Diffusion measurements reveal a difference in apparent diffusion coefficients of intra- and extramyocellular lipids

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Introduction: Skeletal muscle tissue contains two distinct pools of lipids: A) extramyocellular lipids (EMCL) that are located in the fascia along the muscle fibres and B) intramyocellular lipids (IMCL) that are stored as droplets inside the muscle cells [1]. This finding was also confirmed by means of ^{1}H magnetic resonance spectroscopy [2, 3] studies, and it is now well established that IMCL play an important role in energy metabolism and are linked to insulin resistance [4]. To build upon these advances, diffusion spectroscopy might offer further insights into microscopic tissue structure, but due to the low apparent diffusion coefficients (ADCs) [5], measurements of diffusion properties by MRS require large b-values and thus are prone to motion- and vibration-related artifacts. It was shown that using pulse triggering and individual phasing of single acquisitions can significantly reduce artifacts in diffusion measurements [6]. The present work shows the results of an investigation into the diffusion characteristics of IMCL and EMCL, and reports the apparent diffusion coefficients for both lipid pools.

Methods: All spectra were acquired on a clinical 3T system (Trio, Siemens Medical, Germany) using an in-house modified STEAM sequence. A single-loop receive-only surface coil (Rapid Biomedical, Germany) was used to maximize the signal to noise ratio (SNR). The ROI (~ 8 ml) was placed in the tibialis anterior muscle of ten healthy volunteers, and 64 individual acquisitions were stored (TE/TR = 105/1500 ms, TM = 65 and 150 ms, no water suppression). The diffusion gradient strength was varied from 5.2 to 52 mT/m on the space diagonal in 12 steps for TM = 65 ms (resulting in b-values ranging from ~ $3{\cdot}10^2$ to $3{\cdot}10^4$ s/mm^2) and in 8 steps for TM = 150 ms (b-values from ~ $1.6{\cdot}10^3$ to $5.7{\cdot}10^4$ s/mm^2) respectively. For triggering, a standard pulse oximetry sensor was used with a delay of 100 ms. Spectra were processed individually and quantitation was performed using the AMARES algorithm in jMRUI [7]. ADCs were estimated by fitting to an exponential model in MATLAB (Mathworks, USA).

Results: Figure 1 shows a striking difference in diffusion decays between EMCL and IMCL for both TM = 65 and 150 ms. Analogous measurements from bone marrow are included for comparison. The estimated values of ADC are summarized in Table 1. Figure 2 shows how various diffusion weightings affect the EMCL peak more strongly than the IMCL peak. Using the "Gaussian phase distribution" model [8] for restricted diffusion, the IMCL TM = 65 ms data, and the diffusion coefficient of EMCL, the radius of the IMCL droplets was estimated to be ~ 1.35 µm.

	ADC_{EMCL} [mm^2/s]	ADC_{IMCL} [mm^2/s]	ADC_{BM} [mm^2/s]
TM 65	$1.52{\cdot}10^{-5}$ ($1.36{\cdot}10^{-5}$, $1.69{\cdot}10^{-5}$)	$1.95{\cdot}10^{-6}$ ($1.06{\cdot}10^{-6}$, $2.83{\cdot}10^{-6}$)	N/A
TM 150	$1.54{\cdot}10^{-5}$ ($1.43{\cdot}10^{-5}$, $1.67{\cdot}10^{-5}$)	$-1.85{\cdot}10^{-6}$ (-2.810^{-6}, -8.2210^{-7})	$2.26{\cdot}10^{-5}$ ($2.07{\cdot}10^{-5}$, $2.46{\cdot}10^{-5}$)

Tab. 1: *Summary of estimated diffusion coefficients for different lipid pools (single exponential decay model). For IMCL where restricted diffusion is expected, the ADC is shown to allow comparison. The values in brackets correspond to 95% confidence intervals of the fits.*

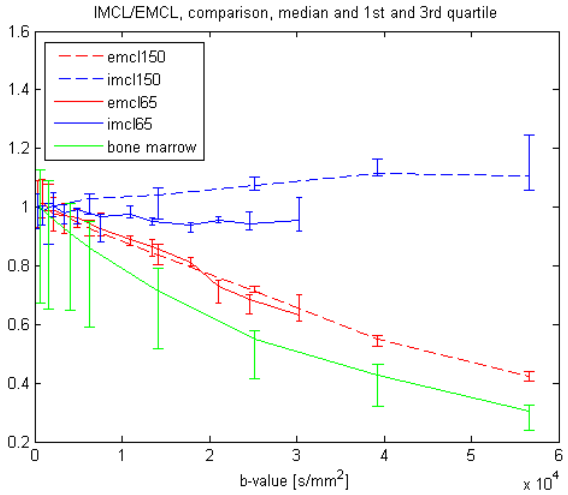

Figure 1: *IMCL, EMCL, and bone marrow diffusion decays. The points represent median of all volunteers and the error bars show 1st and 3rd quartiles. The data are normalized to the first value. The bone marrow data comes from a different study and is presented only as a comparison (TR = 1500 ms, TE = 105 ms, TM = 150 ms; no water suppression; tibia shaft).*

Discussion: The ADC values of EMCL and bone marrow presented here are in the same order of magnitude as would be expected, and are also in good agreement with literature values [5]. However, the ADC of the IMCL is significantly different from published data. Since the extremely low ADC of IMCL does not lead to considerable signal reduction without the application of very strong gradients, its determination is prone to artifacts if the acquisition is not triggered and individually phased. This may explain the factor of 10 times difference from a previous report [5]. Furthermore, the apparent increase of the IMCL signal with increasing b-values for TM=150 ms in Fig.1, which results in a negative ADC, is not physically reasonable and may be a result of the difficulties to phase the noisy single spectra accurately when strong gradients are applied. Nonetheless, these measurements clearly show that the two lipid pools exhibit different diffusion characteristics, specifically, that unrestricted diffusion can be assumed in the case of EMCL, whereas in the IMCL pool, the assumption of restricted diffusion would better explain the findings. As well, the droplet size of the IMCL was found to be ~ 1.35 µm, which is larger than the results from electron microscopy (0.5 µm [9]). The discrepancy might be explained by the fact that the model used in this work did not yet take into account IMCL droplet size distribution. The diffusion characteristics and droplet size reported here provide new insights into lipid storage and metabolism, which may prove useful for future studies of insulin resistance and diabetes [10].

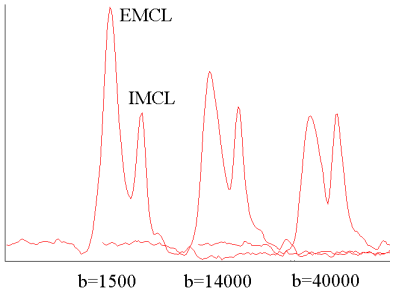

Figure 2: *IMCL and EMCL peaks showing the effect of diffusion weighting, it is easy to notice the differences in decay rate (b-values in s/mm^2).*

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