# Mapping the Creatine Kinase Reaction Rate in Muscles of the Lower Leg Using Progressive Saturation 31P-MRI at 3.0 T.

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**TARGET AUDIENCE**: Those interested in muscle physiology, muscle bioenergetics, or in technical developments in multinuclear MRI. **PURPOSE**: To develop and implement a progressive saturation $^{31}$P-MRI method for imaging the unidirectional conversion rate of phosphocreatine (PCr) to adenosine triphosphate (ATP) through the creatine kinase (CK) reaction at relatively high spatial resolution. The $^{31}$P-MRI method provides full coverage of the lower leg muscle on a high-field (3.0 T) clinical scanner within experimental times that can be relevant for clinical application (~ 45 min). **METHODS**: The CK reaction can be written as:

$$PCr + ADP + H^+ \underset{k_r}{\overset{k_f}{\leftrightarrow}} ATP + Cr \qquad (1)$$

where $k_f$ and $k_r$ the pseudo first-order forward and reverse rate constants. One way of measuring $k_f$ is through the progressive saturation transfer (ST) experiment[1], in which the γ-ATP resonance is saturated for different durations ($t_{sat}$), resulting in PCr signal decrease. Under fully-relaxed conditions, assuming close to complete saturation of the γ-ATP resonance, the magnetization of PCr as a function of $t_{sat}$, is described by the following equation[2]:

$$M(t_{sat}) = c\left[1 + k_f T_1 e^{-(\frac{1}{T_1}+k_f)t_{sat}}\right] \qquad (2)$$

Where $M(t_{sat})$, the magnitude of the PCr signal as a function of $t_{sat}$, and $c$, a parameter accounting for direct spill-over effects. By measuring the PCr signal at several $t_{sat}$, we can estimate $k_f$ through a three-parameter (i.e. $c$, $k_f$ and $T_1$) fit of the data to Eq.2. The constant $k_f$ is multiplied by the PCr concentration to estimate the unidirectional flux of PCr to form ATP, $V_f$. PCr concentration is measured using reference phantoms and the water/fat content of the muscle is accounted for. Ten healthy volunteers (seven men, three women, mean ± standard deviation age 32.0 ± 3.5 years of age), underwent 3.0 T MRI examination, which included saturation transfer $^{31}$P-MRI using the pulse sequence shown in Fig.1, and chemical shift-based water/fat separation imaging[3]. Mean $k_f$ and $V_f$ measurements were compared (one-tailed Student t-test for paired samples) among four major muscles of the lower leg [i.e. Gastrocnemius Lateral (GL), Gastrocnemius Medial (GM), Soleus (S), and Tibialis Anterior (TA)]. Differences with $P$ less than 0.05 were considered significant.

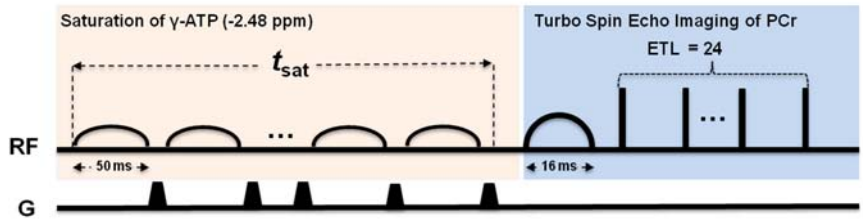


**Fig.1: $^{31}$P-ST Imaging Sequence: A train of 50 ms Gaussian pulses saturates γ-ATP. Spoiler gradients destroy any residual magnetization during a 7 ms inter-pulse delay. The number of Gaussian pulses defines saturation time ($t_{sat}$) in each experiment. A reference image ($t_{sat}$ =0) and eight images with different $t_{sat}$ (range, 0.6 - 6.8 s) were acquired. PCr imaging is performed using a centric ordered 3D-TSE with a frequency selective 90° excitation pulse (16 ms duration, 125 Hz bandwidth), which yields voxel sizes of 0.5 mL.**

**RESULTS**: Figure 2a shows an anatomical cross-section of the lower leg muscles of a volunteer (BMI = 30.4) together with the fat fractions. The decrease of PCr due to chemical exchange with $t_{sat}$ is shown in Fig.2b. By segmenting signals in the PCr images and fitting data to Eq.2, we estimated $k_f$ and $V_f$ for four muscle groups of the leg. In the TA, $k_f$ was 0.26 ± 0.05 s$^{-1}$ (mean ± SD), which was significantly lower than the GL (0.32 ± 0.05 s$^{-1}$, p = 0.0023), the GM (0.31 ± 0.05 s$^{-1}$, p = 0.0289) and the S (0.30 ± 0.04 s$^{-1}$, p = 0.0370). We did not find any significant differences in the $k_f$ among the S the GL and the GM. The metabolic fluxes, $V_f$, in the TA were 8.48 ± 1.56 mM s$^{-1}$ lower than both the GL (10.21 ± 1.41 mM s$^{-1}$, p = 0.00067) and the GM (9.87 ± 1.16 mM s$^{-1}$, p = 0.0431). **DISCUSSION**: Disturbances in the kinetics of the CK reaction in skeletal muscle, which are known to exist in many diseases[4-6] have been studied using unlocalized $^{31}$P-MR spectroscopy with limited volume coverage. However, such methods lack the ability to capture simultaneously the function of several muscle groups with variable fiber composition[7], which can be affected differently by aging and disease[8,9]. The advantage of our method compared to existing $^{31}$P-MRS methods is the large volume coverage and the ability to measure several muscles of the lower leg within a single experiment within clinically relevant acquisition time. **CONCLUSION**: Mapping the kinetics of the creatine kinase reaction rate with large tissue coverage and relatively high spatial resolution is a promising method for the diagnosis and monitoring of several diseases that affect function of skeletal muscle. Saturation Transfer $^{31}$P-MRI can provide insights into patterns of metabolic activity in muscles with different fiber content both in normal aging and diseased populations.

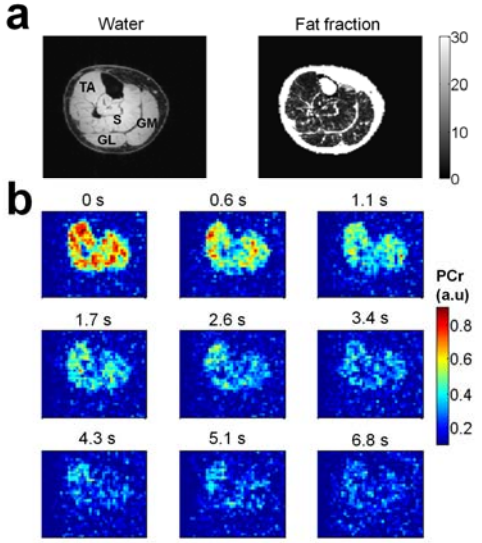


**Fig.2: a) Anatomical $^1$H image and fat/fractions in a cross-section of the lower leg muscles of a volunteer. b) Magnitude of PCr signal decreasing with $t_{sat}$**

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**REFERENCES**: **1**. Forsen S and Hoffman RA. J Chem Phys 1963;39(11):2892-2901. **2**. Horska A and Spencer RGS. MAGMA 1997;5(2):159-163. **3**. Tsao J and Jiang Y. Magn Reson Med 2012;70(1):155-150. **4**.Ingwall JS. Circulation 1993;87(6):58-62. **5**. Radda GK. Science 1986;233(4764):640-645. **6**. Jennings RB and Reimer KA. Am J Pathol 1981;102(2):241-255. **7**. Houmard JA et al. J Appl Physiol 1998;85(4):1337-1341. **8**.Lanza IR et al. J Physiol (Lond) 2007;583(3):1093-1105. **9**. Oberbach A et al. Diabetes Care 2006;29(4):895-900.