MEASURING THE RATE OF PHOSPHOCREATINE RECOVERY IN HUMAN SKELETAL MUSCLE AFTER EXERCISE BY LOCALIZED 1H MRS WITHOUT WATER SUPPRESSION AT 7T

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INTRODUCTION: There has been great interest in measuring ATP synthesis in skeletal muscle using ^{31}P MRS.[1-7] This is typically done either by measuring the rate of chemical exchange between inorganic phosphate (Pi) and γ-ATP in resting muscle using ^{31}P magnetization transfer techniques,[2,3] or by measuring the rate of recovery of phosphocreatine (PCr) after exercise.[1] In muscle, ATP may be derived from substrate-level phosphorylation or oxidative phosphorylation and standard ^{31}P NMR methods do not distinguish these sources. Furthermore, ^{31}P NMR spectroscopy, although attractive in terms of spectral simplicity, is not widely available on most clinical scanners.[3] This work explores the feasibility of an alternative approach for measuring the rate of PCr recovery in muscle after exercise using localized ^{1}H MRS, a technique not only widely available but also suitable for characterizing skeletal muscle of cross-sectional heterogeneity during exercise. This approach is based on the early work by Kreis and colleagues,[4] who assigned the ^{1}H signal at 3.9 ppm to the methylene of PCr, supported by their observation of its proportional response in intensity to the co-registered ^{31}P PCr level after exercise.[4] However, due to residual dipolar coupling, the PCr methylene ^{1}H signal is split into a doublet at low field 1.5 T while the upfield proton signal at 4.1 ppm falls coincidentally at the chemical shift of methine resonance of lactate, a metabolite abundant in muscle after fatiguing exercise.[5] We illustrate here that the increased chemical shift dispersion at 7T allows a clear distinction between lactate and PCr signals in the ^{1}H NMR spectrum, and thus a more confident measurement of PCr recovery.

METHODS:

^{1}H and ^{31}P MR spectra were acquired in an interleaved mode from forearm muscle using a 7T whole-body scanner, with the dominant forearm placed in the center of coil but tilted left-to-right to minimize the effect of residual dipolar coupling. The coil was a partial volume double-tuned ^{1}H /^{31}P T/R coil. ^{1}H NMR parameters: Single-voxel STEAM sequence with TR 2 s, TE 100 ms, NA 8. Non-localized ^{31}P NMR parameters: TR 4 s, NA 1. Four subjects (3 females and 1 male, age 26 - 33 y), participated the study with written consent. Two minutes into data acquisition, the subjects were instructed to squeeze a rubber ball repeatedly every 4 sec at a high intensity level to fatigue the muscle in about 2 min. Data acquisition continued for 20 more minutes after cessation of exercise.

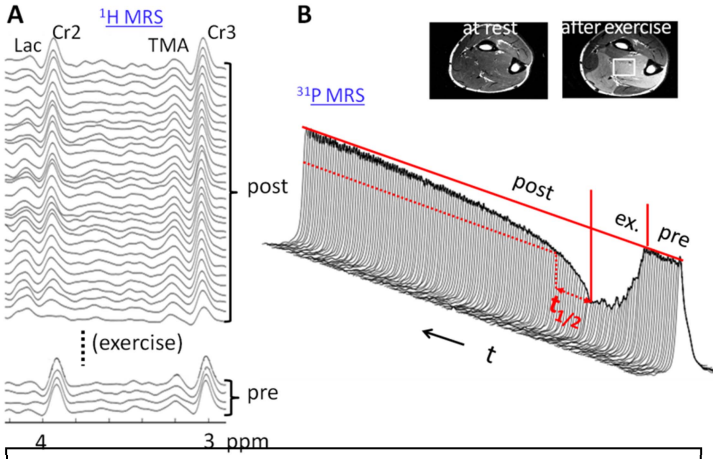

Fig.1 (**A**) Single-voxel ^{1}H MR spectra and (**B**) Non-localized ^{31}P MR spectra, acquired from forearm muscle (T2w image, inset) of a healthy female before, during and after fatiguing exercise. The voxel was placed in flexor digitorum profundus.

RESULTS and DISCUSSION:

A typical ^{1}H MR spectral series shown in Fig.1A clearly illustrates the appearance of the lactate CH signal (4.1 ppm, Lac) and disappearance of the PCr CH_2 signal (3.9 ppm, Cr2) immediately after an intense period of exercise. The time course of Cr2 recovery follows a $t_{1/2}$ constant of 40 sec, which matches well to the recovery of the PCr ^{31}P signal ($t_{1/2}$ = 44 sec, Fig. 1B) in the same time period for this particular subject. The resultant rate constant of 0.027 ± 0.05 s^{-1} ($1/t_{1/2}$, N =4) by ^{1}H MRS is comparable to the observation in tibia anterior muscle (~ 0.03 s^{-1}) by Kreis et al. also using ^{1}H MRS.[4] The high concentration of lactate implies that flux through glycolysis is inhibited in exercised muscle during after exercise. Presumably, the recovery of PCr exclusively reflects ATP synthesis during oxidative phosphorylation. In contrast to Cr2, the signal of Cr3 was only partially reduced immediately after exercise (~20%, Fig.1A), which is consistent with previous observation[4] and can be explained by its relatively long T_2 and small residual dipolar coupling effect.[4,8]

CONCLUSIONS: We demonstrated that the rate of recovery of phosphocreatine after exercise can be measured without interference from residual dipolar coupling and lactate in human forearm muscle using localized ^{1}H MRS without water suppression at 7T.

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