Assessment of resting skeletal muscle alkaline Pi pool and PDE concentration by ^{31}P-MRS at 7T and its relation to mitochondrial capacity and Pi-to-ATP exchange rate

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Introduction: Dynamic phosphorus MR spectroscopy (^{31}P-MRS) during exercise-recovery experiments is an established method for non-invasive measurement of muscle mitochondrial capacity *in vivo*[1]. However, as it requires complex experimental setup and patient compliance, an alternative method for assessing muscle metabolism at rest would constitute a significant advantage. ^{31}P-MRS saturation transfer (ST) probes reaction-kinetics between Pi and ATP at rest that correlate with the findings of dynamic experiments[2], however does not provide direct measure of oxidative metabolism. The use of resting ^{31}P-MR spectra to obtain similar information has been promoted recently, as the concentration of phosphodiesters ([PDE]) was shown to correlate with the Pi-to-ATP flux[3]. Moreover an alkaline Pi (Pi_2) pool detectable at 7T, was related to PCr resynthesis rate after physical exercise[4,5].

The aim of this study was to assess the interrelations between parameters derived from static and dynamic ^{31}P-MRS measurements in quadriceps femoris muscle at 7T in three physiologically different subject groups.

Materials & Methods: In total, data from thirty-seven subjects were included in this analysis and divided into groups based on patient physiological characteristics: overweight-to-obese sedentary subjects prior (group I) and after three months of training (group II), and lean subjects active on regular basis (group III). Details on their clinical characteristics are given in Table 1. ^{31}P-MRS data acquisition was performed on a 7T MR system (Siemens Healthcare, Erlangen, Germany) equipped with a ^{1}H/^{31}P single-loop (10 cm in diameter) surface coil (Rapid Biomedical, Rimpar, Germany). The subjects were examined in prone position with the coil fixed underneath the quadriceps muscle. The coil sensitivity volume was used for localization. The examination protocol was divided into three experiments: (i) acquisition of static spectra (TR=15s, 16 avg.) for quantification of metabolite concentrations and the Pi_2/Pi_1 ratio; (ii) ST experiment (TR=15s, 4 avg. for each saturation position and 2 avg. for the T_1 measurement)[2] for quantification of Pi-to-ATP reaction rate constant (k_{ATP}) and ATP flux (F_{ATP}); and (iii) dynamic examination during knee extension (6min, TR=2s, workload ~30% of maximal voluntary contraction) on a dedicated ergometer (Ergospect, Innsbruck, Austria), and subsequent recovery, for quantification of time constant of PCr recovery (τ_{PCr}) and maximal mitochondrial capacity (Q_{max}). For fitting, the line width of the Pi_2 peak (0.4 ppm downfield from Pi_1) was constrained to the Pi_1 peak[4]. The physiological and ^{31}P-MRS parameters were compared between the groups by a one-way ANOVA and a Tukey post-hoc test and their potential relations by a linear regression.

Table 1. Physiological details about the subject groups and muscle metabolism parameters measured by ^{31}P-MRS at 7T

Group	I	II	III
n (m/f)	14 (9/5)	8 (6/2)	15 (10/5)
Age [y]	35 ± 7	37 ± 8	29 ± 6§
BMI [kg/m^2]	30.42 ± 2.27	30.45 ± 2.00	23.16 ± 2.68*,§
VO_2max [ml/kg/min]	36.81 ± 5.32	42.50 ± 7.23	45.88 ± 3.05*
(i) Static measurement			
PDE [mM]	4.21 ± 1.12	4.12 ± 1.04	2.82 ± 1.00*,§
Pi_2/Pi_1 [-]	0.049 ± 0.025	0.055 ± 0.017	0.077 ± 0.018*,§
(ii) ST measurement			
k_{ATP} [s^{-1}]	0.074 ± 0.019	0.080 ± 0.019	0.080 ± 0.014
F_{ATP} [mM/s]	0.26 ± 0.07	0.28 ± 0.04	0.31 ± 0.05
(iii) Dynamic exercise-recovery measurement			
ΔPCr [%]	39.7 ± 20.2	45.2 ± 23.8	40.3 ± 13.8
τ_{PCr} [s]	39.2 ± 11.0	42.2 ± 12.6	42.6 ± 15.8
Q_{max} [mM/s]	0.52 ± 0.07	0.59 ± 0.07$^{\#}$	0.58 ± 0.07*

n (m/f) – number of volunteers (males/females), BMI – body mass index, VO_2max – maximal whole body oxygen uptake. The values are given as mean ± std; significant differences ($p<0.05$) are noted as follows: $^{\#}$ – between group I and II, * – between group I and III, and § – between group II and III.

Results & Discussion: The results of the ^{31}P-MRS experiments are given in Table 1. Sedentary group prior the training protocol (I) had significantly lower values of Q_{max} in comparison to the active groups. In addition, group III had significantly lower PDE concentration and higher Pi_2/Pi_1 ratio when compared to the other groups (as can be seen already in the MR spectra in Figure 1). The values of Pi_2/Pi_1 ratio in sedentary and active subjects and of [PDE] in overweight and lean subjects are in good agreement with previous reports[3,4]. Significant correlations found between Q_{max} and F_{ATP} ($r=0.569$, $p=0.0002$) and between F_{ATP} and the [PDE] ($r=-0.503$, $p=0.0018$), are consistent with literature[2,3]. Further significant correlations are depicted in Figure 2, i.e., Q_{max} correlated to Pi_2/Pi_1 (A) and [PDE] (B) and Pi_2/Pi_1 correlated to k_{ATP} (C) and [PDE] (D). Thus, the evaluation of Pi_2/Pi_1 ratio and of [PDE] from static ^{31}P-MR spectra seems to provide an alternative biomarker of skeletal muscle mitochondrial capacity.

Conclusion: Our investigation, performed on sedentary and active overweight-to-obese subjects as well as on lean active individuals, shows that resting measurements of Pi_2/Pi_1 ratio and [PDE] correlate with measures derived from dynamic and ST ^{31}P-MRS measurements in skeletal muscle.

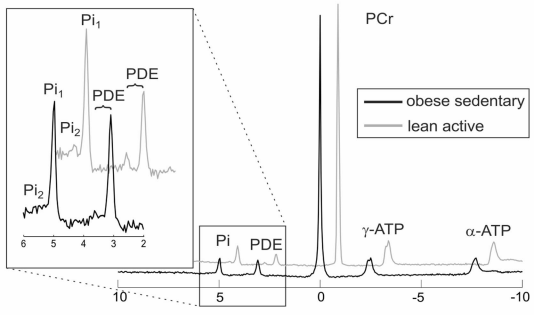

Figure 1 ^{31}P spectra from an obese sedentary and lean active subject, scaled to PCr. The area of Pi and PDE peaks is enlarged. Note higher Pi_2 and lower PDE intensity in the lean subject.

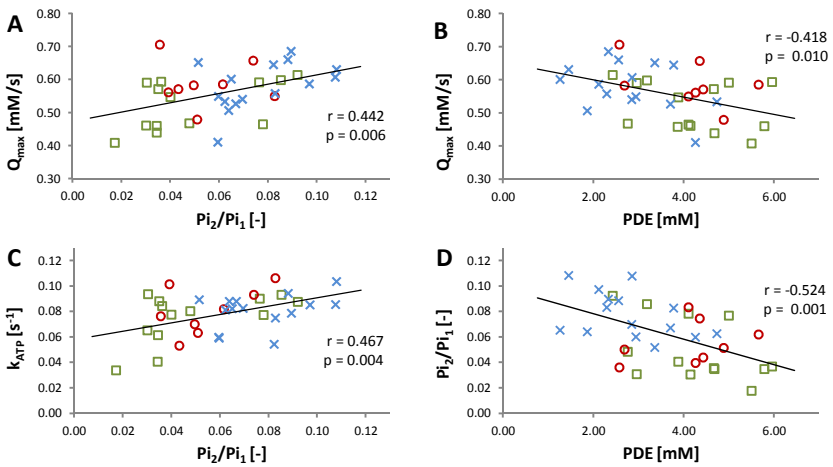

Figure 2 Plots showing linear correlations between measured parameters of muscle metabolism: A) between Q_{max} and Pi_2/Pi_1, B) between Q_{max} and PDE, C) between k_{ATP} and Pi_2/Pi_1, and D) between Pi_2/Pi_1 and PDE. The subject groups are marked as squares (I), circles (II) and crosses (III).

References:

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