Mapping Concentration and Pressure Dependent Transfer Constants in Tumors by Slow Infusion DCE-MRI

Y. Hassid[1], R. Margalit[1], E. Eyal[1], E. Furman-Haran[1], and H. Degani[1]

[1]Biological Regulation, Weizmann Institute of Science, Rehovot, Israel

Introduction

Many solid tumors show an increased interstitial fluid pressure (IFP), which forms a barrier to drug delivery. Herein we present a new DCE-MRI pharmacokinetic method, that takes into account both concentration and pressure gradients between the capillaries and the interstitial spaces and within the interstitium. Using this method, we demonstrate the influence of the pressure gradients on the contrast agent distribution in high IFP tumors.

Methods

The experiments were performed on Human H460 non small cell lung carcinoma cells inoculated subcutaneously 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. All animal procedures were approved by IACUC.

IFP were measured in tumors and Muscle tissue by the 'wick-in-needle' method as previously described (1).

Histological staining included H&E staining for morphological characterization and anti CD31 immunostaining of endothelial cells in order to trace the capillary distribution in the tumors.

The images were acquired with a 4.7 T Biospec spectrometer (Bruker). The MRI protocol included T1 measurements with fast SNAP inversion recovery (IR) sequence applying a non selective inversion pulse, inversion times ranging from 50 ms to 10 s, as well as fast low angle 3D GE acquisition with TE/TR = 2.1/18.3 ms and a 45^0 flip angle, matrix size 256x256, and a FOV of 4 cm.

GdDTPA was administered by slow infusion through the tail vein at a rate of 0.67 mmol/ kg/h for 2 hours. At 20 min of infusion GdDTPA reached steady state concentrations in the plasma. Following blood steady state, the other tissues also reached steady state GdDTPA concentration (1).

The 3D GE measurements were performed during the infusion. Images were analyzed using equations that include terms for the extravasation of the contrast agent from the capillaries and for the interstitial outward convection, as well as for the changes in plasma concentration during the infusion. The analysis yielded parametric maps of concentration gradient dependent transcapillary transfer constants (k^{trans}), pressure gradient dependent transfer constants ($k^{\Delta p}$), extracellular volume fractions (ν_e), and intravascular volume fractions (ν_p).

T1 relaxation measurements were performed before infusion and at 100 min of infusion when GdDTPA concentration in the blood and tissues achieved a steady state. Maps of tissue GdDTPA concentrations at steady state were calculated from the T1 measurements (1). Maps of interstitial GdDTPA concentrations at steady state were calculated by dividing the tissue GdDTPA concentration in each voxel by the corresponding ν_e value calculated from the dynamic experiment described above.

Results

Slow infusion dynamic contrast enhanced MRI studies were performed in eight ectopic H460 human tumors implanted in nude mice. The time courses of GdDTPA distribution in the tumors were monitored during slow infusion by sequential GE images. Pixel by pixel analysis of the images, as described above, yielded parametric maps of k^{trans}, $k^{\Delta p}$, ν_e, and ν_p for each tumor.

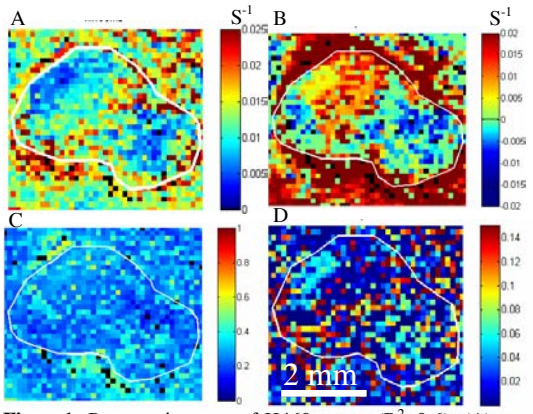

Figure1: Parametric maps of H460 tumor (R^2>0.6). (A) k^{trans} map (B) $k^{\Delta P}$ map (C) ν_e map (D) ν_p map.

Figure 1 demonstrates parametric images of a tumor that exhibited enhancement throughout its whole volume. In this tumor k^{trans} ranged from $0.1*10^{-2}$ to $2.5*10^{-2}$ s^{-1}, ν_e was similar throughout the whole tumor ranging from 0.2 to 0.5, vascular fraction ranged from 1 to 20% with a mean of 6±4%, and $k^{\Delta p}$ was either positive, in the direction of extravasation, ranging from 0 to $6.8*10^{-2}$ s^{-1}, or negative, reflecting convection, ranging from 0 to $-6.5*10^{-2}$ s^{-1}. The highest values of $k^{\Delta p}$ were found at the rim, and lower and negative values were mainly in inner parts.

T1 relaxation rate measurements of these tumors and the values of ν_e enabled us to map interstitial GdDTPA steady state concentration of the tumors. Figure 2 demonstrates a parametric map of the interstitial concentration at steady state of the same tumor as in Fig. 1. We further found a significant correlation ($p<0.001$, Spearman correlation) between $k^{\Delta p}$ and the interstitial steady state concentration, which is related to IFP (1). Pressure measurement in the center of this tumor by means of the 'wick-in-needle' technique indicated IFP of 26 mmHg. The Histopathological analysis and immunostaining of the blood vessels of this tumor performed subsequent to the MRI studies showed homogenous viable and densely cellular tissue and heterogeneous distribution of the blood vessels with microvascular density of 7% over the whole slice, similar to that obtained by the MRI analysis.

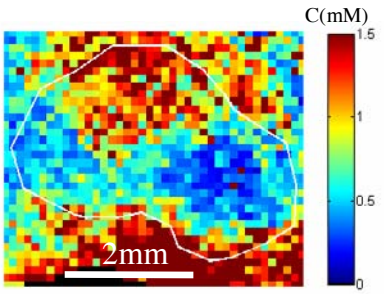

Figure 2: Steady state extracellular GdDTPA concentration map of H460 tumor.

Overall, in all tumors studied, IFP was high, ranging from 18 to 43 mmHg. The tumors were highly viable and the blood vessels density was heterogeneous. In some tumors with very high IFP (>35 mmHg), central parts were not enhanced at all, even after 90 minutes of slow infusion presumably due to strong outward convection.

Conclusion

We developed a model based DCE-MRI method that enabled us to quantify transfer constants driven by concentration gradients and pressure gradients. The significant correlation between the pressure gradients driven transfer constants and the interstitial GdDTPA concentration at steady state served to confirm the presence of such gradients and localize the regions of high IFP in the tumors.

References

1. Hassid, Y., Furman-Haran, E., Margalit, R., Eilam, R., and Degani, H. Noninvasive magnetic resonance imaging of transport and interstitial fluid pressure in ectopic human lung tumors. Cancer Res, *66:* 4159-4166, 2006.