Simultaneous dynamic R_1 and R_2* measurement for AIF assessment combined with DCE MRI in a mouse tumor model

M. Heilmann[1,2], C. Walczak[1,2], J. Vautier[1,2], J-L. Dimicoli[1,2], C. D. Thomas[1,2], M. Lupu[1,2], J. Mispelter[1,2], and A. Volk[1,2]
[1]Institut Curie, Orsay, France, [2]INSERM U759, Orsay, France

Introduction: Dynamic contrast-enhanced (DCE) MRI is extensively evaluated to assess the potential of biomarkers characterizing tumor microvasculature. Current pharmacokinetic models used with clinically approved small molecular weight contrast agents (CA) yield transfer constants (K^{trans}) which generally depends on both, capillary permeability and blood flow. In pre-clinical studies, DCE MRI is typically performed on xenograft models in rodents. The non-invasive assessment of an individual arterial input function (AIF) in mouse models remains a challenge [1]. The aim of this study was to develop a technique addressing both issues: First, combining AIF assessment with DCE MRI in a mouse tumor model without the constraint of colocalization of tumor and heart in the same slice. Second, simultaneous measurement of R_1 and R_2* time courses in the tumor in order to distinguish blood flow and capillary permeability contributions to K^{trans}.

Material and Methods: DCE MRI was performed in 7 nude mice on a colorectal tumor xenograft model at 4.7T (Biospec®, Bruker, Germany) using a home-built quadrature birdcage coil (∅=48mm). Simultaneous dynamic R_1 and R_2* measurement on 2 different slices (heart, tumor) was realized by a double-delay SR-MGE-SNAP [2] sequence ($TR/TE/TS_S/TS_L$=17ms/2.2-14.5ms/80ms/900ms) (**Fig. 1**). Respiration-triggered acquisition resulted in temporal resolution of 2s with the same spatial resolution of (0.5x0.9x2.0)mm^3 in both slices. Before and after 10min DCE MRI with injection of Dotarem®(Guerbet, France) [0.6mmol/kg in 10s], high-resolution (0.1x0.1x1.0mm^3) multiecho SE images (TR/TE=2s/10.7-85.9ms) were acquired. Data analysis performed with home-written software (IDL®, ITT, USA) was based on signal equation and pre-contrast measurement (TS=25ms-10s) for R_1 and on exponential fit for R_2* calculation. Assuming CA relaxivity r_1=4.2$mM^{-1}s^{-1}$ (phantom study), concentration time courses in tumors were analyzed by a 2-compartment model [3] yielding K^{trans} and extravascular extracellular space fraction, v_e, whereas heart curves were fitted to a biexponential function yielding amplitudes A_1 and A_2, and the distribution (m_1) and elimination (m_2) rate constants. For histopathological examination, tumors were resected, and sections of 4µm were stained for visualization of microvessels (Factor VIII) and necrosis (HE).

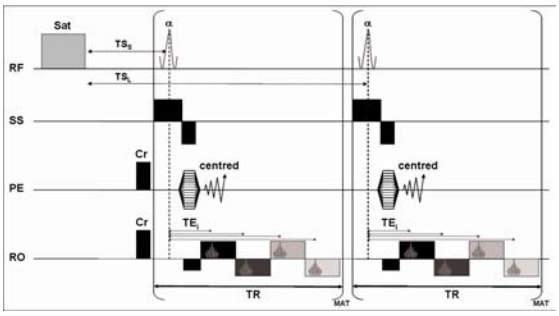

Fig. 1: *The **SR-MGE-SNAP** sequence consists of one global saturation (Sat) followed by two consecutive MGE modules (6 echo times each) – the first one with a short saturation delay, TS_S, for the AIF measurement in the heart, and the second with a long one, TS_L, for the tumor slice. In both modules k-space acquisition started in the center. (Cr: crusher gradients)*

Results and Discussion: Parameters of AIF were reproducible with mean values averaged over all animals: A_1=(5.8±2.4) kg/L, A_2=(3.1±0.3)kg/L, m_1=(1.78±0.37)min^{-1}, and m_2=(0.045±0.016)min^{-1}. In **Fig. 2**, time courses of AIF (**A**) and R_2* changes (**B**) for all animals are presented; the latter showing typical behavior of CA bolus passage. As shown in **Fig. 3**, comparison of tumor parameter maps for K^{trans} (**G**) and v_e (**H**) with immunohistochemically stained tissue sections (**E**: necrosis, **F**: microvessels) revealed lower K^{trans} and higher v_e values in necrotic regions (arrows) with respect to highly vascularized tumor rim (**). Both, time courses of R_1 (**C**) and R_2* (**D**) changes, showed slower and lower increase in the necrotic (ROI#2) compared to the rim region (ROI#3). An intermediate behavior for R_1 but a different one for R_2* changes was observed in region ROI#1 (*), which consisted of viable tissue but less vascularized than the rim. Here, R_2* showed a higher initial increase than in the rim during the first 2min, followed by a decrease ending up at a lower level than found in the rim at 10min after CA injection. Increase in R_1 accompanied by decrease in R_2*, as found in ROI#1 but not in the rim, could be explained by CA extravasation which leads to homogenization of susceptibility gradients. Therefore, based on the combined knowledge of R_1 and R_2*, the lower K^{trans} value of ROI#1 (*) compared to the rim (**) is probably not due to a lower capillary permeability but to a lower blood flow.

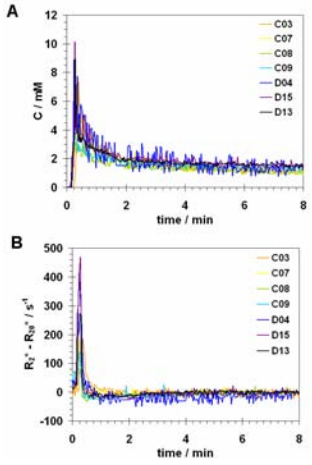

Fig. 2: *AIF (**A**) and temporal evolution of R_2* changes (**B**) obtained from simultaneous measurement of R_1 and R_2* in the heart of 7 nude mice.*

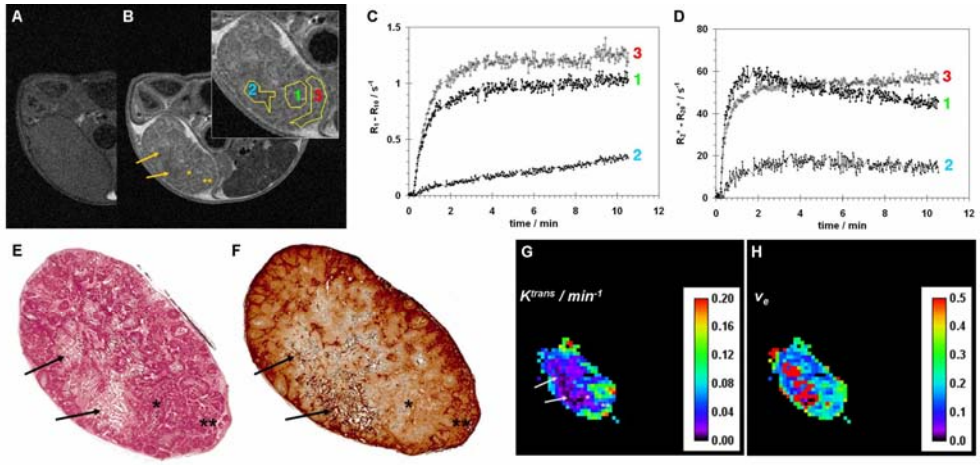

Fig. 3: *High-resolution SE images (**A**: before, **B**: after CA injection) of the tumor slice studied by DCE MRI show the regions-of-interest (ROI#1-3), for which temporal evolution of R_1 (**C**) and R_2* (**D**) changes were compared. Necrotic regions (arrows) are defined on the HE stained tumor section (**E**), whereas distinction between poorly (*) and highly (**) vascularized regions was based on the microvessel staining (**F**). Analysis of concentration time courses by a 2-compartment model [3] were applied to the tumor region yielding parameter maps for K^{trans} (**G**) and v_e (**H**).*

Conclusion: A technique was developed integrating reproducible cardiac AIF assessment in a mouse tumor model – independent of tumor localization – and simultaneous R_1 and R_2* measurement in the tumor. Mean vascular distribution and elimination rate constants for injection of Dotarem® in mice were reported. This study showed the potential of additionally available R_2* time courses in tumors for a better understanding of permeability- and perfusion-contributions to K^{trans}.

References: [1] Zhou R et al. MRM;52:248-257(2004) [2] Heilmann M et al. Proc ESMRMB;26(2006) [3] Tofts PS. JMRI;7:91-101(1997)

Acknowledgments: *Cancéropôle Ile-de-France*, Institut Curie Promoting Research Program *Anti-tumor vectorization*, grant #ACI033159 of French Research Ministry. We thank Fariba Némati (Institut Curie, Paris) for tumor implantation and Renate Bangert (DKFZ, Heidelberg) for providing the HE staining protocol.