Detection of Fast Decaying Lactate in Human Skeletal Muscle after Exercise by 7T 1H MRS

J. Ren[1], I. Dimitrov[1,2], C. Choi[1], A. D. Sherry[1,3], and C. R. Malloy[1,4]

[1]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [2]Philips Medical Systems, Cleveland, Ohio, [3]Department of Chemistry, University of Texas at Dallas, Richardson, Texas, United States, [4]VA North Texas Health Care System, Dallas, Texas, United States

Introduction

Lactate plays a crucial role in energy homeostasis in both physiological and pathological conditions (1). Normal lactate level in blood ranges from 0.5 to 1.6 mM at rest, but can increase 10 or 20-fold following high-intensity exercise. Elevated lactate (typically > 2.1 mM) can be an important marker of mitochondria disease, poor prognosis in acutely ill patients (2), or nutritional deficiency of thiamine (3). Lactate is routinely measured in blood samples but this provides no information about the tissue origin of high lactate. ^{1}H MRS allows non-invasive and repeated measurements directly from the organ of interest typically by detecting the lactate methyl resonance. In muscle, overlapping signals from lipids poses a challenge for detection of lactate and several approaches involving homonuclear editing or using long mixing time (TM) have been reported (4,5). However, the effectiveness of these approaches are questionable considering several practical problems such as chemical shift dispersion of lipid -$(CH_2)_n$- resonances due to varying fiber orientations (6), differences in relaxation times between IMCL and EMCL, pH-dependent changes in lactate resonance frequency (7) due to acid-base disturbance from exercising. Presented in this study is an alternative approach, using a STEAM-based sequence with long echo time to detect the methine resonance of lactate in human skeletal muscle without significant interference for other metabolite resonances The STEAM sequence was chosen due to its insensitiveness in J-modulation to coupled resonances. By using long TE (140 ms), not only the lipid methine overlapping is minimized, but also the water signal is significantly suppressed (at no cost of extra pulses). Additionally, several unwanted effects are eliminated due to attenuated water signal, including the troublesome baseline distortion, sideband artifacts, as well as the shielding of large water signal to the small metabolite signals nearby.

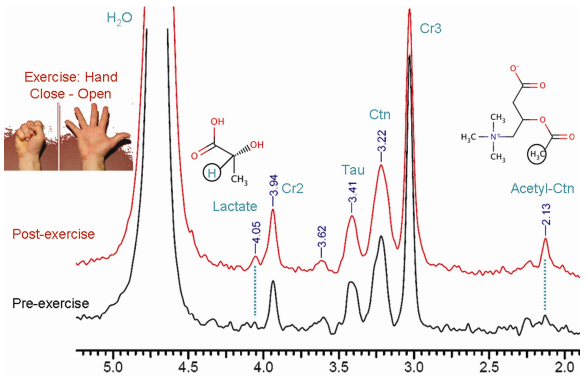

Fig. 1. 7T ^{1}H MR spectra acquired from human forearm muscle pre- and immediately post- 10 min hand close-open exercise (subject #1). Note the exercise-induced lactate signal at 4.05 ppm and acetyl signal at 2.13 ppm.

Methods

The protocol was approved by the Institutional Review Board. Informed consent was obtained from all participants prior to the study. The right forearm of subject was placed on a customized 2-channel T/R partial volume coil, approximately parallel to Bo. The in-magnet exercise protocol is a 10 min of free hand open-close process with a repetition period of 4 sec. Localized single voxel was placed in flexor digitorum profundas muscle ,and ^{1}H MR spectra were obtained using STEAM sequence with TR = 2 s, TE = 140 ms, TM = 13 ms, NSA = 64 or 128, and no water-suppression, at 7T (Achieva, Philips Medical Systems). The spectral data were fitted to Voigt lineshape using ACD software, with frequency referenced to creatine methyl signal at 3.02 ppm. The observed post-exercise signal decay for the methine resonance of lactate at 4.05 ppm and the acetyl resonance of acetyl-carnitine at 2.13 ppm was fit toa mono-exponential equation S(time) = S_a exp(- time/$t_{1/2}$) + S_b.

Results and Discussion

As shown in Figure 1, the ^{1}H MR spectrum acquired from exercised human forearm muscle at long TE of 140 ms clearly revealed lactate methine signal at 4.05 ppm, which was below the detection limit prior to exercise. The elevated lactate methine signal rapidly decayed to the baseline level during recovery with $t_{1/2}$ = 1.5 min (Fig. 2), consistent with the known physiology of fast disposal of lactate after exercise. Muscle lactate can be converted to glucose after circulation to the liver (Cori recycling) or converted to pyruvate which can enter into mitochondria and be further oxidized to acetyl CoA. Because of a reversible acetyl transfer process between CoA and carnitine, the formation of acetyl-CoA in mitochondria can be indirectly detected by acetyl-carnitine. Indeed, a large, sharp acetyl signal from acetyl-carnitine appeared at 2.13 ppm (Figs.1 and 2), as lactate was formed. However, acetyl-carnitine decays at a much slower rate ($t_{1/2}$ = 12.5 min) (Figure 2) during post-exercise recovery. The estimated peak muscle lactate concentration in the exercised muscle was in the range of 15 – 40 mM after 10 min of free hand open-close exercise. With lactate generation, there was a considerable pH drop, as reflected by a 0.05 ppm downfield shift at the lactate methine resonance, but it quickly recovers as lactate returns to pre-exercise levels. To our knowledge, this is the first report of simultaneous observation of lactate and acetyl-carnitine by ^{1}H MRS, and these two metabolites have been reproducibly detected in more than 10 subjects in our lab.

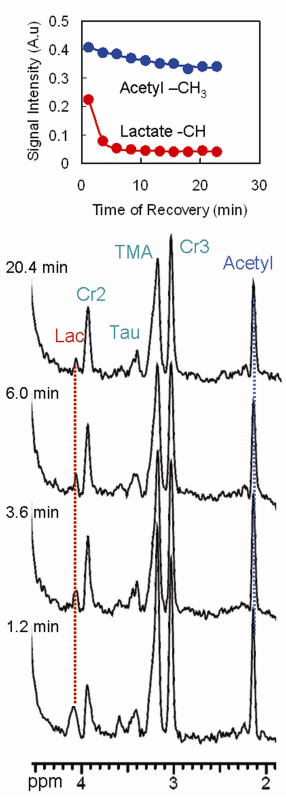

Fig. 2. 7T 1H MRS showing the decay of lactate and acetyl signals in the post-exercise skeletal muscle.

Conclusion

We have demonstrated that muscle lactate and acetylcarnitine can be simultaneously detected in exercised human skeletal muscle by long TE (140 ms) acquisition STEAM sequence without homo-nuclear editing.

References 1. Leverve X et al Crit Care Shock 1998,1:89. 2. Bellomo R Crit Care Shock 1998,1:102. 3. Haas, RH Annu Rev Nutr 1988,8:483. 4. Hetherington HP et al JMR 1989, 82:86. 5. Mercier B et al Eur J Appl Physio 1998,78:20. 6. Khuu A et al MRM 2009,61:16. 7. Pan et al MRM 1991,20:57