

Improving ^{31}P MRS Measurements of Metabolic Kinetics in Skeletal Muscle Using Time Domain Filtering

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Introduction: ^{31}P MRS is the "gold standard" for noninvasive measurements of energy metabolism in exercising muscle. Continuous measurements of phosphocreatine (PCr), adenosine triphosphate (ATP), and inorganic phosphate (Pi) in skeletal muscle before, during and after exercise are obtained. The post-exercise recovery kinetics of PCr are used as an index of mitochondrial oxidative capacity *in vivo*. Mitochondrial dysfunction is increasingly recognized as a cellular mechanism central to a large number of pathologies, including diabetes and metabolic syndrome. *In vivo* ^{31}P MRS measurements, however, suffer from poor inherent sensitivity. A method of improving the S/N of MR spectra that vary in time, known as SIFT (Spectral Improvement by Fourier Thresholding) [1] reduces the noise of the spectra without distorting signal intensity, thus, increasing the accuracy of ^{31}P MRS measured muscle energetics.

Objective: The goal of this study was to compare quantification of ^{31}P MR spectra obtained from an exercise protocol using the following two post-processing procedures: 1) using standard methods (StdP): exponential filtering prior to spectral FT; and, 2) SIFT and exponential filtering prior to final spectral FT. The effects on the observed PCr and Pi resonance S/N and calculations of physiologically relevant time constants are compared.

Methods: Two healthy subjects performed the exercise in a wide bore 3T MRI (Siemens TIM Verio). The exercise was done with a leg extension machine that was secured in the bore of the magnet. Before the protocol the exercise machine weights (outside the bore) were set to 40% of the maximum weight the subject could lift in a single leg extension. The exercise protocol was as follows: 1) rest for the first 120 seconds (s); 2) leg extensions (1 per 2 s) for 180 s (120 to 300 s); and, 3) rest from 300 to 600 s. A single channel ^{31}P tuned transmit/receive surface coil was fixed to the anterior quadriceps muscle of the subject. A ^{31}P 90° pulse sequence was used with TR = 2 s, bandwidth = 3 kHz, 4096 complex data points for a total duration of 10 minutes (300 ^{31}P FIDs acquired). The raw data were analyzed with a custom Python script using the SciPy package. The FIDs were transformed into 4096 point spectra that were subsequently phase corrected using the entropy minimization method¹. SIFT was applied as outlined to the exercise time domain (ETD), i.e., the 300 ^{31}P spectra as described by Doyle et al [1]. Briefly, after the ETD FT, the noise standard deviation (SD) was measured and a threshold operation (2 times SD) was applied. Inverse FT (IFT) of the ETD returned the 300 spectra, which were IFT, exponential filtered and FT, yielding the final SIFT processed spectra. The temporal dimension of the measured signal is composed of high intensity Fourier components of the signal of interest combined with low intensity Fourier components of the noise. Thresholding removes the noise component while preserving the signals of interest. The Pi and PCr peak areas were measured for all StdP and SIF processed spectra. Curve fitting (MATLAB) of the PCr peak area during the recovery was done to calculate the PCr recovery time constants.

Results and Discussion: ^{31}P spectra, Figure 1 (left: StdP; right: SIFT) processed with SIFT show an increase in S/N. During the initial resting portion of the protocol the S/N of the PCr peak increased from 17 (StdP) to 63 (SIFT). Comparable gains were seen in all spectra in both subjects. Figure 2 shows the time dependence of Pi and PCr peak areas, respectively, with (blue) and without (red) using SIFT. Due to the lower S/N, SIFT especially improve Pi peak measurements. Figure 2 (right) also reports the exponential fit (black) of the PCr area during recovery. The R-square values of the fit increased from 0.81 and 0.86 (Subject 1 and Subject 2) to 0.97 (both subjects) with the SIFT method. The time constant of PCr recovery is a marker for mitochondrial

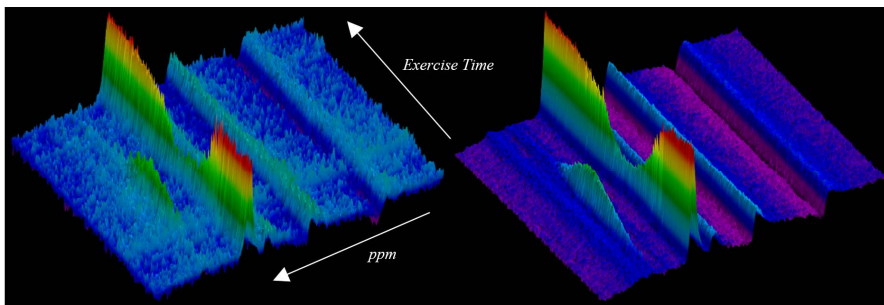


Figure 1: ^{31}P MRS during the exercise protocol with StdP (left) and with SIFT (right)

function in skeletal muscle. The calculated time constants using StdP were 62.9 (95% Confidence Interval (CI): 52.4 to 78.7) and 72.2 (CI: 61.2 to 87.8). With the SIFT method the time constants were 76.3 (CI: 70.3 to 83.4) and 68.7 (CI: 63.9 to 74.2). The CI are notably narrower for the time constants from data processed using the SIFT method. This should allow differences in these time constants to be detected more reliably.

Conclusion: SIFT processing of time dependent MRS data increased spectral S/N (about 3.5 times) compared to conventional methods. SIFT improved the peak area determinations, which allowed more precise fitting to quantify PCr recovery kinetics. Ultimately, the more reliable quantification has potential to make ^{31}P MRS a more sensitive measurement of muscle energetics.

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References: [1] Doyle M et al. *J Magn Reson Series B*. 1994; 103(2):128-133; [2] Chen L et al. *J Magn Reson*. 2002;158(1-2):164-168.

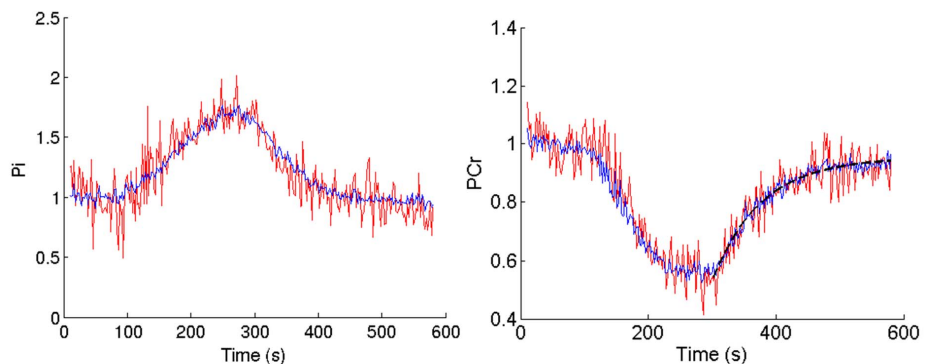


Figure 2: Areas of the Pi (left) and PCr (right) peaks (with StdP is in red, and with SIFT is in blue)