An Improved QUASAR sequence for User-Independent Quantitative and Reproducible Perfusion Measurements

E. T. Petersen[1,2], I. Zimine[1], Y-C. L. Ho[1,2], and X. Golay[1,3]

[1]Neuroradiology, National Neuroscience Institute, Singapore, Singapore, [2]CFIN, Department of Neuroradiology, Aarhus University Hospital, Aarhus, Denmark, [3]Laboratory of Molecular Imaging, Singapore Bioimaging Consortium, Singapore, Singapore

INTRODUCTION: Obtaining quantitative cerebral blood flow (CBF) using non-invasive arterial spin labeling (ASL) techniques is challenging due to uncertainties in bolus arrival time, arterial-input-function (AIF), underlying kinetics and static tissue parameters like blood equilibrium-magnetization (M_{0b}). Blood equilibrium-magnetization is of special importance in longitudinal ASL studies, because M_{0b} is a direct scaling factor in CBF quantification and therefore any error in this parameter will propagate directly to the uncertainty in the perfusion estimate. Unfortunately, measuring this value is not trivial, neither within the ASL experiment itself nor in a separate scan. This is mainly due to partial volume effects with surrounding tissue and pulsating behavior of the blood. In practice, M_{0b} is most often extracted from the sagittal sinus or by using the blood-brain partition coefficient λ, which is defined as the ratio between water content in blood and tissue ($M_{0b} = M_{0t}/\lambda$). A problem in most methods is the user dependency related to the selection of either the sagittal sinus or gray/white matter regions-of-interest (ROI), which can potentially cause great variations in the resulting perfusion estimate. An ASL technique, capable of measuring the AIF and M_{0b} was previously proposed for CBF quantification using model-independent deconvolution [1]. In a second approach [2], M_{0b} estimation was done automatically, based on tissue equilibrium-magnetization M_{0t} and the fact that $M_{0t}/M_{0b} = \lambda$. In this work, we further improve this technique by making it insensitive to RF field inhomogenities and T_2* changes across the brain. To demonstrate its reproducibility, a small test-retest is performed in 6 healthy volunteers in order to get a rough estimate of the reliability of the method.

METHODS: M_{0t} can be calculated on a voxel-by-voxel basis from the saturation recovery data obtained using the QUASAR ASL-sequence [1,2]. However, in this method there remain significant problems related to the fit of T_{1t} from the Look-Locker acquired saturation recovery curve, mainly due to B_1 field variations across the brain. Furthermore, slice profile effects are also play a role and cause the resulting flip angle to appear smaller than the nominal value requested. The actual applied flip angle α is essential in calculating T_{1t} and thereby M_{0t} [2] from:

$$\frac{1}{T_{1t,eff}} = \frac{1}{T_{1t}} - \frac{\ln(\cos(\alpha))}{\Delta TI} \quad \text{(Eq. 1)}$$

?Were ΔTI is the spacing between low flip angle excitation pulses and $T_{1,eff}$ is the apparent relaxation obtained by fitting directly to the Look-Locker curve. By acquiring data at two different flip angles, one can get a map of the needed flip angle correction factor [3] and subsequent correction of T_{1t} and M_{0t} is possible [4]. This correction factor encompasses mainly B_1 field deviations and slice profile variations, although it is likely that other effects such as difference in magnetization transfer effects between low and high flip angle scans are included as well. This method was implemented in the QUASAR sequence in a manner where an optimized flip angle for perfusion is used in the first part of the scan, and the last few repetitions are acquired at lower flip angle, usually one third of the optimized value. These last low flip angle scans are solely used for field inhomogeneity correction. Preliminary test-retest scans were done in 6 subjects (31.8±5.0 year, 2 females) for estimating the reliability of this user-independent quantification method. All subjects gave written informed consent before participation and underwent 5 perfusion measurements, three scans on day 1 and two scans on day 2 which were taken at least one week apart. The second scan was repeated without repositioning the subject, but forcing new scanner calibration steps. The third scan was acquired within 1-2 hour of the first, after repositioning of the volunteer. Repositioning was done based on anatomical landmarks, but no attempt to co-register data was done as this would be realistic in a clinical setup. Scan 4 and 5 were identical to the first two. Reliability was assessed using the Bland-Altman method (comparing difference to mean), the often used Coefficient of Variation (CV = ρ/μ * 100) as well as by calculation of the intraclass correlation coefficient (ICC) which is based on one-way random effects analysis of variance (ANOVA). The protocol was approved by the local ethics committee and performed on a 3T Philips Achieva whole body system. General scan parameters were: TR/TE/ΔTI/TI1=4000/23/300/40 ms, 64x64 matrix, 7 slices, FOV=240x240, flip-angle=35/11.7°, SENSE=2.5. V_{enc}=[∞,4 cm/s], 82 (48 @ V_{enc}=4cm/s, 24 @ V_{enc}= ∞, 10 low flip angle) averages, all implemented in a single sequence.

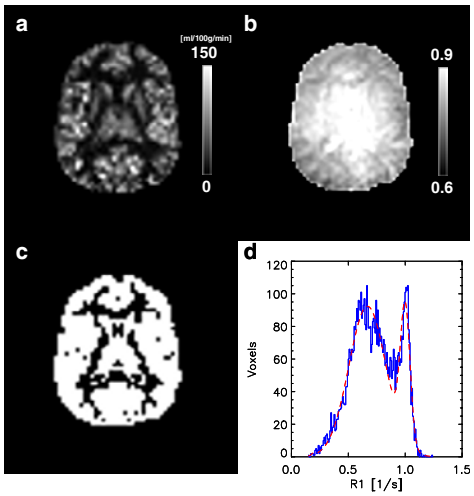

***Figure 1. a**) CBF map, **b**) Flip angle correction factor, **c**) Gray matter mask automatically calculated from **d**) R_1 histogram. The red line is the automatic fitted double Gaussian used for segmentation.*

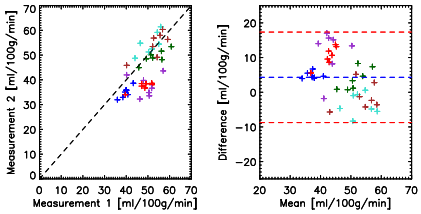

***Figure 2. Left:** Gray matter CBF test-retest values obtained one week apart. Each color represents one subject and values from all 7 slices are plotted. **Right:** CBF difference versus mean for the same data. Red lines are 95% CI and the blue line is the mean difference.*

RESULTS and DISCUSSION: A representative CBF map is shown in Fig. 1a using the correction for the field inhomogenities demonstrated in Fig. 1b. Due to dielectric resonance effects that are more pronounced at higher field strength, it is a common phenomenon, as seen in Fig. 1b where the center of the brain has a higher flip angle than the peripheral. Notice that the flip angle correction factor is consistently less than 1, meaning that on average the applied flip angle is always less than the nominal flip angle. This has to be considered when using a Look-Locker readout for T_1 estimation and a proper estimate is needed especially when the flip angle gets larger. An advantage of the proposed method is that M_{0t} is obtained on a voxel-by-voxel basis, which also means that variations in T_2^* across the brain get included in the further perfusion calculation, as opposed to the situation where a single global M_{0b} is used in the perfusion estimate. However, T_2^* differences between the blood and parenchyma compartments will still remain a potential source of error.

The reproducibility part of this study was a necessary pilot for power calculations of future full fledged test-retest studies of the method. So far, the preliminary results have revealed promising and both CVs of 14-22% and agreement limits are in line with published results from both MRI and Xe-SPECT literature [7,8,9]. The mean of the differences and the corresponding upper and lower agreement limits are summarized in Table 1. Fig. 2 shows the graph for test-retest data obtained one week apart. The intraclass correlation coefficient for all 5 acquisitions is 0.69. Finally, it should be noted that no smoothing has been performed on the data, which is often done to comply with Gaussian field theory [7] and which would improve the apparent reliability.

CONCLUSION: In the present work, a robust and user independent method for quantification of CBF has been developed. Preliminary data suggest good reproducibility. More extensive reproducibility tests are underway.

REFERENCES: [1] Petersen ET et al, MRM 2005;55:219-32 [2] Petersen ET et al, Proc. ISMRM 2006;#2688 [3] Stollberger C et al, Proc. ISMRM 1988;#106 [4] Hinson, WH et al, Med. Phys. 1997;15:551-61 [5] Bland JM et al, Lancet 1986;1:307-10 [6] Shrout PF et al, Psychol Bull 1979;86:420-28 [7] Yen YF et al, MRM 2002;47:921-28 [8] Jahng GH et al, Radiology 2005;234:909-16 [9] Blauenstein UW et al, Stroke 1977;8:92-102

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Table 1. Reproducibility data, calculated from differences between and within perfusion measurements from day 1 and 2. CBF data are from automatic fitted gray matter mask [ml/100g/min]

	Mean	95% CI	Low. AL	Upp. AL	CV [%]
Within session day 1	-2.22	[-3.30, -1.13]	-9.05	4.61	16.6
Between sessions day 1	-2.70	[-4.15, -1.25]	-11.4	10.4	14.4
Within session day 2	-0.38	[-1.99, 1.24]	-10.6	9.80	22.3
Between day 1 & day 2	4.30	[2.23, 6.38]	-8.75	17.6	16.4

CI, Confidence Interval; AL, agreement limit; CV, Coefficient of Variation