3D mapping of creatine kinase reaction rates and metabolic fluxes in the human calf muscle at 3T

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Target Audience: Scientists interested in muscle physiology, metabolism and bioenergetics, and the utilization of multinuclear MRI.

Purpose: The creatine kinase (CK) reaction plays an important role in the transport of ATP and muscle function. Alteration in the kinetics of the CK reaction has been associated with many diseases, such as diabetes, myopathies and heart diseases. Non-invasive measurement of the forward CK reaction rate and metabolic flux can be achieved through phosphorous (^{31}P) magnetization transfer (MT) techniques [1]. In our study, we developed and implemented a novel three-dimensional (3D) ^{31}P-MT imaging sequence on a 3T clinical scanner that maps the forward CK reaction rate and metabolic flux among different calf muscles in clinically relevant times with relatively high spatial resolution.

Methods: All the experiments were performed on a 3T clinical MRI system (Siemens Medical Solutions, Erlangen, Germany) with a dual-tuned (^{31}P/^{1}H) quadrature volume coils (Rapid MRI, Ohio). Images were acquired through a fully centric 3D TSE [2], developed using the 'SequenceTree' software [3]. A 16ms spectrally selective Gaussian pulse with 125Hz bandwidth was used to selectively excite the PCr peak. The TSE parameters are: ETL 24; effective TE and ESP 26 ms; acquisition bandwidth 2.5 kHz; matrix size 48 x 48 x 8; FOV 220 x 220 x 200 mm; voxel size 0.52ml; TR 12 s; resulting in 3.2 min per average. A MT preparation module consisting of a train of 40 Gaussian pulses was employed before the TSE acquisition module, each with 100 ms duration and 360° nominal flip angle, followed by spoiler gradients in all directions (Fig.1). For calculating the forward CK reaction rate (k_{CK}), one 3D image (3 average) without irradiation was obtained, followed by two 3D images (5 average each) where the MT preparation was applied on the γ-ATP resonance (-2.48 ppm) (Fig.2.B) and the mirrored side relative to PCr (+2.48 ppm) (Fig.2.A). T1 in the calf muscle were also measured while the γ-ATP resonance was irradiated. In order to quantify the absolute PCr concentration [PCr], two Pi phantoms with different concentration were scanned separately, after T_1 and B_1 correction the Pi signals were compared with the PCr signal (without irradiation) of the in vivo images. Anatomical images for calf muscles segmentation were also acquired using a proton 3D-GRE with resolution of 1.7 x 1.7 x 5 mm, having the same FOV, imaging center and orientation as the ^{31}P image. Three male and two female healthy volunteers were scanned (30.4 ± 4.0 years old).

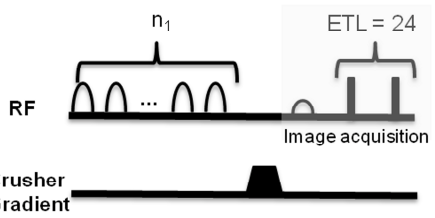

Fig.1. The MT preparation module (40 Gaussian pulses), applied on the γ-ATP peak or the mirror side relative to PCr, followed by a 3D-TSE imaging acquisition.

Results: The forward CK reaction rate can be estimated from the PCr signal obtained while the γ-ATP resonance is irradiated (M_z), and the PCr signal when the mirrored side is irradiated (M_0), and T1 measured while γ-ATP resonance is irradiated [1] using the following Eq.1: $k_{CK} = (1- M_z/M_0) / T_1$. While the metabolic flux of the reaction (V_{CK}) can be calculated from the product of the PCr concentration and the reaction rate constant from Eq.1. An example of k_{CK} map can be found in Fig.2.C. The k_{CK} (s^{-1}) and V_{CK} (mmol/l/s) values calculated in different calf muscles of five volunteers are shown in Table.1.

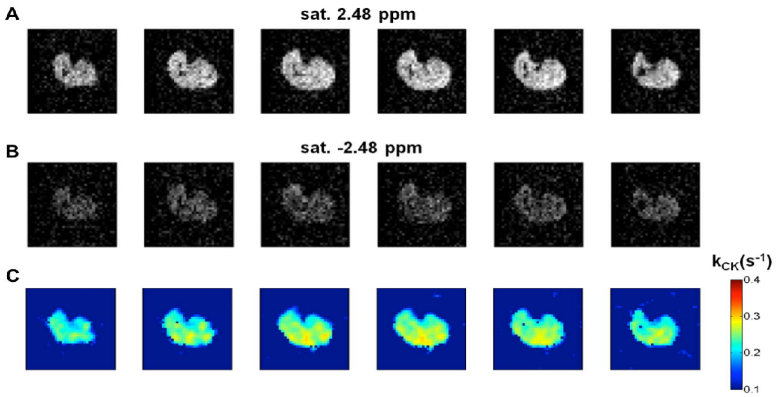

Fig.2. A) Control image acquired with the MT preparation module applied at +2.48 ppm. B) Image acquired with the MT pulse train applied on the γ-ATP peak (-2.48 ppm). C) CK reaction rate kinetic mapping in the calf muscles produced by the ratio of images in A) and B) according to Eq.1 using T_1

Volunteer	TA		TP		S		P		GL		GM	
	k_{CK}	V_{CK}	k_{CK}	V_{CK}	k_{CK}	V_{CK}	k_{CK}	V_{CK}	k_{CK}	V_{CK}	k_{CK}	V_{CK}
1	0.20	6.53	0.21	8.17	0.23	7.79	0.21	6.87	0.22	8.42	0.23	8.40
2	0.24	7.79	0.24	7.70	0.24	7.59	0.26	10.1	0.27	9.36	0.26	8.83
3	0.20	8.28	0.22	8.87	0.26	8.48	0.24	7.62	0.25	9.17	0.23	8.83
4	0.19	6.89	0.19	6.81	0.22	8.31	0.25	8.06	0.25	9.11	0.23	8.41
5	0.21	6.79	0.23	8.11	0.23	6.77	0.21	7.54	0.22	8.51	0.22	7.65
Mean	**0.21**	**7.26**	**0.22**	**7.93**	**0.23**	**7.79**	**0.23**	**8.04**	**0.24**	**8.91**	**0.24**	**8.42**
±SD	**±0.02**	**±0.74**	**±0.02**	**±0.76**	**±0.02**	**±0.68**	**±0.02**	**±1.23**	**±0.02**	**±0.42**	**±0.01**	**±0.48**

Table.1. k_{CK} (s^{-1}), V_{CK}(mmol/l/s) in calf muscles: (TA, TP) tibialis (anterior, posterior), (S) soleus, (P) peroneus, (GL, GM) gastrocnemius (lateral, medial)

Discussion: In this work, we report for the first time the implementation of a 3D ^{31}P-MRI sequence for mapping the CK reaction rate and flux in the calf muscles of healthy volunteers. Our results are in very good agreement with previously reported unlocalized and localized ^{31}P-MT MRS studies [4,5] respectively.

Conclusion: The results suggest that in-vivo 3D-mapping of the CK reaction rates and flux can be achieved at 3T in the skeletal muscle with relatively high spatial resolution, within clinically relevant times. Our method has the potential of detecting spatial variations of the CK reaction kinetics, which might be useful for investigating abnormal heterogeneous patterns of muscle bioenergetics in several diseased states, and could become a valuable tool for monitoring the efficacy of interventions.

References: [1] Alger JR & Shulman RG. NMR studies of enzymatic rates in vitro and in vivo by magnetization. Q Rev Biophys 17:83-124,1984. [2] Parasoglou P, Xia D, Regatte RR. Spectrally selective 3D TSE imaging of phosphocreatine in the human calf muscle at 3T. Magn Reson Med 2012, DOI: 10.1002/mrm.24288. [3] Magland J & Wehrli FW. Pulse Sequence Programming in a Dynamic Visual Environment. Proc ISMRM 14th 2006. [4] Valkovic L, Chmelik M, Kukurova IJ, *et al*. Time-resolved phosphorous magnetization transfer of the human calf muscle at 3 T and 7 T: A feasibility study. Eur J Radiol 2011; DOI: 10.1016/j.ejrad.2011.09.024. [5] Bottomley PA, Ouwerkerk R, Lee RF, & Weiss RG Four-angle saturation transfer (FAST) method for measuring creatine kinase reaction rates in vivo. Magn Reson Med 47(5):850-863, 2002.