The effect of Gd-DTPA on the determination of the Apparent Diffusion Coefficient in liver metastases and healthy liver tissue

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Introduction

Using the Apparent Diffusion Coefficient (ADC) as a biomarker for tumors under therapy is currently under investigation. In most studies contrast enhanced imaging is included in the protocol, which results in the presence of contrast agent (CA) in tissue during the ADC measurement. Does et al. showed that ADCs in rat brains decrease with increasing intravascular susceptibility by measuring the response to step-wise injection of superparamagnetic intravascular contrast agent [1]. Yamada et al. [2] and Firat et al. [3] observed lower ADCs in normal brain, infarct and brain lesion after injection of Gd-DTPA, but the changes were not significant. Our focus is on metastases in the liver using Gd-DTPA as contrast agent. In contrast to superparamagnetic intravascular contrast agent in the brain, Gd-DTPA passes very fast from the vascular system to the tissue in normal liver as well as in metastases in the liver. This difference might change the effect magnitude and sign.

Method

In our investigation we performed diffusion weighted imaging (DWI), using a standard EPI-sequence (TE/TR= 87/900 ms, one slice in one breath hold, 3.1x3.1x10 mm^3, b= 0/100/500 s/mm^2). The MRI was performed at 1.5 T (Magnetom Sonata, Siemens Medical Solutions, Germany). The examinations were an explorative part of a clinical study, investigating PK parameters of a cationic liposomal formulation of paclitaxel (EndoTAG™-1) and its effect on tumor vascularisation. Patients exhibited large variation in tumor size, entity and previous anticancer treatments. DWI examinations were performed in 9 patients before and during the course of treatment. The protocol included one DWI acquisition before and two acquisitions (7±1, 16±1 min.) after CA injection. Gd-DTPA (Magnevist, Bayer-Schering Pharma, Germany) at a dosage of 0.1 mmol/kg body weight was injected. We started with the null hypothesis that Gd-DTPA has no influence on ADCs. Therefore we treated the 32 examinations independently. ADCs were calculated based on logarithm of the signal and linear regression using a tool developed under MATLAB (http://www.mathworks.com). For b-values smaller than 80 s/mm^2 the diffusion weighted signal is flow sensitive because of rapid attenuation due to perfusion in capillary vessels [4]. So ADCs were calculated using different combinations of b-values. The significance of the changes was tested with a two-sided paired t-test. Region of interest (ROI) for tumors included one liver lesion (all metastases). The liver ROIs are composed of 10 small parts, spread over the healthy liver tissue. ADCs were calculated for each pixel and averaged over the ROI.
Simulations of the influence of changes of T1 and T2 caused by the CA on the measurement of ADC, taking partial volume effects into account, were performed using a script developed under MATLAB.

Results

Relative changes comparing the ADC after CA injection to the value before CA were calculated. The mean relative increase of the ADC in the tumor ROIs, using all b-values for the analysis, was 2.9 % with a standard deviation (Std) of 8.4 % and a P-value of 0.05. Using only b=(0;100) and b=(100;500) for calculating ADC the mean relative change was 4.7% and 2.8%. Because of strong variations (Std. 15.8% and 11.2%) these results were not significant, but showed a tendency to a larger effect for small b-values and a remaining effect also without vessel contributions.
The same analysis was performed with a ROI in healthy liver tissue. The mean relative change of ADC including all b-values was 6.2% (Std. 6.7%, $P<0.01$). Using b= (0;100) and (100;500) the relative change of ADC was 10.8% (Std=13.9%, $P< 0.01$) and 4.8% (Std. 8.8%, $P<0.01$). So the tendency observed in tumor tissue is confirmed and even more pronounced in liver.
Simulations turned out that, taking partial volume effects into account, changes of T1 and T2 caused by CA have an influence on the determination of the ADC.

Discussion

We observed increasing ADCs in tissue of liver metastases and healthy liver after injection of contrast agent (Gd DTPA). This is in contrast to the results reported for the brain [1-3]. Chiu et al. reported a tendency to decreasing ADC after Gd-DTPA in liver and liver lesions. But the results were not significant [5]. The difference between the liver and the brain can be attributed to a very fast passage of contrast agent from the capillary system into the extravascular extracellular space (EES) in the liver. This is observed as a pronounced T1 shortening. A possible explanation for the increasing ADC could be that the signal in blood and EES, bearing higher ADCs, is amplified in comparison to the signal in the cells after CA injection. We used a quite short repetition time of TR=900ms for the acquisition so that the whole acquisition fit in one breathhold. Using very long repetition times to prevent T1-weighting is limited in the abdomen, because of movement caused by breathing.
The results of the simulations support the idea that the increasing ADC can be caused by the CA changing the weighting of the influence of the different involved compartments for quite short repetition times. Another explanation may rely on the difference in the structure of microscopic magnetic fields induced by the CA compartmentalised in the EES in the liver and in the vascular bed in the brain. Such fields were proposed as the reason for the ADC reduction in the contrast-doped brain [6]. In conclusion it should be noted that contrast agent can have an influence on the ADC in liver and liver lesions.

[1] Does MD et al., MRM 41:236(1999) **[2]** Yamada K et al., Stroke 33:1799 (2002) **[3]** Firat AK et al., Neuroradiology 48:465 (2006)
[4] Koh DM et al., AJR 188:1622 (2007) **[5]** Chiu FY et al., J Comput Assist Tomogr 29:176 (2005) **[6]** Kiselev VG, JMR 170:228 (2004)