Fast T1-mapping to study biodistribution of nanoparticulate contrast agents

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Introduction

The determination of biodistribution and elimination of contrast agents (CA) is crucial for the development of new CA's, such as e.g. nanoparticulate blood pool agents. Evaluation of CA biodistribution and elimination is usually accomplished by radioactive labeling of the CA molecules and applying scintigraphic imaging [1]. The use of magnetic resonance imaging (MRI) to study biodistribution of the CA is limited due to the fact that usually only relative signal changes due to the injected contrast agent are evaluated to detect an enhancement of the contrast agent. Thereby these relative signal changes depend on the concentration of the contrast agent in the particular tissue, on the detailed MR sequence parameters and on the native T1 of the tissue at hand. Thus for the same CA concentration varying relative signal changes will be observed in different tissues, making a qualitative determination of biodistribution based on MRI problematic. This, however, could be overcome if tissue T1 values were measured directly before and during CA enhancement, whereby the difference of relaxation rates between native tissue and tissue with CA enhancement is directly proportional to the concentration of the CA, with $\Delta R1 = R1 - R1_{native} = r\ c$, where R1=1/T1 is the relaxation rate, c the concentration and r the relaxivity of the CA. It was the purpose of this study to use a fast T1-mapping scheme for the study of CA biodistribution and to apply this method to a new nanoparticulate CA.

Matrials and Methods

For this study nanoparticles, which were intended to act as blood-pool CA, were used based on the biodegradable polymer polylactic acid (PLA) into which Gd labelled albumin was incorporated. The preparation of these nanoparticles is based on an emulsification-solvent evaporation technique as described by Montisci et al. [2]. The resulting nanoparticles had a mean diameter of 35nm and a Gd load of 3000 per nanoparticle. To study biodistribution and elimination of these nanoparticles MRI was performed on male Sprague-Dawley rats, which were anesthetized using a mixture of Ketamin (80-100 mg/kg BW) and Xylasol (10-15 mg/kg BW) and placed in a MR compatible animal holder. For the injection of the CA a Venflon catheter was inserted into a tail vein. MRI was performed on a standard clinical 1.5T whole body MR scanner (Magnetom Avanto, Siemens, Erlangen) using a small flexible receive coil which was tightly wrapped around the animal holder. The experiments were performed after approval by the local animal care committee. For T1-weighted imaging a standard spin-echo sequence was used with the following parameters: TR/TE = 540/14 ms, frequency selective fat saturation, slice thickness: 2 mm, number of slices: 23 (2 concatenations), FOV: 150 mm, acquisition matrix: 256. For fast T1-mapping an inversion recovery snapshot FLASH (IRSFL) sequence as originally described by Haase et al. [3] was implemented. The pulse sequence consists of a preceding non-selective fast passage adiabatic inversion pulse which is followed by a series of T_1-weighted snapshot FLASH (SFL) images (T_R = 3.9ms, T_E = 1.8ms, flip angle α=4°). To guarantee a sufficient accurate sampling of fast relaxation dynamics, as it occurs in tissue after CA application, a centric reordering scheme and the acquisition of a k-space reduced scan matrix of 64x128 (zero filled to 128x128) was chosen. A total of 16 differently T_1-weighted SFL images were acquired after the initial inversion pulse leading to a total acquisition time of 4s for one T_1-map. To cover the whole body of the investigated rats T1-maps were obtained sequentially for up to 16 different slice positions. T_1 maps were calculated by pixel-wise fitting of signal intensities using a low flip angle approximation as described by Deichmann et al. [4]. For the biodistribution studies native T1-weighted SE images and T1-maps were acquired prior to the application of the CA. After bolus injection of the CA the T1-weighted SE sequence and the T1-mapping sequence were repeated in regular intervals to observe the distribution of the CA within the body of the rats.

Results

Using phantom measurements the error of the obtained T1-maps was found to be below 4% for a range of T1 values between 150 and 2000ms. Image 1 shows T1-weighted images before and at different times after injection of the nanoparticles. Strong enhancement is found in liver and kidney. However, an enhancement e.g. in muscle tissue is difficult to detect. After 24h still a strong enhancement in the kidney cortex is found. Figure 2 shows T1 maps obtained in the same rat. A decrease of T1-values due to CA accumulation is easily detected with the used T1-mapping technique even in muscle tissue. The resolution was sufficient to identify different organs of the rat and even to distinguish between kidney cortex and medulla. For the investigated class of nanoparticles an early decrease of T1-values in liver tissue, kidney and muscle tissue is found, likely due to a blood-pool effect. In accordance with the T1-weighted SE images, after 24h clearly reduced T1-values in the kidney cortex are found.

Conclusions

T1-mapping offers a simple method to study biodistribution of a CA in-vivo over a long period of time without the use of radioactive labeling. Knowing the relaxivity of the used CA it is possible to estimate CA concentrations in tissue as a function of time. The reason for the long lasting enhancement of the used class of naonparticles in the kidney cortex is not yet understood and is maybe related to the known long retention time of Gd labelled albumin in the body, which is considered unfavourable for clinical applications.

References

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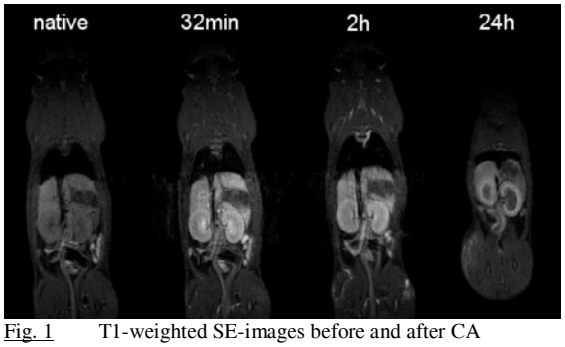

Fig. 1 T1-weighted SE-images before and after CA application

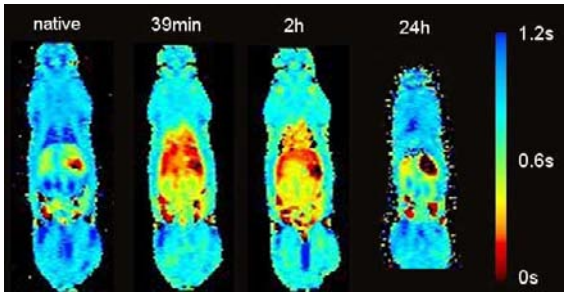

Fig. 2 T1-maps before and after CA application