Rapid Steady State T_1 method for cerebral blood volume fraction mapping using SINEREM as contrast agent and a three dimensional projection reconstruction acquisition mode

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Purpose:

The Rapid Steady State T_1 ($RSST_1$) method, necessitating a blood pool contrast agent (CA), has been used for cerebral blood volume fraction (CBVf) mapping in healthy rat brain with Gd-DOTA and P760 (1) as well as in a C6 brain tumor model with Gd-ACX (2). SINEREM, an ultrasmall superparamagnetic iron oxide (USPIO) CA from Guerbet Laboratories has recently been approved for clinical applications, and has been used as blood pool CA in a C6 rat glioma model (3). This study exploits the longitudinal relaxation and the long blood half life of SINEREM with the $RSST_1$ method for CBVf mapping. A steady state susceptibility contrast (SS ΔR_2*) MRI method for CBVf mapping (4) was used for comparison. The intravascular confinement of SINEREM in an RG2 glioma model in rats was investigated.

Method:

The longitudinal r_1 and transverse r_2 relaxivity of SINEREM in normal saline solution, and the T_1 and T_2 relaxation times in rat blood (n = 3) 5 to 60 minutes after injection of 0.2 mmol/kg SINEREM were measured in vitro at 2.35T and 20°C. The $RSST_1$ method is based on a rapid inversion recovery sequence for signal suppression from brain tissue and blood before CA injection (repetition time TR = 750 ms, inversion time T_{inv} = 325 ms). To reduce the transverse relaxation effect, the $RSST_1$ method was used with a 3D projection reconstruction (3DPR) acquisition mode (FOV = 108 × 108 × 216 mm^3, 31 × 61 projections, duration 24 minutes) enabling a short echo time TE of 0.7 ms, before and after CA injection. The signal in the difference image corresponds to the thermal equilibrium magnetization of blood, and was normalized by an acquisition before CA injection using the following parameters: TR = 1.2 ms, flip angle α = 10°, 31 × 61 projections (duration 38 minutes). At such low flip angles, the longitudinal magnetization is almost independent of the tissue T_1 and the equilibrium magnetization can be deduced by dividing by sin (α). With the SS ΔR_2* method the CBVf is obtained from a ΔR_2* map (before and after CA injection) and the susceptibility difference of blood (4). R_2* mapping was performed using multi gradient echo acquisitions with TR = 6 s, seven TEs between 6 and 42 ms, FOV 32 × 32 mm^2, matrix 128 × 66, seven 2 mm slices (duration 13 minutes). The CBVf in healthy Fischer (n = 3) and RG2 tumor bearing rats (n = 4), 16 to 19 days after implantation, was mapped with both methods using a single SINEREM injection at a dose of 0.2 mmol/kg. During the experiments, the arterial blood pressure and blood gases were controlled. The $RSST_1$-3DPR acquisitions were reconstructed by nearest neighbor interpolation onto a 36 × 36 × 72 grid with a zero filling factor of 4 in all three dimensions. Image processing was carried out with ImageJ for the 3DPR data and with Matlab for the 2D SS ΔR_2* data taking care to delineate similar ROIs on the two data sets.

Figure 1: healthy rat brain

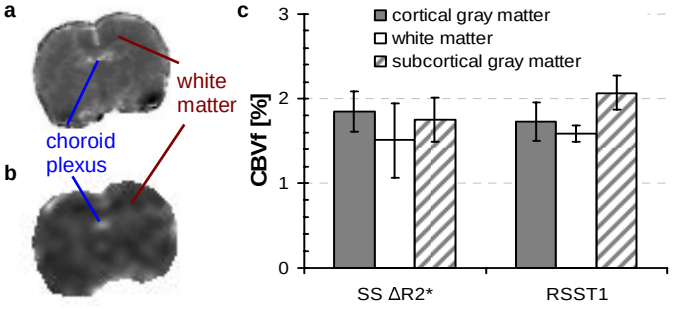
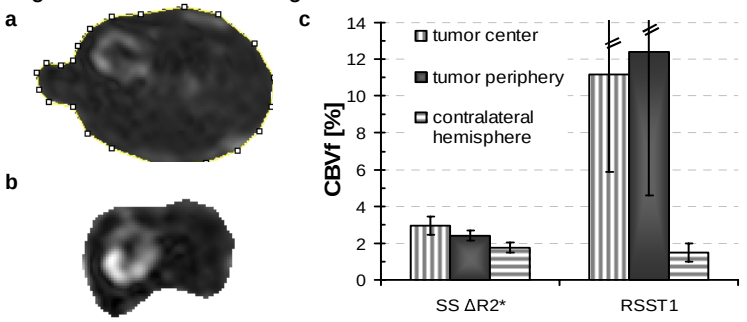


Figure 3: RG2 tumor bearing rat brain



Results:

The relaxivities of SINEREM in normal saline solution at 2.35 T are r_1 = 5.4 and r_2 = 95.6 $s^{-1}mM^{-1}$. After intravenous injection of 0.2 mmol/kg SINEREM the blood T_1 is below $T_{inv}/5$ = 65 ms for one hour assuring full relaxation of the intravascular magnetization for accurate CBVf measurement at T_{inv} = 325 ms. The T_2 ranges from 2.9 ms at 5 minutes post injection to 3.1 ms at one hour necessitating a correction for the T_2 attenuation factor exp(-TE/T_2) = 0.79. Figure 1 shows a coronal ΔR_2*-map (a) and the corresponding CBVf map obtained by the 3DPR-$RSST_1$ method (b) from a healthy rat. The regional normocapnic CBVf obtained with both MRI methods are summarized in the histogram (c). The normocapnic CBVf averaged over the whole coronal slice was 1.7 ± 0.2% with the SS ΔR_2* method and 2.1 ± 0.4% with the $RSST_1$ method in healthy rats. Figure 2 a and b show two orthogonal planes through a RG2 glioma bearing rat brain imaged in the 3DPR mode, illustrating a ring like enhancement pattern in the tumor. The histogram in c summarizes the CBVf in the tumor center and periphery as well as in the contralateral hemisphere obtained with both MRI methods.

Discussion:

The r_2/r_1 ratio of SINEREM at 2.35T is almost 20. The use of SINEREM in combination with the $RSST_1$ technique necessitates a dose of about 0.2 mmol/kg and an acquisition mode allowing a short TE. Owing to the long blood half life of SINEREM, the signal is in the steady state for at least one hour, here exploited for a 3D acquisition for CBVf mapping by the $RSST_1$ method followed by the SS ΔR_2* method for comparison. The local magnetic field distortions around the vessels have no influence on the CBVf quantification by the $RSST_1$ technique since the extravascular signal is suppressed. No statistically significant differences between the regional CBVf in healthy brain and contralateral to the tumor obtained with the two methods were found (Mann-Whitney-test). However, very high blood volume fractions were measured in the tumor with the $RSST_1$ method but not with the SS ΔR_2* method. This result suggests the extravasation of SINEREM in the RG2 tumor model, in which case the susceptibility based methods are known to underestimate the CBVf while the T_1 based methods overestimate the CBVf.

Conclusion:

The $RSST_1$ method can be used for CBVf mapping in combination with any blood pool CA. The use of an USPIO such as SINEREM having a high r_2 requires acquisitions with short TE and correction for the T_2 attenuation factor exp(-TE/T_2), but results in a steady state signal for at least one hour. The regional CBVf are in accordance with values obtained by autoradiography (5), T_1 (6) and T_2 (3) based MRI methods and synchrotron radiation computed tomography (7). In opposite to results reported for the C6 tumor model (3), SINEREM seems to leak from the microvasculature in the RG2 tumor model.

References:

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