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 (Ktrans) 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 T1(t) and T2*(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 (G=52mm, L=70mm). R1 and R2* time courses were measured in two slices (heart, tumor) by a respiratory-triggered double-delay-SR-MGE-SNAP sequence (TR/TE/TSi/TS=17ms/2.2-14.5ms/80ms/900ms, Δx=0.9×0.5×2mm, 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). R1 and R2* 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, R1(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 Ktrans and 2) a mammillary 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 R2* 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:

\[ ΔR2* (t) = R2* (t) - R2* (0) = \kappa_21[C_i(t) - C_p(t)] + \kappa_20[ΔC_p(t)] \]  

(1)
The 2-comp model analysis of ΔR2*(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, ΔR2*(t), could then be fitted to Eq. 1 yielding two parameters related to κ20 and κ21.

Results and Discussion: For the 6kDa CA, Ktrans (mean±std=0.0014±0.0006min⁻¹) and EF (0.63±0.25ml/(100ml·min)) showed a correlation (R²=0.86) indicating that Ktrans 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) 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 (R²=0.90) to Ktrans (0.0073±0.0025min⁻¹) indicating that, here, Ktrans 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 Ktrans values for the low molecular weight CA.

All ΔR2* time courses of the 6kDa CA were analyzed according to Eq. 1 yielding (mean±std=198±54nm/s) and κ21=12.7±8.7nm/s 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 (κ20=0, blue line) and with (κ20=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 (R²=0.78) between κ21 and EF was observed (Fig. 3). As the physiological meaning of κ21 has to be studied in more detail first, here, only a hypothetical interpretation can be given: Assuming that κ21 is related to vascular architecture, the observed correlation could indicate a relationship between vascular architecture and capillary permeability.

Conclusion: In the studied tumor model, the 6 kDa CA was suitable for assessing heterogeneous capillary permeability by measuring Ktrans, whereas the 0.5kDa CA yielded perfusion weighted Ktrans values. Furthermore, a description of R2* 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 κ20 and κ21. 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.


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