Optimal calculation of MR-relaxation rate changes for quantitative tumor blood volume determination at 3.0T

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Introduction The detection of tumors and the monitoring of therapy effects like changing tumor vascularisation and perfusion are supported by quantitative MRI relaxometry. In particular, the measurement of the blood volume in tumors can be assessed by R_2* relaxometry [1,2]. Detecting these therapy effects requires an accurate and quantitative determination of contrast agent concentrations that induce changes in MR relaxation rates R_2 and R_2*. Therefore, a method is required to quantitatively measure these changes of the relaxation rates $\Delta R_2(*)$ before and after contrast agent application. Several commonly used methods suffer either from the influences of susceptibility artifacts or from the fact that the detectable range of ΔR_2* values is limited. We present a robust quantitative method for calculation of $\Delta R_2(*)$ that is free of these limitations.

Materials and Method A common method is to calculate ΔR_2* by fitting an exponential decay function to multi echo datasets, measured before and after contrast agent application. This technique is prone to errors since the relaxation function may deviate from an exponential e.g. due to field inhomogeneities. To become independent of these deviations, ΔR_2* can be calculated from two T2* weighted images before and after contrast agent application:

$$\Delta R_2^* = -\frac{1}{TE}\ln\left(\frac{S_{post}(TE)}{S_{pre}(TE)}\right) \qquad [1]$$

where S_{post} and S_{pre} are the signal intensities before and after the change in relaxation rate. The disadvantage of this approach is that it can only be optimized if the change in relaxation rate is known a priori and that only a small range of ΔR_2* values can be accurately measured. Using a multi-echo readout, the optimal echo time can be chosen by determining the maximum signal difference for every voxel. This approach would omit all other measured data. Therefore, a theoretical model for utilizing all available data has been developed by applying the error propagation function of Eq. 1 as a weighting function for the calculation of the weighted mean ΔR_2^* from all echo times for every voxel:

$$\delta\left(\Delta R_2^*(TE_i)\right) = \sqrt{\left(TE_i \cdot S_0 \cdot \exp\left(\frac{-TE_i}{T_{2\,pre}^*}\right)\right)^{-2} \cdot \sigma(S_{pre}(TE_i))^2 + \left(TE_i \cdot S_0 \exp\left(\frac{-TE_i}{T_{2\,post}^*}\right)\right)^{-2} \cdot \sigma(S_{post}(TE_i))^2} \qquad [2]$$

where $\delta(\Delta R_2^*)$ is the standard deviation of ΔR_2* and $\sigma(S_{pre})^2$, and $\sigma(S_{post})^2$ are the variances of the noise in the images S_{pre} and S_{post}. The relaxation times $T2^*_{pre}$ and $T2^*_{post}$ are obtained from exponential fits to the multi echo datasets before and after contrast agent application. Fig. 1 shows a simulation of this weighting function for low and high ΔR_2^*.

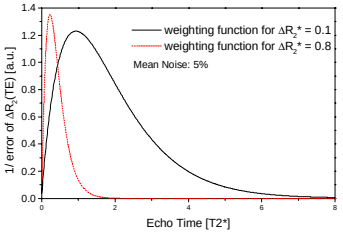

Figure 1: Simulation of the weighting function for low and high ΔR2* in two different voxels.

For the evaluation of this method, a multi gradient echo sequence was applied in phantoms (TR=600ms, ΔTE=2.5ms, 45 echoes) and in vivo (TR=260 ms, ΔTE=7ms, 13 echoes) before and after contrast agent application. It was performed on a 3.0T Philips Intera whole body scanner, for animal imaging a custom-made solenoid coil was used (70mm diameter). In a phantom, different amounts of super paramagnetic iron oxide particles (SPIO, Resovist, Schering AG) were added to water-filled glass tubes. The ΔR_2* calculation was performed by using a fixed echo time of 22 ms as well as the proposed weighted calculation (Fig. 2). To prove the method in vivo, the tumor perfusion in mice was measured by applying a long blood circulating ultra small paramagnetic iron oxide (USPIO, SHU 555C Schering AG), which was i.v. injected into mice, bearing tumors of different vascularity (human breast cancer cell lines: MDA-MB 435 & DU 4475). For three subsequent injections with different concentrations ΔR_2* maps were calculated. In a visually defined ROI the mean ΔR_2* was plotted vs. the total injected amount of USPIO (Fig. 4), and a comparison between the weighted calculation and a fixed echo time was made for the same ROI in one tumor.

Results Fig. 2 shows ΔR_2* maps calculated with only one echo at a fixed echo time of 20ms and by using all echoes weighted with the error propagation function shown in Eq. 2. It demonstrates the high accuracy of the method since the mean standard deviation of ΔR_2* within the glass tubes is 4 times lower in comparison with the standard method (Eq 1). Fig. 3 shows a high resolution ΔR_2* map of a mouse tumor with a large variety of ΔR_2* values. A comparison between the USPIO uptake of tumors with high and low vascularisation shows that quantitatively correct results can be obtained (Fig. 4) (slope values: MDA-MB 435: 0.14 (µmol/kg * s)$^{-1}$, DU 4475: 0.06 (µmol/kg * s)$^{-1}$). ΔR_2* grows linearly with the injected amount of USPIO. The blue dots show the same ROI, analyzed with a fixed echo time of 20ms. A deviation from linearity was observed for high ΔR_2* values. This demonstrates that the ΔR_2* calculation method allows a robust quantitative analysis of tumor vascularisation over a wide range of the contrast agent concentrations.

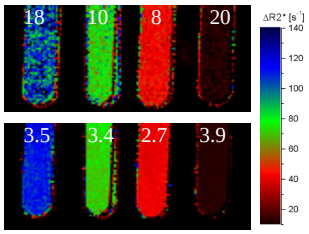

Figure 2: ΔR2* maps of different amounts of SPIO added to glass tubes. Upper: Calculation at fixed TE. Lower: with weighting function of all echo times. Numbers show standard deviation in % of mean ΔR2*.

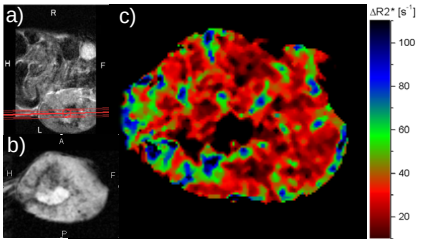

Figure 3: a) Abdominal survey, b) tumor morphology c) ΔR2* map of tumor in mouse after USPIO injection (320 µmol/kg). Calculated by using Eq. 2 as weighting function. Resolution: 200x200x900 µm, median filtered 3x3.

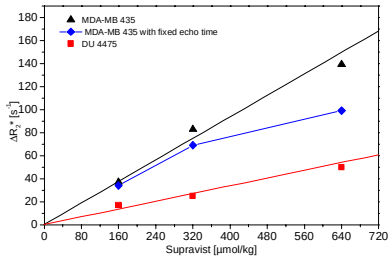

Figure 4: Comparison of ΔR2* in ROI within tumor with low and high vascularisation (black & red points). Blue points: same data as black points but calculated at a fixed TE of 20ms.

Conclusion The application of the error propagation as a weighting function for the ΔR_2* calculation ensures the most accurate determination of ΔR_2* using all available data. The method is independent of the range of ΔR_2* within the image and requires no prior knowledge of the expected ΔR_2*. T_1 could be omitted in these experiments because of sufficiently long TR times. In a further step T_1 effects could be compensated. In comparison to using the signal difference curve as a weighting function, the presented approach is more robust since it takes into account information about the noise and the relaxation time maps. It leads to quantitatively correct results, because all inhomogeneity effects cancel out since only the difference ΔR_2* is calculated.

References [1] Bremer et al.Radiology. 2003 Jan;226(1):214-20. [2] Persigehl et al. Proc Int Soc Mag Res Med 8, 1342 (2004)