Significant alterations on T2-spectra observed in the calf of myopathic patients

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Audience: Researchers interested on NMR-relaxometry methods for studying tissue compartmentation and their clinical applications.

Introduction: T2-mapping of water NMR signal in skeletal muscle (SKM) is known to detect oedematous/inflammatory/necrotic sites, which are all characterized by elevated global (monoexponential) T2-values. Although revealing disease activity, the lack of specificity of such measurement to the underlying pathophysiological mechanism, precludes the application of the monoexponential water T2 as a specific biomarker for the characterization of disease progression. The T2 relaxation of water signals in skeletal muscle is long known to be multiexponential [1] and this has been demonstrated [2] to reveal myowater distribution and exchange between histological compartments (intracellular, interstitial and vascular). The spectroscopic CPMG sequence allows the acquisition of T2-relaxation curves with echo-time sampling and SNR significantly higher than MRI methods, which offers the possibility for robust multiexponential analysis. This method allows extracting a continuous distribution of T2-values (T2-spectrum) that characterizes the investigated volume in the muscle. It has been shown in a recent study [2] that T2-spectra characterizing the soleus muscle of healthy volunteers systematically present two isolated peaks; a *short* one centred at approximately 31 ms, and a *long* one centred at T2-values higher than 120 ms. In this same work [2] it was demonstrated that for physiological transmembrane exchange rates the *short* peak characterizes bulk water in the parenchyma, while the *long* one characterizes bulk water in the vascular space. The different pathophysiological mechanisms occurring in diseased muscles are characterized by different alterations of water distribution and exchange, which shall have an impact on the T2-spectra characterizing these tissues. In the present work we studied the T2-spectra characterising the SKM in the calf of patients diagnosed with neuromuscular disorders. We hypothesise that the analysis of T2-spectra in diseased tissue shall offer specificity to MRI T2 measurements by revealing the pathophysiological mechanisms underlying the observed alterations on the monoexponential T2-value.

Materials and Methods: Localized in vivo T2 relaxation data was acquired with the ISIS-CPMG sequence, described in details in [2]. This technique offers the possibility to acquire fat-saturated T2-decay curves with 1000 echoes and inter-echo spacing of 1 ms. Only even echoes are used resulting in an observation window of 1 s, sampled at 500 Hz. Each decay curve was acquired in 5min. Data were acquired in the soleus of one healthy volunteer and three patients. Visible blood vessels were carefully excluded from VOIs. Examinations were performed on a 3 teslas (3T) whole-body scanner. T2-spectra characterizing the T2-decay curves were extracted using a norm-2 regularized inversion method [2]. In order to evaluate the in-vivo results, a 3 system 2 exchange (3S2X) model representing the histological tissue compartmentation into intracellular, interstitial and vascular spaces was explored to simulate physiological and pathophysiological conditions (Table 1).

TABLE 1: Intrinsic parameters characterizing the simulated systems in order to represent normal, oedematous, inflamed and necrotizing tissue.

	Histological compartment	Normal Conditions	Intracellular oedema	Interstitial oedema	Inflammation	Necrosis
Relative fraction (%)	Intracellular	85[a]	90	70	70	70
	Interstitial	10[a]	7	25	25	25
	Vascular	5[a]	3	5	5	5
Bulk-water T2-value (ms)	Intracellular	31[b]	40	31	31	31
	Interstitial	35[b]	35	70	70	70
	Vascular	180[b]	180	180	180	180
Water residence time (ms)	Intracellular	1000[a]	1000	1000	1000	700
	Vascular	500[c]	500	500	200	200

[a] Values for normal conditions obtained from [Landis et al. 1999. MRM. 42:467-478]
[b] Values for normal conditions obtained from [Araujo et al. 2014. Biophys J. 106:2267-2274]
[c] Values for normal conditions obtained from [Rose et al. 1977. Circul. Res. 41:515-533]

Results: Figure 1 presents the T2-spectrum derived from the T2-relaxation curve for the simulated physiological and pathophysiological conditions. Figure 2 presents the T2-spectra obtained in vivo in a healthy subject and three patients.

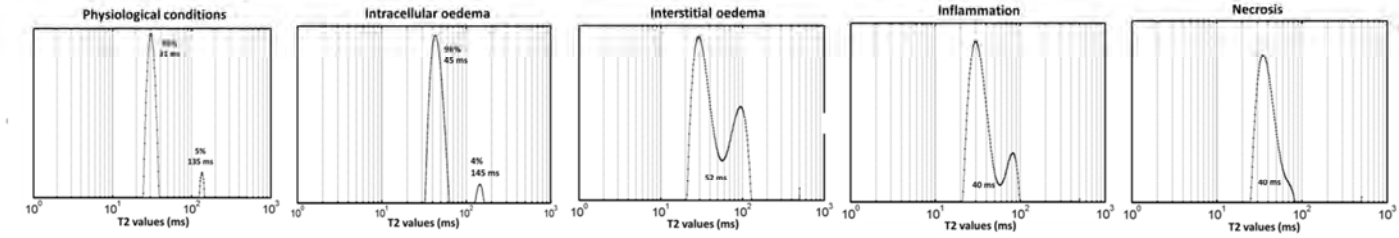

FIGURE 1: T2-spectra extracted from the T2-decay curves simulated with the 3S2X model to represent physiological and pathophysiological conditions

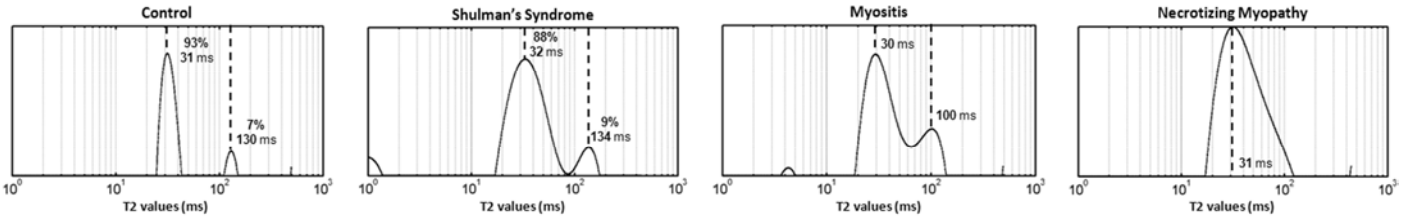

FIGURE 2: T2-spectra extracted obtained in vivo in the soleus of a healthy volunteer (control) and three patients (Shulmans syndrome, Myositis and necrotizing myopathy)

Discussion and Conclusions: Similarities between in-vivo and simulated T2-spectra suggest that specific pathophysiological patterns are identifiable on T2-spectra. The 3S2X model describes healthy conditions accurately and the results from the simulations suggest the following pattern of alterations for the T2-spectra: Related to the simulated normal T2-spectrum, one may observe: (i) for the case of intracellular oedema, a shift of both peaks to higher T2 values; (ii) for the interstitial oedema, a broadening of the *short* and *long* peaks, leading to the merging of both peaks; (iii) for the inflammation, besides the same broadening observed in (ii), there is a shift of the *long* peak towards shorter T2 values; and for the necrosis, besides the reproduction of the effects observed in (iii), there is an intensification of the broadening of the *short* peak, resulting in the complete fusion of both peaks. In the future, we shall apply the presented method in parallel with a technique for measuring the compartmental exchange rates. If the compartmental exchange rates are determined, a quantitative analysis of the T2-spectra can be performed [2], which allows determining the intrinsic volume fraction and T2-value of each histological compartment.

References:

[1] Hazlewood et al. 1974. *Biophys J.* 14:583-606. [2] Araujo et al. 2014. *Biophys J.* 106:2267-2274. [3] Landis et al. 1999. *Magn Reson. Med.* 42:467-478. [4] Rose et al. 1977. *Circul Res.* 41:515-533.