Challenges for Non-Invasive Brain Perfusion Quantification Using Arterial Spin Labeling

I. SOUSA[1,2,3], N. SANTOS[1,2,3], J. SANCHES[1,2], P. VILELA[4], P. FIGUEIREDO[1,2]

[1] Instituto de Sistemas e Robótica; Lisbon, Portugal
[2] Bioengineering Department, Instituto Superior Técnico; Lisbon, Portugal
[3] Healthcare Sector, Siemens, S.A.; Portugal
[4] Imaging Department, Hospital da Luz; Lisbon, Portugal

Key words: *perfusion, MRI, ASL, non-invasive, quantification*

Introduction

Arterial Spin Labeling (ASL) sequences for perfusion Magnetic Resonance Imaging (MRI) have recently become available to be used in the clinical practice, offering a completely non-invasive technique for the quantitative evaluation of brain perfusion. Despite its great potential, ASL perfusion imaging still presents important methodological challenges before its incorporation in routine protocols. Specifically, in some pathological conditions in which the cerebrovascular dynamics is altered, the standard application of ASL may lead to measurement errors. In these cases, it would be possible to estimate perfusion, as well as arterial transit times, by collecting images at multiple time points and then fitting a mathematical model to the data. This approach can be optimized by selecting a set of optimal imaging time points and incorporating knowledge about the physiological distributions of the parameters into the model estimation procedures. In this study, we address the challenges that arise in the measurement of brain perfusion using PASL, due to variations in the arterial transit times, by estimating the errors produced using different types of acquisitions and proposing methods for minimizing such errors. We show by simulation that multiple inversion time ASL acquisitions are expected to reduce measurement errors relative to standard approaches. In data collected from a group of subjects, we further observed reduced inter-subject variability in perfusion measurements when using a multiple versus single inversion time acquisitions. Both measurement errors and variability were further reduced if optimized acquisition and analysis techniques were employed.

Introduction

Arterial Spin Labeling (ASL) offers a completely non-invasive, potentially quantitative method for measuring brain perfusion, or regional cerebral blood flow (rCBF), using magnetic resonance imaging (MRI) [10]. Its developments over the last decade have finally earned ASL a place in the clinical setting, but a number of limitations may still hinder the accurate quantification of perfusion using this technique. In particular, the standard application of ASL may lead to measurement errors resulting from different arterial transit times or the presence of vascular artefacts [16,5,9,14].

The pulsed ASL (PASL) techniques consist in magnetically labeling the water molecules in the arterial blood by applying appropriate inversion radiofrequency pulses and then acquiring the image after a certain time interval, the inversion time (TI).

The difference in the measured magnetization of the tissues, $\bar{\lambda}$ M, between the label image and a control image (without label), can be mathematically described by a kinetic model as a function of TI [1].

In principle, it is sufficient to collect an image at a single TI point to obtain a perfusion measurement, provided that appropriate pulse sequences are used and certain assumptions about the model parameters are verified (*Quantitative imaging of perfusion using a sin-*

Paper presented at the XIX Symposium Neuroradiologicum, 2010.

gle subtraction, second version, QUIPSS II or QUIPSS II with thin-slice TI1 periodic saturation, Q2TIPS)[15,8].

However, this is not always the case, particularly in pathological conditions such as cerebrovascular disease where arterial transit times may be much longer than in the normal brain[2]. In these cases, it would be possible to estimate perfusion, as well as arterial transit times, by collecting images at multiple TI points and then fitting the mathematical PASL model to the data (e.g., Figueiredo et al., 2005)[3]. However, such measurements may be difficult due to the very low intrinsic signal-to-noise ratio (SNR) of ASL images. A greater number of image repetitions can be used to improve the SNR, at the cost of increased scanning time. However, the accuracy of the estimated parameters also strongly depends on the exact values used for TI. A few recent studies have proposed strategies for optimizing such multiple-TI experiments, by selecting a set of optimal sampling points and incorporating knowledge about the physiological distributions of the parameters into the model estimation procedures[16,11]. Information regarding the spatial structure of perfusion maps has also been considered in further methodological developments, resulting in improved quantification of both perfusion and the arterial transit time[4,12,13]. In this study, we address the challenges that arise in the measurement of brain perfusion using PASL, due to variations in the arterial transit times, by estimating the errors produced using different types of acquisitions and proposing methods for minimizing such errors.

Methods

The methods used to compare multiple-TI with single-TI PASL acquisitions are first presented. The multiple-TI data acquisition strategies and associated perfusion, f, and arterial transit time, Δt, estimation methods are then described.

Numerical simulations were performed in order to predict quantification errors in each case and, in this way, compare the different methodologies under study. Finally, empirical PASL data were collected from a group of healthy subjects in order to demonstrated the applicability of these methodologies and show the improvements achieved with our proposed techniques.

Multiple-TI vs single-TI PASL methods

We aimed to establish the need for multiple-TI acquisitions for perfusion quantification using PASL, when very long arterial transit times occur. In order to achieve this, we performed numerical simulations to predict the errors incurred in perfusion quantification when using a standard, single-TI acquisition, at a typical TI point (2000ms). Perfusion values were computed using:

$f = \dfrac{\Delta M(TI)}{2\alpha\lambda M_0 \tau \varepsilon^{-T_{1b}TI}}$, where $f(ml/100g/\mathrm{min})$ is the cerebral perfusion; $\Delta M(TI)$ is the magnetization difference at a certain TI point; M_0 is the baseline magnetization; λ is the blood-brain partition coefficient; τ is the time width of the label; T_{1b} is the blood relaxation time. The following values were assumed: α=90%; λ=0.9; T_{1b}=1600 ms[7] and τ=750 ms.

We then compared these errors with the ones that would be obtained by instead employing a multiple-TI acquisition scheme, at a set of TI points set of uniformly distributed TI points covering the interval 200-2400 ms in regular steps of 200 ms, and then adjusting an appropriate PASL kinetic model to the data:

$$\Delta M(TI) = \frac{2\alpha M_0 f}{\lambda\kappa}$$

$$\begin{cases} 0, & TI < \Delta t \\ e^{-T_{1b}^{-1}TI}(e^{\kappa(TI-\Delta t)}-1), & \Delta t \le TI < \Delta t+\tau, \\ e^{-T_{1b}^{-1}TI}(e^{\kappa(TI-\Delta t)})-e^{\kappa(TI-\Delta t-\tau)}), & TI \ge t+\tau \end{cases}$$

where Δt is the arterial transit time;
$k = T_{1b}^{-1} - T_1^{-1} - f/\lambda$ is related to the tissue longitudinal relaxation constant, T_1=1300 ms.

We performed the simulations as described in the section *Numerical Simulations*, using typical values of perfusion and transit time, both in healthy conditions (f~72⁓.24 ml/min/100 ml and Δt~500⁓400 ms) and in arterial transit time delaying pathology (f~72⁓.24 ml/min/100ml and Δt~1000⁓400 ms; Δt~1500⁓400 ms; Δt~2000⁓400 ms).

Multiple-TI data sampling strategy

Two different PASL multiple-TI acquisition strategies were investigated for obtaining quantitative brain perfusion and arterial transit time maps:

Uniform: a set of uniformly distributed TI points covering the interval 200-2400 ms in regular steps of 200 ms [6]; and

Optimal: a set of optimal TI points determined according to an algorithm previously proposed by our group, based on a Bayesian Fisher information matrix criterion, taking into account the uncertainty in the a priori knowledge of the model parameters (24 ml/100 g/min for f and 300 ms for Δt) as well as the amount of noise in the data: 370, 750, 1090, 1400 and 1700 ms [11].

Multiple-TI parameter estimation method

Two different perfusion and transit time estimation methods from PASL multiple-TI were investigated:

StdLS: a standard least squares fitting method is employed;

Bayesian: our previously proposed Bayesian method is employed, incorporating the following a priori information on the normal distributions of the perfusion and transit time values: f~72⁀.24 ml/min/100 ml and Δt~700⁀300 ms [12]. A total variation spatial prior is also employed in order to accommodate the spatial variations of the parameters, which are smooth within regions but relatively abrupt across regions [13].

Numerical simulations

In order to compare the multiple-TI and single-TI acquisitions and also our new proposed multiple-TI sampling and estimation methods with the standard ones, we performed Monte Carlo numerical simulations. In each run, an artificial dataset was generated based on the mathematical PASL kinetic model [1], using realistic distributions of the relevant physiological parameters, and random Gaussian noise was added. Perfusion and transit time measurements were then obtained and the respective errors were computed by comparing them with the true parameter values used in the artificial data generation. In each condition, a total of 1000 runs were performed and the relative errors in the perfusion and transit time measurements were averaged.

Empirical data

A group of seven healthy volunteers (two males, aged 23-26) was studied on a Siemens Verio 3.0 T system (Siemens, Erlangen) with a 12-channel head coil, using a PASL PICORE-QUIPSS II sequence with a gradient echo planar imaging (GE-EPI) readout and TR/TE=2500 ms/19 ms, TI_1=750 ms.

The labelling region was 10 cm thick and the gap between the labelling slab and the proximal slice was 18.8 mm. The acquisition slab contained nine contiguous axial slices, acquired in ascending order and positioned parallel to the AC-PC line, with a resolution of 3.5×3.5×5.0 mm^3. PASL images were collected using the two acquisition schemes under study (*Uniform* and *Optimal*).

The resulting perfusion measurements were then obtained using the two methods under study (*stdLS* and *Bayesian*). Due to the lack of gold standard measures, we chose to assess the quality of the parameter quantification by calculating the inter-subject coefficient of variation (CV), for each sampling scheme and estimation method, using:

$CV_f = 100 \times \frac{\sigma_f}{\bar{f}}(\%)$, where $\bar{f}$ and σ_f are the mean and standard deviation of f across subjects and slices; and

$CV_{\Delta t} = 100 \times \frac{\sigma_{\Delta t}}{\overline{\Delta t}}(\%)$, where $\overline{\Delta t}$ and $\sigma_{\Delta t}$ are the mean and standard deviation of Δt across subjects, for each slice. Since the value of the arterial transit time is dependent on the slice, average across slices is done afterwards.

Results

The results obtained by both numerical simulations and analysis of empirical data are presented here, for the comparison between multiple-TI vs single-TI PASL methods.

Numerical Simulations

Our results show that the standard single-TI PASL acquisitions may lead to severe perfusion measurement errors in some circumstances. In fact, as shown in Figure 1, while they yield relatively good results when arterial transit times are within a limited range, we show that they produce severe perfusion quantification errors when arterial transit times are increased beyond their normal values (up to 80% for 2000ms transit times). In these cases, multiple-TI acquisitions are still able to provide accurate perfusion measurements.

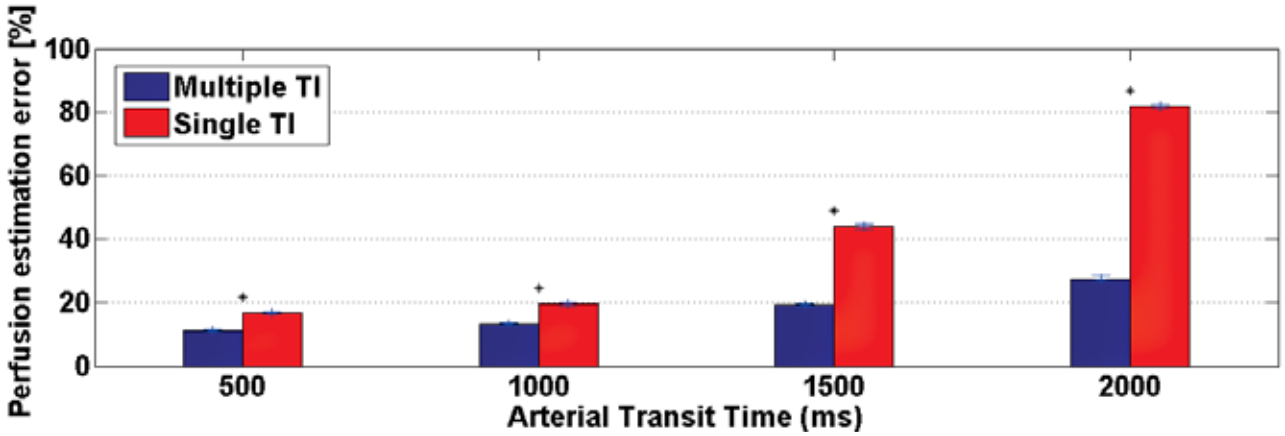

Figure 1 Simulation results: perfusion estimation errors predicted for a standard single-TI acquisition and a uniform multiple-TI acquisition. * denotes statistically significant error differences.

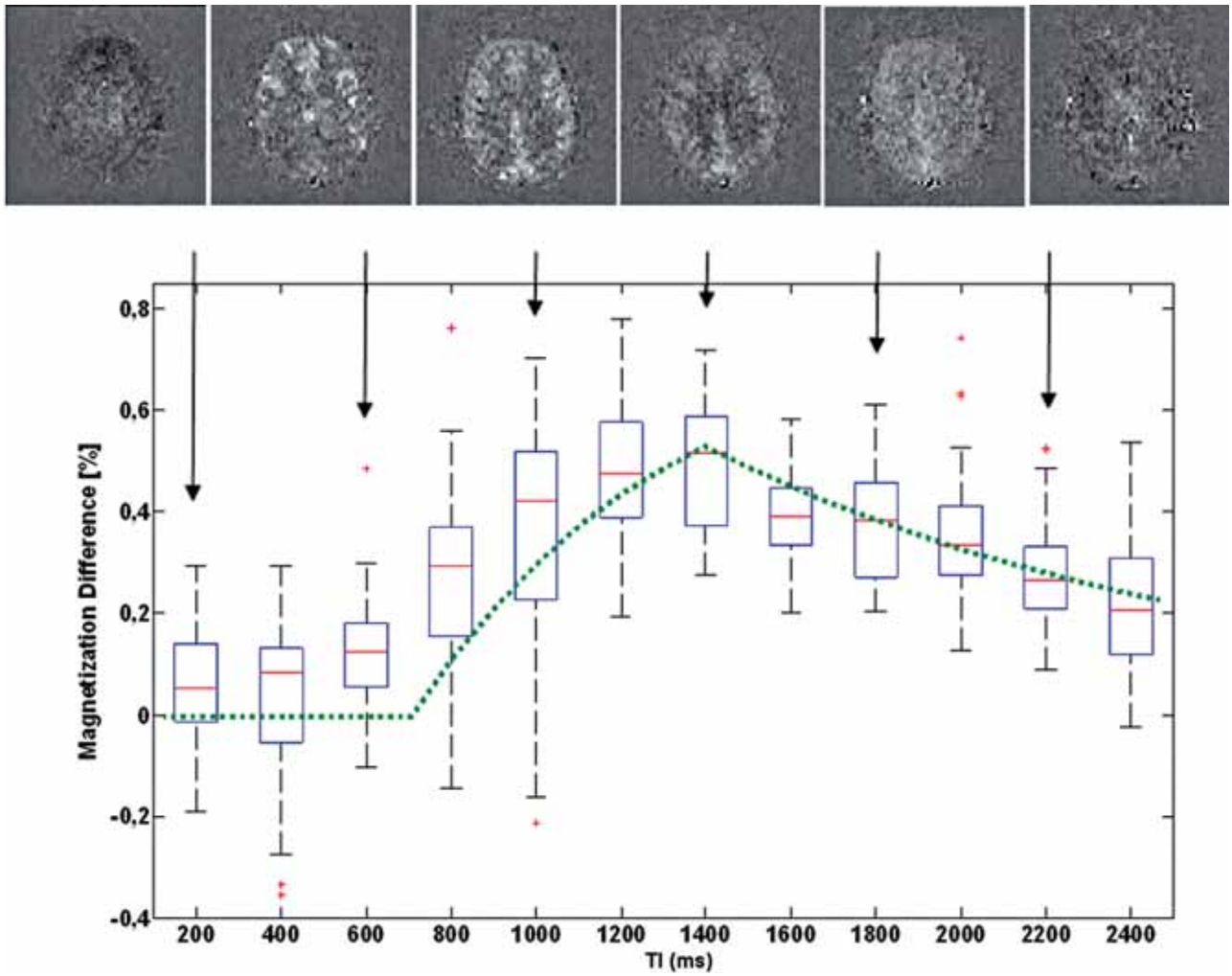

Figure 2 PASL data collected at multiple TI's using a uniform sampling strategy. Top: magnetization difference images of one brain slice collected at 6 illustrative TI's, for one subject. Bottom: box plots of the distribution of magnetization difference values collected for all brain slices and all subjects, at all TI's, and overlaid expected kinetic model curve (green). The median of the distributions is shown in red and the boxes are bounded by the 25th and 75th percentiles.

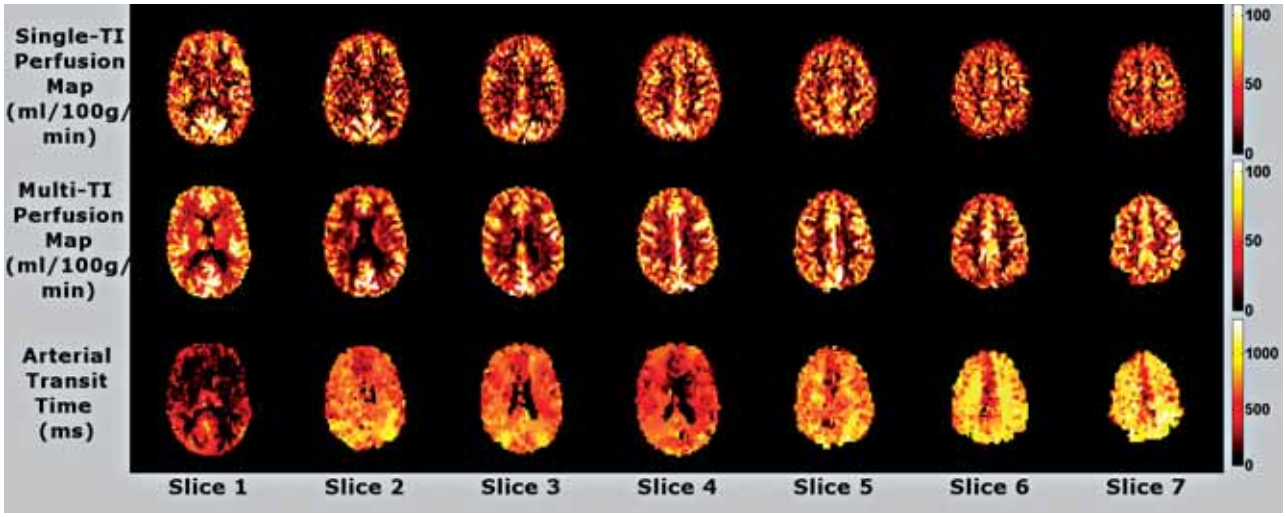

Figure 3 Quantitative maps obtained for one healthy subject, using the single-TI method, for perfusion (first row), and the optimized multiple-TI method, for perfusion (second row) and arterial transit time (third row).

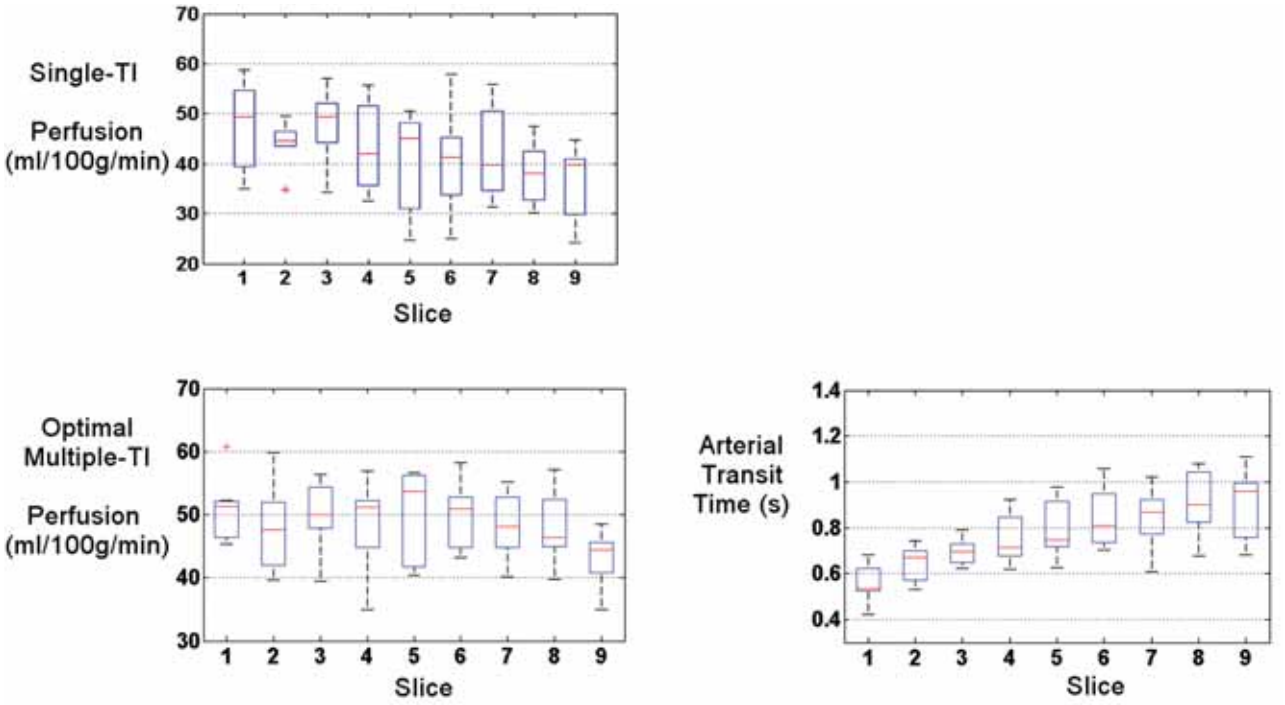

Figure 4 Box plots of the parameters measured across all subjects, for each of 9 slices: perfusion obtained using the single-TI method (top) and perfusion (left) and arterial transit time (right) obtained with the optimized multiple-TI method (bottom). The median of the distributions is shown in red and the boxes are bounded by the 25th and 75th percentiles. Outliers are represented by the red crosses.

Empirical data

Figure 2 shows data from the uniform multiple-TI acquisition. We can see that the global magnetization difference signal for all slices and subjects is closely related to the theoretical signal described by the mathematical kinetic model used [1]. Identical findings were encountered for the optimal sampling acquisition (results not shown).

In Figure 3, the perfusion and transit time maps obtained using the single-TI method and the optimized multiple-TI method, for 7 brain slices in one subject, are shown. The perfusion

maps show higher perfusion values in gray matter regions relative to white matter, as expected due to vascularization differences. Arterial transit time maps show increasing values with slice as the distant from the labeling slab also increases. Single-TI perfusion maps are noisier, although, as expected, the perfusion patterns are consistent with the optimal multiple-TI perfusion maps, especially for the first slices, where the arterial transit times are within the normal range and the single-TI method assumptions are met. The effect of including a spatial prior containing information regarding the spatial variations of the parameters is visible. The noisy aspect of the maps obtained without spatial prior is strongly attenuated, without performing any spatial smoothing.

Perfusion and arterial transit time mean gray matter values obtained using the optimal multiple-TI method, for all subjects studied per slice, shown in Figure 4 (top), are in good agreement with the values reported for gray matter in healthy young volunteers. The increase of the arterial transit times with the slice reveals longer transit time for the upper slices, as described above. The perfusion mean gray matter values obtained using the single-TI method, for all subjects studied per slice, shown in Figure 4 (bottom), reveal larger boxes which imply higher inter-subject variability and a slight underestimation of perfusion.

The inter-subject CV is a measure of the inter-subject variability of the perfusion and transit time measurements. The inter-subject CV obtained for single-TI perfusion quantification was 20.6%, whereas using multiple-TI standard techniques the inter-subject CV was reduced to 14.5% and using the combination of the optimal sampling scheme with the Bayesian estimation method this value was further reduced to 12.4%. The lower inter-subject CV is of great importance in order to achieve great sensitivity in the detection of pathology. It also allows greater statistical power in group studies. This therefore demonstrates, in practice, the advantage of using the proposed multiple-TI method relative to single-TI acquisitions, when performing perfusion quantification PASL studies.

Discussion

Perfusion imaging based on ASL acquisitions, commercially available and already implemented in clinical workstations, generally use a single-TI acquisition, presenting short scanning times and allowing straightforward perfusion quantification. However, our simulation results indicate that such a single-TI approach may incur in severe measurement errors, especially when arterial transit times are increased beyond their normal values. We therefore suggest that multiple-TI strategies should, in general, be preferred for accurate perfusion quantification using ASL. Not only do such acquisitions produce smaller perfusion measurement errors, but they also allow the simultaneous estimation of additional physiological parameters of interest, such as the arterial transit time.

We have previously shown that it is possible to improve these multiple-TI acquisitions, by employing optimal sampling strategies in order to reduce scanning time as well as measurement errors [11]. We further demonstrated that combining such multiple-TI optimal sampling schemes with Bayesian fitting methods produces even lower quantification errors [12,13]. Application of the proposed methodology to real data collected from a group of healthy individuals further showed reduced inter-subject coefficients of variation for the estimated parameters, compared to standard approaches. Lower inter-subject variability allows greater sensitivity in the detection of perfusion alterations correlated with pathology. Therefore we conclude that multiple-TI Bayesian sampling and estimation methods effectively improve perfusion and arterial transit time estimation from PASL data.

In summary, we have shown that it is possible to obtain fully quantitative brain perfusion and arterial transit time maps using commercially available ASL sequences, but that it is in general preferable to select a multiple-TI acquisition scheme for perfusion quantification with pulsed ASL. The limited SNR of such PASL acquisitions and associated difficulties in obtaining accurate perfusion measurements may then be overcome by employing optimized methodologies. The continuous effort in the improvement of both acquisition and analysis techniques therefore should contribute to the pursuit of accurate and clinically meaningful non-invasive quantitative perfusion images.

Acknowledgements

We thank the technicians Ana Cristina Santos, Fernando Gonçalves and Ruben Teixeira,

as well as the remaining staff from the Imaging Department of Hospital da Luz for their assistance with scanning. We acknowledge logistic support from the Hospital da Luz. The investigators IS, NS, JS and PF also acknowledge the financial support by the Portuguese Science Foundation (FCT) through Project PTDC/SAU-BEB/65977/2006, FCT grant SFRH/BDE/33365/2008 and the ISR/IST plurianual funding through the PIDDAC Program funds.

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Patrícia Figueiredo, DPhil
Instituto Superior Técnico
Av. Rovisco Pais, 1
1049-001 Lisboa, Portugal
Tel.: +351 218417288
Fax: +351 218419013
E-mail: patricia.figueiredo@ist.utl.pt