Reproducibility of the Quantification of Arterial and Tissue Contributions in Multiple Postlabeling Delay Arterial Spin Labeling

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Purpose: To evaluate the reproducibility of estimation of cerebral blood flow (CBF), bolus arrival time (BAT), and arterial blood volume (aBV) from arterial spin labeling (ASL) data acquired at multiple postlabeling delays (PLDs).

Materials and Methods: CBF, BAT, and aBV parameters were estimated from flow-suppressed and nonflow-suppressed multiple-PLD PICORE-Q2TIPS ASL using model-based Bayesian and least-squares fitting frameworks, and aBV was also obtained from a model-free approach. Reproducibility of these parameters was assessed by computing the within- and between-subject coefficients of variability (CVw and CVb).

Results: CVw and CVb were comparable across model-based approaches, but were greater for the aBV from the model-free approach. Overall, the Bayesian model estimation procedure was found to provide the best compromise between reliability and reproducibility, yielding CVw/CVb values of 21/21, 3/4, and 24/26% for CBF, BAT, and aBV, respectively. Although a CBF range of 45 mL/100g/min to 59 mL/100g/min was found on average and a BAT of 0.7–1.0 seconds across methods, the corresponding maps were comparable in terms of the parameters’ spatial distributions, and in particular in the identification of macrovascular locations, as assessed through comparison with time-of-flight images.

Conclusion: Reproducible estimates of CBF, BAT, and aBV values can be obtained from non-macroweighth liquid suppressed ASL using both least-squares and Bayesian model-based methods.

Key Words: arterial spin labeling; reproducibility; kinetic modeling; macrovascular; arterial blood volume

ARTERIAL SPIN LABELING (ASL) techniques rely on magnetic labeling of the arterial blood spins that flow into the capillary bed and exchange with tissue unlabeled spins, which can be described using a general kinetic model (1) to estimate cerebral blood flow (CBF) and bolus arrival time (BAT). Since many voxels in the imaging region contain feeding or traversing arteries, this nonexchanging arterial compartment will also contribute to the total ASL signal, but the separation of tissue and arterial contributions is not straightforward.

In pulsed ASL (PASL) acquisitions with a single postlabeling delay (PLD), it is possible to limit the bolus width by saturating its trailing edge, which together with the use of a long PLD eliminates the intravascular arterial contribution: this is the principle underlying QUIPSS-type (QUantitative Imaging of Perfusion using a Simple Subtraction) pulse sequences (2–4). In continuous and pseudo-continuous ASL (CASL and pCASL), the use of a long PLD is sufficient to ensure intravascular labeled blood elimination, since these techniques already provide implicit control over the label duration. However, both shortening the bolus width and elongating the PLD lead to ASL signal loss due to the magnetization difference decay with the T1 of blood. Moreover, the required assumption of a maximum BAT is not suitable whenever the observed BAT is much longer than expected values, particularly in cerebrovascular disease. In multiple-PLD acquisitions, the intravascular arterial signal is present at short PLD values, showing as bright foci in macrovascular locations. If unaccounted for, this contribution will lead to significant CBF overestimation. Ye et al (5) proposed the use of bipolar crusher gradients to dephase the rapidly moving spins and eliminate the signal from large arteries. Although this approach is effective in removing most of the arterial intravascular contamination and has been widely used, it also causes a reduction in the signal-to-noise ratio (SNR). Moreover, recent ASL implementations, for example, 3D GRASE-ASL (6), employ the Carr-Purcell-Meiboom-Gill echo sequence, which is not
The only multiple-PLD ASL study employing kinetic model fitting for CBF and BAT estimation was performed by Parkes et al (18), who reported good within-subject reproducibility using multiple-PLD CASL data at 1.5T. The “QUASAR reproducibility study” was the most extensive ASL reproducibility study conducted so far, and employed a model-free approach for CBF, BAT, and aBV measurement (19). Several MRI centers and a total of 275 subjects were included, and good reproducibility was found for all measurements. QUASAR has also been used in other reproducibility studies in comparison with single-PLD ASL methods (20) and other imaging modalities (21). Most of the ASL reproducibility studies performed thus far focused on the CBF parameter only, on the one hand, and on global or region-of-interest (ROI) measurements, on the other hand. Regional variability patterns are only reported for CBF maps obtained using single-PLD PASL (15,20) and single-PLD CASL and pCASL (20).

In this study we had three major aims. The first aim was to assess the reproducibility of global values and regional patterns of macroflow-suppressed and nonflow-suppressed multiple-PLD ASL derived parameters CBF, BAT, and aBV. Second, we aimed to compare standard least-squares and Bayesian frameworks in the estimation of these parameters. Finally, we aimed to compare aBV estimation using model-based and model-free approaches from non-QUASAR data.

**MATERIALS AND METHODS**

The methods employed for parameter quantification from ASL data are first described and the experimental data acquisition and analysis procedures are then presented.

**Parameter Quantification Methods**

**Theory**

The general kinetic model proposed by Buxton et al (1) describes the control-tag magnetization difference measured from the tissues in PASL, $\Delta M_{\text{tiss}}$, as:

$$\Delta M_{\text{tiss}}(\text{PLD}) = \frac{2\alpha M_0 \text{CBF}}{k} \begin{cases} 0 & \text{if PLD} < \text{BAT} \\ e^{-\text{PLD}/T_{1b}(e^{\text{PLD-BAT}}-1)} & \text{if BAT} \leq \text{PLD} < \text{BAT} + \tau \\ e^{-\text{PLD}/T_{1b}(e^{\text{PLD-BAT}}-e^{\text{PLD-BAT}-\tau})} & \text{if PLD} \geq \text{BAT} + \tau \end{cases}$$

with $k = T_{1b}^{-1}T_{1}^{-1}\cdot\text{CBF}/\lambda$, where $M_0$ is the equilibrium magnetization of the arterial blood; BAT is the bolus arrival time; $\tau$ is the bolus duration; $T_{1b}$ is the blood longitudinal relaxation time constant; $T_1$ is the tissue longitudinal relaxation time constant; $\lambda$ is the blood-tissue partition coefficient; and $\alpha$ is the labeling (inversion) efficiency.

The extended kinetic model including intravascular signal proposed by Chappell et al (8) adds an extra component describing the ASL signal arising from intravascular labeled water, $\Delta M_{\text{art}}$ to the general kinetic model, by taking into account the arterial blood volume fraction, aBV:

$$\Delta M_{\text{art}}(\text{PLD}) = 2\alpha M_0 \begin{cases} 0 & \text{if PLD} < \text{aBAT} \\ e^{-\text{PLD}/T_{1b}\text{aBV}} & \text{if aBAT} \leq \text{PLD} < \text{aBAT} + \tau a \\ 0 & \text{if PLD} \geq \text{aBAT} + \tau a \end{cases}$$

where aBAT is the intravascular bolus arrival time and $\tau a$ is the intravascular bolus duration. The total
magnetization difference measured in each voxel is then given by:

\[ \Delta M_{\text{total}}(\text{PLD}) = \Delta M_{\text{NS}}(\text{PLD}) + \Delta M_{\text{FS}}(\text{PLD}) \]  

The model-free aBV quantification proposed by Petersen et al (7) consists of computing the area under the curve \( \Delta M_{\text{NS}}(t) - \Delta M_{\text{FS}}(t) \), where \( \Delta M_{\text{NS}}(t)/\Delta M_{\text{FS}}(t) \) are the control-tag magnetization differences of nonflow-suppressed/flow-suppressed ASL data. This area is then adjusted for \( T_1b \) compared as a ratio to the value in a blood-filled voxel, estimated as \( 2M_0\alpha a \) and divided by the inversion efficiency, \( \alpha \).

\[ aBV = \frac{\int_{-\infty}^{\infty} (\Delta M_{\text{NS}}(t) - \Delta M_{\text{FS}}(t)) e^{\lambda T_1b} dt}{2\alpha M_0\alpha a} \]  

In the original version, this method was used with the QUASAR implementation of ASL with Look-Locker readout, and the multiple saturation pulses due to the Look-Locker readout were taken into account by adding an extra term with flip angle dependence, not needed when using EPI readouts.

**Model Estimation Methods**

The first model estimation method used was a nonlinear curve-fitting in the least-squares sense based on the trust-region-reflective algorithm (22) from MatLab (MathWorks, Natick, MA), which we will abbreviate as the least-squares (LSQ) algorithm. The LSQ algorithm was used to estimate: 1) CBF and BAT by fitting the general kinetic model (1) to flow-suppressed data; and 2) CBF, BAT, and aBV by fitting the extended kinetic model (8) to nonflow-suppressed data. Whenever using the extended kinetic model with LSQ estimation, aBAT was set to 70% of the BAT. This assumption regarding the relationship between aBAT and BAT was based on a previous study (23), and had the purpose of allowing some variation in the value of aBAT while avoiding the need to estimate this additional parameter.

The second estimation method was based on fast Bayesian inference (24) incorporated in the tool BASIL from FSL (25–27). CBF and BAT were estimated from flow-suppressed ASL data at multiple-PLD. For nonflow-suppressed ASL data the intravascular compartment was also estimated in order to quantify the macrovascular arterial signal contribution in terms of aBV (8). In order to achieve CBF, BAT, and aBV estimation aBAT is also estimated as an intermediate step and the priors described in (8) are used.

The model-free aBV quantification was implemented in a self-written MatLab routine. The area under the curve of the subtraction of flow-suppressed and nonflow-suppressed datasets was computed and appropriately scaled. The aBV map obtained was used as a known parameter of the extended kinetic model, and CBF and BAT were then retrieved by fitting the general kinetic model to the nonflow-suppressed data using the LSQ algorithm.

Independently of the estimation method or model used, certain additional assumptions were made. Both arterial and tissue bolus duration (\( \tau \) and \( \tau a \)) were fixed by the sequence parameter \( T_11 = 750 \) msec, since the Q2TIPS module was used for longer PLD values. The relaxation constant of labeled arterial blood \( T_1b \) was set to 1.6 seconds. \( T_1 \) of tissue to 1.3 seconds, \( \lambda \) was 0.9, and the inversion efficiency was assumed to be 90%. The PLD was obtained for each slice by considering the specific slice acquisition time (a difference of 50 msec was found between each consecutive slice).

**Experiments**

**Data Acquisition**

Multiple-PLD PASL data were acquired from nine healthy volunteers (22.9 ± 5.6 years, 4 males) during rest in two sessions 1 week apart. Written informed consent was obtained from all the volunteers and the study was approved by the local Ethics Committee. A PICORE-Q2TIPS (4) sequence was used, with GE-EPI readout, TR/TE = 2500/25 msec. The PLD corresponds to the sequence parameter TI2, which was varied as TI2 = 400–2400 msec in steps of 200 msec, with each control-tag pair repeated eight times. The Q2TIPS module allowed limiting the labeling width (7) to a maximum of 750 msec by adjusting TI1 and TI1s for each TI2: for TI2 below 1000 msec TI1 and TI1s were set to TI2 minus 25 msec and for TI2 above 1000 msec TI1 was set to 750 msec and TI1s to 900 msec. The adiabatic hyperbolic secant pulse (4) was applied to a 10-cm-thick labeling region, positioned 18.8 mm below the proximal imaging slice. Both flow-suppressed and nonflow-suppressed datasets were collected in each session, yielding a total of 22 separate PICORE-Q2TIPS runs and a total acquisition time of 14 minutes and 40 seconds. The flow-suppressed dataset was acquired with flow limit 3 cm/s in the foot-head direction. Images were collected from nine slices with voxel resolution of 3.5 × 3.5 × 5.0 mm³. In the first session, a T1-weighted structural image was obtained using an MPRAGE sequence, with TR/TE = 2250/2.26 msec, and a voxel size of 1 × 1 × 1 mm³, and a time-of-flight (TOF) image was also obtained with TR/TE = 20/2.1 msec and voxel size 0.78 × 0.78 × 0.5 mm³.

**Data Analysis**

The data were analyzed using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and MatLab. The two multiple-PLD ASL datasets (with and without flow-suppression) were aligned to each other and motion corrected using FLIRT (28). The control-tag pairwise differences were computed to yield the mean \( \Delta M \) maps for each PLD. The off-resonance effects caused by imperfect inversion slice profile in multislice imaging were corrected as in (29). The resulting maps were then normalized by \( M_{\text{iso}} \), obtained from the saturation recovery of the control images averaged across a tissue region and divided by \( \lambda \). A total of five different analysis procedures were carried out, using the two datasets (flow-suppressed and nonflow-suppressed) and the three parameter estimation methodologies (LSQ, BASIL,
and LSQ with aBV from model-free), as summarized in Table 1. From the flow-suppressed dataset, the general kinetic model was fitted using the LSQ or BASIL, for estimation of CBF and BAT only. Estimation of CBF, BAT, and aBV was achieved by fitting the extended kinetic model using LSQ or BASIL. Alternatively, aBV was obtained by the model-free approach from flow-suppressed and nonflow-suppressed data, and it was then fed to the extended kinetic model for estimation of CBF and BAT using LSQ.

Individual CBF, BAT, and aBV maps were coregistered with the individual’s structural image, and in turn with the standard MNI brain (MNI152, non-linearly derived, McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada), using the FSL tool FLIRT and Boundary-Based-Registration (BBR) algorithm (28,30). The registered maps were averaged first across sessions in the voxels common to the two sessions and then across subjects in all voxels for which the nine subject maps were different from zero.

In order to compute the maximum intensity projection (MIP) of the mean aBV maps and TOF map, each map was first thresholded at 150% of its median. The thresholded aBV/TOF maps were averaged across subjects and sessions in the nonzero voxels of the BAT maps of the nine subjects. The MIP was then taken across the three dimensions. The sensitivity for large vessel detection was measured as the percentage of voxels in the aBV map intersecting the TOF map, normalized by the total number of voxels in the TOF map.

The within- and between-subject variability were assessed by computing the respective standard deviation (SDw and SDb) as described by Bland–Altman (31). SDb is the usual definition of standard deviation for the group of subjects and sessions and SDw is defined by $SDw = \sqrt{\frac{\sum (x_i - x_w)^2}{N}}$, where $N$ is the number of subjects and $x_i - x_w$ is the difference a given parameter (CBF, BAT, or aBV) between two sessions for subject $i$. The within- and between-subject coefficients of variability (CVw and CVb) were obtained by dividing SDw and SDb by the parameter mean. These variability measures were computed for each parameter estimated both voxelwise and in the intersection of the previously defined ROI and the standard MNI brain gray matter segmentation.

### Statistical Analysis

A repeated measures analysis of variance (ANOVA) with factors flow-suppression (Yes, No), estimation method (LSQ, BASIL), and session (1, 2) was carried out for CBF and BAT values. A two-way ANOVA was also conducted for aBV with factors estimation method and session and a post-hoc Tukey test was also conducted. Differences were considered statistically significant if $P < 0.05$.

### RESULTS

The maps of parameter estimates averaged across subjects and sessions, as well as the respective SDw and SDb maps, resulting from the five different analysis procedures described in Table 1, are shown in Fig. 1. Higher CBF values in gray versus white matter and in the medial posterior region were observed consistently across methods. The CBF maps obtained from the nonflow-suppressed dataset presented generally higher CBF values than those from the flow-suppressed dataset, especially in vascular locations. The CBF within- and between-subjects variability maps have similar spatial patterns across methods, with higher variability in the posterior region and locations of vascular structures. Important differences were found in the BAT estimates, which were higher for the methods using LSQ estimation than for those using BASIL estimation, especially for the method including model-free aBV estimation. The other two more standard LSQ methods show lower variability in regions of lower BAT, which are consistent with basal ganglia and macrovascular regions. The high aBV locations are consistent across methods; however, aBV levels vary considerably. Higher aBV variability is found in the regions of higher aBV.

The average CBF, BAT, and aBV values obtained in gray matter in the two sessions, for each of the analysis procedures, are shown in Fig. 2. Statistically significant CBF and BAT differences were found for flow-suppression factor ($P < 0.05$) but not for session factor ($P = 0.22$ and $P = 0.83$). Main effects of the estimation method were observed for BAT ($P < 0.05$) but not for CBF ($P = 0.08$). No significant factor interactions were found for CBF (flow-suppression and estimation method: $P = 0.17$; flow-suppression and session: $P = 0.81$; estimation method and session. $P = 0.99$; flow-suppression, estimation method and

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**Table 1**

Summary of Analysis Procedures, in Terms of Datasets, Models, Estimation Method, and Estimated Parameters

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Model</th>
<th>Estimation method</th>
<th>Estimated parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS-LSQ</td>
<td>Flow-suppressed</td>
<td>General kinetic model</td>
<td>LSQ: 2 parameters CBF, BAT</td>
</tr>
<tr>
<td>FS-BASIL</td>
<td>Flow-suppressed</td>
<td>General kinetic model</td>
<td>BASIL: 2 parameters CBF, BAT</td>
</tr>
<tr>
<td>NS-LSQ</td>
<td>Nonflow-suppressed</td>
<td>Extended kinetic model</td>
<td>LSQ: 3 parameters CBF, BAT, aBV</td>
</tr>
<tr>
<td>NS-BASIL</td>
<td>Nonflow-suppressed</td>
<td>Extended kinetic model</td>
<td>BASIL: 3 parameters CBF, BAT, aBV</td>
</tr>
<tr>
<td>NS-LSQ with</td>
<td>Flow-suppressed + Nonflow-suppressed</td>
<td>Model-free</td>
<td>Model-free aBV</td>
</tr>
<tr>
<td>model-free aBV</td>
<td>Nonflow-suppressed</td>
<td>Extended kinetic model</td>
<td>LSQ: 2 parameters CBF, BAT</td>
</tr>
</tbody>
</table>

$: FS = flow-suppressed dataset; NS = non-flow-suppressed dataset; LSQ = least-squares based estimation; BASIL = Bayesian inference for arterial spin labeling framework; CBF = cerebral blood flow; BAT = bolus arrival time; aBV = arterial blood volume.
session: $P = 0.79$), but a significant interaction between flow-suppression and estimation method was found for BAT ($P < 0.05$). The lowest CBF estimates averaged in gray matter were obtained for the flow-suppressed dataset (LSQ: 45.5 ± 29.2 mL/100g/min and BASIL: 43.8 ± 27.3 mL/100g/min). For the nonflow-suppressed dataset the lowest CBF estimate, which is in better agreement with the flow-suppressed CBF estimates, was obtained for BASIL (52.0 ± 36.6 mL/100g/min) followed by the LSQ with model-free aBV (59.5 ± 38.8 mL/100g/min) and finally the LSQ (60.1 ± 39.6 mL/100g/min). The lowest BAT gray matter averages were obtained with the two BASIL methods (flow-suppressed: 0.71 ± 0.18 sec, nonflow-suppressed: 0.70 ± 0.16 sec), while the LSQ BAT averages were higher (flow-suppressed: 0.82 ± 0.41

Figure 1. Parameter estimates group average maps and respective within- and between-subject SDs ($n = 9$, two sessions) obtained using the five different analysis procedures, for one representative MNI slice.
sec, nonflow-suppressed: 0.87 ± 0.40 sec) and the LSQ with model-free aBV even higher (0.97 ± 0.50 sec). Main effects were observed for aBV estimation method factor (\(P < 0.05\)) but not for session factor (\(P = 0.06\)), and the interaction of the two factors was not statistically significant (\(P < 0.05\)). The post-hoc test revealed that the aBV obtained with NS-LSQ method (0.35 ± 0.73\%) was significantly lower than with BASIL (1.17 ± 1.75\%) or the model-free approach (1.10 ± 1.06\%).

The CVw and CVb values obtained for the gray matter CBF, BAT, and aBV parameters across subjects and sessions, using the five analysis procedures, are presented in Table 2. The procedure yielding lowest CVw and CVb for CBF is the FS-LSQ; however, the variability of FS-BASIL parameters is not considerably higher. For the nonflow-suppressed dataset, LSQ with model-free aBV is the method yielding the lowest variability of CBF estimates. In general, the BASIL methods show much less BAT variability than the remaining methods. For aBV estimation, NS-LSQ and NS-BASIL show considerably less variability than the model-free approach.

The MIP images of the group average aBV maps obtained using the three relevant analysis procedures and the respective TOF map are displayed in Fig. 3. The MIP images show consistent locations of large vessels for the three methods, although with differences in the sensitivity of vessel detection. The BASIL aBV estimation shows the best sensitivity (57\%), followed by the LSQ estimation (31\%) and model-free method (19\%).

**DISCUSSION**

For multiple-PLD PICORE-Q2TIPS ASL data both least-squares and Bayesian model-based estimation methods yield reproducible estimates of CBF and BAT from flow-suppressed data and CBF, BAT, and aBV from nonflow-suppressed data. The within-subject coefficients of variation are in general agreement with previous studies (19). CBF and BAT estimates obtained from macroflow-suppressed and nonsuppressed acquisitions show similar within- and between-subject variability; however, CBF values are generally higher in the last case. While aBV values were comparable, the model-free approach yields the most variable and less sensitive aBV maps and was therefore considered not so appropriate for nonflow-suppressed PICORE-Q2TIPS data analysis. We also found that all methods yielded consistent spatial distributions of CBF, BAT, and aBV parameters, despite some differences in the average parameter values. In terms of aBV, a Bayesian model-based method was able to detect macrovascular locations with the highest sensitivity, as assessed through comparison with TOF images.

A summary of the results obtained by the studies in the literature addressing ASL reproducibility is presented in Table 3. The average CBF maps obtained in our study are generally in agreement with the literature. In particular, the higher CBF found in posterior regions has also been reported in previous studies.

| Table 2 | Coefficients of Variation for the Three Parameters and Five Analysis Procedures |
|---------|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|
|         | Flow-suppressed data            | Nonflow-suppressed data         |
|         | LSQ    | BASIL  | LSQ    | BASIL  | LSQ with model-free aBV |
| CBF     | CVw (%) | 10     | 10     | 16     | 21     | 16 |
|         | CVb (%) | 15     | 16     | 18     | 21     | 17 |
| BAT     | CVw (%) | 10     | 5      | 5      | 3      | 13 |
|         | CVb (%) | 12     | 5      | 11     | 4      | 13 |
| aBV     | CVw (%) | —      | —      | 22     | 24     | 41 |
|         | CVb (%) | —      | —      | 25     | 26     | 39 |

CBF = cerebral blood flow; BAT = bolus arrival time; aBV = arterial blood volume; CVw = within-subject coefficient of variation; CVb = between-subject coefficient of variation; LSQ = least-squares based estimation; BASIL = Bayesian inference for arterial spin labeling framework.
a slightly lower global BAT in gray matter of 0.760. The sampling strategy was the same as in our study, but using a two-parameter fitting procedure. The multiple-PLD PASL data to the general kinetic model healthy young subjects by fitting nonflow-suppressed to the borderzones of the arterial territories. MacIntosh transit times in the usual locations corresponding to agreement with the prior studies (33–35), with longer would lead to an apparently higher CBF. when using the LSQ and model-free methods, which suggest that macroflow-suppression may indeed be less effective in the posterior circulation. In fact, the macrovascular crusher gradients in our sequence were applied only in the inferior–superior direction and, therefore, due to geometry of the posterior arteries, there may be labeled spins flowing perpendicular to the gradients that are not suppressed.

The CBF maps obtained from nonflow-suppressed data are generally higher than the ones from macroflow-suppressed data, independently of the estimation method. However, the average difference was not significant when using BASIL. This may indicate underestimation of the intravascular contributions to the ASL signal when using the LSQ and model-free methods, which would lead to an apparently higher CBF.

The BAT maps obtained in our study are also in agreement with the prior studies (33–35), with longer transit times in the usual locations corresponding to the borderzones of the arterial territories. MacIntosh et al (33) mapped BAT in a relatively large group of healthy young subjects by fitting nonflow-suppressed multiple-PLD PASL data to the general kinetic model using a two-parameter fitting procedure. The sampling strategy was the same as in our study, but a slightly lower global BAT in gray matter of 0.760 seconds was found. Our simulations (results not shown) and data from a BAT comparison study (34) show that in the two-parameter general kinetic model fitting, not accounting for intravascular signal will result in BAT underestimation; therefore, this value is likely to be underestimated. The distance from the labeling to the imaging region is also a key parameter influencing the absolute BAT value (34). Moreover, uncrushed BAT is more sensitive to label location, since it reflects direct macrovascular changes (34). Santos et al (35) estimated CBF and BAT in a flow-suppressed dataseries using a LSQ and a Bayesian algorithm and obtained an average BAT of 0.790 seconds in gray matter, which is in closer agreement with our results.

In spite of presenting similar regional patterns, the BAT maps obtained using the different analysis procedures display different ranges. The lowest BAT averages were obtained with the BASIL method, while the LSQ values were higher and the LSQ with model-free aBV values even higher. These differences are likely bound to specific methodological issues in each approach. The Bayesian approach uses a prior value for BAT of 700 msec, which may bring the estimated BAT values down (closer to this prior value) in the presence of high noise levels. The fact that the dispersion of BAT values across the brain is also much smaller when using this method compared to the others further supports this hypothesis. In the case of LSQ with model-free aBV, the relative overestimation of BAT would be expected in case the aBV value is overestimated (simulation results not shown). This may indeed be the case, particularly outside the macrovascular locations, as assessed by inspection of the respective aBV maps.

The quantitative comparison of aBV values among prior studies may be hampered by variations across brain regions, in the caliber of the vascular segments included in the ROI, vascular anatomy, and other macro-circulation factors such as blood pressure and cardiac cycle. However, our comparison between methods should be fair since we used the same subjects and regions of interest. BASIL and the model-free method provided similar average aBV estimates of about 1%. This value is in agreement with the value obtained for gray matter by Petersen et al (7) in the original model-free study (0.93 ± 0.06%) and the positron emission tomography (PET) literature (1.5 ± 0.3%) (36). In the QUASAR study (19), the flow limit used for flow-suppression was higher (4 cm/s), which explains the lower aBV average reported (0.67 ± 0.16). The aBV estimate obtained by LSQ was lower, which would be expected according to our simulations using a three-parameter LSQ fit (results not shown).

Despite the amplitude differences, the three methods show similar spatial patterns, largely in agreement with the TOF images (although the vessel segments appear thicker in the aBV derived MIPs, probably due to partial volume effects). These ratio differences are probably related to the use of an automatic relevance determination (ARD) prior to aBV estimation by the BASIL framework, while MIP thresholding was equivalent for the three methods.
Table 3
Summary of Literature Studies on ASL Reproducibility

<table>
<thead>
<tr>
<th>Field strength (T)</th>
<th>Sequence</th>
<th>Subjects</th>
<th>Interval between the sessions</th>
<th>CBF (ml/100/min)</th>
<th>BAT (s)</th>
<th>aBV (%)</th>
<th>CVw (%)</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASL 1.5</td>
<td>Multiple-PDL CASL</td>
<td>$n = 10$ 20–67 years</td>
<td>20 minutes</td>
<td>CBF $63 \pm 13$ Gray matter</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floyd 1.5</td>
<td>Single-PDL CASL (45 pairs)</td>
<td>$n = 125$ male 27 ± 8 years</td>
<td>6 ± 3 days</td>
<td>CBF $56 \pm 14$ Whole brain</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermes 1.5</td>
<td>Single-PDL CASL (80 pairs)</td>
<td>$n = 38$ 19 male 20–29 years</td>
<td>7 weeks</td>
<td>CBF $72 \pm 13$ Gray matter</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gevers AJNR 2009</td>
<td>Single-PDL CASL(50 pairs)</td>
<td>$n = 10$ 5 male</td>
<td>3 weeks</td>
<td>CBF $56 \pm 11$ Whole brain</td>
<td>9</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCASL 3</td>
<td>Single-PDL TILT(75 pairs)</td>
<td>$n = 126$ male 61–80 years</td>
<td>3 months</td>
<td>CBF $42 \pm 10$ Gray matter</td>
<td>14</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu JMRI 2011</td>
<td>Single-PDL pCASL PDL = 2.5s (29 pairs)</td>
<td>$n = 87$ male 27–41 years</td>
<td>10–15 days</td>
<td>CBF $48 \pm 5$ Gray matter</td>
<td>5</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASL 1.5</td>
<td>Single-PDL FAIR(31 pairs)</td>
<td>$n = 129$ male 32–71 years</td>
<td>1 – 4 weeks</td>
<td>CBF $64 \pm 12$ Gray matter</td>
<td>11</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jhang Radiology 2005</td>
<td>DIPLOMA PICORE EPISAR (Q2TIPS)</td>
<td>$n = 134$ male 29–64 years</td>
<td>2 hours</td>
<td>Whole brain</td>
<td>7</td>
<td>0.8</td>
<td></td>
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<tr>
<td>Wang Neuroimaging 2011</td>
<td>Single-PDLPICORE Q2TIPS(50 pairs)</td>
<td>$n = 105$ male 27 ± 8 years</td>
<td>1 week</td>
<td>CBF $58 \pm 10$ Cortex</td>
<td>6</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen Neuroimaging 2010</td>
<td>Multiple- PDLQUASAR Model-free</td>
<td>$n = 27534$ ± 9 years</td>
<td>13 ± 10 days</td>
<td>CBF $47 \pm 8$ BAT 0.8 ± 0.1</td>
<td>CBF 10</td>
<td>aBV0.7 ± 0.2</td>
<td>aBV 22</td>
<td></td>
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<tr>
<td>Henrikson JMRI 2012</td>
<td>Multiple-PDLOQUASAR Model-free</td>
<td>$n = 178$ male 20–30 years</td>
<td>90 minutes</td>
<td>CBF $24 – 40$</td>
<td>16</td>
<td></td>
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<tr>
<td>CASL, pCASL, PASL</td>
<td>CASL, pCASL, PASL</td>
<td>$n = 6.5$ male 25–50 years</td>
<td>1 to 3 weeks</td>
<td>CBF $24 – 40$</td>
<td>16</td>
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</tbody>
</table>

CBF = cerebral blood flow; BAT = bolus arrival time; aBV = arterial blood volume; CVw = within-subject coefficient of variation; ICC = intraclass correlation coefficient (reflects the ratio between the data variance of interest and the total data variance); CASL = continuous arterial spin labeling; PASL = pulsed arterial spin labeling; pCASL = pseudo-continuous arterial spin labeling; PLD = postlabeling delay.
Flow-suppressed data provide lower CBF variability than the methods based on nonflow-suppressed data, indicating that the incorporation of bipolar crusher gradients is beneficial for accurate and reproducible CBF mapping. BASIL shows considerably lower BAT variability than the other methods; however, this low BAT variability may be counterbalanced by increased CBF variability due to the incorporation of prior information on BAT values. Model-based methods show considerably less variability in aBV estimation than the model-free approach, probably due to increased variability added by the requirement of using both flow-suppressed and nonflow-suppressed datasets with inherently longer acquisition times prone to increased motion artifacts.

Our variability values are in general agreement with the literature, as summarized in Table 3. The only study using multiple-PLD ASL data and fitting of a kinetic model (18) used a CASL sequence at 1.5 T and 10 subjects scanned in two sessions 20 minutes apart. A CVw of 4.1% for CBF was reported; this very low variability compared to ours may be related to the shorter time interval between sessions. In the ”QUASAR reproducibility study,” QUASAR data were analyzed using a fully model-free approach (19), yielding CBF, BAT, and aBV estimates with CVw values of: 9.9%, 5.6%, and 22.4%, respectively. Possible explanations for the reduced variability reported in this study are the fact that a standardized protocol requiring minimum user-dependency including the use of a slice repositioning software, and that the age range was limited despite the high number of subjects (33.7 ± 8.9 years). Our CVw values for CBF are only slightly above those of the QUASAR study; while those for BAT are larger using the LSQ with model-free aBV, but are actually remarkably low when using BASIL. However, our CVw for model-free aBV is almost twice the one of the QUASAR study; this discrepancy may be justified by differences in data acquisition, namely: lower SNR, lower temporal resolution, and longer acquisition times, which may have led to increased motion between the two datasets and increased subtraction errors. Nevertheless, NS-LSQ and NS-BASIL methods yielded aBV CVw of 22 and 24%, respectively, which are in the range of the values reported in the QUASAR reproducibility study. Gevers et al (20) used the general kinetic model to retrieve CBF from QUASAR nonflow-suppressed data and reported a CVw of 23%. This higher variability is probably related to the fact that the intravascular component was not separated and reflects both tissue and vascular flow variability.

The estimated parameter maps generally show higher variability in vascular regions and lower variability in the basal ganglia. The higher within-subject variability in vascular regions is probably related to differences in cardiac cycle, leading to alterations in the inflow of fresh labeled spins. The larger signal at vascular locations yields also higher subtraction errors. As we were careful to only include the slab common to both sessions, diversity in vascular anatomy would add to these factors only in the case of the between-subject variability maps. The deep gray matter regions are less subject to partial volume effects, due to their higher tissue homogeneity and this is probably at least partly the reason for the lower variability reported.

The BASIL approach yields the most similar CBF and BAT values between flow-suppressed and nonflow suppressed data and the most sensitive aBV with average aBV values more in agreement with previous studies. BASIL has been shown to provide the best compromise between reliability (coherence in the parameter values) and reproducibility, as within-subject variability of CBF, BAT, and aBV was not considerably different from LSQ. Nevertheless, it is worth noting that in the BASIL approach adjustments in the priors may be needed in pathology applications or whenever significant changes in the normal transit times occur, in order to allow increased flexibility in the estimation of time parameters.

One limitation of our study is the lack of comparison of model-based and model-free approaches for CBF and BAT estimations in addition to aBV. It would be interesting to compare the model-based approaches with the entirely model-free approach originally proposed by Petersen et al (7). However, the deconvolution procedure associated with this method would not be sufficiently stable when applied to our data, given the relatively low temporal resolution used to sample the label kinetics and the poor SNR. In fact, with the sequence employed in this study, increasing the number of PLD values used to sample the kinetic curve would lead to forbiddingly long acquisition times. Nevertheless, the comparison of the full model-free method with BASIL in terms of CBF quantification from QUASAR data has been previously presented (9), showing that the CBF estimates obtained by the two approaches are fairly comparable. We extended the previous work (9) by comparing model-based and model-free approaches applied to non-QUASAR data, in terms of aBV estimation and its reproducibility. We found out that model-free approach is not so appropriate for aBV estimation and, as these maps were needed for the deconvolution of nonflow-suppressed data, the final result would probably be less accurate.

In conclusion, we have shown that a PICORE-Q2TIPS ASL sequence in a multiple-PLD nonflow-suppressed acquisition scheme can be used to obtain estimates of perfusion, arterial transit times, and intravascular volumes with good within-subject reproducibility and low intersubject variability, by fitting an extended kinetic model.

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REFERENCES


