Reference region based modeling in DCE-MRI allows reliable therapy response monitoring despite drug induced systemic changes in a rat liver tumor model

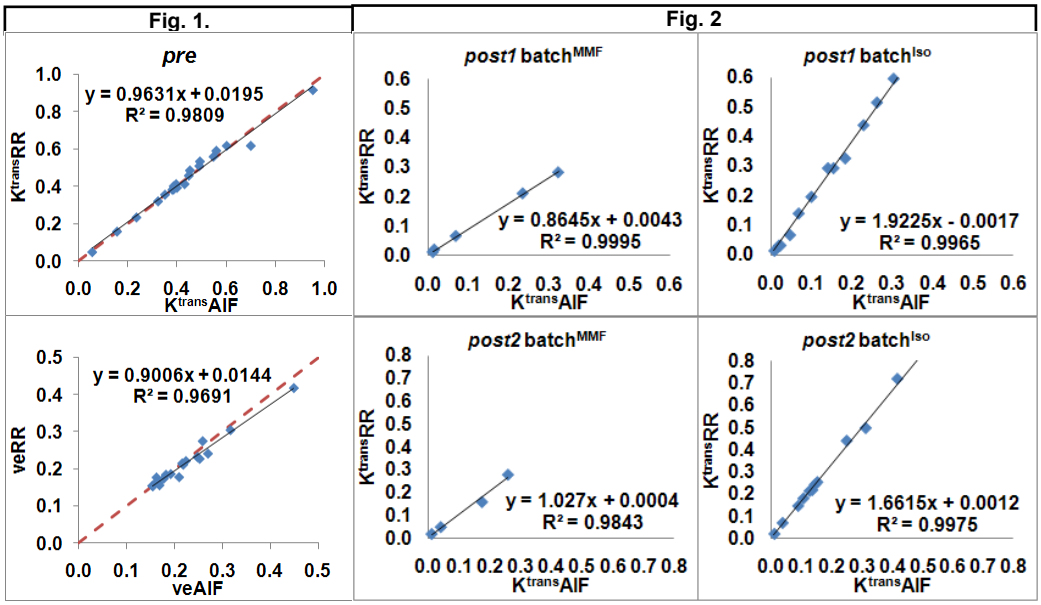
A. Steingoetter[1,2], J. Svensson[3], Y. Kosanke[1], E. Rummeny[1], and R. Braren[1]

[1]Institute of Radiology, Klinikum rechts der Isar der TU München, Munich, Germany, [2]Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Switzerland, [3]Department of Medical Radiation Physics, Malmo University Hospital, Lund University, Malmo, Sweden

Introduction: A persistent limitation in quantitative DCE-MRI is the difficulty of the simultaneous measurement of the arterial input function (AIF), and the CA concentration in the tumor tissue. The use of an AIF previously determined in a small population (population AIF (popAIF) model) or the concurrent measurement of CA uptake in a reference tissue (reference region (RR) model) are proposed alternatives. However, in longitudinal therapy response studies, changes in the AIF would introduce systematic errors when using a popAIF. In contrast, such changes should be reflected in the reference tissue data and may favour the use of the RR model. In this study, two different anaesthesia protocols, resulting in ~ - 30% change in heart rate, were used to simulate systemic changes in the AIF to analyze the robustness of popAIF [1] vs RR [2] modeling in longitudinal therapy response monitoring of an orthotopic hepatocellular carcinoma (HCC) rat tumor model.

Methods: All animal experiments were approved by the local ethics committee. 18 buffalo rats bearing unifocal HCC were imaged 12 days after tumor cell implantation (right lateral liver lobe) and imaged using a human wrist coil in a 1.5 Tesla MRI system (Achieva, PMS, The Netherlands) the day before (*pre*) and one day (*post1*) and three days after (*post2*) transarterial embolization (EmboCept®), respectively. *Pre* treatment, rats were all anesthetized by i.m. injection of a mixture of midazolam, medetomidine and fentanyl (MMF). At day *post1* and *post2*, rats were anaesthetized by gaseous infusion of isofluorane ($batch^{Iso}$, n=12) or by i.m. injection of MMF ($batch^{MMF}$, n=6). DCE-MRI experiments were performed during free breathing using a previously described dynamic radial T1 mapping technique (LLGC) [3]. Pharmacokinetic (PK) modeling was performed using an open two-compartment model [4] applying either a previously CT derived population AIF [1] or the RR method described in [2] using rat back muscle. KK^{trans} and ve of tumor tissue (K^{trans}, ve) were computed for both methods. Initially, individual reference parameters of muscle ($K^{trans}{}_m$, ve_m) were determined from the *pre* treatment data using the popAIF method. Mean reference $K^{trans}RR_m$ and $veRR_m$ values were then calculated and subsequently applied in the RR method for computation of K^{trans} and ve [2].

Results: The treatment strategy resulted in tumors exhibiting different grades of necrosis and parameter values in the range of 0.01 to 0.81 min^{-1} for K^{trans} and 0.01 to 0.48 for ve. As expected highly necrotic tumors showed the lowest values for K^{trans} and ve. Mean $K^{trans}RR_m$ and $veRR_m$ values were 0.09 ± 0.02 min^{-1} and 0.12 ± 0.02, respectively. PopAIF and muscle RR parameter values showed a strong linear correlation *pre* treatment with no significant difference for K^{trans} and ve (**Fig. 1**). Separate analysis of $batch^{Iso}$ and $batch^{MMF}$ groups for *post1* and *post2* showed good correlation within groups. However, there was a significant systematic offset in $batch^{iso}$ with lower values for popAIF compared to RR (ΔKtrans < -40 ± 3% and Δve < -26 ± 7%). In contrast, no significant difference was detected in $batch^{MMF}$ (ΔKtrans < 10 ± 10 % and Δve < 6 ± 6%) (**Fig. 2**).



Discussion: This study highlights, within a realistic setup resembling a preclinical therapy response study, the robustness and feasibility of the reference region approach. MMF induces a drop in rat cardiac frequency of ~ 30% compared to isofluorane and thereby affects AIF properties resulting in systematic modeling errors. Latter was further demonstrated in a separate parallel study. Despite no direct measurement of individual AIFs, this study gives indirect evidence that the applied RR model, to a large extend, accounts for drug induced systemic changes, here simulated by use of different anesthesia.

References: 1. Svensson J. et al, Proc 17th ISMRM 2009 (4368); 2. Yankeelov TE. et al, MRI 23:519-29 (2005); 3. Steingoetter A. et al, Proc 17th ISMRM 2009 (1487); 4. Tofts P. et al JMRI 10:223-232 (1999).