Towards Functional MRI in Blood Free Rats

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Introduction: In spite of the widespread use of BOLD fMRI many aspects of the relationship between the recorded signal and the underlying physiology remain poorly understood. In addition, novel fMRI contrast mechanisms have been proposed, such as diffusion (1) and neural current imaging (2), which may be better understood *without* the confounding effects of blood oxygenation changes. Fluorinated blood substitutes have the advantage of high oxygen carrying capacity without the paramagnetic effects of hemoglobin. Fluorinated agents have been used in several MRI studies (e.g. 3) and fluorinated blood substitutes have been used for complete removal of circulating blood for the purpose of measuring intrinsic optical signals (4). We investigated the use of Oxycyte (Synthetic Blood International Inc.) as a blood replacement agent during an isovolumic exchange transfusion with concurrent MRI monitoring in rats.

Methods: Experiments were performed on male Sprague-Dawley rats (300-350g); anesthetized (3% Isoflurane in 70% air/30% oxygen), tracheostomized and mechanically ventilated. Temperature and pulse oximetry parameters (SaO_2, HR) were monitored and recorded and arterial blood gasses and hematocrit measured periodically. Oxycyte is an emulsion of 60% w/v PFC in water. We experimented with three different transfusion mixtures. 1) physiological saline (as a control), 2) 100% Oxycyte emulsion, 3) a mixture of 60% Oxycyte and 40% blood plasma (from donor rats) by volume. The mixtures were injected into a femoral vein using an MR compatible syringe pump, while simultaneously withdrawing whole blood from the contralateral femoral artery either manually or using a modified syringe pump. The transfusion was started after placing the animal and probe cradle in a 4.7T Bruker Biospec scanner, equipped with 40G/cm gradients. At baseline and every 15 minutes thereafter, multi-slice whole brain coronal EPI was used to measure T_2, T_2^*, ADC and FA.

Results: Exchange transfusion with saline (0.1ml/min) resulted in progressive systemic hypoxia (decreasing brain T_2, T_2^* and ADC) followed by cardiac arrest after 100 minutes. All rats transfused with Oxycyte survived, however best results were obtained with the Oxycyte/plasma mixture, exchanged at a rate of 0.33ml/min. Figure 1 shows physiological and MRI data from an animal which survived a 90% reduction in hematocrit after an exchange of 36ml of fluid (over 2.5 times its total vascular volume) over 2 hours with no T_2 or T_2^* decrease, ≤6% ADC reduction and good blood gas values (PCO_2, PO_2) and mean arterial blood pressure.

Conclusions: Our initial results suggest that an appropriate blood substitute mixture involving Oxycyte can maintain rats in a physiologically stable condition. This may permit blood-free MRI measurements of brain activation and provide insights into the BOLD effect as well as novel fMRI contrast mechanisms.

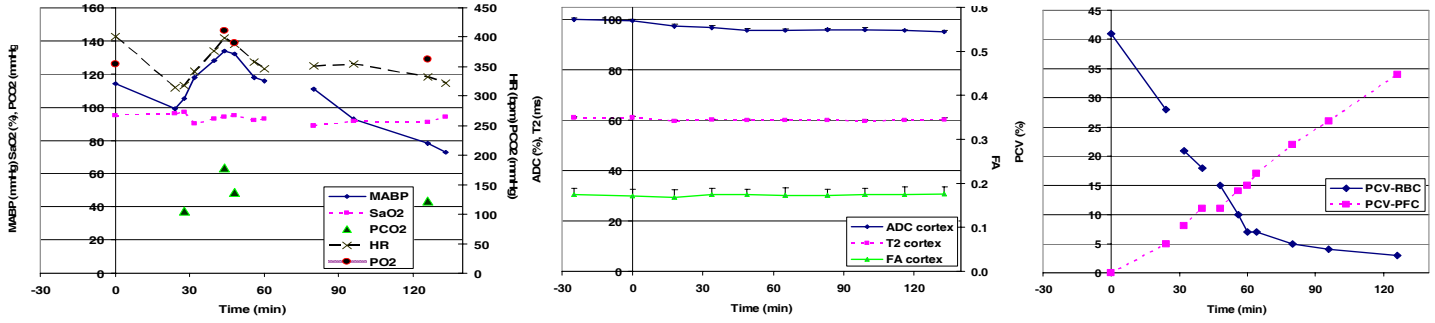

Figure 1: (Left) physiological parameters, (Top-center) Rat brain T_2, ADC(%) and FA values measured in the cortex. (Right) hematocrit and %PFC content. Reasonable blood gasses were maintained and there was no evidence for anoxic depolarization.

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