Comparison of T1, T2 and T2* contrast agents in the perfusion assessment of a glioma rat model

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Introduction

Cerebral perfusion assessment by Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) involve the intravenous administration of a bolus from a paramagnetic contrast followed by the rapid, time-resolved, MR imaging of its first pass through the microvasculature of the imaged slice[1,2]. This approach relies both on the chemical nature of the contrast agent (CA) used and on the inherent properties of the MR technique implemented. Most protocols combine the use of conventional contrast agents and rapid Echo Planar MRI methods to resolve in time the transit of a bolus of the contrast medium. In the case of the brain, analysis of the kinetic curves allows for the determination of the blood volume (CBV), blood flow (CBF), mean transit time (MTT) and eventually capillary permeability[3]. In this study we compared the results obtained from bolus tracking measurements performed in a rat high grade glioma model by using contrast media with different relaxation and plasma half-life properties: Gd-DTPA (a T1 convectional CA), Dy-DTPA (a home-made T2 CA), and two iron oxide nanoparticles with increased retention time in the vasculature and employed as T2* contrast agents, Endorem® (USPIO nature) and Resovist (SPIO nature). Our last goal is to determine the most optimal method for validating the effectiveness of antiangiogenic therapies in glioma murine models.

Methods

High grade gliomas were induced in Wistar rats (200-220 g) by stereotaxic injection of C6 cells in the right caudate nucleus. MRI evaluations were carried out in a horizontal 7T system (Bruker Pharmascan®) with a ^{1}H selective birdcage resonator of 38 mm and a gradient insert of 360 mT/m. Animals were anesthetized with isofluorane 1.5 % in oxygen, placed in a heated probe and physiologically monitored during the studies. Perfusion weighted imaging studies were performed using single-shot EPI acquisition and a 0.2 M solution of the contrast medium. CA solution was rapidly injected in the tail vein as a bolus (1 mL/kg bw) 10 seconds after starting acquisition. The same protocol was followed for all the contrast media assessed. Acquisition parameters were the following: TR= 250 ms, TE = 7 ms, Av = 1, flip angle = 30^o, acquisition matrix = 64×80 corresponding to an in-plane resolution of 594x475 μm^2, number of repetitions = 150, total acquisition time = 38 seconds. Parametric perfusion maps (CBF, CBV and MTT) were generated on a pixel by pixel basis. Data were computed with a home-made software application written in MatLab. Pixel time-evolution signals were obtained, and the values corresponding to the first seconds of each temporal series were considered to set the basal level. The following expression was fitted: $\Delta R_2^*(t) = -k.\ln(S(t)/S_0(t))$. Parametric maps were obtained for six slices (1.5 mm slice thickness) in each animal and four different regions (cortex, white matter, peripheral tumor and core tumor) in every case. Parametric maps were analysed with Image J by selecting manually four brain regions containing at least 20 pixels each one and yielding a value for every slice and every rat.

Results and discussion

Figure 1 summarizes the cerebral blood volume data measured in the brain regions by employing the four contrast agents previously mentioned in a glioma developed in rats between 20-25 days after C6 cells injection. Figure 2 depicts some examples of CBV maps with each contrast medium. It can be noted that mean values measured by using Gd-DTPA, Endorem® or Resovist® are very similar in all the brain regions and even higher employing Gd-DTPA (a T1 CA) than the T2* contrast nanoparticles. Nevertheless, the use of a Dy chelate, a T2 CA with almost no effect in T1, yielded the higher CBV values by avoiding the underestimation of haemodynamic parameters associated with the T1 effect in the PWI MR signal. In all cases, the DSC studies shown that the core of the tumors was necrotic, not allowing the arrival of the contrast agent to this region. Similar behaviours were found for CBF and MTT measurements (data not shown).

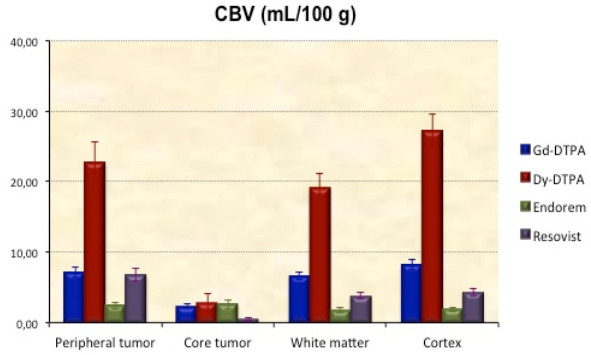

Figure 1. Mean CBV values measured in four brain regions by employing four different contrast media in a PWI-DSC study of C6 glioma rat model

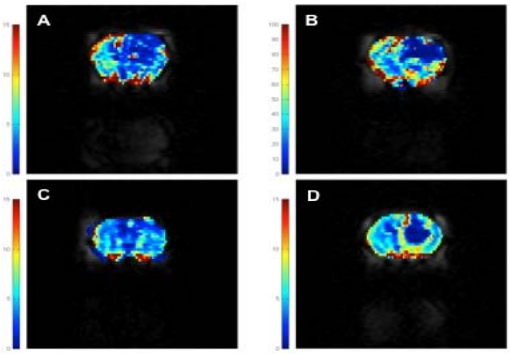

Figure 2. CBV maps from DSC-MRI studies in a high grade glioma rat model by injecting different CA's. A: GD-DTPA, B: Dy-DTPA, C: Endorem (USPIO), D: Resovist (SPIO)

Conclusions

Beside contrast media with higher T2* relaxivity and retention time in vascular system would be supposed to present improved perfusion parametric measurements, our results show that the use of Dy as paramagnetic susceptibility contrast agent in DSC MRI studies, yields the higher effects in measuring perfusion than the use not only of Gd but of iron oxide nanoparticles. Dy complexes remain then as the better choice in perfusion MRI analysis in brain tumors because of their higher influence in the T2 of the tissues, not shortening T1 values.

Bibliography

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