Tracer kinetic analysis of a simultaneous T1- and T2* measurement in a tumor model

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INTRODUCTION Two measurement approaches exist for the quantification of tissue perfusion and permeability with a bolus-tracking experiment: T1-weighted dynamic contrast enhanced MRI (DCE-MRI), and T2*-weighted dynamic susceptibility contrast MRI (DSC-MRI). The latter has the advantage of strong signal changes even when the tracer is compartmentalized in a small fraction of the tissue volume. One the other hand, DSC-MRI does not allow for absolute quantification since the relaxivity of the contrast agent differs strongly between tissue and arterial blood [1]. Moreover, when the tracer extravasates out of the vasculature the loss of microscopic gradients may lead to a gradual reduction in T2* relaxivity during the acquisition. The aim of this study is to measure the magnitude of the error introduced by these effects using a sequence that allows for simultaneous measurement of T1 and T2* at high temporal resolution [2].

MATERIALS AND METHODS The measurement sequence is described in detail in [2]. It combines a saturation-recovery Turbo-Flash sequence with a multi-gradient-echo sequence with a temporal resolution of 1.8s. Data were obtained from three mice, measured during the passage of a bolus of 0.6 mmol/kg Gd-DOTA (Dotarem, Guerbet, France) injected in 10s. For each mouse, signal-time curves were measured in the heart to determine the arterial input function, and in three different regions within subcutaneously implanted fragments of a human colorectal cancer: in the necrosis, and in a highly- and poorly vascularized part of the tumor. Data were processed in IDL 6.4 (ITT Visual Information Solutions, Boulder, CO). Relaxation rates R1 and R2* were quantified for each dynamic using the signal analysis presented in [2]. R1 and R2* time curves were fitted independently to a full two-compartment model [3], which produces four independent parameters: the plasma flow F_P, the plasma mean transit time T_P, the extraction flow F_E across the capillary wall, and the mean transit time of the interstitium T_I . These parameters can be combined using the central volume theorem to determine the volumes V_P and V_I of plasma and interstitium, respectively. To verify the dependence of the T2* relaxivity on the distribution of the tracer within the tissue, the fitted model parameters for the T1 data were used to determine the tracer concentrations $C_P(t)$ and $C_I(t)$ in the plasma and interstitium, respectively. From these time curves, a partition coefficient $\lambda=(C_P-C_I)/(C_P+C_I)$ was determined as a function of time. With this definition, $\lambda = 1$ if the tracer is purely intravascular, $\lambda = -1$ if the tracer is purely extravascular, and $\lambda = 0$ when the tracer is equally distributed over both compartments. The T2* relaxivity was measured as a function of time by $k2^*=\Delta R2^*/(V_PC_P+V_IC_I)$, and plotted as a function of the partition coefficient λ.

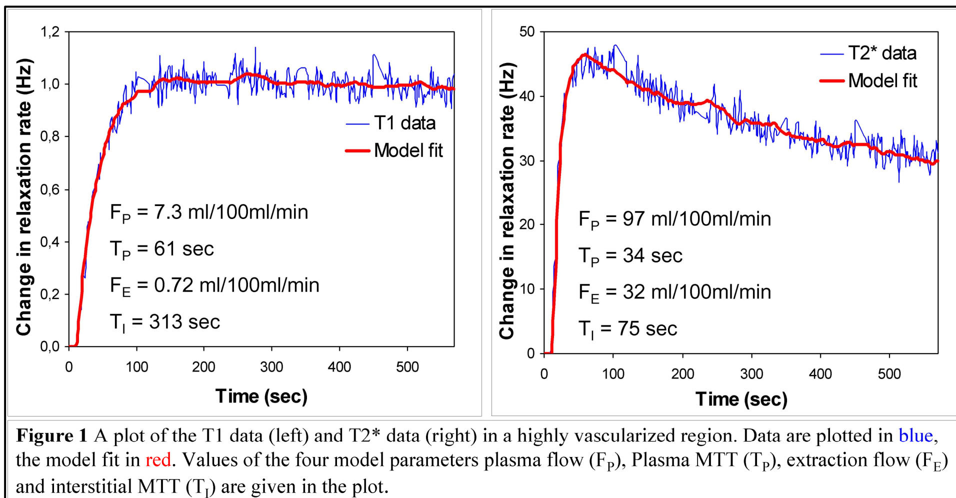

Figure 1 A plot of the T1 data (left) and T2* data (right) in a highly vascularized region. Data are plotted in blue, the model fit in red. Values of the four model parameters plasma flow (F_P), Plasma MTT (T_P), extraction flow (F_E) and interstitial MTT (T_I) are given in the plot.

RESULTS An example of the data and the model fits to R1 and R2* data is given in figure 1. The R2* curves typically decrease more rapidly after the initial vascular fase, but the model fits are equally accurate for both types of curves. The flow- and volume parameters calculated from the R2* curves are significantly higher than those of the R1 curves: on the average, F_P values are higher by a factor 18, V_P by a factor 9.5, F_E by a factor 35 and V_I by a factor 13. The mean transit times are lower when measured from R2* curves: a factor 0.5 for T_P and a factor 0.3 for T_I. With one exception, the total volume of distribution V_P+V_I calculated from R2* was unphysical (mean 160 ml/100ml) but in all cases it was within acceptable ranges for R1 (mean 15 ml/100ml). Plasma mean transit time values are overestimated with both methods, presumably due to large bolus dispersion between the arterial site and the tissue. The T2* relaxivity is plotted in figure 2 for four examples. The partition coefficient never reached negative values, and has a minimum near $\lambda = 0.5$ for tissue types with slower extravasation. In all cases the function $k2^*(\lambda)$ was increasing on the interval [0,1]. The equilibrium relaxivity $k2^*(0)$ ranged between 100-200 Hz/mM, and the relaxivity $k2^*(1)$ of the intravascular tracer ranged from 300-700 Hz/mM. Figure 2 also shows that the regions differ in the rate and the manner in which the relaxivity decreases to its equilibrium value.

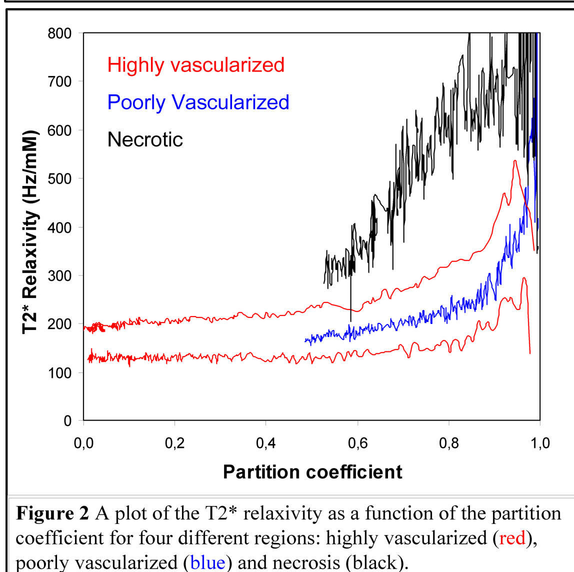

Figure 2 A plot of the T2* relaxivity as a function of the partition coefficient for four different regions: highly vascularized (red), poorly vascularized (blue) and necrosis (black).

DISCUSSION/CONCLUSION The results provide experimental confirmation of two different quantification errors in DSC-MRI. First, the effect of the difference in T2* relaxivity between pure blood and tissue [1] produces a serious overestimation in all flow- and volume parameters. Second, the T2* relaxivity changes when the contrast agent redistributes within the tissue due to extravasation. The loss of T2* effects leads to an apparent wash-out of tracer which cannot be distinguished from actual wash-out by tracer kinetic analysis, leading to underestimated values for the mean transit times. This is independent on T1-related leakage effects [4], which also lead to T2* signal increase during extravasation, but which are eliminated here by the fact that T2* values are measured dynamically. As such, these results indicate that tissue permeability cannot be measured from T2* data alone. On the other hand, they show that the combination of T1- and T2* data produces additional information in the form of the $k2^*(\lambda)$ curves. The T2* relaxivities measured in this tumor model are significantly higher than the value of 40 Hz/mM predicted for normal brain tissue [1], which suggests a strong sensitivity to tissue type. If a theoretical model is developed that provides a deeper understanding in the parameters affecting the behaviour of $k2^*(\lambda)$, additional parameters may be derived that allow a more complete characterization of the tissue geometry.

REFERENCES [1] Kiselev (2005) *JMRI* **22**: 693-696, [2] Heilmann et al. (2007) *MAGMA* DOI 10.1007/s10334-007-0082-2, [3] Brix et al (2004) *MRM* **52**: 420-429, [4] Quarles et al (2005) *MRM* **53**: 1307-1316