Improved assessment of angiogenesis-related MRI-readouts by using macro-molecular contrast agents

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Introduction

Tumor blood volume (TBV) and vascular permeability can be used as biomarkers for the measurement of tumor neo-vascularization and to evaluate treatment efficacy of anti-angiogenetic drugs. Vascular permeability can be assessed *in vivo* by dynamic-contrast enhanced (DCE) MRI, measuring the leakage of extra-cellular paramagnetic contrast agent (CA) from the circulation into the tissue by T1-weighted gradient echo sequences. Measurement of TBV is generally based on dynamic-susceptibility-contrast (DSC) MRI. Application of DSC-MRI for tumor imaging either requires the use of complex data correction procedures (where applicable) or blood-pool CA. Hence, parallel assessment of permeability and TBV has until now been based on the serial acquisition of two imaging sequences often employing different CAs. However, for many applications it would be attractive to extract this information from a single data set. Presently, new classes of CA with different pharmaco-kinetic profiles become available, which potentially can improve the assessment of these readouts.

In this study, it will be demonstrated that local TBV and vascular permeability can both be calculated form the temporal profile of a dynamic T1-relaxation measurement after a single injection of the macro-molecular contrast agent Vistarem™ in rats bearing mammary BN472 tumors. Values obtained for TBV will be compared with those derived from a DSC-measurement using small particles of iron oxide (SPIO).

Material and Methods

MRI: (A) Dynamic T1-weighted IR-recovery sequence (TI=1200msec, TR=10msec, TE=3msec, α=12°), 128 images, temporal resolution of 5.7 s/image. The relative concentration of CA in tissue (C_t) was calculated from the signal intensities in the T1-weighted images and a reference image, which was acquired without the IR-pulse. (B) Dynamic T2-weighted GE-sequence (TR=10.7 msec, TE=3.1 msec), 40 images, temporal resolution of 1 s/image.

Contrast agent: (A) P792 (Vistarem™, Guerbet, Paris) was injected as a bolus at a dose of 1.4 ml/kg body weight. (B) AMI-25 (Endorem™, Guerbet, Paris) was injected as a bolus at a volume of 400µl.

Animal model: Orthotopic mammary BN472 tumors in Brown-Norway rats.

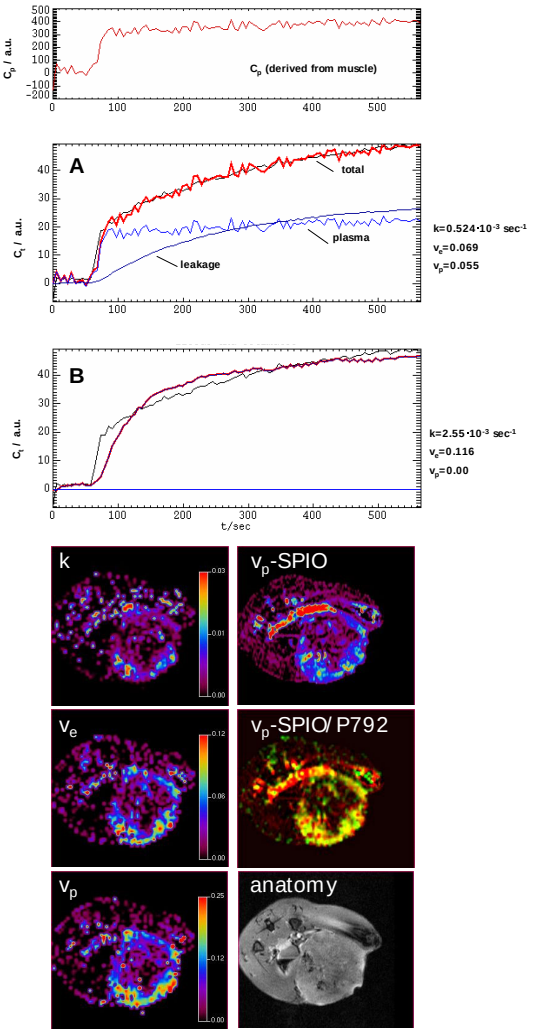
Data analysis: A 2-compartment model was used to describe the temporal profile of the CA concentration in tumor tissue (C_t) allowing to estimate the permeability surface product k, the leakage space v_e and the fractional blood volume v_p:

$$C_t(t) = k\int_0^t \exp\left(-k/v_e\,(t-t')\right) C_p\,dt' + v_p C_p \qquad \text{(Eq. 1)}$$

The plasma concentration C_p can be derived from muscle tissue since P792 is a blood pool agent confined to the vascular space in normal tissue. A constant C_p of 3% was assumed for muscle tissue. Analysis was carried out on region-of-interest (ROIs), which comprised areas close to the tumor rim and for individual pixels.

Result

Figure 1 (top) shows the least-square fit for relative concentration time curves of plasma (derived from muscle signal) and tumor signal for the full model (A) and C_p=0 (B). The least square fit in (A) reveals a very good match of measured data and the model. On a qualitative level, the initial signal slope clearly shows two phases: an initial steep rise corresponding to the arrival of the tracer in the local circulation and a slower increase reflecting leakage of CA into the tissue. In contrast, neglecting the contribution of C_p (B) to the signal leads to a poor fit result and an overestimation of k. The lower panels show parametric maps, which display the results of the regression procedure for individual pixels. Vascular permeability k, leakage space v_e and fractional blood volume are largest in the rim of the tumor. Moreover, a good spatial match was found for v_p calculated by the DCE-method (green) and v_p calculated from the DSC-measurement (red).



Discussion

The data demonstrates the feasibility to measure vascular permeability and TBV by a single dynamic T1-weighted image sequence. Due to the weak leakage of P792 from the circulation into tumor tissue in BN472 tumors, two characteristic contributions to the signal enhancement profiles are observed: one corresponds to the arrival of CA in the tumor vasculature (fast) and another one corresponding to the leakage of CA into tissue (slow). When using low molecular weight contrast agents these two processes are of the same time scale and, hence, cannot not be separated, rendering the extraction of v_p by Eq.1 difficult. Modeling the contribution of C_p to the MR signal improves the accuracy of the estimate for k, which is of relevance in highly vascularized tumor regions. Finally, it could be demonstrated that v_p as calculated from the DCE-approach closely matches v_p derived from DSC-MRI, which is currently the methodological reference for TBV measurements in animal studies. In conclusion, the DCE-approach described here allows assessment of two important markers for tumor physiology. The main advantage of the method is its translatability into clinical studies provided that macromolecular CA will be approved for use in humans in the next future.