The effect of bolus length and dispersion on Arterial Spin Labeling flow quantification

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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. In this work, we focus on the effects from the shape and length of the AIF on CBF quantification. Traditionally, when quantifying pulsed ASL, the bolus is assumed a boxcar-function only undergoing T1 decay before it reaches the exchange site. However, bolus dispersion will be present and differences in vessels sizes, length and tortuousness will result in dispersion differences, not only in between subjects, but also across the brain [1]. Generally, the bolus length is often expected to be well defined using QUIPSS II type of approaches [2], where the end of the bolus is cut off at a predefined time. However, from ultra sound studies it is known that large variability in blood velocities exist in brain arteries (65±19cm/s in distal ICA) [3] and according to where and how wide the label slab has been defined, the blood may have left the label region at typical cut-off times of 0.6-0.8s.

Here the aim was to show the variability in dispersion and bolus duration, based on data acquired as part of the worldwide test-retest "*The QUASAR reproducibility study*" [4]. Quantification errors using standard models are simulated for AIF variations within normal ranges of velocities and dispersion.

METHODS: The results from the QUASAR reproducibility study consist of data from 28 sites and 284 (164 Male, 120 Female, 34±9 years) healthy volunteers. All subjects gave written informed consent before participation according to local ethics regulations and underwent 4 ASL scans in two sessions separated on average by two weeks (13±10 days). All sites were equipped with 3T Philips Achieva whole body systems with automatic planning capabilities, which was used for automatic slice repositioning between sessions. The QUASAR experiment is based on multi-slice acquisition at multiple inversion time-points [5]. General scan parameters were: TR/TE/ΔTI/TI1=4000/23/300/40 ms, 0.64s QUIPSS II bolus length, 64x64 matrix, 7 slices, FOV=240x240, flip-angle=35/11.7°, SENSE=2.5. V_{enc}=[∞,4 cm/s], 84 (48 @ V_{enc}=4cm/s, 24 @ V_{enc}= ∞, 12 low flip angle) averages, all implemented in a single sequence. The QUASAR sequence allows the extraction of AIF's on a voxel-by-voxel basis from where the actual bolus length and dispersion can be extracted. The characteristic of the AIFs were assumed to approximate the Gaussian dissipation function proposed by Hrabe et al [6]. It is basically a convolution of the ideal AIF by a Gaussian distribution, applying a higher weighting of the longer traveling trailing edge. Because dispersion to some extent can mask the actual bolus length and visa versa, the actual bolus length was fitted in "parallel" within multiple AIFs from each dataset. This resulted in a global bolus duration and a dispersion parameter for each individual AIF. Only AIFs from voxels with a reasonable SNR were included. The accuracy of the method was tested using Monte-Carlo simulations and the actual AIF fit to real AIFs were compared to the gamma function which is also widely used for describing dispersed boluses. The effect of dispersion and unexpected bolus shortening is simulated for a standard 3-parameter (2 when using QUIPSS II) fit to multi time-point data as well as single TI acquisition at typical sample times of 1.5 and 1.8s. For the single TI quantification, a distinction has been made between the situation where tissue T1, arrival time etc is unknown (q=1 in [2]) and the situation where these parameters are known (q=true). General simulation parameters (results are average errors within these ranges): Blood T1=1.65s, tissue T1=1.2s, λ=0.9, CBF=20-60ml/100g/min, transit time=0.4-1.0s, bolus duration=0.5-0.7s (Fig. 1b only), dispersion std.=0.0-0.2s (Fig. 1d only).

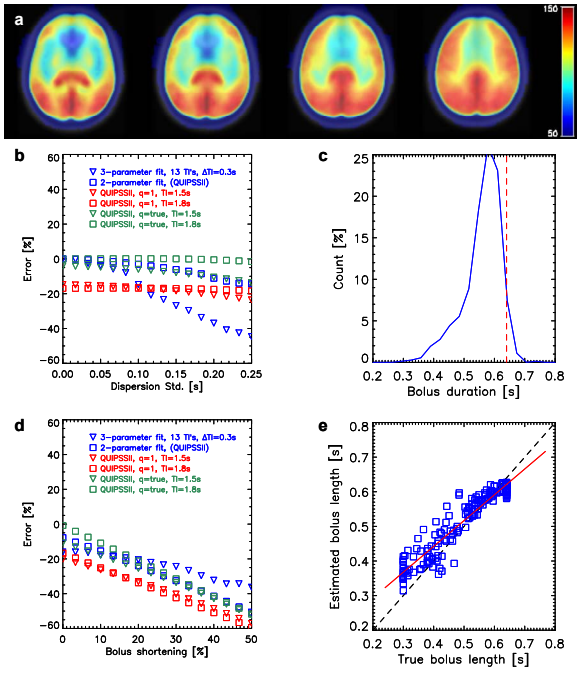

Figure 1. a) *Average Gaussian dispersion of the AIF's (N=960). Notice the increased dispersion in distal regions and the posterior territory.* ***b)*** *Quantification errors as a function of dispersion for typical model based methods.* ***c)*** *Distribution of estimated bolus length (N=960). The bin-size is 30ms and the red vertical line represents the QUIPSS II bolus cut-off time applied to all data (0.64s).* ***d)*** *Quantification errors as a function of unexpected bolus shortening (as compared to 0.7s) for typical model based methods.* ***e)*** *Monte-Carlo simulations of the bolus width estimation. Red line represents the systematic errors of the method.*

RESULTS and DISCUSSION: Fig. 1a shows the average dispersion estimated from 284 subjects (960 scans). As expected the dispersion increases in distal parts of the perfusion territories and interestingly, there is more dispersion in the posterior territory, probably due to the smaller feeding arteries (as compared to both ICAs) and longer travel distance. Fig. 1b shows the quantification errors one could expect across the brain in healthy volunteers due to dispersion. In general the QUIPSS II based methods are robust to dispersion especially if long TIs are used, however in the case of q=true, it should be noticed that transit time measures will be affected by dispersion, resulting in larger errors. The 3 parameter fit on the other hand performs poorly with larger amount of dispersion. Fig. 1c shows the distribution of the estimated bolus width from the 284 subjects. I general the distribution is leaning towards the nominal cut-off (0.64s) but the majority are actually closer to the 0.5-0.6 range, suggesting that in general one should rather use 0.5s or less to ensure appropriate bolus saturation. One could argue that the observation is a result of "over-fitting" the data and thereby returning larger dispersions instead of longer boluses. However, when locating the lower slice at the base of the brain, then the labeling is performed at the level of the ICA (15cm label in this study) where mean blood velocities are approximately 40cm/s [3,7], resulting in mean bolus durations as low as 0.38s. The problem is further exaggerated in studies where flow reactivity is assessed using either CO_2 or acetazolamide which significantly increase the velocity in the feeding vessels [7]. Fig. 1d show the possible quantification errors related to shorter than expected boluses and as expected the 3-parameter fit is less sensitive to this, however the dispersion effects tend to increase with shorter bolus, leading to an underestimation in this case as well. In Fig. 1e, the accuracy of the AIF bolus length estimation is shown for similar acquisition and SNR as in the real data. The root-mean-square error fitting the Gaussian dissipation to the AIFs is significantly better than fitting to a gamma function ($p<0.0001$) which is often used in tracer kinetics. This suggests that viewing the dispersion as a random process could be appropriate in reality. Another interesting observation from the data is the fact that sites having lower average CBF across subjects also seem to have shorter bolus durations ($r=0.63$, $p<0.001$). This could be due to differences in the spatial extent and homogeneity of the RF field delivered by the body coil for inversion. Finally, females tend to have 17ms shorter bolus than males ($p<0.01$) and correcting for bolus length did not improve CBF's within subject standard deviation.

CONCLUSION: The effects from variation in the shape of AIF can potentially introduce large quantification errors across as well as within subjects and should be considered for CBF quantification. Short bolus cut-off time should be applied to account for even normal variations in flow velocities of the feeding vessels.

QUASAR reproducibility study: The group includes scientists from the following sites: **Australia:** Symbion Clin. Res. Imag. Centre. **Belgium:** Leuven University. **Canada:** University of British Columbia. **Denmark:** Glostrup Hospital. **Germany:** University Hospital of Schleswig-Holstein. **Japan:** Kumamoto Hospital, Kyushu University, Tohoku University in Sendai. **Korea:** Bundang National University Hospital, Kyung-Hee University, Samsung Medical Center, Severance Hospital Yonsei University. **Netherlands:** University Medical Center Groningen. **Singapore:** National Neuroscience Institute. **Sweden:** Lund University. **Switzerland:** Lausanne University Hospital**. Thailand:** Ramathibodi Hospital. **UK:** Imperial College London, University of Nottingham, University of Manchester. **USA:** Adv. Imag. Res. Center UTSW, Columbia University, Dallas Children, Johns Hopkins University, NIH, Vanderbilt University, University of Michigan, Thomas Jefferson University.

REFERENCES: [1] Gall P et al, Proc. ISMRM 2008;#627 [2] Wong EC et al, MRM 1998;39:702-8 [3] Lee VS et al, Radiology 1999;212:493-8 [4] Petersen ET et al, NeuroImage 2010;49:104-13 [5] Petersen ET et al, MRM 2006;55:219-32 [6] Hrabe et al, JMRI 2004;167:49-55 [7] Eicke BM et al, Stroke 1999;30:75-80

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