBF without the need for a prolonged TI-stepping protocol. Application of saturation pulses to the tagging band at time TI\(_1\) imposes a controlled value for \(\tau\), satisfying this requirement for absolute quantification of perfusion. It is critical, however, that these saturation pulses be applied before the trailing edge of the bolus leaves the labeling region. If the pulses are applied too late, they will have no effect on the delivered tag bolus and the actual value of \(\tau\) will depend on a combination of geometric and hemodynamic variables. This violates the assumption that \(\tau\) is equal to TI\(_1\) and renders subsequent flow estimates inaccurate. In some cases the results may be highly misleading. For example in our functional ASL experiment to detect flow increases in response to hypercapnia, acquisitions using a 700 ms TI\(_1\), 1400 ms TI\(_2\), and 100 mm tag thickness suggested only a marginal flow increase in response to CO\(_2\) inhalation, which is incorrect (23). This error was due to compression of the tag duration to a value significantly less than 700 ms during hypercapnia, resulting in an ASL signal that was similar to that seen at normocapnia at the delay time (TI\(_2\)) used for imaging. Under such conditions, the effect of the
QUIPSS II saturation pulses is essentially nullified and the acquisition behaves like a simple PICORE acquisition, subject to the types of error described previously (14,20).

In practice, the situation described above can arise if the inversion band is not wide enough to provide enough tagged blood to begin with, or if $T_{I1}$ is too long. In both cases, perfusion will be underestimated, since true delivery time $\tau$ is less than assumed delivery time $T_{I1}$, causing a fractional underestimation of perfusion ($FE_1$) equal to:

$$FE_1 = \frac{\tau - T_{I1}}{\tau}$$

[3],

Without QUIPSS II temporal definition $\tau = \tau_{\text{geometric}}$, and it is impossible to know $\tau_{\text{geometric}}$ from only a single-TI experiment. Moreover, $\tau_{\text{geometric}}$ will vary from voxel-to-voxel, due to variable blood flow in the brain. Single-TI absolute quantification is thus only possible if $T_{I1}$ is less than $\tau_{\text{geometric}}$ (condition 1), which forces $\tau = T_{I1}$ for all voxels (14).

Assuming the requirement of $T_{I1} < \tau_{\text{geometric}}$ is met, tagged blood within the inversion band will be effectively eliminated at saturation and will not contribute to signal at the imaging slab. After this time, inverted blood can be thought of as being in two spatial locations; some will remain in the physical gap and some will have reached the imaging slab. Imaging immediately or soon after saturation (i.e. $T_{I2}$ slightly greater than $T_{I1}$) would ignore tagged blood trapped in the physical gap. The resulting perfusion map would not consider the entire temporally defined bolus, and the calculated flow would again underestimate the true flow. Since tagged blood begins to arrive at the imaging slab at $\Delta t$, a time $T_{I2} > \Delta t + T_{I1}$ (transit delay plus delivery time) is necessary to consider complete bolus delivery (condition 2) (14). In other words, an appropriate choice for $T_{I2}$ will allow sufficient time between saturation and imaging.
for the bolus to be completely delivered to the imaging slice. If condition 2 is violated, the fractional underestimation of perfusion \((FE_2)\) is given by:

\[
FE_2 = \frac{TI_1 + \Delta t - TI_2}{TI_1 + \Delta t} \tag{3}
\]

Additionally, it is unadvisable to make \(TI_2\) too long, since the lifetime of the ASL tag is limited, and is subject to \(T_1\)-decay and clearance effects.

Based on these theoretical criteria, we performed experiments to explore the practical importance of optimizing ASL parameter values when using PICORE-QUIPSS II. More generally, however, these considerations apply to any quantitative pASL method that incorporates post-labeling saturation. The experiments demonstrate the value of using a multi-TI acquisition to characterize tag delivery dynamics, especially in situations of systemic manipulation (like hypercapnia) and functional activation studies.

Results from Experiment Set I show that using published parameter values of \(TI_1 = 700\) ms, \(TI_2 = 1400\) ms, and tag width = 100 mm, can result in an underestimation of perfusion. The multi-TI normocapnia-hypercapnia experiments demonstrate that bolus delivery dynamics can change considerably during a global flow perturbation (i.e. hypercapnia), resulting in delivery times substantially less than 700 ms. A PICORE-QUIPSS II experiment using a \(TI_1\) of 700 ms would therefore result in late application of saturation pulses (since \(TI_1 > \tau_{\text{geometric}}\)). Even at baseline normocapnia, observed delivery times were less than 700 ms. Had single-TI, QUIPSS II experiments been performed, absolute perfusion would have been underestimated during both hypercapnia and normocapnia. Based on equation 3, the fractional error would be more severe for hypercapnia, since hypercapnic delivery times are considerably less than normocapnic
delivery times. Thus, the error is not a systematic one, and instead is a function of delivery time. Because of this disparity, there is not only a miscalculation in absolute blood flow, but also in the relative perfusion change between the two states. Figure 2 highlights this idea. Hypercapnia causes a clear increase in blood flow, as indicated by the much sharper rise in signal intensity (after the initial delay) compared to the normocapnia state. However, the clearance phase of the inflow curves for both states are roughly coincident. The QUIPSS II experiment would give similar signal intensity values for both states (at TI\(_2\) = 1400 ms), and since the delivery time is assumed to be TI\(_1\) = 700 ms for both, only a modest increase in flow. To confirm this idea, we can compare flows calculated with the standard single-TI approach to flows calculated with a multi-TI, standard kinetic model approach (Table 1). Only because TI\(_1\) > \(\tau_{\text{geometric}}\) does such a single-TI analysis hold; in these situations the non-QUIPSS II experiment is equivalent to the QUIPSS II experiment. Thus, a QUIPSS II approach using TI\(_1\) = 700 ms would cause a substantial underestimation in perfusion increase for all three subjects, since the true delivery time \(\tau\) is significantly less than TI\(_1\) in hypercapnia. Condition 2, however, is satisfied; by the time imaging occurs (TI\(_2\) = 1400 ms), the bolus will have been completely delivered to the imaging slab.

There are two ways to ensure that TI\(_1\) is less than \(\tau_{\text{geometric}}\). The most straightforward is to reduce TI\(_1\) to a value that will always be less than \(\tau_{\text{geometric}}\), to guarantee that some tagged blood will remain in the inversion band at saturation. In these particular normocapnia-hypercapnia experiments, a TI\(_1\) of 450 ms or lower would be acceptable, based on the SKM-computed \(\tau_{\text{geometric}}\) (table 1). However, choosing a suitable TI\(_1\) a priori, without first doing a multi-TI experiment, can be difficult, since bolus delivery characteristics are not known and typical published values may not be ideal. Furthermore, because of the dramatic variation in flow
values and delivery times across experiment types and subjects, literature values specific to the application may not even exist. Because of these difficulties, studies may end up using lower than necessary TI \(_1\) times, to assure tag saturation for the study population. While substantially lowering TI \(_1\) will indeed prevent error, perfusion sensitivity will be sacrificed. In other words, a lower TI \(_1\) will result in less tagged spin delivery and consequently, lower SNR. Since functional ASL is, in the best of circumstances, SNR-limited (<1% of total unsubtracted signal contributes to the perfusion map (7,24)), lowering TI \(_1\) is likely to result in an unacceptable degradation of sensitivity. An alternative approach, which potentially avoids a TI \(_1\) reduction, is to increase delivery time of the geometric bolus, \(\tau_{\text{geometric}}\). This can be readily achieved by using a wider inversion band on systems where a body coil is available for RF transmission. It is worth noting that much of the earlier experimental work cited in this article was performed on systems using smaller head volume coils to transmit labeling pulses. Additionally, use of a receive-only phased-array head coil in conjunction with body coil excitation and labeling will further improve SNR.

Experiment set II explores the relationship between inversion band thickness and delivery time. The results summarized in Figure 3 and Table 2 demonstrate that increasing inversion band thickness increases delivery time substantially; in these experiments, \(\tau_{\text{geometric}}\) increases 56% +/- 22% when going from a 50 mm tag to a 100 mm tag, and 58% +/- 31% when going from a 100 mm tag to 200 mm tag, on average. A 200 mm tag width increases delivery time well beyond 700 ms in gray matter, and would permit substantially larger TI \(_1\) values. Figure 4 demonstrates the clear increase in SNR as a function of tag thickness; a \(-250\%\) increase from 50 mm to 100 mm and a \(-60\%\) increase from 100 mm to 200 mm is observed. It is important to note that as tag thickness increases, new regions of anatomy with different blood volume and
flow characteristics will be included; therefore, there is not a simple relationship between tag width and \( \tau_{\text{geometric}} \) or SNR.

Experiment set III uses a functional block design experiment to illustrate how inappropriate parameter values can result in false negative findings. Only with a 200 mm tag is a statistically significant increase in cortical blood flow seen; the experiment using a 100 mm tag fails to detect the perfusion increase.

Experiment set IV uses a visual cortex activation paradigm to illustrate how parameter optimization can lead to increased functional sensitivity. Scan 1 of the fourth experiment set uses standard ASL parameters, and yields expected activation in the visual cortex, as seen in figures 6a,c. Scan 2, however, uses optimized parameters, based on the results of experiment set II. As indicated in table 2, a 200 mm tag width results in much longer delivery times, permitting the use of larger \( T_{I1} \) values in the QUIPSS II scheme. For all three experiments in set II, \( \tau_{\text{geometric}} \) for a 200 mm tag width was greater than 1000 ms; we thus chose a new \( T_{I1} \) of 1000 ms for scan 2, satisfying condition 1. \( T_{I2} \) was left unchanged at 1400 ms; given the above choice for \( T_{I1} \) and the reported transit delay times for a 200 mm tag, we assumed condition 2 would not be violated. The optimization resulted in much larger activation regions, as seen in figures 6b,d and reported in table 3.

The results from this study highlight the importance of choosing appropriate parameter values when performing quantitative pASL experiments. Published values for ASL parameters may be adequate for detecting functional changes in focal activation studies, but may be doing so with suboptimal sensitivity. More serious perfusion biases may arise when absolute quantification is required or when flow changes are global (as in hypercapnia).
Since optimal parameter values will vary between ASL applications, from scanner to scanner, and from subject to subject; we recommend explicitly optimizing ASL parameters by performing a full multi-TI acquisition with a large inversion band (e.g. 200 mm) for each experiment, or at least on a few representative members of the anticipated subject population. While in this study we have used rather lengthy scans to highlight results, it should be possible to generate adequate inflow curves in a fraction of the time (e.g. 6 min) by decreasing spatial resolution. After fitting the curves with the SKM, delivery time $\tau_{\text{geometric}}$ and transit delay $\Delta t$ can be used to appropriately select $T_{I1}$ and $T_{I2}$, by adhering to the aforementioned guidelines. In this way, it will be possible to perform quantitative and highly sensitive single-TI ASL experiments.
5. Conclusions

Pulsed ASL with post-labeling saturation is subject to substantial perfusion errors if parameters are not chosen correctly. For the technique to be accurate, certain critical ASL parameters including inversion times and inversion band thickness must be optimized. Our results show the importance of parameter selection and suggest that use of typical published inversion times can lead to errors in perfusion calculation, particularly during global challenges such as hypercapnia. These perfusion errors are due to the incorrect assumption of the bolus delivery time $\tau$ if incorrect $T_{I_1}$ and $T_{I_2}$ values are used. Accuracy and sensitivity can be improved by using wider tagging thicknesses, particularly when a body transmit coil is available. Because ASL has been recently finding utility in many clinical applications, accurate and sensitive single-TI perfusion quantification is critically important.
6. Acknowledgments:

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7. References


Table 1
ASL parameter results from experiment set I

<table>
<thead>
<tr>
<th>Subject</th>
<th>Transit Delay (ms)</th>
<th>Delivery Time (ms)</th>
<th>Multi-TI flow (ml/100g/min)</th>
<th>Single-TI flow (ml/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normo-capnia</td>
<td>Hyper-capnia</td>
<td>Normo-capnia</td>
<td>Hyper-capnia</td>
</tr>
<tr>
<td></td>
<td>Δt (ms)</td>
<td>τ_{geometric} (ms)</td>
<td>% Flow increase</td>
<td>% Flow increase</td>
</tr>
<tr>
<td>1</td>
<td>601</td>
<td>339</td>
<td>588</td>
<td>451</td>
</tr>
<tr>
<td>2</td>
<td>653</td>
<td>506</td>
<td>597</td>
<td>504</td>
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<td>3</td>
<td>657</td>
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Table 2
Transit delays (Δt) and Delivery times (τ_{geometric}) for experiment set II

<table>
<thead>
<tr>
<th>Subject</th>
<th>Transit Delay $\Delta \tau$ (ms) at tag width</th>
<th>Delivery Time $\tau_{geometric}$ (ms) at tag width</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mm</td>
<td>100 mm</td>
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<tr>
<td>4</td>
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<td>250</td>
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<tr>
<td>5</td>
<td>306</td>
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<td>6</td>
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Table 3
Functional sensitivity in experiment set IV

<table>
<thead>
<tr>
<th>Subject</th>
<th>NAV</th>
<th>% Change</th>
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</thead>
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<tr>
<td></td>
<td>Scan 1</td>
<td>Scan 2</td>
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<tr>
<td>8</td>
<td>274</td>
<td>449</td>
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<tr>
<td>9</td>
<td>131</td>
<td>397</td>
</tr>
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</table>
FIG 1. Representative PICORE perfusion-weighted image maps acquired with a multiple inversion time approach, as a function of TI$_2$. Perfusion images correspond to TI$_2$ values from 150 ms to 1450 ms in steps of 100 ms, from left to right and top to bottom.
FIG 2. ROI inflow profiles during normocapnia and hypercapnia for subjects 1 (a), 2 (b), and 3 (c). Inflow profile data are fit with SKM. ROI’s are shown in perfusion map insets.
FIG 3. ROI inflow profiles for 50 mm, 100 mm, and 200 mm tags, for subjects 4 (a), 5 (b), and 6 (c). Inflow profile data is fit with the SKM. ROI’s are shown in perfusion map insets.
FIG 4. Representative perfusion maps at TI = 1400 ms, for tagging bands of 50 mm (a), 100 mm (b), and 200 mm (c), all equally windowed at the same noise level. Gray matter SNR is substantially increased when larger tag widths are used, leading to higher perfusion sensitivity.
FIG 5. Comparison of functional activation t-statistic maps for normocapnia-hypercapnia block design experiments. 

a: map generated using ASL parameters $T_{I1} = 700$ ms, $T_{I2} = 1400$ ms, and tag width = 100 mm. 
b: map generated using ASL parameters $T_{I1} = 700$ ms, $T_{I2} = 1400$ ms, and tag width = 200 mm.
FIG 6. Comparison of visual cortex functional activation maps acquired with default ASL parameters $T_{I1} = 700 \text{ ms}$, $T_{I2} = 1400 \text{ ms}$, and tag width = 100 mm (a: subject 8, c: subject 9) and optimized ASL parameters $T_{I1} = 1000 \text{ ms}$, $T_{I2} = 1400 \text{ ms}$, and tag width = 200 ms (b: subject 8, d: subject 9). Activation maps are overlaid on original EPI images, and thresholded to show activations corresponding to $t > 4.81 \ (p < 0.00001)$. 