Determination of maturity and functionality of tumor vasculature by MRI: Correlation between BOLD MRI and DCE MRI using P792 in experimental fibrosarcoma tumors

C. Baudelet[1], G. O. Cron[1], B. Gallez[1]

[1]Biomedical Magnetic Resonance Unit, Catholic University of Louvain, Brussels, Belgium

Introduction: Both BOLD MRI and DCE MRI have emerged as useful techniques for noninvasive imaging of tumor vasculature. While the utility of BOLD MRI for assessment of vessel maturation and function and DCE MRI in tumor imaging is well recognized, it is still currently unclear how both techniques are related. In the present study, we compared BOLD contrast using hypercapnia and carbogen as functional markers of vessel maturation and vessel function with DCE MRI using P792 (Vistarem®), a macromolecular Gd-based contrast agent with rapid blood clearance. A pharmacokinetic analysis allowed us to extract three parameters, namely K^{Trans}_{in}, the influx volume transfer constant, k_{ep}, and vp. The aim of this work was to answer the following questions: 1) To what extent is vessel immaturity, revealed by BOLD MRI, correlated with contrast agent uptake (or efflux) rate, a marker of capillary permeability? In the classic view of angiogenesis, immaturity of tumor vasculature is associated with transendothelial hyper-permeability. 2) To what extent is vascular function, as assessed by BOLD MRI, correlated with contrast agent arrival, another marker of tumor vessel perfusion status? 3) Is the magnitude of the BOLD signal change during carbogen breathing correlated with contrast agent uptake (or efflux) rate? Since the magnitude of the BOLD change was found to be governed by regional vascular density, and since K^{Trans}_{in} or k_{ep} can reflect sustained angiogenesis, a positive correlation might exist between these parameters. 4) Are the magnitude of the BOLD signal change during carbogen breathing and the fractional plasma volume, two parameters related to blood volume, correlated?

Methods: Intramuscularly implanted FSa II fibrosarcoma-bearing mice were imaged at 4.7T (n=7). BOLD MRI employed T2*-weighted GRE imaging with the following parameters: TR=200 ms, TE=18 ms, flip angle=45°, 12.5 kHz receiver bandwidth, matrix= 64 x 64, linear encoding order, FOV= 4 cm, 1.6 mm slice thickness, 2 averages (avg), 25.6 sec/image. A run of 140 sequential images were acquired. Maturation and functionality of the tumor vasculature were determined from the GRE images acquired during inhalation of air (first 20 scans), air containing 5% CO2 (next 30 scans), air again (30 scans), carbogen (95% O2, 5% CO2, 30 scans), then again air (last 20 scans). VD or VF were calculated from T2* weighted signal changes due to hypercapnia or carbogen breathing, respectively. DCE T1-weighted gradient-recalled echo images were obtained with the following parameters: TR=40 ms, TE=4.9 ms, 1.6 mm slice thick., α=90°, matrix=64 x 64, FOV=4 cm, 25 kHz SW, resulting in an acquisition time of 2.56 s per scan. The enhancement kinetics were continuously monitored for 8 min (200 total scans with 1 avg) and then for 1h (60 scans with 24 avg). A proton density weighted image was acquired before DCE MRI using the above cited GRE sequence but with the following parameters: TR=8s, TE=4.9 ms, 2 avg. The tracer concentration changes were fitted to a two-compartment pharmacokinetics model. Vp, K^{Trans}_{in}, and k_{ep} maps were then generated.

Results-Discussion: Our results showed that there was no correlation between vessel maturity and contrast agent uptake (K^{Trans}_{in}) or efflux (k_{ep}) , revealing uncoupling between vessel maturation and reduced permeability. In addition, DCE MRI provided higher estimates of the number of functional vessels than did BOLD MRI. This could be explained by the presence of plasma channels or by the low sensitivity of conventional BOLD MRI. The two putative markers of regional vascular density, i.e. the magnitude of BOLD signal change during carbogen challenge (VF) and the fractional plasma volume were more generally related, although the degree of correlation was very weak (r^2 in individual tumors ranging from 0.02 to 0.14). Furthermore, VF showed no correlation with K^{Trans}_{in}. A positive correlation was observed (r^2=0.75) between mean tumor VF and k_{ep}, but only when averaged over the whole tumor (not when computed on P792 enhancing tumor regions). This would merely have revealed a relation between perfusion status and the capacity to respond to carbogen breathing.

Conclusion: Characterizations of tumor microvasculature imaging by using BOLD MRI and DCE MRI appear to be largely complementary, given the weak correlations between their corresponding derived parameters.

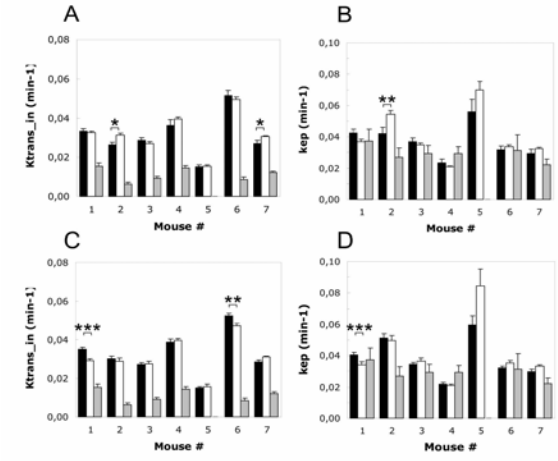

Fig. 1 (left) A. Mean K^{trans}in values for hypercapnia BOLD responsive voxels (black) versus non responsive voxels (white).
B. As for A but kep values.
C. Mean K^{trans}in values for carbogen BOLD responsive voxels (black) versus non responsive voxels (white).
D. As for C but kep values. Grey bars in plots are mean K^{trans}in (A-C) or kep (B-D) in contralateral muscle. means ± SEM. *:p<.05

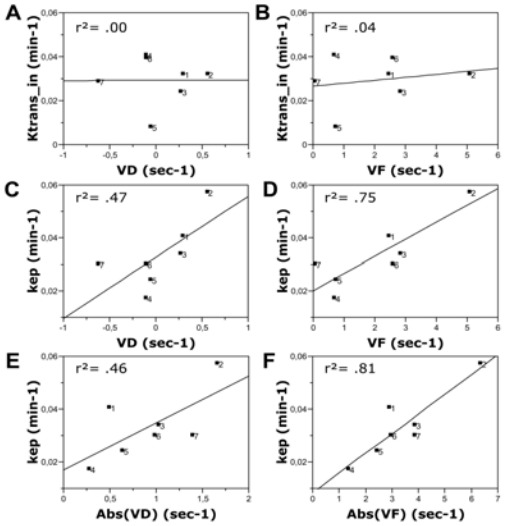

Fig. 2 (right) Mean tumor DCE MRI-derived parameters versus VD or VF BOLD MRI-derived parameters. Linear fit, R^2, and tumor labels are given.