Separation of the Intra- and Extracellular Apparent Diffusion Coefficients (ADC) of Water in Rat Skeletal Muscle using Spectroscopic MEMRI

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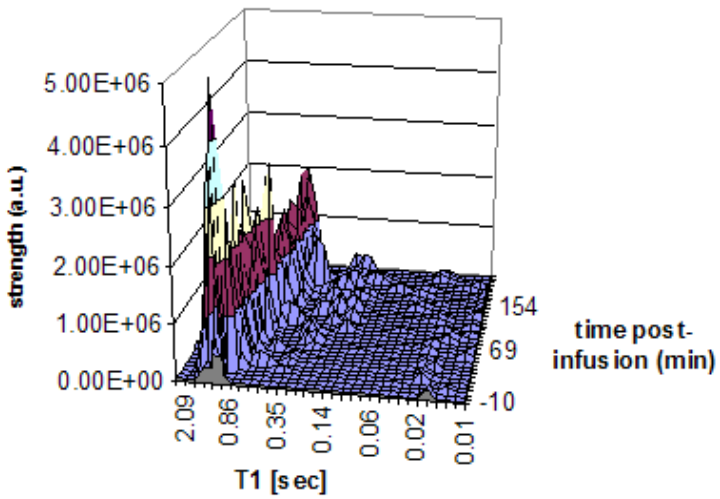
Introduction: A previous study of skeletal muscle[1] has shown that, with even a moderate concentration of a contrast reagent (CR), water exchange may not be in the fast exchange limit. This implies that with a high enough concentration of CR, it may be possible to measure the intracellular (IC) and extracellular (EC) apparent diffusion coefficients (ADC) with minimal interference from water exchange between the two compartments. We use here a graduated infusion schedule of $MnCl_2$ and a diffusion-weighted (DW) inversion-recovery (IR) spectroscopic sequence to measure DW-IR data sets that are first fit to a biexponential form to extract the compartmental M_0 values.[2] These sets of DW compartmental M_0 values are then fit for the ADC of each compartment.

Materials and Methods: Experiments were performed on a GE CSI-II 2.0T/45-cm imaging spectrometer operating at a ^1H frequency of 85.56 MHz with ±20 G/cm gradients. A 22 mm (ID), 4-turn solenoid RF coil was placed around the right thigh of 3 Sprague-Dawley rats (270 - 420 g). Circular copper endcaps were placed on the sides of the coil to restrict the RF excitation to the coil region eliminating the need for gradient-localized spectroscopy. The $MnCl_2$/PBS solution was infused into the catheterized femoral vein. Sequential infusions of 0.8532 mL were performed at concentrations of 20, 30, 40, 50, 60 and 70 mM over a period of 32 min at a flow rate of 0.0266mL/min. IR data, using an adiabatic inversion pulse, were acquired pre-infusion, every 6 minutes throughout the infusion schedule, and at the end of all data acquisition. Either of two sets of inversion times (TI) of 5.0 ms – 15.000 sec or 5.0 ms – 7.000 sec were used. The latter TI-value set was used after sufficient $MnCl_2$/PBS solution had been infused to shorten the overall T_1 of the tissue. Diffusion-weighted (DW) IR data were acquired pre-infusion and at 25 min into the 70 mM infusion period using a DW spin-echo pulse sequence with an adiabatic inversion pulse. Sequence parameters were: Δ = 20.5 ms, δ = 5.0 ms, TE = 25.5 ms, TR = 7 sec, SW = 10000, number of points = 4096. A T_1-weighted image was acquired pre-infusion, once in the middle of each infusion period, and after the final DW data set to monitor the distribution of $MnCl_2$. The IR data was analyzed using an Inverse Laplace Transform (ILT); which yields a distribution of T_1 relaxation times.[1] The ILT was used to determine that the IC and EC water signals were separable. DW data was analyzed using a biexponential fit to the IR data and the resulting compartmental M_0 values at each diffusion weighting were then fit to calculate the ADC for each compartment. For comparison, the DW M_0 values generated from single exponential fits to the same data were used to calculate an 'averaged' ADC.

Results: A representative surface plot of the ILT results for one rat is shown in the Figure. The T_1 scale is logarithmic. Pre-infusion data sets are shown at negative times. Note that by ~ 1 hr post-infusion, a shoulder has developed at the side of the main T_1 peak. This shoulder decreases in T_1 values with increasing $[Mn^{2+}]$ at longer infusion times. The main T_1 peak also shifts to shorter values as the infusion proceeds. For the three animals, the mean T_1 of the main (IC) peak is centered at 1220 ± 10 ms before infusion and decreased to 600 ± 50 ms by the end of the 70 mM infusion period. The mean T_1 of the EC distribution shifted to 110 ± 30 ms by that point. The additional peaks at shorter T_1 values are artifacts due to incomplete inversion. The mean ADC values for the two compartments determined from the biexponential fitting were $1.4 \pm 0.2 \times 10^{-3}$ mm^2/s and $2.2 \pm 0.2 \times 10^{-3}$ mm^2/s for Compartments A and B, respectively. Compartment A was assigned to the longer of the two compartmental T_1 values (presumably IC). A monoexponential fit to the data gives a mean ADC = $1.4 \pm 0.1 \times 10^{-3}$ mm^2/s. The mean fraction for Compartment B was 7.8 ± 0.5%, but this signal is heavily T_2-weighted. **Discussion**: The data shows that water signals can be separated using MEMRI in muscle. These results are in contrast to Landis *et al*. who, using $GdDTPA^{2-}$, did not achieve two separated components. The observed separation can be attributed to the greater relaxivity[3] of Mn^{2+}. Note that the long T1 compartment has the smaller of the two ADC values; this is consistent with its assignment to the IC space. This implies that, for the duration of the experiment, the Mn^{2+} ions do not enter the IC space in appreciable numbers. Both the IC and single exponential mean ADC values and the compartment fractions are consistent with those in the literature[1,4].



References: 1. Landis CS, *et al*, Magn. Reson. Med., 1999; **42**: 467-478. 2. Silva MD, *et al*, J. Magn. Reson., 2002; **156**: 52-63. 3. Wedland MF, NMR in Biomed., 2004; 71:581-594. 4. Heemskerk, AM Magn. Reson. Med., 2005; **53**: 1333-1340.