Design and setup of dynamic contrast enhanced experiments for longitudinal preclinical studies of tumor response to anti-angiogenic therapy

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Purpose: Dynamic contrast enhanced (DCE)-MRI is seen as a promising biomarker for assessing tumor angiogenesis and the effects of antiangiogenic therapy because of its sensitivity to properties of the microvasculature [1]. DCE provides measures of tumor vascular function, i.e. tumor vessel permeability during the course of the treatment. Particularly DCE experiments in preclinical models in small animals can help to better verify effects of anti-angiogenic drugs on certain tumors, by permitting repeated measurements with a given tumor during the course of the treatment [2]. Although, DCE-MRI is common in clinical routine it is not yet standardized in small animals and the experimental DCE designs and setups are only barely documented in literature. An accurate and reproducible setup is, however, crucial to conduct reliable DCE experiments. Thus, the purpose of this work was to report in detail our DCE design and setup in order to monitor the treatment effects of anti-angiogenic drugs in tumor bearing mice.

Materials and Methods: Non-selective saturation recovery (SR) and in slice direction flow compensated FLASH images were acquired on a 7T animal MRI (ClinScan, Bruker) to measure the magnetization recovery in a single shot (snapshot) with 16 time points for TI = 82-3344.5 ms with ΔTI = 217.5 ms, TE = 1.53 ms, FA = 5°, echo spacing = 2.7 ms, TR = 3562 ms, acquisition matrix: 128x80, FoV: 32x25 mm², 6/8 Partial Fourier, BW = 550 Hz/pixel. The SR-snapshot method was calibrated using a phantom made of four Eppendorf tubes filled with 2 ml saline and aqueous solutions of Gd-DTPA (0.1, 0.2, 0.3, 0.4 mM) at about 30°C [4]. Matlab (MathWorks Inc.) was used for data processing. The relaxation calibration curve of the SR-snapshot FLASH sequence shows higher relaxation rates, but similar relaxivity, i.e. 1/2 relaxation rates obsolete. This setup is used in our institution to consecutively measure the tumor response to anti-angiogenic drugs reliably and reproducibly. This is corrected by the hematocrit (hct), where the hematocrit was assumed to be 45% [4]. Matlab (MathWorks Inc.) was used for data processing.

The transfer constant (Ktrans) is shown as an overlay to an anatomical image in Fig.3 and DCE curves with the fitted model parameters were plotted in Fig.4.

Discussion/Conclusion: We were able to design an experimental setup for reliable DCE measurements. Due to the small dead volume of our injection line we can keep the total injection volume low which is of importance in mice whose physiology is most likely affected by larger injection volumes. Another improvement of our design is the calibrated SR-snapshot sequence which numerically measures the relaxation rate and makes the use of another method for acquisition of reference relaxation rates obsolete. This setup is used in our institution to consecutively measure the tumor response to anti-angiogenic drugs reliably and reproducibly. This is essential for the successful completion of longitudinal preclinical studies.

References:

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