Cerebral blood volume fraction mapping in a C6 brain tumor model using RSST$_1$-MRI with an intravascular contrast agent: Gd-ACX

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Introduction

The recently developed Rapid Steady State T_1 (RSST$_1$) method (1,2) is used for cerebral blood volume fraction (CBVf) mapping in a C6 tumor model in rats. Gadolinium complexed to an experimental α-cyclodextrin derivative (ACX) (3) results in a MRI contrast agent (CA) with about twice the longitudinal and transversal relaxivity of Gd-DOTA and characterized by an intravascular confinement in Gd-DOTA permeable tumor vasculature (4). In this work, its potential for the assessment of tumor angiogenesis is demonstrated.

Subjects and Methods

3 healthy and 8 male Wistar rats 21 days after intrastriatal injection of 10^5 C6-tumor cells were imaged at 2.35T with an Inversion-Recovery-FLASH sequence (TR = 750 ms, T_{inv} = 325 ms), which suppresses the signal from extravascular tissue characterized by T_1 > 1 s while allowing complete relaxation of the compartment containing the CA. Coronal images containing tumor sections, contralateral cerebral tissue and temporal muscles were acquired for 5 minutes to observe the signal evolution just after injection of 0.05 mmol/kg Gd-ACX, and 60 minutes later after injection of 0.1 mmol/kg Gd-DOTA. CBVf maps were obtained by subtracting the signal acquired before CA injection from the post injection signal divided by the equilibrium signal from both compartments acquired with TR = 10 s. Each signal is averaged over one minute at constant amplitude. After the MRI experiments, the brains were frozen in liquid nitrogen one minute after intravenous injection of 6 mg Hoechst 33342 (fluorescent marker with similar diffusion properties as Gd-DOTA) (5).

Results

Fig. 1 shows a typical signal evolution averaged over two regions of interest in tumor and contralateral tissue from one brain. A signal decrease would indicate CA loss with an increase of blood T_1 above T_{inv}/5. A continuous signal rise as observed in tumor tissue after Gd-DOTA injection for the entire acquisition time is due to CA extravasation, while the constant signal amplitude obtained from healthy brain tissue after Gd-ACX and Gd-DOTA injection reflects the thermal equilibrium magnetization of the intravascular compartment. In the brain tissue contralateral to the tumor the mean CBVf (n = 8) is 0.94 ± 0.16% with Gd-ACX and 1.03 ± 0.23% with Gd-DOTA (Fig. 2). The mean global CBVf in healthy rats (n = 3) is 1.43 ± 0.44% and 1.49 ± 0.39%, respectively. Contrary to the signal after Gd-DOTA injection, the signal from tumor tissue remains constant after Gd-ACX injection, yielding a CBVf of 1.32 ± 0.40% in the tumor periphery. Fig. 3a shows a representative CBVf-map and Fig. 3b the corresponding fluorescent microscopy image revealing low tumor vascularization with sparse highly Hoechst permeable vessels.

Discussion and conclusion

Contrary to Gd-DOTA, Gd-ACX remains intravascular in a C6-tumor, and has therefore a potential for MRI perfusion measurements, as demonstrated here for CBVf measures in tumor tissue after injection of 0.05 mmol/kg Gd-ACX. The low CBVf in this tumor model is qualitatively confirmed by microscopy. The low contralateral CBVf obtained with both CAs might be explained by the mass effect of very large C6-tumors.

Potential applications of the RSST$_1$ method in combination with Gd-ACX are the intravital monitoring of tumor angiogenesis and the assessment of the antiangiogenic efficacy of drugs in preclinical studies.

References

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Fig. 1: Signal enhancement in tumor periphery and contralateral cerebral tissue obtained by the RSST$_1$-method

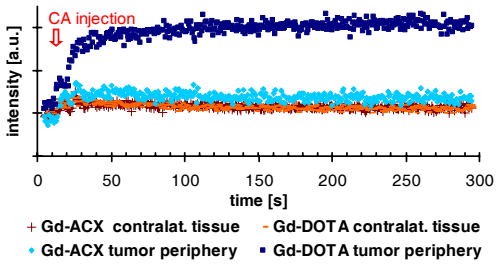

Fig. 2: Mean (n = 8) cerebral blood volume fraction obtained from three different C6-tumor regions and from contralateral cerebral tissue

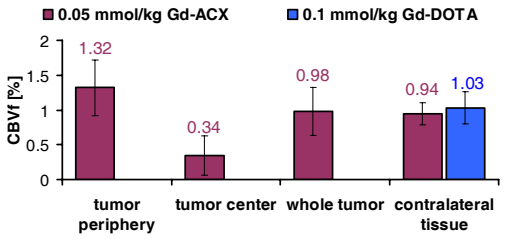

Fig. 3a: Coronal CBVf-map of a C6-tumor bearing rat. **b:** Hoechst fluorescent microscopy of the tumor section used for CBVf-measurement