Accounting for Pre-Capillary Signal in Arterial Spin Labelling Perfusion Measurements

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Introduction: It is generally assumed that the main source of signal in an Arterial Spin Labelling (ASL) experiment arises from labelled water that has reached the capillaries and is undergoing exchange into the tissue. A recognised confounding source of signal is that arising from labelled water still within arteries, which can be removed either through the use of flow suppression gradients [1] or by modelling of this macro vascular (MV) signal [2]. However, both approaches may fail to account for blood that is in small pre-capillary (PC) vessels. This blood may have a flow speed both too low to be effectively suppressed and that would result in a signal shape different from that assumed of the MV signal in model-based correction. In this work we sought to investigate the effect of the PC signal on perfusion quantification for multi-inversion time pulsed ASL (pASL). We hypothesised that within an existing two component (tissue and MV) model-fitting method the pre-capillary signal was potentially being accounted for by both tissue and MV components leading to a bias in estimation of both cerebral blood flow (CBF) and arterial blood volume (aBV).

Methods: We adapted the two component model of [2] that includes a model of MV and tissue signals, to which was added a pre-capillary component. The MV component was parameterized by aBV, MV bolus arrival time (BAT) and assumed a rapid blood flow velocity such that label does not reside for any significant length of time within the voxel. Thus this component could be written in terms of the classic arterial input function for a pASL label. The tissue component followed the 1-compartment rapid exchange model of [3] and was parameterized by CBF and capillary BAT. The pre-capillary component was parameterised by CBF, BAT and a PC mean transit time (pcMTT), the sum of the latter two giving the capillary BAT for the tissue component. The PC model assumed that the PC vessels were impermeable and that blood remained within them during the pcMTT, (c.f. the impermeable solution in [4]). The pcMTT can be related to the CBF and PC blood volume (pcBV) by the central volume theory in the same manner as other kinetic models. Note that the tissue and capillary components share the CBF parameter, thus both contribute to the estimation of CBF. Both the MV and PC components were assumed to have the same arterial blood T1 value. The model used was similar to that in [5], except that we include an independent MV component to account for large artery signal and we adopt a simpler more computationally efficient model for the tissue component.

Model fitting was performed using the same probabilistic algorithm that has previously been employed to fit the two-component model to pASL data [3] with the same prior values as employed in that work. These priors included a shrinkage prior for the MV component that removed it (by forcing aBV to zero) if the data did not support the inclusion of this extra component of the model. Prior information was also included (by means of a Gaussian distribution) for pcMTT taking a mean of 0.5 s (corresponding to a typical CBF of 0.01 s^{-1} and pcBV of 0.5%) with standard deviation of 0.3 s.

Resting state ASL images were collected in four healthy subjects. Using a pulsed ASL preparation with GE-EPI readout with and without flow crushing (b=10 s/mm^2) (TR/TE 3520/18 ms, 4x4x6 mm, 64x64 matrix, 5 slices, Q2TIPS saturation after 0.7 s [4], 10 TIs, 10 averages). Four models that varied the components that were included were fit to the data: tissue, tissue + MV, tissue + PC, tissue + MV + PC. T1 of tissue was taken as 1.3 s and T1 blood as 1.6 s. Analysis was performed within a brain mask derived from the data using the FSL tool BET (www.fmrib.ox.ac.uk/fsl). Significance in the differences in parameter values between the pairs of models were tested using a paired t-test (two-tailed, p=0.05) across all voxels from all subjects within their brain masks.

Results: Figure 1 shows CBF, capillary BAT, aBV and pcMTT images from a representative subject, a reduction in CBF was observed when all components were included along with an increase in voxels exhibiting a substantial aBV value. A reduction in estimated CBF was found when adding either a MV or PC component to the model (18 and 26 % respectively), a further reduction was found when adding both components to the model (38% compared to tissue only), each of these differences were significant. An increase in aBV was found by including a PC component in the tissue + MV model (30%, significant at p=0.05). Using the tissue + MV + PC model crushing was found to have negligible effect on the CBF estimate (<1%, not a significant difference at p=0.05), unlike the tissue only model (9% reduction, significant difference at p=0.05). The crushing was found to cause a reduction in aBV (48%), pcBV (5%) and pcMTT (4%), all significant at p=0.05.

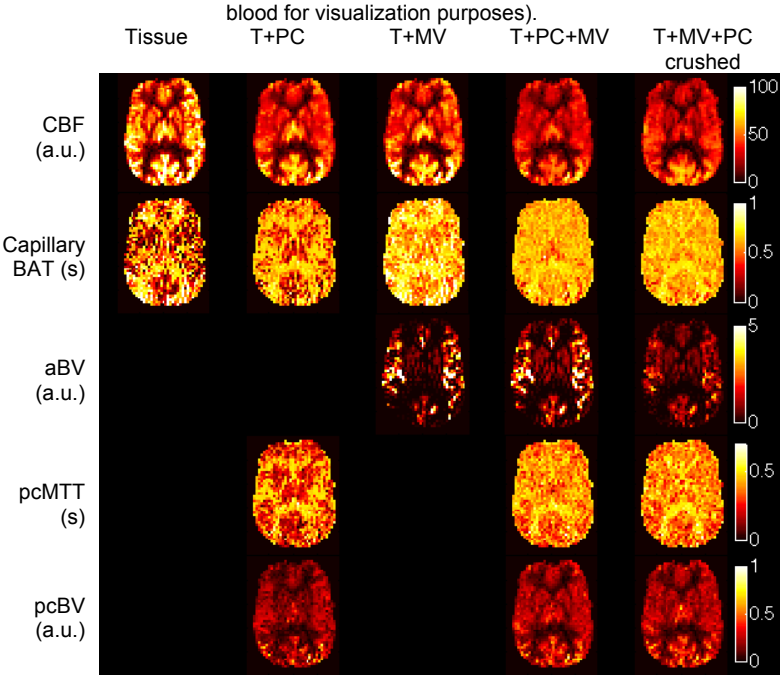

Figure 1: Resulting parameter images from a representative subject for the 4 different models. (CBF, aBV and pcBV are in arbitrary units, having been scaled by an empirical value for the equilibrium magnetization of arterial blood for visualization purposes).

Discussion: The results support the hypothesis that a pre-capillary ASL signal can be isolated from tissue and MV components. Without a PC component the analysis results in an over estimation of CBF and under estimation of aBV. The increase in aBV was surprising, since merging MV and PC components into one might be expected to give a larger value for aBV overall. The result may be explained by poorer estimation of MV signal by the tissue + MV model primarily in regions of low aBV, since the aBV images for the three component model showed a more contiguous arterial component across the brain. In such low aBV regions the MV component may be shifted to later TIs by the tissue + MV model to account for the PC signal and thus some of the earlier arriving MV signal may have been neglected.

The flow-suppressed data considered here supported the potential to account for PC flow within ASL analysis. Flow suppression had the effect of substantially reducing the MV component, with a small reduction in the PC signal and no effect on the tissue signal. However, work is still needed to confirm that a PC signal can be reliably identified in ASL data. A promising approach would be to extend the use of flow suppression to multiple diffusion values to more closely examine label at different stages within the vasculature.

An important extension to the model is to consider the rate of exchange of label once it reaches the capillary space, since here a single well-mixed compartment has been assumed for the tissue signal. The presence of an impermeable PC space would increase the time the label spends in the blood over existing two compartment models of exchange, with implications for the resulting permeability estimates.

References: 1. Ye, et al., MRM 37:226, 1997; 2. Chappell *et al.*, MRM 63(5):1357-1365, 2011 ; 3. Buxton *et al.*, MRM 40:383-396, 1998; 4. Parkes *et al.*, MRM 48(1):27-41; 5. Li *et al.,* MRM 53(3):511-518.