Limits on quantification of perfusion and capillary permeability surface area product using FAIR ASL

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Introduction: Arterial spin labelling (ASL) is an important technique for investigating tissue function in both animals and humans. ASL provides a non-invasive method to measure perfusion (*F*) and has been proposed as a method of estimating capillary permeability surface area product (*PS*). ASL techniques make use of blood water as an endogenous tracer and model the evolution of the signal change observed due to inflow of the labelled water into the imaging voxel [1]. In order for ASL to make the step into widespread use reproducible quantifiable measurements need to be achievable in a reasonable acquisition time. However, such measurements are challenging due to the intrinsically low SNR associated with ASL. Although *F* and *PS* measurements have been reported in the brain [2,3,4] the error on such measurements is often neglected. As ASL suffers from such an intrinsically low SNR it is essential to be able to estimate the magnitude of the measurement error prior to interpreting measured differences (for example between patient and healthy populations) in fitted values. In this study we look specifically at the use of ASL in normal brain of rats and humans to measure *F* and *PS*. We investigate the experimental limits on *F* and *PS* quantification using simulations and experimental verification in rat brain at 9.4 T. We ascertain the expected error on FAIR-based *F* and *PS* measurements and quantify the % changes in these parameters that can be resolved experimentally. Our results allow us to judge the feasibility of *PS* measurements the precision of *F* using FAIR ASL.

Methods: Monte Carlo simulations were performed to investigate the accuracy and precision of the two-compartment model for measuring *F* and *PS* under different noise levels. The signal that would be expected from a FAIR ASL experiment was simulated using the two-compartment model [2 3] for typical human grey matter and typical rat brain tissue parameters under a variety of *F* and *PS* conditions. Gaussian noise was added to the data and fitted estimates of *F* and *PS* were obtained. This was repeated 1000 times at each noise level. The mean and median fitted *PS* and *F* were recorded along with their standard deviation (SD). From these simulations the coefficient of variation (which gives the percentage error associated with the measurement) that would be expected on an ASL measurement of *F* or *PS* was quantified for different signal to noise ratios (SNRs). *In vivo* experiments were performed on 4 rats on a Varian 9.4 T system. Anaesthesia was induced with 2% isofluorane in air and maintained with 1-1.5 % isofluorane throughout the duration of the scan. Breathing rate and temperature were monitored though out the experiment and body temperature maintained at 37 degrees. The sequence used was based on the FAIR sequence proposed by Pell et al [5]. A 3.8cm diameter quadrature birdcage RF coil was used as this was the smallest coil that would fit the rats meaning optimum SNR could be achieved. A sech180 inversion pulse was used for the FAIR preparation. A slice was selected through the centre of the brain with a slice thickness of 2 mm and a slice thickness ratio (STR) of 3 [5]. For the imaging sequence a gradient spoiled centric phase encoded TURBO FLASH sequence was used. (TE= 3 ms , TR=5 ms, matrix = 128 (read) x 64 (phase)). Slice selective and non slice selective images were acquired at delay times of TI = 1, 1.5, 2, 2.5, 3, 4, 5 s. 6 averages were taken and each acquisition lasted approximately 25 minutes. A normalization image with 6 averages was taken after each acquisition. A subtraction image is shown in figure 1(a). Regions of interest (ROIs) were drawn manually over whole brain, grey matter and cortex regions. Typical ROI size for whole rat brain was 800 voxels. A Levenberg-Marquardt fitting routine was used to fit the fast exchange two-compartment model [2] (with *PS* either fixed or as a free variable) and the single compartment model [6] to time course data from the regions and an error estimate was calculated from the covariance matrix using the curve fitting package Microcal Origin.

Results:

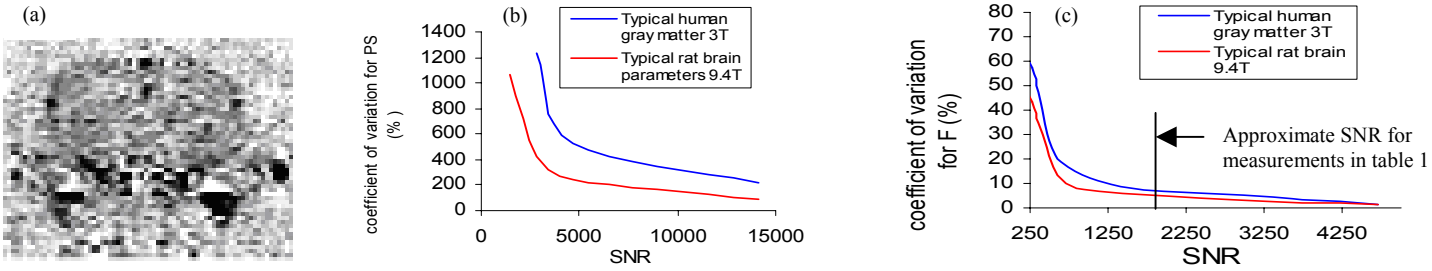

Figure 1(a) Perfusion weighted subtraction image of rat brain at TI = 1 s. (b) Coefficient of variation in *PS* as a function of image SNR for typical human grey matter parameters at 3 T and typical rat brain parameters at 9.4 T. (c) coefficient of variation in *F* as a function of image SNR for typical human grey matter parameters at 3 T and typical rat brain parameters at 9.4 T.

	PS and *F* fitted to 2 comp fast model		*F* fitted to 2 comp fast model *PS* set to 1.5		*F* fitted to single comp model
	F(ml blood)/min/(100ml tissue)	*PS*(ml water)/min/(ml tissue)	*F*	*PS*	*F*
Rat 1	143±11	1±2E13	166±15	1.5	135±11
Rat 2	138±15	3±4E13	152±18	1.5	131±10
Rat 3	157±12	2±3E13	171±10	1.5	145±13
Rat 4	164±16	5±7E13	179±14	1.5	157±13

Table 1: Summary of fitted *F* and *PS* values obtained over ROI in rat brain using single [6] and two compartment models [2]. When *PS* and *F* were both fitted as free parameters the error for *PS* was greater than the value on each measurement showing it was not possible to measure experimentally.

Discussion: We have defined the precision with which estimates of *F* and *PS* may be made across a range of SNRs. The fitted perfusion values and error matched well with known literature indicating comparable levels of SNR [5]. We found that quantitative measurements on a pixel by pixel basis for our SNR of 70 would produce *F* errors in excess of 100%. To generate quantitative measurements regions were drawn and, as SNR increases proportionally with the square root of the number of pixels, ROI analysis increased the SNR to levels that made quantitative measurements of perfusion possible (Fig. 1(c)). However, we found the SNR required to measure *PS*, even on large regions, with just a 100% coefficient of variation would require an SNR increase of approximately 2 orders of magnitude over our acquired data. We therefore conclude that although with current MR capabilities the measurement of *F* using FAIR ASL demonstrates acceptable precision, similarly acceptable levels of precision in the measurement of *PS* are not possible.

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