Characterization of Tumor Perfusion; DCE-MRI During Slow Infusion

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Introduction

Various physiological models served as a basis for analyzing dynamic contrast enhanced MRI. In these models several assumptions were made, which may not hold for all types of tumors. In order to characterize better the factors contributing to dynamic contrast enhanced MRI of tumors and improve the physiological model we have designed and applied a slow infusion-"drip" protocol that allowed us to characterize better the vascular characteristics and mechanisms of contrast enhancement.

Methods

MDA-MB-231 human breast cancer cells were inoculated in the mammary of SCID mice. H-460 human non small cell lung carcinoma (NSCLC) cells were inoculated in the flank of nude mice. The mice were anesthetized throughout the experiments by exposure to 1% isoflurane in an O_2/N_20 (3:7) mixture. Images were acquired with a 4.7T Biospec spectrometer (Bruker). The imaging protocols included a gradient echo sequence (GE) and a fast inversion recovery (IR) sequence. The GE sequence was applied sequentially before and during the infusion. The IR sequence was applied before infusion and during infusion at steady state (90 minutes after start of infusion). The parameters of the 2D GE were were: TR/TE = 36.7/2.8ms, flip angle 60º, matrix size 128:128 FOV 3 cm in the lung cancer model and 4.5 cm in the breast cancer model. The parameters of the IR sequence were: TR=15 msec TE=3.5 msec TI range 10-10000 msec, matrix size 128:128, and FOV as in the GE sequence. The effective GdDTPA concentration per pixel [Ct] was calculated from the T1 data before administration (1/T10) and at steady state of GdDTPA (1/T1), using the fast exchange limit (Ct ~ extracellular volume fraction x concentration in this fraction), according to : $1/T1 = 1/T10 + R1[Ct]$ where R1 is the T1 relaxivity = 4.3 $sec^{-1}mM^{-1}$

Slow infusion - drip protocol: A solution of GdDTPA at 0.05 M is infused through the tail vein using a special pump, at a rate of 5.5 µl/min=330 µl/hour (=0.0165 mmol/hour / 25 g) for ~ 2 hours. No adverse reaction or death of the mice were observed.

Results

The time course of GdDTPA distribution in different organs, using the "drip" protocol was monitored by sequential GE images. Figure 1 shows changes in the normalized signal intensity during the infusion measured in different organs. 60 minutes after the beginning of the infusion steady state of GdDTPA concentration was reached. Hence, at this state the rate of infusion equals the rate of clearance into the urine and the intravascular and extravascular-extracellular concentration of GdDTPA became similar.

T1 measurements at steady state in regions with high vascular density (i.e. heart) or high extracellular volume (tumor cyst) indicated that the steady state concentration of GdDTPA is less then 1 mM. This suggested that the decrease in 1/T1 at the extracellular volume of the tumor was not enough to induce slow exchange conditions. Hence, this experiment enabled us to map the effective concentration of GdDTPA per pixel, Ct. Differences in signal intensity in the same organ and in different organs predominantly reflected changes in the intravascular + extracellular volume fraction. Figure 2 demonstrates the concentration distribution of GdDTPA at steadt state in breast cancer. Figure 3 demonstrates parametric maps of T1 and effective concentration in lung cancer. The histology of the breast tumor confirmed the presence of a cyst in the center. T1 maps before the infusion and at steady state show a decrease in T1 due to increased GdDTPA concentration. The largest increase in GdDTPA concentration was found in the cyst where the extracellular volume fraction is ~1. From the ratio between the cyst and the viable tumor effective concentration we have deduced an extracellular volume fraction of ~ O.2 for the latter. In the lung cancer model we observed at steady state a reduction in T1, and in the effective contrast concentration but large parts were completely not accessible to GdDTPA, presumably due to IFP. Correlation with the histological slice showed an homogeneous distribution of dense cells throughout the tumor slice. Hence the only explanation for the absence of contrast material appeared to be increased IFP and convection into areas surrounding the tumor.

Conclusions

The slow infusion protocol provided a means to explore the mechanism of contrast enhancement and extract the physiological parameters that characterize tumor perfusion and delivery. Algorithms to analyze the ""drip" data in conjunction with "bolus" data are now being developed.

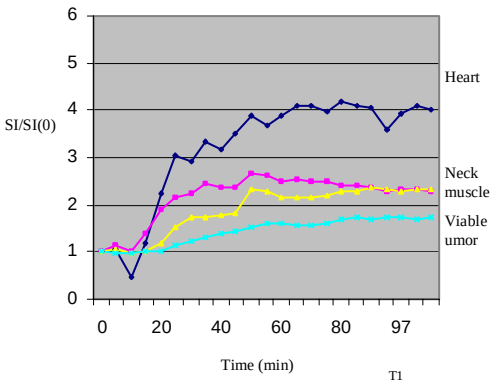

Figure 1: signal intensity in different organs of a SCID mouse bearing MDA-MB-231 tumor before and during infusion of GdDTPA.

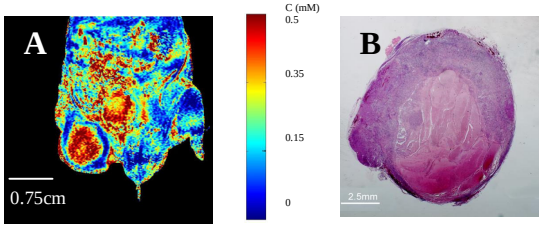

Figure 2: GdDTPA concentration map, A, in orthotopiccaly implanted human MDA-MB-231 and H&E stained histology, B, of the tumor (note the presence of the cyst).

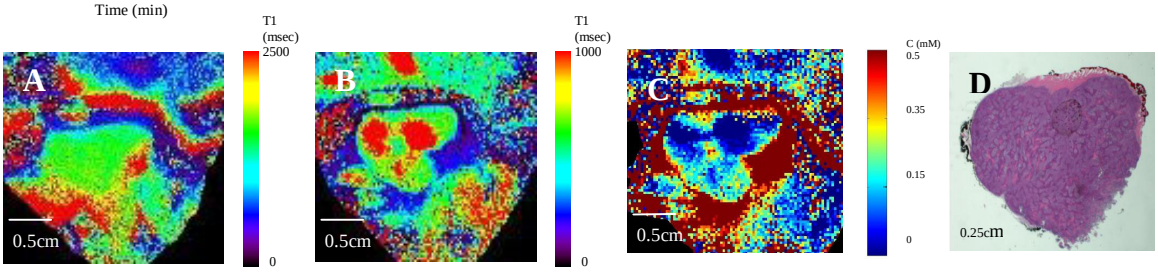

Figure 3: Parametric images of human H- 460 lung cancer implanted in the flank of nude mice: A) T1 map before infusion. B) after 90 minutes of infusion C) GdDTPA concentration map assuming extra-intracellular fast exchange D) H&E stained histology of the tumor E) GE image at 90 min of infusion that demonstrates convection due to interstitial fluid pressure (IFP).