Is Arterial Spin Labeling Ready for Prime Time? *Preliminary results from the QUASAR Reproducibility Study*

E. T. Petersen[1], X. Golay[1,2], and T. QUASAR Reproducibility study[3]

[1]Neuroradiology, National Neuroscience Institute, Singapore, Singapore, [2]Laboratory of Molecular Imaging, Singapore Bioimaging Consortium, Singapore, Singapore, [3]22 Centers

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, underlying kinetics and static tissue parameters like blood equilibrium-magnetization. Blood's equilibrium-magnetization is of special importance in longitudinal ASL studies, because it 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. On top, ASL is a low signal-to-noise measurement and altogether these challenges have resulted in ASL being portrayed as a perfusion tool only working in dedicated highly specialized settings. However, development efforts over the years as well as the recent move towards high-field systems, in particular in the clinical settings, have solved many of these problems. In this work, we evaluated the QUASAR [1-2] implementation, which allows user independent CBF estimation, in a worldwide test-retest study dubbed "*The QUASAR reproducibility study*". The aim was to show that ASL firstly is a reliable option for perfusion measurements and secondly that it can easily be used across centers without the need for special hardware or dedicated personnel.

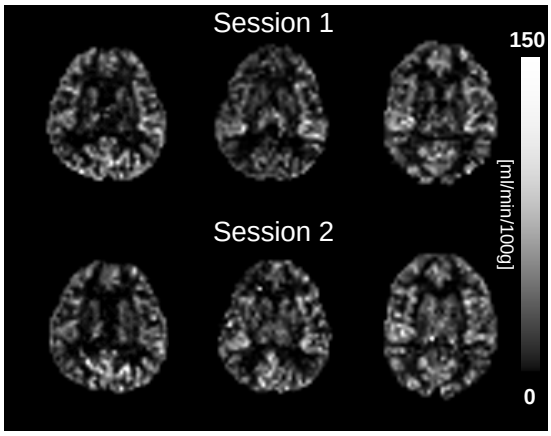

Figure 1. *CBF maps from three different subjects at three different sites. The upper row is from session 1 and the lower row is from session 2. Notice the good match of location between the two scan sessions.*

METHODS: These preliminary results from the QUASAR reproducibility study consist of data from 22 sites and 199 (116 Male, 83 Female, 33±8 years) healthy volunteers. All subjects gave written informed consent before participation according to local ethics regulations and underwent 3 high resolution 3D anatomical scans as well as 4 ASL scans in two secessions separated on average by two weeks (13±10 days). Any personal information from subjects was removed in accordance with local patient protection regulation (HIPAA in the US). All sites were equipped with 3T Philips Achieva whole body systems running on the same software release with automatic planning capabilities also called SmartExam [3] which was used for slice repositioning between sessions. The QUASAR experiment is based on multi-slice acquisition (with a gap between slices) and therefore correct repositioning is crucial with regards to the interpretation of the reproducibility. The three 3D MPRAGE scans were used to estimate the precision of the repositioning algorithm and these results have been submitted as a separate abstract. The main conclusions were that we can expect average translations and rotations up to 1.26 ± 0.44mm and 1.50 ± 0.64° respectively, due to repositioning errors and subject motion. Four perfusion measurements were obtained, two during session 1 where the second scan was acquired after repositioning the volunteer and two during session 2 where the second scan was repeated without repositioning the subject, but forcing new scanner calibration steps. This allowed the evaluation of different factors such as physiological variation, planning inaccuracies as well as acquisition errors which together make up the overall variability between repeated measurements. Both sessions were performed in random orders across sites and volunteers. For these preliminary results, full brain gray matter T1-based masks were used. Reliability was assessed using the Bland-Altman methods (repeatability = $\sqrt{2}\times1.96\times SD_w$; 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). General scan parameters were: TR/TE/ΔTI/TI1=4000/23/300/40 ms, 64x64 matrix, 7 slices (6mm/2mm gap), 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.

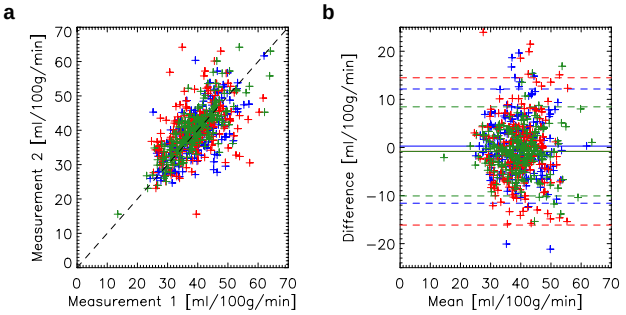

Figure 2. a) *Gray matter CBF test-retest values obtained within session 1(blue), session 2 (green) and between sessions (red).* ***b)*** *CBF difference versus mean for the same data. Dotted lines are 95% CI's and the solid lines are the mean difference. Notice the narrower CI within session 2 (no subject repositioning) as compare to within session 1 (subject repositioning) as compared to between sessions (repositioning + physiological variation).*

RESULTS and DISCUSSION: Representative CBF maps from three sites are shown in Fig. 1. As can be seen, the anatomical location is fairly accurate between the two sessions. The mean gray matter CBF were 39.5 [ml/100g/min] with a significantly higher GM CBF in females than in males 40.4 vs. 38.8 [ml/100g/min] (p=0.004). The overall within-subject standard deviation, repeatability and coefficient of variation for the four scans were 4.96 and 13.8 [ml/100g/min] and 12.6 [%], respectively. Bland-Altman plots are shown in Fig. 2 where the difference in repeatability for scans within session 1 can be seen in blue, within session 2 in green and in between sessions in red. As expected the repeatability is largest between sessions where one could expect variations of physiological origin, or due to planning as well as the acquisition and subsequent post-processing of the ASL data. The repeatability within session 2 is the smallest because no repositioning happened between scans and the variability is only due to eventual subject motion, acquisition and post-processing errors. The corresponding intraclass correlation coefficients (ICC type 1&2) were 0.55 and 0.83 respectively. These results are in line with previously published results from both MRI and Xe-SPECT literature [4-7]. Finally, it should be noted that no smoothing has been performed on the data and all data was included. It can be noted from inspection of the data that the quality is variable between sites and subjects and for subsequent analysis the clinical usefulness needs to be scored as well. The repeatability for individual sites ranged from 8-20 [ml/100g/min] and whether this spread is correlated with scanner performance remains to be investigated. Also the separation of the different effects and their significance will be investigated using variance component analysis methods as part of continued work.

CONCLUSION: The accuracy of the slice-planning as well as the overall and in-between site reproducibility of ASL was tested. Good slice repositioning was achieved and the test-retest showed reasonable reproducibility across sites, suggesting that ASL is ready for use within and across centers in future clinical multi-centre studies. At the very least, the reproducibility was found to be within the same range as Xe-CT, the declared gold-standard for measurement of perfusion [8].

QUASAR reproducibility study: The group includes scientists from the following sites ordered by country: **Australia:** Symbion Clin. Res. Imag. Centre. **Belgium:** Leuven University. **Canada:** University of British Columbia. **Germany:** Hospital of Schleswig-Holstein. **Japan:** Kumamoto University Hospital, Kyushu University, Tohoku University in Sendai. **Korea:** Seoul National University Bundang Hospital, Kyung-Hee University. **Singapore:** National Neuroscience Institute. **Sweden:** Lund University. **Thailand:** Ramathibodi Hospital. **UK:** Imperial College London, University of Nottingham, University of Manchester. **USA:** Adv. Imag. Res. Center UTSW, Columbia University, Children's Medical Center in Dallas, Johns Hopkins University/Kennedy Krieger Institute, National Institute of Health, Vanderbilt University, University of Michigan.

REFERENCES: [1] Petersen ET et al, MRM 2005;55:219-32 [2] Petersen ET et al, Proc. ISMRM 2007;#2688 [3] Young S, et al. SPIE 2006 [4] Hermes M et al, Mag. Res. Mat. Phy. [5] Yen YF et al, MRM 2002;47:921-28 [6] Jahng GH et al, Radiology 2005;234:909-16 [7] Blauenstein UW et al, Stroke 1977;8:92-102 [8] Latchaw RE, et al. Stroke 2003;34:1084-1104.

ACKNOWLEDGEMENT: Philips Medical Systems, NMRC/0919/2004