Quantitative Magnetization Transfer in *In Vivo* Healthy Human Skeletal Muscle at 3T

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Introduction

MRI is of increasing value in the investigation of skeletal muscle affected by neuromuscular diseases [1]. The magnetization transfer (MT) effect, describing cross-relaxation between protons in different macromolecular environments, has been shown to be sensitive to muscle pathology by magnetization transfer ratio (MTR) measurements [3-6]. Measures derived from quantitative MT (qMT) modelling, a technique well-established in the brain, are less hardware and implementation dependent than MTR and provide more specific physical insights. Previous muscle qMT measurements have focussed on *ex vivo* animal samples. The aim of this work was to apply a qMT model to human muscle *in vivo* in order to investigate its potential as a quantitative biomarker in neuromuscular diseases [2].

Theory

In a 2-pool model of MT [7], the Bloch equations can be formulated to describe the longitudinal steady state magnetizations of the free-water proton pool (a), M_0^a, and the restricted pool protons (b), M_0^b, irradiated at an off-resonance frequency Δ. Ramani *et al.* [8] described the signal measured in the presence of MT saturation given in Eq.(1), where $f = M_0^b / \left(M_0^a + M_0^b\right)$ is the restricted pool fraction, R is the exchange rate between the 2 pools, R_b is the longitudinal relaxation rate of pool b, R_{RFb} is the RF absorption rate of pool B, ω is applied saturating pulse amplitude and g is a scaling factor. To approximate pulsed MT saturation, the continuous wave power-equivalent (CWPE) amplitude may be calculated for a given pulse-shape using the expressions in [8]. Data acquired at various combinations of Δ and ω may thus be fitted to Eq. 1 in order to estimate the remaining MT parameters.

$$S = gM_0^a\left[\frac{R_b\left(\frac{RM_0^a}{R_a(1-f)}\right)+R_{RFb}+R_b+RM_0^a}{\left(\frac{RM_0^a f}{R_a(1-f)}\right)\left(R_b+R_{RFb}\right)+\left(1+\left[\frac{\omega}{2\pi\Delta}\right]^2\left[\frac{1}{R_a T_2^a}\right]\right)\left[R_{RFb}+R_b+RM_0^a\right]}\right] \quad Eq.(1)$$

Methods

Imaging was performed at 3T (Siemens Tim Trio) operated with a body transmit coil. Ten healthy subjects aged 33.6±8.7 (mean ± SD) years were scanned feet-first and supine. The signal was received from the mid-right calf with a matrix surface-coil array. Images were acquired with 128x128x16 matrix and 180x180x160mm FOV unless stated. MT prepared images were acquired using a custom-made slice-selective spoiled 3D-FLASH sequence (TR/TE=50/3ms, α=6°) that allowed for free choice of the MT saturation [9]. A 12ms Gaussian pulse with Δ = 1,2,5,10,20,50 and 100 kHz repeated at nominal flip angles of 350° & 500° corresponding to CWPE amplitudes of 304 and 434 rad/s respectively were used to generate a set of images with 14 different MT weightings. T1 maps were obtained by fitting to the 3D-FLASH signal acquired at 3 different flip angles (5°, 15° & 25°). High resolution 2D-TSE T1w images were obtained for placing ROIs. Maps of the B1 transmit deviation were obtained using an optimized actual flip angle imaging approach [10, 11] (α=60°, TRs = 50, 150ms, 64x64x16 matrix) and used to compensate for deviations from the nominal flip angle, θ_{nom}, in the T1 and MT measurements. The total acquisition time was less than 15 min. The 4 central partitions of each volume were registered to the anatomical T1w images on which ROIs were placed over 4 different muscles for each subject. The 14 MT-weighted measurements were fitted to the 2-pool qMT model in Eq (1) in order to estimate the parameters T_2^b (via R_{RFb}), RM_0^a, $f/(R_a(1-f))$ and $1/(R_a T_2^a)$ with R_b=1 and gM_0^a determined form the data. Fitted parameters and their uncertainties were combined with the measured T1 values [7] to obtain the f and T_2^a in each region [8]. Voxel-wise muscle qMT parameter maps were also computed.

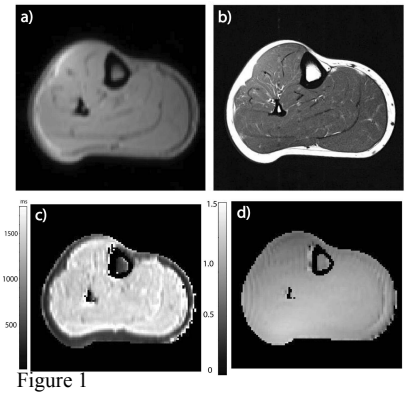

Figure 1

Results

Fig. 1 shows an example of a) MT-weighted image (Δ= 20kHz, θ_{nom}= 350°) b) T1w image, c) T1 map and d) relative B1 map (as a fraction of θ_{nom}). Fig. 2a) shows a fit to the data for a region in a single ROI (medial-gastroc muscle). Mean qMT parameters in the soleus muscle were $1/(R_a T_2^a)$=51±4, $f/(R_a(1-f))$=0.15±0.01s, T_2^b=5.9±0.2μs, RM_0^a=17±4, T_{1obs}=1.51±0.05s, T_1^a=1.58±0.06s, f=0.08±0.01, T_2^a =31±4ms. Fig. 2b) shows a calculated parameter map for T_2^b.

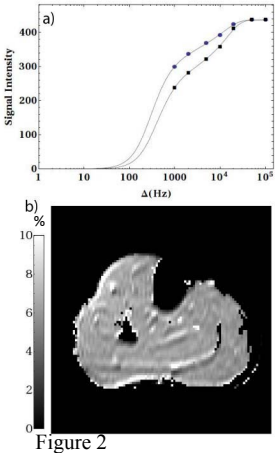

Figure 2

Discussion

The quantitative 2-pool model with CWPE approximation described the data well and a moderately fast pulsed qMT evaluation of muscle was possible at 3T within SAR limitations. The B1 maps of 10 subjects were qualitatively similar with a slowly varying spatial distribution and deviations of less than 40%. A super-Lortentzian function as the restricted-pool rf absorption lineshape gave superior fits to a Gaussian function for *in vivo* muscle (data not shown). The parameter RM_0^a varied widely and was not discriminate, consistent with previous studies in other tissues. The parameter T_2^b varied very little between subjects and was slightly reduced compared with previous *ex vivo* animal muscle measurements [12]. The parameters $1/(R_a T_2^a)$ and $f/(R_a(1-f))$ converged well in the fits and, when combined with the T1 measurements, the parameters f and T_2^a were adequately estimated: these may provide further physical insight into the abundance of hydrophilic macromolecules in healthy muscle. Deviations from the observed restricted pool fraction of f=8%, if observed in future studies, may prove a useful future marker of disease. Its precise underlying determinants, whether at a cellular or more macroscopic scale require further investigation. Alternative pulsed qMT models may improve the relative sensitivities of the qMT parameters in healthy muscle, and their value when applied to studies of e.g. inflammatory muscle disease or exercise physiology is promising.

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