Combination of DCE and DSC MRI: Added value in the study of tumor vascularization

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Introduction: Dynamic contrast-enhanced (DCE) MRI combined with pharmacokinetic modeling yields transfer constants (K^{trans}), which typically reflect a mixture of perfusion and permeability, depending on the contrast agent (CA) as well as local characteristics of the tumor vasculature. Dynamic susceptibility-contrast (DSC) MRI combined with an intra-vascular CA is a complementary technique to study tumor perfusion. The purpose of this study was to combine DCE and DSC MRI and to demonstrate for CA of different molecular weights (MW) that this approach holds potential to better characterize tumor vascularization.

Material and Methods: Combined DCE-DSC MRI, i.e. by simultaneous measurement of $T_1(t)$ and $T_2^*(t)$, was performed in 7 nude mice with subcutaneous colorectal tumor xenografts (TC302, Institut Curie, France) at 4.7T (Biospec®, Bruker, Germany) using a home-built quadrature birdcage coil ($\varnothing$=52mm, L=70mm). R_1 and R_2^* time courses were measured in two slices (heart, tumor) by a respiration-triggered double-delay SR-MGE-SNAP sequence (TR/TE/TS$_S$/TS$_L$=17ms/2.2-14.5ms/80ms/900ms,Δx=(0.9×0.5×2mm^3,Δt=1.6-2.0s) [1]. A 0.5kDa CA (Gd-DOTA, Dotarem®, Guerbet, France) was injected in the first group (n=4) at dose D=0.318mmol/kg, and a 6kDa CA (P792, Vistarem®, Guerbet, France) at D=0.2mmol/kg in the second group (n=3). R_1 and R_2^* time courses were calculated with a home-written software (IDL®, ITT, USA) [1] for the heart and different tumor regions, latter chosen with respect to heterogeneities found in corresponding histological sections.

For DCE MRI, $R_1(t)$ was analyzed with 1) the Tofts model [2] (applying a mono-(6kDa CA) or bi-exponential (0.5kDa CA) function to describe the arterial input function (AIF)) yielding K^{trans} and 2) a mammilary 2-compartment model [3] (using the measured AIF) yielding plasma flow (PF) and extraction flow (EF). For the 0.5kDa CA, latter had to be replaced by a 1-comp model yielding the flow (F), because the two compartments could not be distinguished correctly with the 2-comp model. For DSC MRI, we expanded the linear relationship between R_2^* and voxel concentration, which is valid for intra-vascular CA, by an additional term accounting for the time-dependent susceptibility gradients due to CA leakage:

$$\Delta R_2^*(t) = R_2^*(t) - R_2^*(0) = \kappa_{20} \cdot C(t) + \kappa_{21} \cdot \left[C_p(t) - C_i(t)\right] \tag{1}$$

The 2-comp model analysis of $\Delta R_1(t)$ provided the CA concentrations of the voxel, $C(t)$, the plasma, $C_p(t)$, and the interstitial space, $C_i(t)$. Relaxation rate changes, $\Delta R_2^*(t)$, could then be fitted to Eq. 1 yielding two parameters referred to as κ_{20} and κ_{21}.

Results and Discussion: For the 6kDa CA, K^{trans} (mean±std: 0.0014±0.0006min^{-1}) and EF (0.63±0.25ml/(100ml·min)) showed a correlation (R^2=0.86) indicating that K^{trans} was a good measure for CA extravasation and therewith reflected capillary permeability (Fig. 1). Furthermore, a mean plasma flow of PF=(4.2±3.2)ml/(100ml·min^{-1}) was measured in this tumor model. For the 0.5kDa CA, only a 1-comp model could be applied, for which F (2.7±0.9ml/(100ml·min)) was correlated (R^2=0.90) to K^{trans} (0.0073±0.0025min^{-1}) indicating that, here, K^{trans} was essentially perfusion weighted (Fig. 1). It should be noted that F was of the same order of magnitude than PF, which even strengthened the hypothesis of perfusion weighted K^{trans} values for the low molecular weight CA.

All ΔR_2^* time courses of the 6kDa CA were analyzed according to Eq. 1 yielding (mean±std) κ_{20}=198±54mM^{-1} s^{-1} and κ_{21}=12.7±8.7mM^{-1} s^{-1}. In Figure 2, two representative examples (a: low EF, b: high EF) are given showing the measured data (black) overlaid by the model fit (Eq. 1) without (κ_{21}=0, blue) and with ($\kappa_{21}\neq$0, red) CA leakage correction. The model fit described the measured data well when CA leakage was corrected. In contrast, without accounting for CA leakage the model fit differed from measured data. This mismatch was more important in the early kinetic phase as well as for regions with high extraction flows (Fig. 2b). Furthermore, a correlation (R^2=0.78) between κ_{21} and EF was observed (Fig. 3). As the physiological meaning of κ_{21} has to be studied in more detail first, here, only a hypothetical interpretation can be given: Assuming that κ_{21} is related to vascular architecture, the observed correlation could indicate a relationship between vascular architecture and capillary permeability.
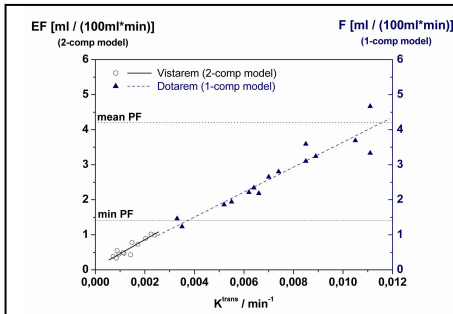

Fig. 1: Comparison of K^{trans} with extraction flow (2-comp model) for the 6kDa CA (R^2=0.86) and with flow (1-comp model) for the 0.5kDa CA (R^2=0.9) showed a correlation. Horizontal lines indicate mean/min. plasma flow obtained from 2-comp model analysis of the P792 data.
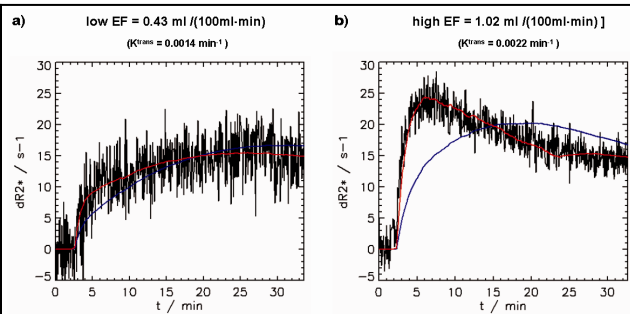
Fig. 2: Example curves of relaxation rate changes, $\Delta R_2^*(t)$, analyzed without (κ_{21}=0, blue line) and with ($\kappa_{21}\neq$0, red line) correction of contrast agent leakage (Eq. 1) for **a)** low and **b)** high extraction flow. $\Delta R_2^*(t)$ was always better described when considering an additional term accounting for susceptibility gradients created by CA exchange between plasma and interstitial space than without.
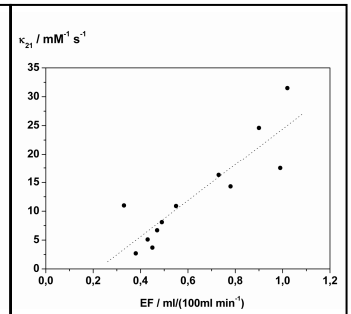
Fig. 3: Parameter κ_{21}, correcting $\Delta R_2^*(t)$ for susceptibility gradients due to CA leakage (Eq. 1), showed a correlation with the extraction flow (R^2=0.78) obtained from the 2-comp model analysis of $\Delta R_1(t)$.

Conclusion: In the studied tumor model, the 6 kDa CA was suitable for assessing heterogeneous capillary permeability by measuring K^{trans}, whereas the 0.5kDa CA yielded perfusion weighted K^{trans} values. Furthermore, a description of R_2^* time courses in the presence of CA leakage was proposed, which accounts for additional susceptibility gradients due to CA extravasation and depending on the concentration gradient between intra- and extra-vascular space. The combination of DCE and DSC MRI in one single measurement yielded the parameters κ_{20} and κ_{21}. Their physiological meaning will be studied further in order to better understand whether and how they are related to intra-voxel cellular distribution and vascular architecture.

References: [1] Heilmann M et al. Magn Reson Mater Phy (2007) DOI:10.1007/s10334-007-0082-1 [2] Tofts PS. JMRI (1997) 7:91-101 [3] Brix G et al. Magn Reson Med (2004) 52:420-429