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3D ^{23}Na MRI of human skeletal muscle at 7 Tesla: initial experience

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Abstract

Objective—To evaluate healthy skeletal muscle pre- and post-exercise via 7 T ^{23}Na MRI and muscle proton T_2 mapping, and to evaluate diabetic muscle pre- and post-exercise via 7 T ^{23}Na MRI.

Methods—The calves of seven healthy subjects underwent imaging pre- and post-exercise via 7 T ^{23}Na MRI (3D fast low angle shot, TR/TE=80 ms/0.160 ms, 4 mm × 4 mm × 4 mm) and 1 week later by ^{1}H MRI (multiple spin-echo sequence, TR/TE=3,000 ms/15–90 ms). Four type 2 diabetics also participated in the ^{23}Na MRI protocol. Pre- and post-exercise sodium signal intensity (SI) and proton T_2 relaxation values were measured/calculated for soleus (S), gastrocnemius (G), and a control, tibialis anterior (TA). Two-tailed *t* tests were performed.

Results—In S/G in healthy subjects post-exercise, sodium SI increased 8–13% ($p<0.03$), then decreased ($t_{1/2}$=22 min), and ^{1}H T_2 values increased 12–17% ($p<0.03$), then decreased ($t_{1/2}$=12–15 min). In TA, no significant changes in sodium SI or ^{1}H T_2 values were seen (−2.4 to 1%, $p>0.17$). In S/G in diabetics, sodium SI increased 10–11% ($p<0.04$), then decreased ($t_{1/2}$=27–37 min) without significant change in the TA SI (−3.6%, $p= 0.066$).

Conclusion—It is feasible to evaluate skeletal muscle via 3D ^{23}Na MRI at 7 T. Post-exercise muscle ^{1}H T_2 values return to baseline more rapidly than sodium SI. Diabetics may demonstrate delayed muscle sodium SI recovery compared with healthy subjects.

Keywords

Ultra high field MRI; Muscle; Sodium; T_2 mapping; Diabetes

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Introduction

It has been well documented that skeletal muscle proton T_2 relaxation values increase following exercise, which leads to increased muscle signal intensity on T_2-weighted ^{1}H MR images [1–4]. This results predominantly from the intra-cellular accumulation of metabolites (lactate, phosphate) and osmotic shifts of water from the extracellular to the intracellular space [3, 5–7]. T_2 maps of muscle can provide information on the spatial pattern of muscle activation in both normal and abnormal states [8, 9].

^{23}Na MRI also has the potential to provide insight into muscle physiology. Within the intracellular space, skeletal muscle contains a low concentration of sodium (10–30 mM/L) and a high concentration of potassium (140 mM/L) relative to the concentrations in the extracellular space (sodium 145 mM/L, potassium 4 mM/L) [10]. This concentration gradient across the cell membrane is maintained by the Na^+–K^+ ATPase, which pumps out 3 Na^+ ions in exchange for 2 K^+ ions. When an action potential (leading to muscle contraction) is generated, there is a rapid, passive influx of sodium ions and efflux of potassium ions via other types of channels. During intense contractile activity, there is a persistent influx of sodium ions and efflux of potassium ions, which degrades the transmembrane Na^+ and K^+ gradients, leading to loss of membrane excitability and muscle contractility [10, 11]. Such loss of membrane excitability is believed to represent one of the main mechanisms of muscle fatigue [12].

Previous studies at 1.5 T have demonstrated the feasibility of observing increased skeletal muscle sodium signal intensity in healthy subjects after exercise [13, 14], in subjects with myotonic dystrophy [13] and in subjects with paramyotonia congenita [15, 16]. As numerous disease states, such as diabetes, starvation and hypothyroidism, have been documented to decrease Na^+–K^+ ATPase activity in skeletal muscle [10], ^{23}Na MRI has the potential to play a role in imaging of these disorders as well. However, the detection of sodium signal at standard clinical field strength (1.5–3 T) can be technically challenging secondary to: (1) the low gyromagnetic ratio of sodium (16.8 MHz at 1.5 T), (2) the low tissue concentration of sodium compared with hydrogen (ca. 22,000 times less signal), and (3) the rapid biexponential T_2 decay of sodium in tissue (0.5–8 ms and 15–30 ms).

Because signal-to-noise ratio (SNR) scales roughly with the magnitude of B_0, ultra high field (UHF) MRI (7–9.4 T) has the potential to provide improved imaging of sodium compared with standard clinical field strength. The goals of this study were: (1) to determine the feasibility of performing ^{23}Na MRI of skeletal muscle at 7 T and assess how skeletal muscle sodium signal intensity changes before and after exercise over several time points; (2) to compare these results with corresponding post-exercise changes in skeletal muscle proton T_2 relaxation values; and (3) to assess skeletal muscle sodium signal intensity before and after exercise in a small set of subjects with impaired exercise capacity (type 2 diabetics).

Materials and methods

Phantom studies

To evaluate the relationship between sodium signal intensity and NaCl concentration, five phantoms composed of varying concentrations of NaCl (100, 150, 200, 250 and 300 mM/L) suspended in 4% agarose underwent imaging via ^{23}Na MRI at 7 T. To evaluate the variability in signal measurements made via ^{23}Na MRI, the phantoms were repeatedly scanned every 7 min from 0 through 35 min. To simulate the imaging protocol for human subjects (see below), after the initial image at 0 min, the phantoms were removed from the coil, repositioned and then imaged serially from 7 through 35 min. These phantoms were

also included with every subject (taped to the anterior aspect of the leg) when they were imaged via ^{23}Na MRI as a quality control measure.

B_1 field homogeneity was evaluated by using the double angle method [17] to image a phantom of 15 cm in diameter composed of 300 mM/L NaCl suspended in 4% agarose.

Healthy human subjects

This study had institutional review board approval and all subjects provided written informed consent. We recruited seven healthy subjects (mean age = 29±3.6 years, 4 males, 3 females, no concurrent medical issues).

Exercise protocol

After an initial baseline image at rest, the subject got down off the MR couch, then hopped on one leg (the leg of their choice) until they reached fatigue. Mean exercise time was approximately 2±0.6 min. Subjects were then re-imaged serially every 7 min until a final time point of 35 min was reached.

^{23}Na MRI

Imaging was performed on a 7 T whole body MRI unit (Siemens, Erlangen, Germany) using a quadrature ^{23}Na knee coil (Rapid MR International, Columbus, OH, USA). We implemented a 3D-GRE sequence with a radial k-space acquisition (TR/TE=80 ms/0.160 ms, bandwidth (BW)= 130 Hz/pixel, signal average=10, number of projections= 512, 64 readout points, spatial resolution = 4 mm × 4 mm × 4 mm, acquisition time=6 min 50 s) using the manufacturer's provided pulse sequence development environment (IDEA).

The *x, y* and z components of the readout gradient were computed by using the equations

$$G_x = G\sin\theta\cos\varphi G_y = G\sin\theta\sin\varphi G_z = G\cos\theta$$

where < represents the polar angle ($0 < \theta < \pi$) and φ represents the azimuthal angle ($0 < \varphi < 2\pi$) in *k*-space; *k*-space was filled from the centre to the periphery of a sphere, following cones from north to south of the sphere [16, 18]. A non-selective radiofrequency pulse with a duration of 200 μs was used and the signal was sampled during ramp-up of the readout gradient [19]. The resulting effective TE was $TE = \tau RF/2 + \tau Delay = 160$ μs.

^{1}H MRI

Immediately following each ^{23}Na MRI, subjects were imaged by ^{1}H MRI at 7 T to delineate muscle anatomy. We utilised a ^{1}H quadrature knee coil (Rapid MR International, Columbus, OH, USA) and performed a gradient echo sequence (3D fast low angle shot (FLASH), TR/TE= 20/4.5 ms; flip angle=10°; bandwidth =130 Hz/pixel; one signal acquired; 50 axial images with resolution 0.195 mm × 0.195 mm, 1-mm slice thickness).

To assess changes in skeletal muscle proton T_2 relaxation values after exercise, healthy subjects returned 1 week later (to ensure that subjects were fully rested) and underwent H MRI at 7 T before and after performing the same identical exercise protocol described above (i.e. the same number of hops). A multiple spin-echo imaging sequence (TR=3,000 ms, TE=15, 30, 45, 60, 75, 90 ms, 0.585 mm × 0.585 mm, 1-mm slice thickness) was performed every 7 min until a final time point of 35 min to replicate the timing of the sodium MRI.

^{23}Na and ^{1}H MR image analysis

The scanner workstation software was used to draw 1-cm-diameter regions of interest (ROI) on proton images in flexor muscles used in the exercise, soleus (S) and medial gastrocnemius (G), and these were copied to the sodium images. An ROI was also drawn around a dorsiflexor muscle not used in the exercise, the tibialis anterior (TA), which served as an internal control.

For ^{23}Na MRI, pre- and post-exercise sodium signal intensity (SI) was measured, and percentage change versus baseline was calculated as: [(post-exercise SI) – (resting SI)]/(resting SI).

For ^{1}H MRI, pre- and post-exercise muscle T_2 values were calculated by fitting the six echoes to a monoexponential decay by using the equation $M = M_0 \times e^{-t/T2}$. Half-lives ($t_{1/2}$) for plots were estimated by obtaining a best-fit curve (Microsoft Excel, Redmond, WA, USA).

Statistical analysis

All statistical analyses were performed with SPSS (Chicago, Illinois). Group mean values were calculated for each muscle of interest. The coefficient of variation was calculated as the standard deviation divided by the mean signal intensity. Wilcoxon signed rank tests were utilized to determine statistical significance of measurement differences before and after exercise. Two-tailed *t* tests were performed to determine statistical significance of differences in half-lives.

Diabetic subjects

Finally, to determine if ^{23}Na MRI might be able to detect alterations in muscle physiology in subjects with disease, we then recruited four subjects with longstanding type 2 diabetes (mean age=44±6.5 years, 2 males, 2 females, mean number of years since diagnosis of type 2 diabetes=7.8±4.3 years) to participate in the ^{23}Na MRI protocol. Similar image and statistical analyses were performed.

Results

Phantom studies

Maps of B_1 field homogeneity demonstrated less than 5% variation in the B_1 field along both horizontal and vertical axes when this phantom was imaged via ^{23}Na MR at 7 T (not shown). Figure 1 is a plot of sodium signal intensity vs. phantom NaCl concentration, with background signal intensity plotted as 0 mM/L NaCl. The results of three experiments performed on different days are plotted. The plot demonstrates that there is a linear relationship between the ^{23}Na MR signal and NaCl concentration. When phantoms were serially imaged every 7 min from 0 through 35 min, the coefficient of variation is less than 2% over time for all phantoms. Of note, the phantoms were repositioned in between the 0-min and 7-min images in order to replicate the human imaging protocol.

Muscle ^{23}Na MRI post-exercise in healthy subjects

Representative resting ^{23}Na, immediate post-exercise ^{23}Na, and axial ^{1}H MR images from two subjects are shown in Fig. 2. In the proton image (Fig. 2c), there is radio-frequency coil/field inhomogeneity artefact anteriorly and posteriorly. A subtle increase in signal intensity within plantar flexor muscles used in the exercise (soleus and gastrocnemius) can be seen on the post-exercise images. In healthy subjects, compared with rest, there was a statistically

significant percentage increase in immediate post-exercise sodium signal intensity in S (8±4%, p= 0.028) and G (13±8%, p=0.028), but not in TA (0.5±5%, p=0.92) (Fig. 3).

Over the next 35 min, mean SI in both S and G decreased to near baseline in an exponential fashion (Fig. 3) with a $t_{1/2}$ of approximately 22 min for both S and G. There was no statistically significant change in sodium signal intensity in TA (−2.4±5%, p=0.46) at 35 min.

Muscle proton T_2 relaxation values post-exercise in healthy subjects

Figure 4 demonstrates the change in muscle proton T_2 relaxation values before and after exercise. Mean pre-exercise proton T_2 relaxation values for TA, S and G were 33.9±3.78 ms, 36.8±4.2 ms and 36.7±4.67 ms, respectively. After exercise, there was a statistically significant increase in proton T_2 relaxation values for S (12±3%, p= 0.01) and G (17±8%, p=0.029), but not for TA (1±2%, p= 0.18). Proton T_2 relaxation values in both S and G gradually returned to baseline in a logarithmic fashion with a $t_{1/2}$ of approximately 15 min for S and 12 min for G. When compared with the half-lives for recovery of sodium signal intensity, the difference in half-lives was statistically significant (p=0.049 for S, p=0.012 for G).

Muscle ^{23}Na MRI post-exercise in subjects with diabetes

In subjects with diabetes (Fig. 5), compared with rest, there was also a statistically significant increase in immediate post-exercise sodium signal intensity in S (10±6%, p= 0.034) and G (11±4%, p=0.009), but not in TA (−3.6±4%, p=0.066). Over time, mean SI in both S and G gradually decreased to near baseline with a $t_{1/2}$ of approximately 37 min for S and 27 min for G. SI in TA decreased by approximately 7±5% at 35 min; this difference compared with rest was not statistically significant (p=0.066). When compared with the half-lives for recovery of sodium signal intensity in healthy subjects ($t_{1/2}$ 22 min for both S and G), the difference in half-lives was statistically significant (p= 0.05 for S and G).

Discussion

This study demonstrates the feasibility of performing 3D ^{23}Na MRI of human skeletal muscle at 7 T in vivo. Specifically, the results demonstrate the feasibility of monitoring physiological changes that occur in skeletal muscle after exercise via sodium MRI. In addition, this study provides evidence that changes in skeletal muscle sodium signal intensity following exercise follow a different time course than corresponding changes that occur in skeletal muscle proton T_2 relaxation values. Finally, the results suggest that sodium MRI may be able to detect alterations in muscle physiology in subjects with diabetes.

Sodium imaging in this study was facilitated by imaging at 7 T (SNR scales roughly with B_0; for full discussion, see Collins et al. [20]) and by the implementation of a 3D radial acquisition sequence with an ultra-short TE of 0.160 ms.

Sodium has a biexponential T_2 decay with a fast component of 0.5–8 ms and a slow component of 15–30 ms, which account for approximately 60% and 40% of the signal, respectively [14]. The use of an ultra-short TE sequence will therefore decrease T_2* signal loss. This echo time is shorter than those utilized in previous ^{23}Na MR imaging studies. The 3D radial sequence is well suited for short TE imaging since no slice selection pulse is required, thus minimizing the delay between excitation and data acquisition. In addition, the k-space trajectory begins at the origin of k-space, allowing efficient sampling of low frequency, high amplitude data with tolerable streaking artefacts.

The phantom studies demonstrate that there is a linear relationship between sodium signal intensity and NaCl concentration and little variability in measurements for serial images made during the same day. Such demonstration of reproducibility of measurements is important if comparisons are going to be made between scans performed on the same day and if quantitative ^{23}Na MR imaging is to be performed in the future.

The increase in muscle sodium signal intensity after exercise in healthy subjects is in agreement with: (1) results of studies in the physiology literature, in which skeletal muscle sodium content increases (in an intracellular fashion) after muscle stimulation [21–23], and (2) other ^{23}Na MRI studies of skeletal muscle in human subjects in vivo [13, 14]. In the latter studies, 34±7% [13] and 16– 22% [14] increases in sodium signal intensity were observed after exercise. In a study by Weber et al. [15], no significant increase in calf muscle sodium signal intensity was observed in healthy subjects after exercise. However, these subjects performed only 30 calf raises while standing on both legs as opposed to our and previous studies in which up to 200 hops on one leg were performed. The lack of increased muscle sodium signal intensity in Weber et al.'s study may have been due to a less vigorous exercise protocol. However, their goal was to evaluate subjects with paramyotonia congenita, who have persistently depolarised muscle cells; thus the exercise protocol was likely kept to a minimum in order not to induce motor difficulties in the patient population.

The results also demonstrate an apparent approximate 3–7% decrease in sodium signal intensity in the control muscle, tibialis anterior, at the 35-min time point for both healthy subjects and diabetics. Though this difference was not statistically significant (p=0.46 for healthy subjects, p=0.066 for diabetics), the number of subjects in the study is small. The authors can only conjecture that the activation of physiologic mechanisms to maintain sodium homeostasis after exercise (i.e. mechanisms which function to decrease muscle sodium content after it rises) might nonspecifically affect the entire leg. For example, blood perfusion to the leg, which is augmented after exercise and functions in part to remove metabolites that have accumulated, might cause a small decrease in sodium content in the tibialis anterior muscle even though it was not stimulated. This is an avenue of research that is worth pursuing in the future.

The biophysical basis for the increase in sodium signal intensity in muscle after exercise is probably multifactorial. This increase in sodium signal could be due to: (1) an increase in total muscle sodium content and/or (2) alterations in sodium's T2 relaxation values or in the proportions of slow- and fast-T2-relaxing pools of sodium.

With regard to changes in the total muscle sodium content, the sodium signal measured represents the sum of sodium contained in the intracellular (i) and extracellular (e) compartments (Total sodium content = $[Na]_i \times Volume_i + [Na]_e \times Volume_e$), with the extracellular compartment comprising approximately 7–14% of the total skeletal muscle volume [3,24]. Furthermore, the extracellular compartment is composed of the interstitial space and the vascular space. Although the extracellular sodium concentration (ca. 140 mM/L) remains essentially constant in a patient with normal renal function and constant blood perfusion, the volumes of the intracellular and extracellular compartments increase after exercise [3], and the intracellular concentration of sodium increases during muscle cell depolarisation [21–23]. Therefore, the increase in sodium signal intensity following exercise could reflect changes in the quantity of sodium in both compartments.

With regard to alterations in muscle sodium T_2 relaxation values after exercise, it is believed that the rapid-T_2-relaxing pool of sodium corresponds to fast tumbling, free sodium in solution and the slow-T_2-relaxing pool of sodium corresponds to sodium interacting with macromolecules [14]. Therefore, if after exercise, there is an increase in the T_2 relaxation

value of either pool of sodium or an increase in the proportion of slow-T_2-relaxing pool of sodium, there would be less signal loss and greater signal measured for a given echo time. Future work will involve quantifying not only the contributions of the intracellular and extracellular compartments to the sodium signal, but also quantifying the contributions of slow- and fast-T_2-relaxing sodium pools to the sodium signal, and determining how these contributions are altered in various disease states.

The recovery of skeletal muscle proton T_2 values back to baseline ($t_{1/2}$ 12–15 min) was faster than the recovery of skeletal muscle sodium signal intensity back to baseline ($t_{1/2}$ 22 min). The difference in recovery time for these two processes likely stems from the fact that they reflect different physiological phenomena. The increase in muscle proton T_2 relaxation values after exercise is related to the accumulation of intracellular metabolites (lactate, phosphate) and osmotic shifts of water from the extracellular to the intracellular space [3, 5–7]. If phosphate and lactate are cleared relatively rapidly from the cell via enzymatic processes (regeneration of adenosine triphosphate (ATP) via oxidative phosphorylation, reduction in lactate via the Cori cycle), then fluid shifts between the extracellular and intracellular compartments will in turn rapidly reverse, and muscle proton T_2 relaxation values will normalise. However, normalisation of the sodium signal requires clearance of sodium from the intracellular compartment (which depends on Na^+–K^+ pump activity), as well as the ability of the flowing blood to remove extruded sodium ions from the extracellular space. This may simply require more time compared with the time required to clear intracellular muscle metabolites, resulting in slower recovery of the sodium signal intensity to baseline compared with the proton T_2 relaxation values.

Finally, the results of this study suggest that post-exercise skeletal muscle sodium signal intensity in diabetics recovers to baseline more slowly compared with healthy subjects. One possible explanation for this observation may be related to the decreased Na^+–K^+ pump activity as well as the altered tissue microvasculature in diabetics. According to exercise physiology literature, Na^+–K^+ pump activity helps protect muscles against fatigue by maintaining Na^+ and K^+ concentration gradients across the cell membrane, thereby preserving muscle membrane excitability [10, 25]. Diabetics, however, have decreased Na^+–K^+ pump activity and decreased numbers of Na^+–K^+ pumps on the muscle cell membrane, which has been attributed to insulin resistance [10, 26–28]. Decreased Na^+–K^+ pump activity would result in a decreased ability to extrude intracellular sodium ions into the extracellular space and result in persistently elevated muscle sodium content with a slower recovery to baseline. The latter would manifest as increased signal intensity on ^{23}Na MRI and a longer $t_{1/2}$ for recovery to baseline values, as observed in this study. Furthermore, diabetics demonstrate altered tissue microvasculature and poor tissue perfusion; a decreased ability of flowing blood to remove extruded sodium ions from the extracellular space could also result in persistently elevated muscle sodium content and persistently elevated muscle sodium signal intensity. ^{23}Na MRI might eventually be applied to patients with diabetes in order to better evaluate those who are at risk of diabetic muscle infarction—a grave complication of longstanding diabetes—as the calf is one of the most frequent sites of involvement [29, 30].

There are several limitations to this study. First, as a pilot study, the number of subjects was small. Second, although subjects performed the same exercise protocol, it is possible that subjects exercised with different intensities, which could affect the results. Third, there was no gold standard validation of measurements, as muscle biopsy would have been invasive, potentially dangerous and unethical in this patient population. Fourth, at the 130 Hz/pixel bandwidth used in this study, the total readout time is 7.69 ms; therefore, fast sodium T2 decay during this readout time will result in blurring of high frequency components on the images. Finally, based on the plot generated by phantom studies, the calculated total muscle

sodium content in our healthy subjects at rest is approximately 44 mM, or about 50% greater than values reported in previous muscle sodium imaging studies [13, 14]. The greater values obtained in this study may stem from the use of a highly undersampled radial acquisition sequence. In future studies, protocols with less undersampling may have to be implemented in order to accurately perform quantitative ^{23}Na MRI. It should be noted, however, that changes relative to baseline may ultimately represent the more important quantitative imaging biomarker.

In conclusion, this study demonstrates the feasibility of monitoring physiological changes in muscle before and after exercise via 3D ^{23}Na MRI at 7 T. Compared with the changes that occur in muscle proton T_2 relaxation values after exercise, muscle sodium signal intensity requires more time to return to baseline. Finally, the results of this study suggest that ^{23}Na MRI might be able to detect alterations in muscle physiology after exercise in subjects with diabetes. ^{23}Na MRI could potentially be used as a non-invasive method of gaining physiological and metabolic information about skeletal muscle.

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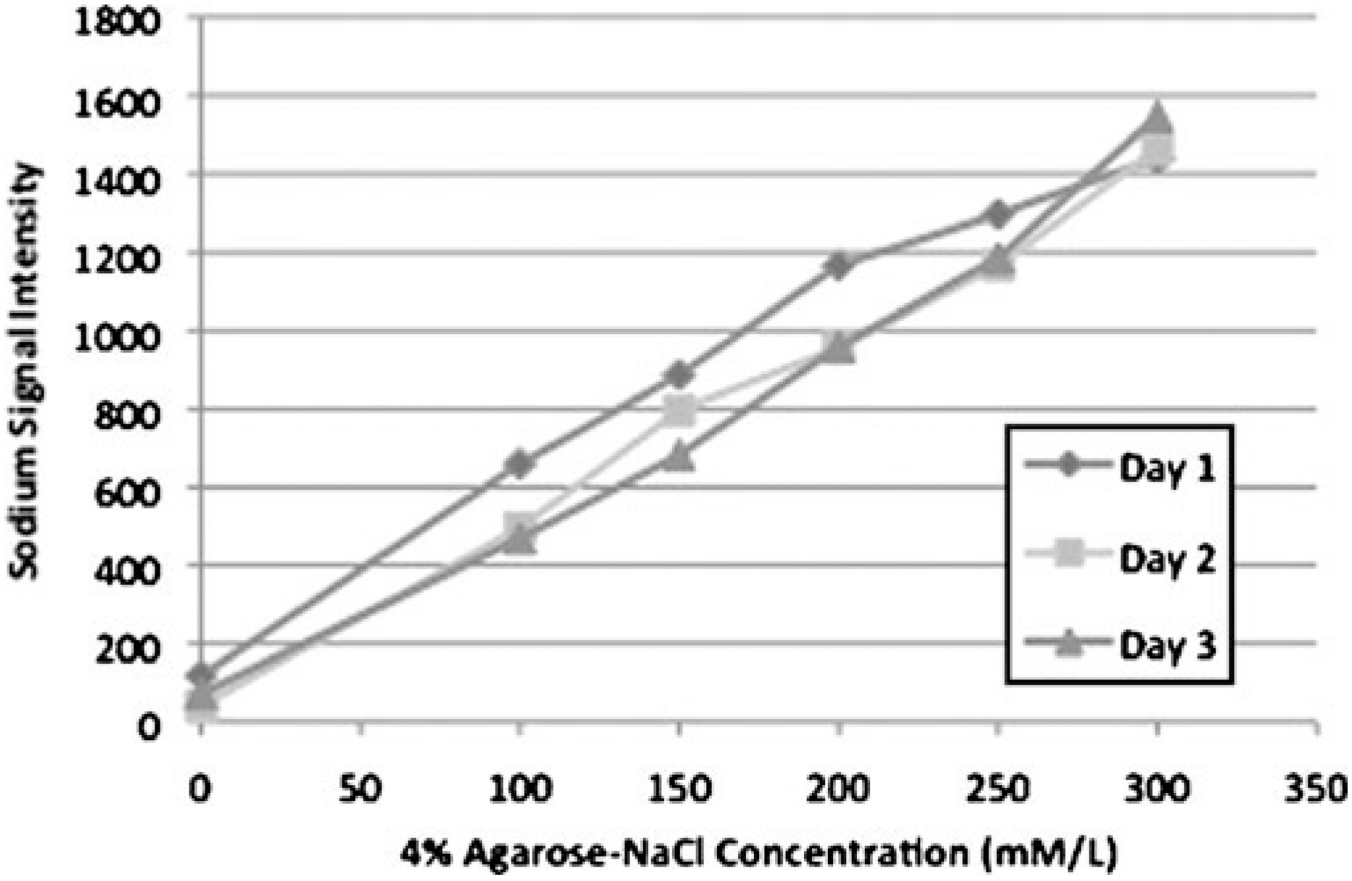

Fig. 1.

Plot of sodium signal intensity vs. phantom NaCl concentration (100–300 mM/L) with background signal intensity plotted as 0 mM/L NaCl. There is a linear relationship between sodium MR signal and NaCl concentration. The results of three experiments performed on different days are plotted

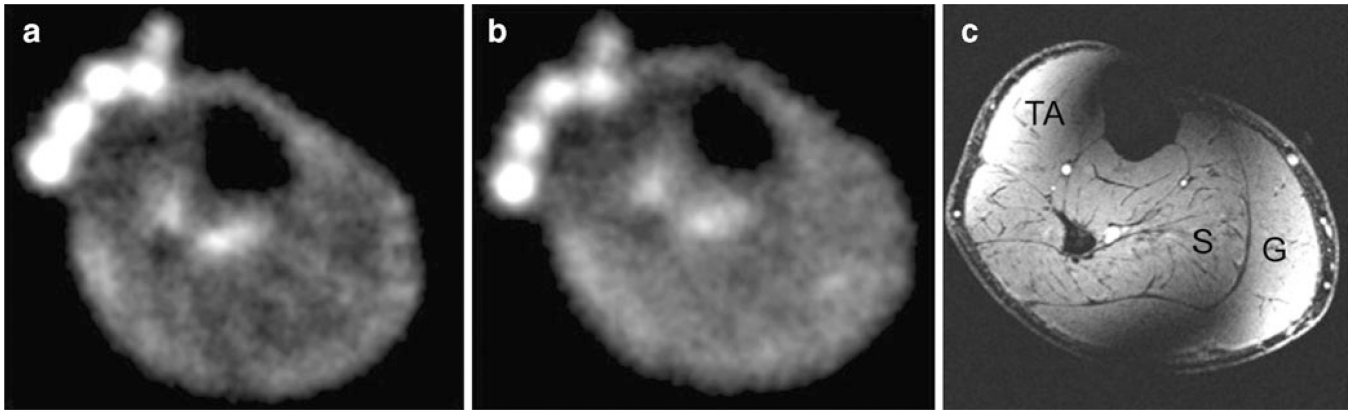

Fig. 2.

a Resting sodium MR image (TR=80 ms, TE=0.160 ms, 4 mm × 4 mm × 4 mm) from the calf of a healthy volunteer. The NaCl phantoms can be seen at the anterior aspect of the leg. **b** Immediate post-exercise sodium MR image from the same volunteer, showing subtle increase in sodium signal intensity within the posterior compartment muscles. **c** Corresponding proton 3D fast low angle shot (FLASH) MR image (TR=20 ms, TE=5 ms, 0.195 mm × 0.195 mm, 1-mm slice thickness) from the same volunteer, which was performed after the sodium MRI to delineate muscle anatomy. *TA* tibialis anterior, *S* soleus, *G* gastrocnemius. Coil inhomogeneity artefact is seen at the anterior and posterior aspects of the leg

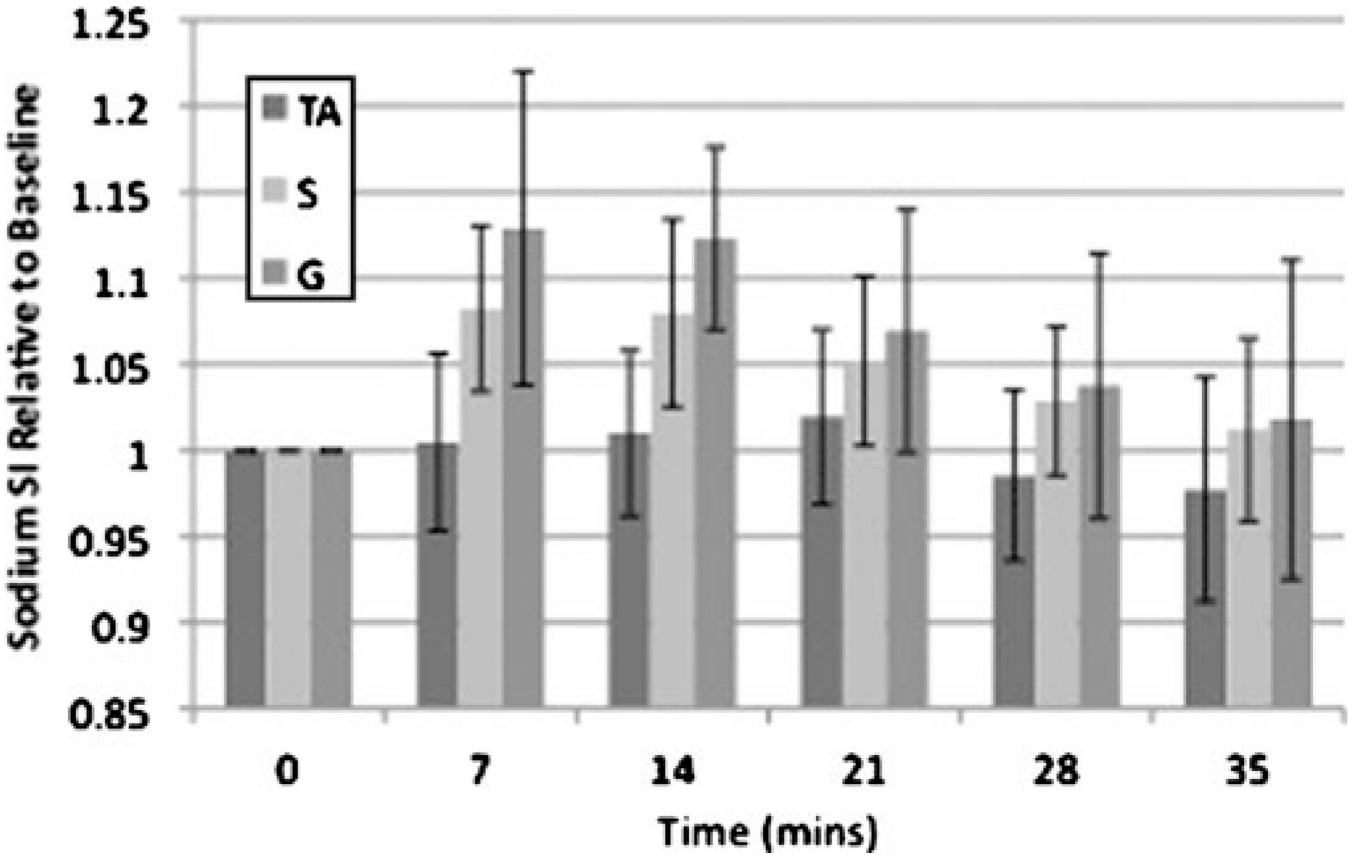

Fig. 3.

Bar graph demonstrating the time course of recovery for sodium signal intensity after exercise in healthy subjects. Immediately after exercise, sodium signal intensity increased in S (8±4%, p=0.028) and G (13±8%, p=0.028), but not in the dorsiflexor control muscle TA (0.55%, p=0.92). Sodium signal intensity then decreased to near baseline in an exponential fashion with a $t_{1/2}$ of approximately 22 min for both S and G

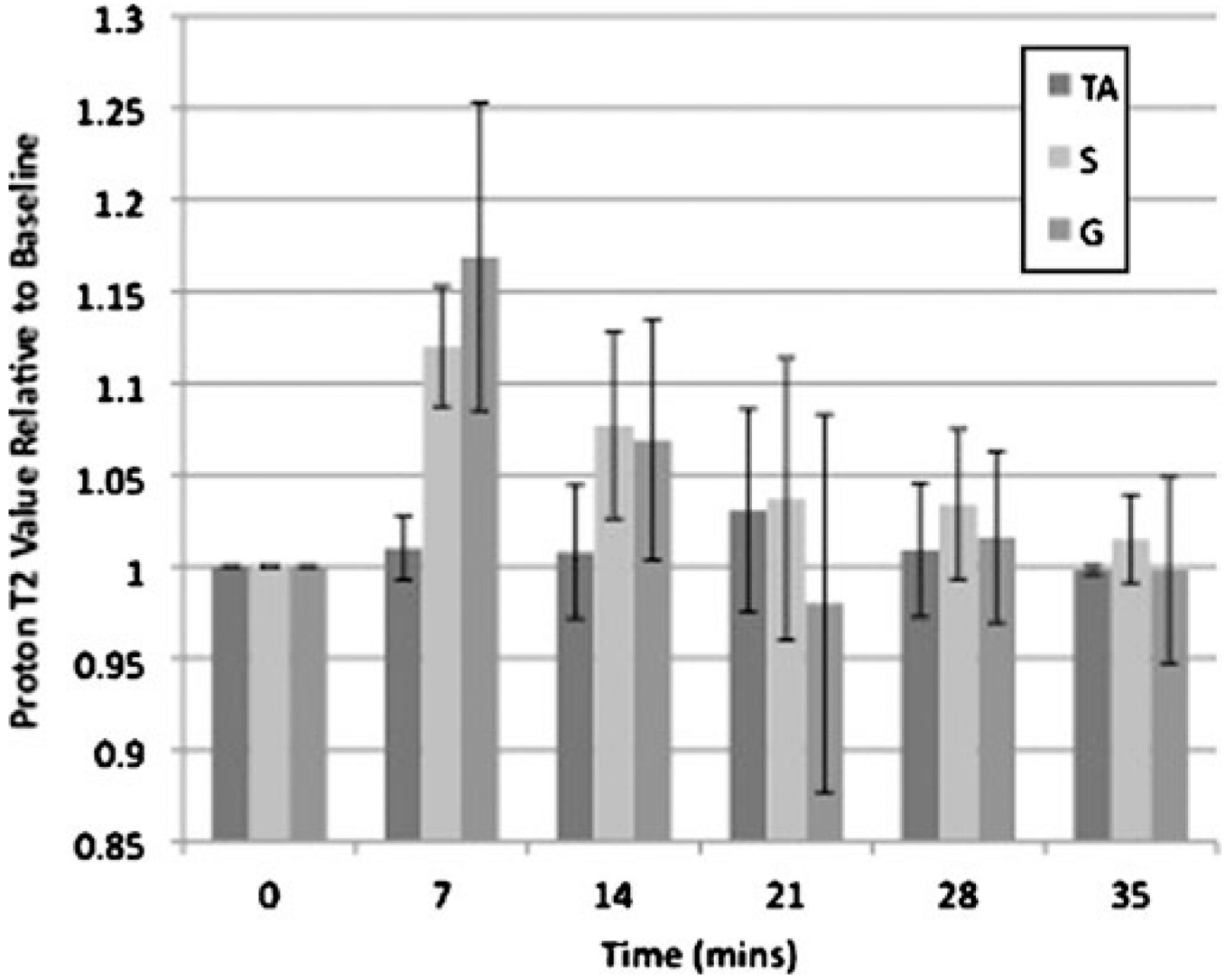

Fig. 4.

Bar graph demonstrating changes in proton T_2 relaxation values before and after exercise. Baseline T_2 relaxation values for tibialis anterior (TA), soleus (S) and gastrocnemius (G) were 33.9± 3.78 ms, 36.8±4.2 ms and 36.7±4.67 ms, respectively. Immediately after exercise, T_2 relaxation values increased in S (12±3%, p=0.01) and G (17±8%, p=0.029), but not in TA (1±2%, p=0.18). T_2 relaxation values in S and G then decreased in a logarithmic fashion with half-lives ($t_{1/2}$) of approximately 15 and 12 min, respectively

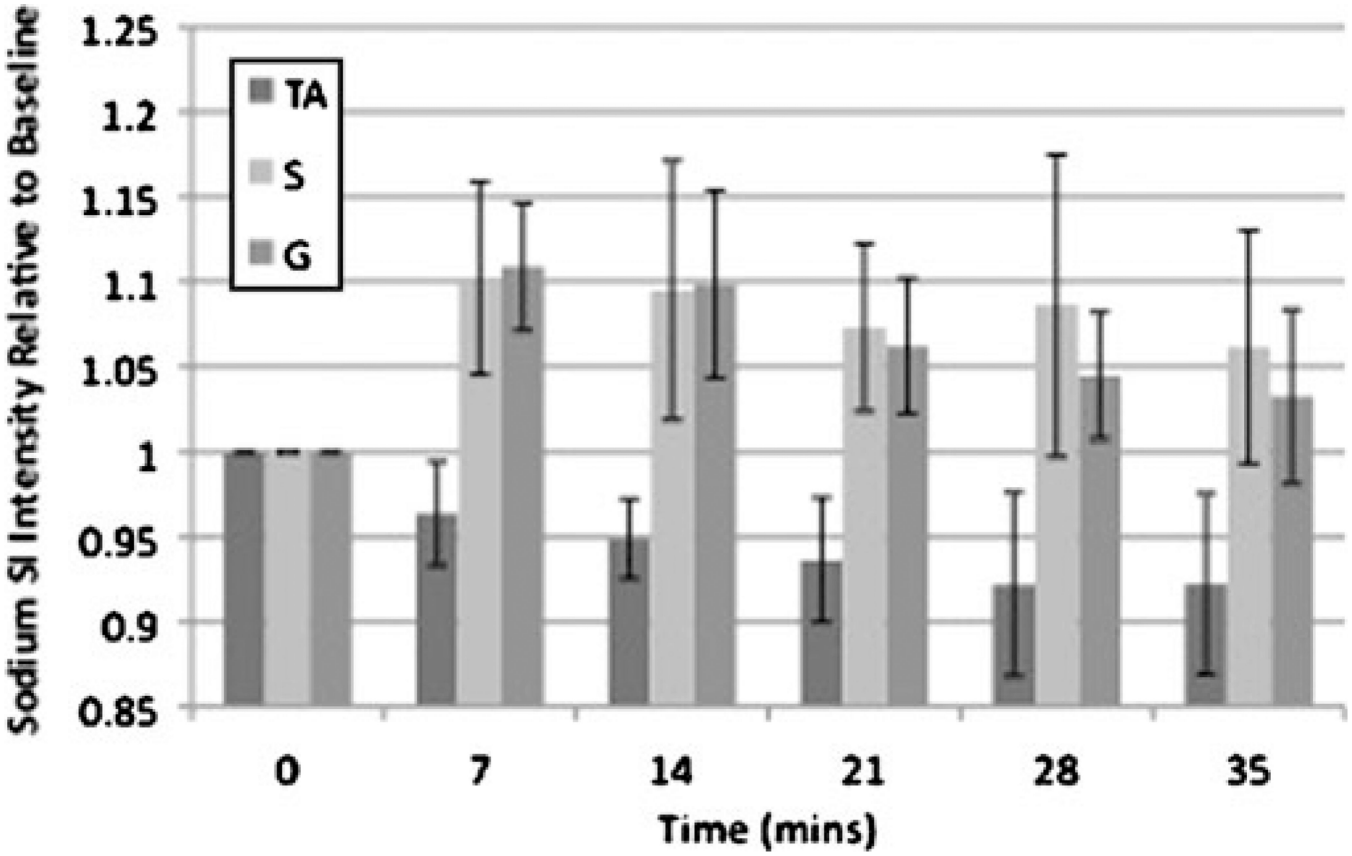

Fig. 5.

Bar graph demonstrating the time course of recovery for sodium signal intensity after exercise in diabetics. Immediately after exercise, sodium signal intensity increased in S (10±6%, p=0.034) and G (11±4%, p=0.009), but not in TA (−3.6±4%, p=0.066). Over time, sodium SI in S and G gradually decreased with half-lives ($t_{1/2}$) of approximately 37 and 27 min, respectively