In vivo quantification of myowater anatomical compartmentation with proton T2-relaxation studies using a three site two exchange (3S2X) model

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Introduction: Proton T2-relaxation has been shown to be multi-exponential in many biological tissues. This behaviour is believed to reflect physic-chemical characteristics of the tissue. In muscle tissue at least three exponential components are systematically observed; a "short" one (T2<10ms) accounting for less than 15% of the signal, an "intermediate" component (20<T2<50ms) accounting for 75 to 95%, and a "long" one (T2>100ms) accounting for less than 15%. There is general agreement that the "short" component reflects water from hydration shells of macromolecules (*hydration-water*). However, interpretation of the "intermediate" and "long" components is still controversial, and two main theories have been proposed over the years: (i) one theory states that each of these components reflects a distinct anatomical compartment with intrinsic T2-value determined by the local concentration of macromolecules (1); (ii) the second theory states that these components reflect chemical-exchange processes between *free-water* and *hydration-water* occurring at distinct intermediate rates in all anatomical compartments (2). The objectives of this work were: (i) to look for experimental evidence of the anatomical compartmentation theory; and, if succeeded, (ii) to look for a compartmental exchange model capable of explaining the observed "intermediate" and "long" T2 components. A two site exchange (2SX) model reflecting the intra and extracellular compartments, and a three site two exchange (3S2X) model, representing the intracellular, interstitial and vascular spaces were investigated. Transverse magnetization evolution of both systems is described by equations (1,2), where $-1/\gamma_i$ are the eigenvalues of the system-characteristic matrix A, and T is a $(N \times N)$ matrix whose columns are the corresponding eigenvectors.

$$\frac{dM}{dt} = \mathrm{A} \times M \quad (1)$$

$$M(t) = T \times \begin{pmatrix} e^{-\frac{1}{\gamma_1}} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & e^{-\frac{1}{\gamma_N}} \end{pmatrix} \times T^{-1} \times M(0) \quad (2)$$

$$A_{2SX} = \begin{pmatrix} -1/T2_i - 1/\tau_i & \frac{1}{\tau_e} \\ \frac{1}{\tau_i} & -1/T2_e - 1/\tau_e \end{pmatrix}$$

$$A_{3S2X} = \begin{pmatrix} -1/T2_i - 1/\tau_i & \frac{1}{\tau_{ei}} & 0 \\ \frac{1}{\tau_i} & 1/T2_e - 1/\tau_{ei} - 1/\tau_{ec} & \frac{1}{\tau_c} \\ 0 & \frac{1}{\tau_{ec}} & -1/T2_c - 1/\tau_c \end{pmatrix}$$

Materials and Methods: Localized in vivo T2 relaxation data were acquired with the ISIS-CPMG sequence, graphically described in Fig.1. The sequence was implemented on a 3T whole-body scanner (Tim Trio, Siemens Healthcare). Excitation and refocusing were done with a 250 and a 500µs hard pulses, respectively. Sequence parameters were TE=1ms, ETL = 1000 and TR = 18.75s. Fat saturation was applied after each of the ISIS cycles resulting in T2 decay curves without contributions from lipids. The signal from *hydration-water* has been verified to be saturated by the long inversion pulses in the ISIS module. Each decay curve was acquired in 5min. Data were acquired from within the soleus of 8 healthy volunteers under different vascular filling conditions (*vascular-draining, normal and vascular-filling*). Visible blood vessels were excluded from VOIs. Data were fitted to a biexponential model by means of non-negative least mean squares. Characteristic relaxation curves for each vascular filling condition were defined from the results of the biexponential fitting (Tab. 1). Unknown intrinsic parameters of the 2SX and 3S2X models were estimated within realistic intervals by fitting the characteristic curves to Eq. 2. Intracellular T2-value, $T2_i$, was set to 31ms for both models. For the 3S2X model the residence time, τ_i, was set to 1s (3), the plasma T2-value, $T2_c$, was measured with the same CPMG sequence and set to 189ms, interstitial and capillary relative fractions, interstitial T2-value and intracapillary residence time were free to vary within the intervals $P_e \in [5{,}10]$ %, $P_c \in [1{,}15]$ % , $T2_e \in [30{,}200]\ ms$ and $\tau_c \in [150, 10^4]\ ms$, respectively.

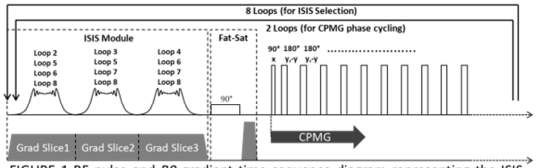

FIGURE 1 RF pulse and *B0* gradient time sequence diagram representing the ISIS-CPMG method.

Results: Different T2-relaxation curves were observed for each vascular filling condition. Figure 2 presents examples of obtained T2 decay curves for each vascular filling condition. Results obtained from biexponential fitting for the relative fractions and corresponding T2 values by means of mean±SD between subjects for each vascular filling condition are presented in Table 1. The 2SX model only succeeded to fit the data for abnormally high intracellular residence times (τ_i > 20s), which implies slow exchange regime. On the other hand characteristic curves were well adjusted to the 3S2X model (Fig. 3) for realistic transmembrane exchange rates (τ_i,τ_c ~ 1s) (3,4). The results for the estimated intrinsic parameters of the 3S2X system for the different vascular conditions are presented in Table 2.

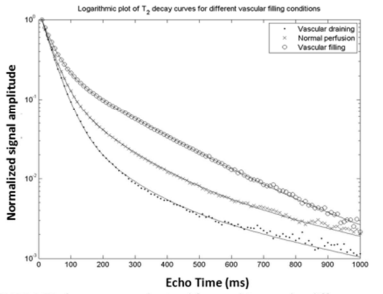

FIGURE 2 T2 decay curves obtained for a subject under different vascular filling conditions, along with corresponding fitted curves (*lines*).

TABLE 1 Results obtained from biexponential fitting for the relative fractions and corresponding T2 values by means of mean±SD between subjects for each vascular filling condition.

Vascular condition		intermediate	long
Vascular draining	Rel. Fraction (%)	94.6(1.5)	5.4(1.5)
	T2 (ms)	31.7(0.5)	139(23)
Free perfusion	Rel. Fraction (%)	92.0(2.4)	8.0(2.4)
	T2 (ms)	32.1(0.4)	159(25)
Vascular filling	Rel. Fraction (%)	85.8(4.7)	14.2(4.7)
	T2 (ms)	32.6(0.7)	181(20)

TABLE 2 Extracted intrinsic capillary relative fraction, P_c, and residence time, τ_c, intracellular to interstitial volume ratio, P_i/P_e, and interstitial T2, T_e, for the three vascular filling conditions.

Vascular condition	P_c (%)	P_i/P_e	T_e (ms)	τ_c (ms)
Vascular draining	4.3	8.6	41	558
Free perfusion	6.9	8.3	47	1188
Vascular filling	13.6	7.6	52	9019

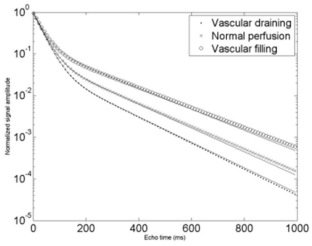

FIGURE 3 Characteristic relaxation curves characterizing the different vascular filling conditions. The lines through the points correspond to the fitted decay curves with the 3S2X model.

Conclusions:

i) Multicomponent T2-relaxation in muscle tissue reflects water anatomical compartmentation.

ii) T2-relaxation data cannot be predicted with a 2SX model, representing an intra/extracellular compartmentation.

iii) The 3S2X model representing intracellular, interstitial and vascular spaces predicts T2-relaxation data correctly even when transmembrane exchange is taken into account.

ii) The 3S2X fitting indicates that the observed "intermediate" T2 component reflects water within the intracellular and interstitial spaces while the "long" T2 component reflects water within the vascular space.

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