Quantification of perfusion and blood volume in the brains of rats breathing carbogen using ASL and a two compartment model

J. Carr[1], D. Buckley[1], J. Tessier[2], and G. Parker[1]

[1]ISBE, University of Manchester, Manchester, Greater Manchester, United Kingdom, [2]AstraZeneca, Macclesfield, Cheshire, United Kingdom

Introduction Arterial spin labelling (ASL) is an important technique for investigating tissue function in both animals and humans and provides a non-invasive method to measure perfusion (*F*). A single compartment model that assumes immediate equilibration of labelled blood water protons in the capillaries with the extra-vascular space has been used most extensively to quantify *F* [1, 2]. However, this equilibration assumption is known to be inaccurate and may therefore lead to errors in quantified results. A more complex two compartment model that accounts for the limited permeability of the capillary wall to water molecules has been proposed [3, 4]. A two compartment model will supply a more accurate description of the imaging voxel and also allow extra parameters to be quantified from ASL data. Although ASL has been used to estimate *F* and *PS* simultaneously [3] the error on the *PS* estimate has been shown to be very large [5]. 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 differences in fitted values (for example between white and gray matter or between disease states) and be aware of any bias that may be caused by inaccurate modeling. In this study we explore the ASL modeling and demonstrate the difference in the single compartment and two compartment model sensitivities to changes in the T_1 of the extravascular space (T_{1e}). The two compartment model sensitivity to *F*, *PS* and v_b is also investigated.

Methods To compare the relative importance of the contributions from different parameters included in the 2 models we assess the sensitivity of the ASL signal to variations in each parameter. ASL signals were simulated over a large range of *F*, T_{1e}, *PS* and v_b for the two compartment model for typical rat brain parameters at 9.4 T. A large range of each parameter was selected to extend beyond the maximum physiological range to gain a comprehensive understanding of the model behaviour at extremes. *In vivo* experiments were performed on 3 rats on a Varian 9.4 T system. Anesthesia was induced with 2% isofluorane in air and maintained with 1-1.5 % isofluorane throughout the scan. Breathing rate and temperature were monitored throughout the experiment and body temperature maintained at 37° C. The sequence used was based on the FAIR sequence proposed by Pell et al [6]. 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 [6]. For the imaging sequence a gradient spoiled centric phase encoded turboFLASH 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 = 0.6, 1, 1.5, 2, 2.5, 3, 4, 5 and 15 s (for normalization). 4 averages were taken and each acquisition lasted approximately 20 minutes. ASL datasets were acquired with the rat breathing air and carbogen. A transition time of 10 minutes was allowed between scanning in each condition for steady state to be reached in the physiological parameters of interest. Regions of interest (ROIs) were drawn manually over the whole brain and a Levenberg-Marquardt fitting routine was used to fit the two compartment model [3] with v_b either fixed or fitted as a free variable to ASL data. A T_1 map was used to calculate regional T_{1e} and other two compartment model parameters were given assumed values as follows: T_{1b} = 2.2s, PS = 1.5 ml water (ml tissue)$^{-1}$ (min)$^{-1}$, v_b = 0.05, v_{bw} = 0.7 ml water (ml blood)$^{-1}$ and v_{ew} =1 ml water (ml tissue)$^{-1}$. An error estimate was calculated from the covariance matrix associated with the fit and the coefficient of determination (COD) was recorded to measure the goodness of fit.

Results

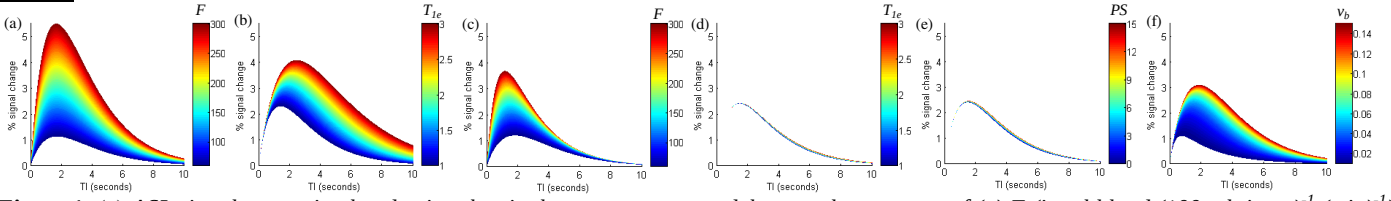
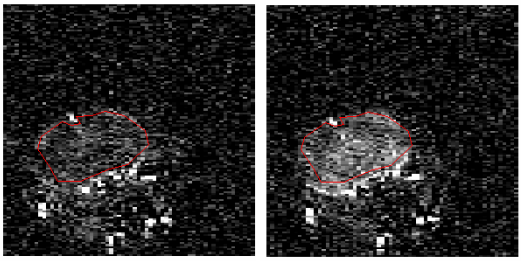


***Figure 1*:** (a) *ASL signal curve simulated using the single compartment model over a large range of (a) F (in ml blood (100 ml tissue)$^{-1}$ (min)$^{-1}$) and (b) T_{1e} (s) and using the two compartment model over a large range of (c) F (d) T_{1e} (e) PS (in ml water (ml tissue)$^{-1}$ (min)$^{-1}$) and (f) v_b (in ml blood (ml tissue)$^{-1}$) for typical rat brain parameters at 9.4 T.*



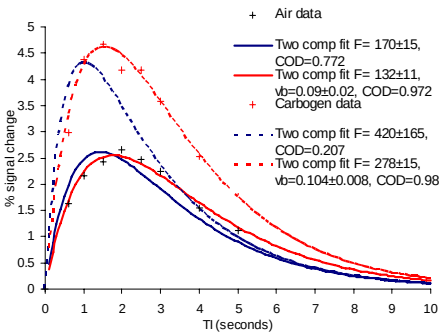


Figure 2: *Subtraction image taken at TI = 1.5 s with rat breathing (a) air and (b) carbogen. (c) Typical whole brain ROI data set with model fits of two compartment model with only F fitted (blue lines) and F and v_b fitted (red lines) for air (solid lines) and carbogen (broken lines) breathing.*

	F only fitted	*F* and v_b fitted	
	F	*F*	v_b
Rat 1	153±14	123±19	0.07±0.03
Rat 2	162±17	155±12	0.06±0.04
Rat 3	170±15	132±11	0.09±0.02
Rat 1 **C**	406±171	255±21	0.09±0.02
Rat 2 **C**	423±152	291±27	0.08±0.04
Rat 3 **C**	420±165	278±15	0.10±0.01

Table 1: *Two compartment model fitted F (ml blood (100 ml tissue)$^{-1}$ (min)$^{-1}$) and v_b (ml blood (ml tissue)$^{-1}$) values when only F fitted and when F and v_b fitted for whole brain ROI.* **C** *indicates fitted result after carbogen administration.*

Discussion Figure 1 (b) and (d) show how the single compartment model is over-sensitive to T_{1e} when compared with the two compartment model. This is a due to the assumption of immediate equilibration of labelled blood water protons in the capillaries with the extra-vascular space and demonstrates how estimates of *F* made using the single compartment model will be biased towards T_{1e}. A similar result was found when typical human brain parameters were used to simulate the signal (data not shown) and this highlights the importance of using a two compartment model to accurately quantify *F* for both animal and human data. Figure 1 (e) and (f) show the two compartment model is much more sensitive to v_b than *PS*, indicating that fitting for *F* and v_b may be optimal. A subtraction image taken with the rat breathing air and carbogen is shown in Fig. 2(a) & (b). The large signal change due to carbogen can clearly be seen and is reflected in the ASL time series shown in Fig. 2(c). Fitting for *F* and v_b is shown to increase the accuracy of the fit (measured by the COD) especially at high *F*. Table 1 shows there to be a large increase in *F* due to carbogen inhalation in all rat brains. The errors on *F* with carbogen breathing are reduced when fitting both *F* and v_b to the two compartment model. The inclusion of v_b in the fit reduces the effect of carbogen on *F* from an increase by a factor of approximately 2.5 to and increase by a factor of approximately 2. In conclusion we have shown that the single compartment model is oversensitive to T_{1e} and that ASL in combination with a two compartment model can be used to simultaneously estimate *F* and v_b.

References **1**. Kwong et al, *MRM*, 1995 **34**:878-887; **2**. Buxton et al, *MRM*, 1998 **40**:383-396; **3**. Parkes et al, *MRM*, 2002 **48**:27-41; **4**. Zhou et al, *JCBM*, 2001 **21**:440-55; **5**. Carr et al, *MRM*, 2007 **58**:281-289; **6**. Pell et al *MRM*, 2004 **51**:46-54.