Visualization of SPIO labeled mesenchymal stem cells in knee joints by R2* mapping

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Introduction

We propose a visualization method base on parametric R_2* mapping with rejection criteria of error of fit and minimal relative signal decay. The method will be demonstrated on ex-vivo rat knees injected with SPIO labeled mesenchymal stem cells (MSCs).

In cartilage repair mesenchymal stem cells (MSCs) have emerged as a promising therapy because they are capable of new cartilage formation as well as the secretion of growth factors and anti-inflammatory factors[1-2]. Although the application of MSCs in degenerative joint disease models shows improved cartilage quality, their mechanisms of action are still unclear.

We demonstrate that we are able to track attachment of SPIO labeled MSCs into a variety of structures in the knee joint. Previously we reported on the application of SPIO labeled cells in short T_2 species[3] and on quantification of SPIO by MRI[4].

Our method relies on quantitative voxel based R_2* mapping, which enables SPIO visualization. The method is demonstrated on ex-vivo rat-knees injected with different amounts of SPIO labeled cells, and has also been demonstrated on in-vivo rat-knees. This allows us to visualize a negative contrast agent in a non-homogeneous environment.

Methods

Knees were injected with rat MSCs labeled with ferrumoxides-protamine sulfate as previously described by our group[3]. Ex vivo injections were performed with saline only (control) and 250,000 SPIO-labeled and formalin-fixated cells.

In the ex-vivo rat-knees the R_2* values were mapped using a 3D FSPGR sequence with TR=52.5 ms, and TEs: 1.3, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50 ms and voxelsize 26 x 26 x 500 μm^3. MRI experiments were performed on a preclinical GE 7T Discovery system.

Post-processing employed a MATLAB protocol to fit the Rician MR magnitude signal model through the measured intensities at each voxel as a function of TE, using a Maximum Likelihood approach. R_2* value follows for each voxel, with an error in ms as expressed by the square roots of the Cramer-Rao lower bounds.

The R_2* values can be translated to a color as displayed in Figure 1 top middle and top right. The post processed color maps (Figure 1 top) a filter was applied, requiring a signal decay of at least 66% of it's intensity at the longest TE compared to the shortest TE. In that way, bone cortex got eliminated by a lack of signal decay (Figure 1 bottom). Note that bone core has been excluded from the ROI making up the color map.

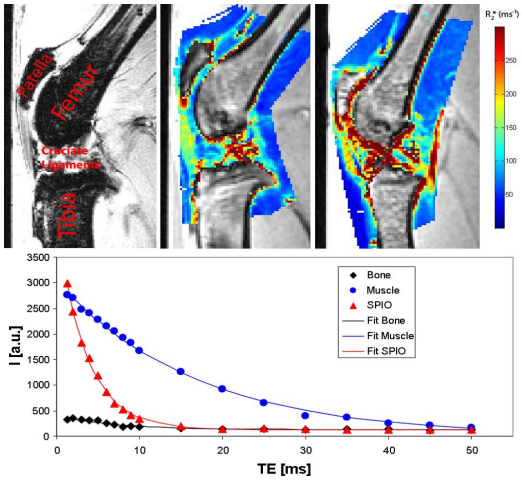

Figure 1. *Top left*: MRI image of rat knee marking different structures of the knee. *Top middle*: Color encoded R_2* map of rat knee injected with saline. *Top right*: R_2* map of rat knee injected with 250,000 SPIO-labeled MSCs. *Bottom*: Relaxation profiles of 3 distinct regions of interest from bone, muscle and SPIO exhibit marked differences in R_2*

Results

In the MR images of the rat knee several structures can be distinguished as shown in Figure 1 left. When looking at the R_2* color map (Figure 1 top middle), the tendons around the knee show a slight increased R_2* as compared to muscle tissue. The cruciate ligaments show relatively high R_2* values

Comparing the color maps of the rat knees injected saline, and the one injected with SPIO (Figure 1 top middle and top right), a clear difference in R_2* values between both knees can be appreciated, indicating regions of SPIO in the intra-articular space between patella and femur. SPIO labeled cells also attach to the cruciate ligaments and the patellar tendon, as indicated by high R_2* values in combination with blooming effects. Due to susceptibility effects, the hypointensities in magnitude FSPGR R_2* images associated with cruciate ligaments typically appear larger than the ligaments themselves. Since these hypointensities occur in regions of low spin density, it is unreliable to be detected by looking at signal voids.

Conclusions

We are able to visualize SPIO-labeled MSCs in the knee by means of voxel-based mapping of R_2* values, where visualization/identification of SPIO based on the occurrence of 'signal voids' is not reliable. We have demonstrated that we are able to distinguish between bone cortex and SPIO labeled cells with our proposed method.

References

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