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$R_{1\rho}$ dispersion and sodium imaging in human calf muscle

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Abstract

Purpose: To evaluate the magnitude of chemical exchange effects and $R_{1\rho}$ dispersion in muscle and their relationship to tissue sodium levels with aging.

Methods: Seven healthy volunteers (aged 24 to 87 years, median age 47) underwent MRI to assess tissue sodium levels and water $T_{1\rho}$ values at different spin-locking frequencies in calf muscles. $T_{1\rho}$ values at each locking field were computed based on a three-parameter mono-exponential model to fit signals obtained at different locking times, and $R_{1\rho}$ ($= 1/T_{1\rho}$) rates were compared at different locking fields. In particular, the dispersion of $R_{1\rho}$ ($R_{1\rho} = R_{1\rho}(0 \text{ Hz}) - R_{1\rho}(500 \text{ Hz})$) was examined as a function of subject age. Muscle sodium content was calculated by comparing signal intensities between tissues and reference standards within the same image. The variations of $R_{1\rho}$ with age and sodium were analyzed by linear regression.

Results: $T_{1\rho}$ values and sodium content both increased with age. $R_{1\rho}$ dispersion also increased with age and showed a strong linear correlation (correlation coefficient $r = 0.98$, $P = 0.000578$) with sodium content.

Conclusion: $R_{1\rho}$ reports on the contribution of labile protons such as hydroxyls which may be associated with macromolecule accumulation in the extracellular matrix (ECM). An increase of sodium signal suggests an enlarged ECM volume fraction and/or an increase in sodium concentration, which occurs during normal aging. The strong correlation between $R_{1\rho}$ and sodium is likely the consequence of increased ECM and density of total charged sites within the matrix from molecules such as collagens and proteoglycans. The results from this study show the potential use of $R_{1\rho}$ dispersion and sodium imaging in the assessment of pathological changes in muscle such as fibrosis.

Keywords

$T_{1\rho}$; $R_{1\rho}$ dispersion; Sodium MRI; Muscle

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1. Introduction

The spin lattice relaxation time in the rotating frame, $T_{1\rho}$, modulates the signal and contrast in MRI sequences employing spin locking pulses, and has shown promise for the detection of biochemical changes in the extracellular matrix (ECM) of certain biological tissues [1–3]. At higher fields (3 T and beyond), $T_{1\rho}$ (and thus also the relaxation rate $R_{1\rho} = 1/T_{1\rho}$) is strongly influenced by chemical exchange between water and labile protons, mainly amides, amines and hydroxyls [4–6] rather than just slow molecular motions. $T_{1\rho}$ imaging involves the application of radiofrequency (RF) locking fields that can partially reverse the influence of such exchange processes so that the values of $T_{1\rho}$ and $R_{1\rho}$ vary with the strength of the RF pulses used. This dispersion of the relaxation rate $R_{1\rho}$ with locking field amplitude may be used to analyze and quantify parameters of the exchange processes of protons, and $R_{1\rho}$ (the difference in rate between low and high locking fields) largely reflects the contribution of chemical exchange to relaxation, which therefore reflects the concentration of protons in tissue that exchange at an appropriate rate [7,8]. Biological tissues with high macromolecular protein content demonstrate a considerable dispersion, especially at higher fields, but fat and water rich tissues typically exhibit negligible $R_{1\rho}$ dispersion. $T_{1\rho}$ imaging has been exploited in studies of several human tissues, including brain, cartilage, breast, liver, and heart, but most studies have used lower magnetic fields and/or have used a single locking field amplitude only, so $T_{1\rho}$ imaging in muscle at 3T or above is relatively rare and we are unaware of any previous study performing $R_{1\rho}$ dispersion at high field in human muscle.

Recently, there has also been a renewed interest in sodium MRI due to the availability of higher magnetic fields, improved hardware and pulse sequences [9–13], which have allowed acquisitions of sodium images with reasonable signal to noise ratio and spatial resolution in practical times. Sodium is the most abundant cation in the human body, and is vital for cellular function and integrity [14,15]. Normally, the intracellular space accounts for $\approx 80\%$ of tissue volume with a sodium concentration of 10–15 mM, separate from an extracellular volume fraction of $\approx 20\%$ with a sodium concentration of 140–150 mM. This relatively stable concentration difference is primarily maintained by the sodium potassium Na^+/K^+ -ATPase pump, which pumps sodium out of cells while pumping potassium into cells. Leaky cell membranes or impaired Na^+/K^+ exchange kinetics potentially change the cytosolic total tissue sodium, making sodium changes potential indicators of a wide range of disease states. Typically, an increase of total tissue sodium concentration indicates a loss of tissue viability associated with an increase of intracellular sodium due to the loss of integrity of the cell, and also an increase of extracellular volume when cells are injured [14,16–20]. Decreases in sodium are often associated with loss of negatively charged moieties such as proteoglycans (PGs) [15,21].

Human skeletal muscles are mostly attached to bones by bundles of collagen fibers (tendons) that allow movement and provide support. Skeletal muscle is composed mainly of multinucleated cells (myofibers), connective tissues, blood vessels and nerves. The skeletal muscle extracellular matrix is composed of collagen, proteoglycans, glycoproteins, matricellular proteins, growth factors, cytokines, and matrix remodeling enzymes, which form a complex, three-dimensional network among the muscle fibers [22–24]. In normal

tissue, collagen and PGs comprise the major structural components of ECM, and PGs bind to collagen in specific locations and are present in different ratios throughout ECM that maintain the structure and organization of the matrix. ECM not only provides structural support for muscle integrity, but also plays an important role in muscle fiber force transmission, maintenance, and repair. Nearly every pathological change and normal aging reported in muscle, is associated to some degree with ECM fibrosis [25]. Fibrosis is a complex process characterized by excessive production of ECM components, which negatively impact muscle plasticity and function, so quantifying matrix changes could help to understand mechanisms involved in the development of fibrosis and be used to evaluate therapeutic targets. To date the methods for assessing ECM composition have mainly relied on invasive immunochemical and biochemical analyses of biopsies, so a reproducible and reliable non-invasive method would facilitate the assessment of changes in ECM.

Both $T_{1\rho}$ and sodium MRI have potential to evaluate the progression of tissue physico-chemical changes in ECM. For example, changes in the negatively charged glycosaminoglycans (GAGs) within PG can affect the signals in both sodium and $T_{1\rho}$ imaging in certain tissues [21]. In this study, we used $T_{1\rho}$ imaging and measured $R_{1\rho}$ dispersion to evaluate changes in skeletal muscle in normal aging. Because aging is accompanied by fibrosis in muscle, these measurements were predicted to reflect biochemical changes in the extracellular matrix. We computed $R_{1\rho}$ as a degree of $R_{1\rho}$ dispersion to assess changes specifically in chemical exchange processes in aging muscle, possibly from the expected accumulation of charged macromolecules in ECM. We found $R_{1\rho}$ decreases with age in muscle for all locking fields, consistent with observations in liver fibrosis [26,27] and with an overall dilution of macromolecular content and increase in extracellular volume and water content. $R_{1\rho}$ dispersion on the other hand was found to be smaller than in cartilage at 3T [28], but robustly measurable and increased with age (as measured by $R_{1\rho}$), suggesting that there are increasing fractions of labile protons and/or increases in their exchange rates. We also acquired and compared sodium images of the same muscles and observed that sodium levels in muscle also increased with aging. Comparing these changes, the strongest correlation was the variation of $R_{1\rho}$ with sodium content, which was statistically significant even after adjusting for age. The increases of sodium signal and $R_{1\rho}$, as well as their correlation, are potentially the consequence of increased specific charged sites within ECM caused by fibrosis. This study suggests a way to non-invasively map the distribution of changes in ECM as a biomarker of disease progression, as well as to evaluate the treatment effects.

2. Methods

This study was approved by the Institutional Review Board (IRB) of Vanderbilt University. Seven healthy volunteers (aged 24 to 87 years, median age 47) participated and were appropriately consented prior to imaging.

$T_{1\rho}$ and sodium images were acquired in one imaging session using a Philips 3T Achieva scanner (Philips Healthcare, Best, the Netherlands). The lower leg of each subject was placed in a quadrature knee coil tuned to sodium (Rapid Biomedical GmbH, Rimpar, Germany) and scanned together with four calibration phantoms (NaCl aqueous solutions of

10 mM, 20 mM, 30 mM, and 40 mM), see Fig. 1. These calibration phantoms served as reference standards for computing relative sodium content in tissue *via* linear regression analysis. Proton $T_{1\rho}$ imaging data were acquired using the scanner body coil without repositioning the subject between scans, assuring an accurate spatial registration between $T_{1\rho}$ and sodium data. Finally, an mDixon scan (for structural information, with the same isocenter as $T_{1\rho}$ and sodium scans) was acquired to guide the drawings of region of interests (ROIs).

2.1 MR imaging

For $T_{1\rho}$ imaging, a B_0/B_1 inhomogeneity self-compensated $T_{1\rho}$ prepulse sequence was used [29] followed by a Turbo Spin Echo (TSE) data acquisition. A single axial slice was scanned with FOV: $192 \times 192 \text{ mm}^2$, pixel size: $1 \times 1 \text{ mm}^2$, slice thickness: 4 mm, TR/TE: 4000 ms/10 ms, TSE factor: 15, NEX: 1. Five spin-locking times (TSL) [2 ms, 22 ms, 42 ms, 62 ms, 82 ms] were combined into a single scan for $T_{1\rho}$ calculations, resulting in a scan time of 4 min 4 s. The $T_{1\rho}$ experiment was repeated at different spin-locking fields (FSL) [0 Hz, 100 Hz, 300 Hz, 500 Hz] to evaluate the dispersion in muscle. After acquisition, $T_{1\rho}$ values at each FSL were calculated on a pixel-wise basis by fitting the signal intensity *vs* TSL to a three-parameter mono-exponential model: $S = S_0 \exp(-TSL/T_{1\rho}) + C$, where S is the acquired MR signal, S_0 is the signal intensity without locking pulse, and C is a constant. $R_{1\rho}$ values were calculated by taking the reciprocal of $T_{1\rho}$, and $R_{1\rho}$ dispersion in muscle was assessed by plotting $R_{1\rho}$ *vs* FSL. In addition, the mDixon scan was acquired at the same position of the $T_{1\rho}$ image, with parameters of FOV: $192 \times 192 \text{ mm}^2$, resolution: $1 \times 1 \text{ mm}^2$, five slices at a thickness of 6 mm. TR/TE: 200 ms/4.6 ms. Four types of image (water, water fat in-phase, water fat out-of-phase, and fat) were generated for each slice.

For sodium data acquisitions, an optimized 3D gradient-echo sequence was used with FOV: $192 \times 192 \times 210 \text{ mm}^3$, voxel size: $3 \times 3 \times 30 \text{ mm}^3$, bandwidth: 434 Hz/pixel, TR/TE/FA: 50 ms/0.99 ms/85°, NEX: 64, and total scan time 15 min 2 s. Sodium quantification was performed by comparing signal intensities between tissue and calibration phantoms. First, a linear relationship (sodium concentration *vs* signal intensity) was assessed based on the phantom data, and then the slope and intercept from the linear regression were applied to the tissue regions to quantify relative sodium contents assuming the same T1 and T2 values for tissue and solutions.

2.2 Data analysis

The mDixon, $T_{1\rho}$, and sodium scans were aligned with each other in the middle of their imaging slabs, so the center slice of each scan was taken for analysis. To facilitate the analysis, the sodium image was first interpolated to the same in-plane resolution as the mDixon image (which is also equal to the resolution of the $T_{1\rho}$ images). Muscle ROIs including five subregions (anterior compartment, peroneus, soleus, medial gastrocnemius, and lateral gastrocnemius) were drawn on the mDixon images and then overlaid onto the $R_{1\rho}$ and sodium maps to extract data. Sodium and $T_{1\rho}$ (or $R_{1\rho}$) values were expressed as median $\pm$ SD (standard deviation).

To examine the age associated changes in muscle, $R_{1\rho}$ values (at each FSL) and sodium content were plotted against age. We calculated the $R_{1\rho}$ difference between low and high FSLs: $R_{1\rho} = R_{1\rho}(0 \text{ Hz}) - R_{1\rho}(500 \text{ Hz})$, which describes the degree of the dispersion and we plotted that *vs* sodium content to assess the correlation between the amount of exchangeable protons and sodium content in ECM.

ImageJ (NIH, version 1.49v) was used for ROI drawing and signal intensity measurements. Other processing was performed using Matlab (R2015b).

3. Results

Fig. 2 shows an example of the mDixon water image, sodium image, as well as $R_{1\rho}$ map of a 24-yrs male subject. Muscle regions were first drawn on the mDixon images then overlaid on sodium and $R_{1\rho}$ maps, from which data can be extracted.

Fig. 3 displays the $R_{1\rho}$ value (at each FSL) and sodium content *versus* age, in which each correlation was assessed by linear correlation coefficient (r) and P value as shown on the plots. Note that at each FSL, $R_{1\rho}$ shows strong correlation with age, which is confirmed by $r \approx 0.9$ and $P < 0.05$. There is also a strong trend relating sodium and age which did not reach statistical significance (for a significance level of 0.05).

Fig. 4 shows the relationships of the dispersion $R_{1\rho} (=R_{1\rho}(0 \text{ Hz}) - R_{1\rho}(500 \text{ Hz}))$ with age and with sodium content.

There is a strong correlation ($r = 0.98$, and $P = 0.000578$) between $R_{1\rho}$ and sodium in muscle. We also fitted a multiple linear regression model in which the $R_{1\rho}$ was the outcome variable and sodium was the main explanatory variable while age was added to the model as a confounder. It showed that sodium was still a statistically significant effect ($r = 0.96$, $P = 0.0094$) on $R_{1\rho}$ while age did not reach significance ($P = 0.4259$).

4. Discussion

A variety of changes in molecular composition may occur in the extracellular space of tissues prior to morphologic changes, associated with either pathologies or normal aging. Changes in relaxation times potentially reflect biochemical alterations in the extracellular matrix. For instance, in articular cartilage, increases of $T_{1\rho}$ have been observed in both normal aging [1] and osteoarthritis [30], probably reflecting a loss of proteoglycans that promote water relaxation. However, in human spine disc samples, $T_{1\rho}$ in the nucleus pulposus is inversely correlated to the degenerative degree [31]. Although both disc nucleus pulposus and articular cartilage are primarily comprised of water, proteoglycan, and type II collagen, their relative compositions and degenerative processes (the degree/type of collagen cross-linking and proteoglycan aggregation in ECM) differ [32], which may affect $T_{1\rho}$ relaxation differently. Also, the loss of GAGs is not always an indication of tissue degeneration. Greater deposition of sulfated GAGs in dystrophic muscles has been reported through biopsy analysis [33]. $T_{1\rho}$ is reportedly sensitive to fibrosis in liver [26,27], but these studies differ in the choice of locking field and main magnetic fields. Fibrosis occurs in

muscles in normal aging as well as in diseases (such as dystrophies and diabetes) [25], so it may be expected that $T_{1\rho}$ changes occur in muscular degeneration.

In this study, we aimed to evaluate the potential role of $T_{1\rho}$ dispersion measurements for assessing biochemical changes in skeletal muscle in normal aging. We found $R_{1\rho}$ decreases with age, suggesting an overall loss of fractional macromolecular content and increase in water fraction. On the other hand, $R_{1\rho}$ dispersion, as represented by $\Delta R_{1\rho}$, increased with age, suggesting a greater abundance (or possible an increased exchange rate) of exchangeable protons within the tissue. Moreover, the strong correlation with the increased levels of sodium signal suggests there is a corresponding increase in ECM volume and number of charged sites.

Because the extracellular space has nearly a 10-fold greater sodium concentration than the intracellular space, an increase of extracellular volume fraction would lead to a total sodium increase in an imaging voxel. If fibrosis is present, the increased ECM may accommodate more labile protons associated mainly with amides, amines and hydroxyls, even if the total average concentration of proteins in tissue decreases. Thus increased chemical exchange with free water at 3T increases the $R_{1\rho}$ dispersion even as $R_{1\rho}$ values overall decrease with age.

In conclusion, although this initial study was limited to a relatively small sample size and normal aging, the results highlight the potential use of $R_{1\rho}$ (and $\Delta R_{1\rho}$) and sodium imaging in the assessment of a range of muscular diseases that involve changes in macromolecular contents. $R_{1\rho}$ dispersion, perhaps as an alternative to sodium measurements, may provide complementary and more specific information to characterize changes in muscle in clinical practice.

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Fig. 1.

(a) Lower part of the 3T sodium knee coil. Inside the coil there are four calibration standards fixed in a phantom holder. A concave cover with a hard smooth surface (as pointed out by the white arrow) is slid open to display the phantoms. (b) During imaging, the skin is in direct contact with the surface of the concave cover.

Fig. 2.

Images of a 24-yrs male subject at 3T. (a) mDixon water image with five muscle subregions labeled: anterior compartment (tibialis anterior and extensor digitorum longus) – red, peroneus – green, soleus – blue, medial gastrocnemius – cyan, and lateral gastrocnemius – gold. (b) Sodium image was interpolated to the same in-plane resolution as the mDixon image, then it could be overlaid directly on the muscle ROI from (a). Four calibration standards are shown at the bottom of the image, with sodium concentrations (from left to right) of 10 mM, 20 mM, 30 mM, and 40 mM. (c) Pixel-wise $R_{1\rho}$ map at the same muscle position (FSL = 500 Hz).

Fig. 3.

(a) Correlation between $R_{1\rho}$ (at each FSL) and age for all seven volunteers, showing that $R_{1\rho}$ decreases with age for all the FSLs, and the decrease is greater at higher FSL. (b) A trend between sodium content and age can be readily identified (one subject failed to complete the sodium scan, so sodium data from the other six subjects ($N = 6$) were included into the analysis).

Fig. 4.

(a) $R_{1\rho}$ ($=R_{1\rho}(0 \text{ Hz}) - R_{1\rho}(500 \text{ Hz})$) shows a strong positive correlation with age. (b) $R_{1\rho}$ shows an even stronger correlation with sodium content in calf muscle. When adjusted for age, sodium still has a statistically significant effect ($r = 0.96$, $P = 0.0094$) on $R_{1\rho}$.