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The Feasibility of Measuring Phosphocreatine Recovery Kinetics in Muscle Using Single-Shot ^{31}P RARE MRI Sequence

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Abstract

Rationale and Objectives—Heterogeneity of skeletal muscle structure, composition and perfusion results in spatial differences in oxidative function between muscles and muscle regions. The simultaneous measurement of the post-exercise phosphocreatine (PCr) recovery rate across all muscles of a human limb cross-section may provide new insights into normal physiology and disease states. The objective of this work was to assess the feasibility of acquiring PCr rapid acquisition with relaxation enhancement (RARE) images with sufficient temporal and spatial resolution to accurately measure PCr recovery kinetics in a cross-section of a human limb.

Materials and Methods—One normal subject performed a finger exercise until fatigued. At cessation of exercise surface coil localized pulse-and-acquire phosphorus-31 MR spectra (^{31}P -MRS) of the forearm were acquired at 6 S intervals for 4 minutes. The exercise protocol was repeated 7 days later and axial PCr RARE images of the forearm were acquired following exercise with 5.6 cm³ voxels at 6 S intervals for 4 minutes.

Results—The PCr recovery time constants for the PCr RARE and ^{31}P -MRS measurements were 91.0 and 91.1 seconds, respectively based on a monoexponential fit. A Pearson correlation test showed that the PCr recovery data that resulted from the RARE PCr imaging were highly correlated with the data resulting from the ^{31}P -MRS ($r = 0.91$, $p < 0.0001$).

Discussion—Data from selected regions of RARE PCr images acquired at 6 S intervals compare well to those acquired using surface coil ^{31}P MR spectroscopy and can provide an accurate assessment of PCr recovery kinetics.

Keywords

MRI; phosphocreatine recovery kinetics; RARE MRI; muscle function; phosphorus MRI

Introduction

Substantial variation in the biochemical properties, vascular supplies, and composition (e.g. fiber type) among human skeletal muscles has been well documented (1–6). These characteristics influence the mitochondrial capacity to varying degrees in different muscles in normal and athletically trained individuals (2, 4). Further changes in these characteristics occur due to normal aging (7) and some disease states, which may result in a heterogeneous pattern of altered metabolic function (4–6).

The rate of resynthesis of phosphocreatine (PCr) in skeletal muscle following exercise is an index of the capacity of the mitochondria to carry out oxidative metabolism (2, 8, 9). Phosphorus-31 magnetic resonance spectroscopy (^{31}P -MRS) with surface coil localization is an accepted method for measuring the post-exercise recovery rate of skeletal muscle PCr (9, 10) and can provide insights into normal physiology and pathophysiology in disease states (2). A limitation of surface coil ^{31}P -MRS is that it does not provide precise spatial information and is limited to superficial muscle regions. It is also uncertain whether the acquired signal is from only a single muscle or from multiple muscles with different characteristics within the sensitive region of the surface coil (2). Current ^{31}P -MRS localization methods require times that are too long for the precise assessment of post-exercise PCr recovery kinetics (2, 11, 12).

Forbes and coworkers measured the rate of PCr recovery simultaneously across several muscles in the human lower leg using a low intensity gated exercise protocol (13, 14) and ^{31}P chemical shift imaging (^{31}P -CSI) (11, 12). Although low intensity gated exercise protocols allow the measurement of PCr recovery without the confounding effects of muscle acidification, the ^{31}P -CSI method is time consuming and results in a long data acquisition period.

A fast imaging method for acquiring dynamic PCr recovery information through a cross-section of a human limb may provide more information about altered metabolic function by allowing the simultaneous assessment of recovery kinetics in all of the muscles in the cross-section. Such a method may reveal patterns of disease progression and information that would help elucidate the mechanisms responsible for metabolic changes that occur as a result of exercise training, aging and disease. It has been demonstrated that the Rapid Acquisition with Relaxation Enhancement (RARE) pulse sequence can be used to produce MR images that reflect the ^{31}P content in resting skeletal muscle with much smaller voxel sizes and shorter scan times than other localized ^{31}P MRS methods at 3T and higher field strengths (15, 16).

In this work we investigated the use of the ^{31}P RARE pulse sequence at 3T for the measurement of post-exercise PCr recovery kinetics in a cross-section of the human forearm. A novel aspect of this study is the demonstration of the feasibility that PCr recovery kinetics can be measured with a temporal resolution and a signal-to-noise ratio (SNR) that is comparable to that of surface coil localized ^{31}P -MRS but with a spatial resolution that is comparable to current ^{31}P -MRS localization methods that are used in resting muscle studies (2, 11, 12).

Materials and Methods

Study Subject

One healthy 56-year-old man was recruited for this study. The subject was recreationally active but was not involved in any training programs to specifically strengthen the forearm and did not use any medications. The subject provided written informed consent approved

by the local institutional review board. Data were acquired on a 3T whole body clinical MRI system (General Electric, Waukesha, WI) equipped with broadband transmit and receive channels. Phosphocreatine RARE MR images and ^{31}P MR spectra were acquired in two separate sessions 7 days apart following an identical exercise protocol.

Exercise Protocol

The same exercise protocol was used for ^{31}P MRS and PCr RARE MRI measurements. The subject lay prone on the scanning table with his right forearm extended above his head. One ^{31}P spectrum or one PCr RARE image was acquired with the forearm muscles at rest for baseline information. The exercise protocol consisted of repeatedly squeezing a firm rubber block between the thumb and index finger. Audio cues for the contraction and rest periods were provided by a computer-based metronome. The duration of the contractions and rest periods were 1 second each. The subject was signaled to begin exercise and continued to exercise until exhaustion was experienced. The subject reported exhaustion at approximately 90 seconds after beginning exercise for both the ^{31}P spectroscopy and imaging studies. Forty-one images or spectra were acquired at 6-second intervals beginning immediately at the cessation of exercise. The total post-exercise measurement time was 240 Seconds. Healthy muscle with resting levels of PCr will appear bright on a PCr image. As the concentration of PCr is reduced during exercise the signal intensity of muscle tissue appears darker until it is at the level of the background noise during sustained exhaustive exercise. Squeezing the rubber block with only the thumb and index finger results in depletion of PCr in only a subset of the forearm muscles, mainly the flexor muscles near the location of the surface coil used for the ^{31}P MRS portion of this study (volar surface of the forearm). Muscles not recruited in the exercise protocol, will appear consistently bright throughout the recovery period and provide a visual reference during times when the regions of muscle that are exercised intensively have signal intensities near the noise level.

MR Spectroscopy

A 7.5-cm circular ^{31}P transmit/receive surface coil was placed on the volar surface of the mid forearm in close proximity to the flexor digitorum as shown in Figure 1b. The center of the coil was 5 cm distal to the elbow joint. Spectra were acquired using a pulse-and-acquire free induction decay (FID) sequence. The MRS acquisition parameters were: sweep width, 2048 Hz; number of complex points, 1024; TR, 3 S; signal averages, 2; time per acquisition, 6 S. The acquisition range was limited to 2.5 cm in the axial direction by a slice selection gradient.

Mapping the region of sensitivity of the ^{31}P surface coil—To determine the region of sensitivity of the ^{31}P surface coil a map of the RF (B1) field was generated, as previously described (17, 18), by placing one of the flat end surfaces of a 16 cm diameter $\times$ 25 cm long cylindrical phantom containing a solution of 50 mM inorganic phosphate (Pi) onto the 7.5 cm circular ^{31}P surface coil. The spatial resolution of the RF field map was chosen to match that of the PCr RARE images.

MR Imaging

A double-tuned ($^{31}\text{P}/^1\text{H}$) low-pass quadrature birdcage RF coil with a diameter of 12 cm and a length of 12 cm was used for all image acquisitions for this study (17). All imaging was performed in an axial plane located 5 cm distal to the elbow joint.

Measurement of RF excitation pulse width—The bandwidth of the 15 ms RF excitation pulse (19) was measured by acquiring a series of images of a 500 ml bottle containing an 85% solution of phosphoric acid (Fisher Scientific A242–500) placed within

the double-tuned birdcage coil. The scanner's transmit/receive frequency was incrementally stepped in 10 Hz increments from 300 Hz below to 300 Hz above the sample's center frequency and an image was acquired at each step resulting in 61 images. The following scan parameters were prescribed to acquire an axial view of the sample: slice thickness = 25 mm, field-of-view (FOV) = 30 cm, acquisition matrix = 32×32 , receiver bandwidth = 32.25 KHz, TR = 2 S and total scan time = 2 S. After the images were reformatted to 256×256 pixels for display on the scanner console the average signal intensity of an 8×8 pixel region of interest (ROI) was measured at the center of the phantom in each of the images.

Mapping of the static field—Static field (B_0) mapping in the axial plane of the forearm was performed as previously described (20) at the location where the ^{31}P RARE imaging was performed.

Proton imaging—Prior to the ^{31}P RARE imaging, a ^1H T2-weighted spin echo scan was performed for anatomical reference: section thickness, 2.7 mm, axial plane, number of sections, 9; TR, 1.5 S; TE, 40 ms; receiver bandwidth, 16.0 KHz; FOV, 15 cm^2 ; matrix, 256^2 . The number of sections and their thickness were selected to have the same axial coverage as the thicker ^{31}P MRS and MRI acquisitions.

PCr imaging—A modified 2D fast spin echo (FSE) pulse sequence which allowed the acquisition of imaging data through the scanner's broadband transmit/receive hardware was used (16). The acquisition of images based on the PCr resonance was accomplished using the spectrally selective excitation pulse centered on the PCr peak with slice selection defined by the refocusing gradient pulses. Forty-one single-shot acquisitions were performed in the axial plane at 6-second intervals beginning at the end of exercise. The imaging parameters were: echo train length, 20; section thickness, 25 mm; effective TE, 27 ms; FOV, 30 cm; matrix, 20×20 ; voxel size, $1.5 \times 1.5 \times 2.5 \text{ cm}$; receiver bandwidth, 1 kHz; and no signal averaging. The adenosine triphosphate (ATP) resonances were suppressed using the method proposed by Chao, et al (16). J-couplings among the three resonances of the ATP molecule result in phase and amplitude modulations of the ATP signals following excitation. When the ^{31}P signal is acquired by a refocusing echo train following the excitation pulse, the individual ATP signals will be arbitrarily in and out of phase by varying degrees at each echo and contribute to the image signal. By setting the spacing between echoes to 26 ms the ATP signals cancel at each echo and the contribution from ATP is eliminated (16).

Data Analysis

Spectroscopy—Phosphorus-31 spectral data were processed using IDL software (Version 6.0. Research Systems, Inc. Boulder, CO). Each FID was processed with 3–5 Hz exponential line broadening without zero filling. Spectra were manually phased using zero and first-order phase corrections. The areas of the PCr peaks were calculated and the results for all post-exercise data time points were normalized to the pre-exercise value. The pH at the end of the exercise portion of the ^{31}P -MRS study was calculated from the chemical shift between the Pi and PCr spectral peaks (2, 8, 9).

Imaging—The voxels (target voxels) from the PCr images, generated using the birdcage coil, were matched to the same anatomic region that contributed to the signal received during surface coil ^{31}P -MRS. These target voxels were identified by comparing the PCr images to the surface coil B_1 map and a ^1H anatomical image (Figure 1c). For each of the 41 post-exercise PCr images, the signal intensity of the eight target voxels were averaged and then normalized using the pre-exercise signal intensity.

Calculation of recovery time constants: All PCr recovery data were normalized to the average pre-exercise value and fitted to a monoexponential recovery function.

The Pearson correlation coefficient was calculated for the ^{31}P MRS (FID) data and the PCr RARE recovery data.

SNR Measurements: The SNR of the MRS study was calculated from the integrated area of the PCr peak and a region containing only noise in a resting muscle spectrum. The SNR of the PCr RARE MRI study was calculated from the average signal intensity of the eight target voxels and the average signal intensity of the background voxels in a resting PCr image.

Results

The RF field map of the ^{31}P surface coil is shown in Figure 1a. Only 10 voxels in 1a have B1 values that are above the noise level (6 bright voxels on the bottom row and 4 darker voxels on the top row). This pattern approximates the familiar sensitivity pattern that is typical of circular surface coils. The gray-scale on the right side of the figure relates variations in B1 relative to the normalized mean value of all of the pixels that contained signal. The goal of this work was to demonstrate that modeling the PCr recovery based on the signal in the voxels in the post-exercise PCr RARE images that correspond to the region of sensitivity of the surface coil used for the ^{31}P MR spectroscopy measurements would provide the same post-exercise PCr recovery time constant value as the area under the PCr peaks in the post-exercise ^{31}P spectra. The region of the forearm that contributed to the ^{31}P MRS signal is shown by overlaying the surface coil RF field map onto a ^1H anatomical image (Figure 1b). Eight of the ten voxels identified by the RF field map contain muscle tissue. In Figure 1c the RARE PCr image that was acquired with the subject's forearm at rest is shown superimposed onto the same ^1H anatomical image as Figure 1b with white lines to identify the 8 voxels (target voxels) that correspond to the region of sensitivity of the ^{31}P surface coil used during the ^{31}P MRS measurements.

The real component of ^{31}P spectra acquired while the forearm muscles were resting (Pre-Exercise), at the beginning of the recovery period (End-Exercise) and at the end of the recovery period (End-Recovery) are plotted in Figure 2. The PCr signal at the End-Exercise time point (Figure 2b) is substantially diminished and returns to nearly the Pre-Exercise level at the end of the measured recovery period (Figure 2c). The End-Exercise pH was 6.53.

A plot of the experimentally derived RF excitation pulse bandwidth is shown in Figure 3. The full width at half maximum (FWHM) was 240 Hz and the width at the base of the skirt was 380 Hz.

An axial plane B0 field map of the subject's forearm at the location where the ^{31}P information was acquired is shown in Figure 4a along with a histogram of the B0 map in Figure 4b. Since PCr recovery only involves muscle tissues only the width of the "Muscle" chemical shift peak in the histogram need be considered for assessing the B0 field homogeneity. The histogram indicates a total variation of approximately 19 Hz at the base of the peak that represents the muscle tissue.

Figure 5 shows a subset of the PCr images obtained during the 4-minute recovery measurement period. The Extensor Carpi and Brachioradialis muscles (upper right forearm in the images) were not recruited during the two-finger exercise protocol and provide a bright visual anatomical reference during the early recovery period while the signal intensities of the exercised muscles are near the background noise level. The signal intensity

from the 8 target voxels in the first image ($t = 0$ Seconds) demonstrates substantial PCr depletion in the target voxel region by the exercise protocol. The signal can be seen gradually recovering to near pre-exercise intensity in the exercised muscle regions at the end of the 4-minute measurement period ($T = 240$ Seconds).

The SNR of the resting MRS spectrum was 8.89 and the SNR of the resting RARE image target voxels was 8.05.

The RARE and ^{31}P -MRS PCr recovery time constants were 91.0 and 91.1 seconds as determined by fitting a monoexponential function to the PCr recovery data (Figure 6). The Pearson correlation coefficient for the ^{31}P RARE data and the ^{31}P FID MRS data is 0.91 ($p < 0.0001$).

Discussion

We have demonstrated the feasibility of acquiring dynamic PCr recovery images of a human forearm with a temporal resolution of 6 S and a voxel volume of 5.6 cm^3 using a RARE pulse sequence. This spatial resolution is comparable to that of ^{31}P chemical shift imaging studies that typically takes nearly an hour to perform (11, 12). We have also shown here that the resulting recovery kinetics measurements in a defined region of the PCr RARE images are similar to those measured with surface coil MRS. Phosphocreatine recovery kinetics studies could be performed in groups of voxels in other regions, in single voxels within specific muscles or in multiple muscle regions following a single exercise session. The SNR of the dynamic PCr recovery images is nearly equal to that of the PCr peak area in unlocalized ^{31}P spectra acquired with the same temporal resolution. The measured spectral width of the excitation pulse is sufficiently narrow at the measured range of B_0 field values to avoid exciting the inorganic phosphate (Pi) peak, which resonates at approximately 260 Hz from the PCr peak at 3T.

Surface coil localization is the accepted method for dynamic PCr recovery studies (2, 8–11). There are three important limitations associated with using surface coils as a localization method for MRS studies: 1) there is a spatially dependent variation in signal throughout the sensitive region due to the non-uniform flip angle distribution (2, 21); 2) only one region can be sampled per exercise study; 3) the ability to acquire information from deep-lying regions is limited.

Spatially localized PCr recovery kinetics data is important because different muscle regions have different oxidative, circulatory, and motor properties (2, 3, 5). The oxidative capacity of individual muscles varies with fiber type, aging, disease and physical activity (2). In normal muscle, perfusion patterns vary between muscles and are heterogeneous within individual muscles (3). The structure of human skeletal muscle is complex and its composition is also heterogeneous both between muscles and within the same muscle (2). This distribution of fiber types and blood flow in human muscle tissue results in a heterogeneity of myocellular chemistry (2). Various disease states further impose alterations in the spatial distribution of the fiber composition and blood flow in muscles (2, 5). These differences may be important considerations for interpreting the results of experiments involving myocellular energy metabolism.

While the pH at the end of the exercise portion of the protocol was similar to that of other post-exercise PCr recovery studies (2, 8, 22) it was substantially lower than that of normal resting muscle, indicating lactate accumulation. This may have had an effect on the monoexponential behavior of the recovery. This has been acknowledged in previous ^{31}P -MRS surface coil PCr recovery studies (2, 8, 22). With gated low-intensity exercise protocols (13, 14) pH is unchanged and muscle acidification does not occur; however,

substantially longer acquisition times are required to simultaneously measure PCr recovery in multiple muscles. A method called Changing Rate Utilization Resource (CRUR) has been introduced for modeling biological systems where the rate of recovery of biological markers changes over the duration of the recovery period (23). This method may be useful in future studies to model the rate of PCr recovery following exhaustive exercise where muscle acidification causes variations in the recovery rate. The method was not used for this study because it introduces additional parameters to model the recovery curve that are not in widespread use and may introduce confusion in interpreting the results at this time.

A limitation of this study is the lack of quantitative measures and controls associated with the exercise protocol. An MRI compatible exercise ergometer with adjustable resistance to the pressure applied by the subject as well as a measure of applied force will improve the intersubject repeatability of the protocol, improving the probability that the subjects exercise in an identical manner for the MRS and MRI data acquisitions. This would also facilitate a larger study involving more subjects to study the effects of disease on muscle function and the response to therapies.

Use of localized PCr recovery kinetics may be valuable for both biological research and patient care. Studies evaluating how muscle fatigue may relate to patient falls or response to specific exercise regimens will likely require the simultaneous study of muscles with different motor functions. A localized imaging assessment of the metabolic impact of peripheral vascular disease through a section of a limb may provide complementary information to standard arteriograms to guide surgical and non-surgical vascular interventions and would also provide a unique tool for visually assessing the response to such interventions. Skeletal muscle PCr recovery has been used as an outcome measure for clinical trials of subjects with heart failure (6). Studying multiple muscles may determine whether muscles with a specific predominant muscle fiber type are the best surrogates for heart failure.

Pre-clinical abnormalities have been detected in resting diabetic foot muscles using the ^{31}P RARE technique owing to improved spatial resolution compared to other localized MRS methods (24). Exercise studies may reveal abnormalities in skeletal muscle oxidative capacity that are not detectable under resting conditions. The combination of post-exercise PCr recovery measurements and the spatial resolution that is achievable with gradient localized RARE imaging of the cross-section of a limb may result in further improvement in the sensitivity of detecting abnormalities.

In conclusion, this work demonstrates the feasibility of an imaging method for measuring PCr recovery kinetics in well-proscribed muscle regions that cannot be accomplished using current standard MRS methods. To the best of our knowledge, this is the first report of an imaging method for measuring PCr recovery rates in muscle with a temporal resolution that is similar to that of typical ^{31}P MRS methods for measuring PCr recovery. In this study the SNR and the post-exercise PCr recovery kinetics obtained from RARE images are comparable to those of ^{31}P spectra acquired with the same temporal resolution. A method for non-invasively measuring the post-exercise PCr recovery kinetics simultaneously over different areas of a cross section of a human limb may provide insights into the mechanisms of disease, response to therapy and normal physiology.

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Figure 1.

The image in a. is a ^{31}P B1 map of the surface coil that was used for the unlocalized MRS PCr recovery study. In b. the B1 map is shown superimposed onto a ^1H image of the subject's arm that was acquired at the same level as the ^{31}P RARE images. The position of the surface coil during the in vivo PCr recovery and phantom B1 map acquisitions was used to align the B1 map with the subject's anatomy to determine which portion of the sensitive region of the surface coil contributed to in vivo signal reception (pixels blocked out with dark lines). A pre-exercise ^{31}P RARE image is similarly overlaid on the ^1H image and the corresponding target voxels that were combined to measure the relative PCr signal during recovery are outlined with white lines.

Figure 2.

Phosphorus-31 spectra acquired before the start of exercise (a), at the cessation of exercise (b) and at the end of the measured recovery period (c). All post-exercise spectral amplitudes are shown normalized to the pre-exercise PCr peak amplitude.

Figure 3.

The bandwidth profile of the 15 ms chemical-shift selective RF excitation pulse. The bandwidth of the pulse is narrow enough to avoid exciting the spins of the Pi resonance while being wide enough to excite all of the spins at the PCr resonance based on the forearm B0 map information.

Figure 4.

A B0 map of the subject's forearm acquired immediately before the exercise protocol began (a). A histogram of the static field across the forearm in units of degrees (b). The large peak in the center of the histogram represents water tissues and the small peak that extends from approximately -10.0 to -20.0 Hz represents the fat/lipid tissues. The imaging parameters were not selected to account for the fat/water chemical shift.

Figure 5.
A representative subset of the ^{31}P RARE images obtained during the 4-minute post-exercise recovery period demonstrating the recovery of the PCr concentration in the region contained by the 8 target voxels.

Figure 6. The PCr recovery data for both the ^{31}P spectroscopic and RARE PCr image acquisitions are plotted together with the monoexponential fit results. The correlation between the ^{31}P -MRS and PCr RARE recovery data was significant ($p < 0.0001$).