Novel pharmacokinetic model for fractional blood volume quantification with the Rapid Steady State T_1 MRI technique in tumors with Gd-DOTA permeable vasculature

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Introduction: Noninvasive quantification of tumor blood volume fraction (BVf) by magnetic resonance imaging (MRI) using clinically approved gadolinium-based contrast agents (CA) is of great interest for tumor classification and grading [1], and in particular for monitoring antiangiogenic therapies [2]. However, tumor neovasculature is often permeable to these low-molecular weight CA, preventing BVf quantification with most MRI techniques that are based on the vascular confinement of the CA. The Rapid Steady State T_1 ($RSST_1$) technique [3] for BVf quantification, originally developed [4] and validated [5] using blood pool CA, was extended for the case of permeable vasculature [6] by modeling the transendothelial CA leakage without requiring the arterial input function. The present work aims at validating the $RSST_1$ technique for BVf quantification in a C6 brain tumor model with vasculature permeable to Gd-DOTA. A ΔR_2* steady state technique employing an iron-oxide-based blood pool CA known to remain confined to the tumor vasculature in the C6 tumor model [7] and BVf estimations obtained from histological sections were used as reference methods.

Material and methods: All animal experiments were approved by the institutional ethic committee. Eight Wistar rats were imaged at B_0 = 4.7T in a 47/40 Bruker Biospec USR AV III scanner with a homogenous coil for transmission and a mouse head surface coil for reception 11 days after intrastriatal inoculation of C6 tumor cells [4]. The rats were anesthetized with 2% isoflurane in air. Body temperature, arterial blood pressure and respiration rate were monitored continuously and maintained within physiological ranges.
The $RSST_1$ acquisitions were performed with a 3D Inversion Recovery prepared MDEFT sequence (FOV 32 × 32 mm^2, matrix 32 × 32, 8 coronal slices × 2 mm, non-selective adiabatic inversion pulse, TE = 1.2 ms, TR_{echo} = 6.5 ms, excitation flip angle = 10°). A proton density map for signal normalization was acquired first (TR = 10 s, T_{inv} = 9 s, duration 1 min 20 s). Gd-DOTA (Guerbet Laboratories, Aulnay-sous-Bois, France, 0.6 mmol/kg) was injected intravenously during a dynamic $RSST_1$ acquisition (TR = 750 ms, T_{inv} = 306 ms, 6 s/repetition). One hour was allowed for CA washout without removing the rat from the scanner. ΔR_2* steady state imaging was performed with the same slice geometry using a Multi Gradient Echo sequence (matrix 64 ×128, TR = 6 s, 30 echoes at TE = 3 ms, 6 ms, …, 90 ms, 2 averages, duration 12 min 48 s) prior to and 4 minutes after injection of 0.2 mmol/kg MoldayION (BioPAL, Worcester, MA). At the end of the experiment, the brains were excised for immunofluorescent staining (anti-collagen IV, Southern Biotechnology Associates., Birmingham, AL) of the epithelial basal lamina.
The $RSST_1$ signal was normalized according to $S_{norm}(t) = (S_{post}(t) - \langle S_{pre} \rangle)/S_0$, where $S_{post}(t)$ is the post contrast signal and $\langle S_{pre} \rangle$ is the average pre contrast signal, while S_0 is the proton density signal providing the equilibrium signal from the vascular and extravascular compartment. In a large vessel and in brain tissue with intact blood brain barrier, $S_{norm}(t)$ reaches a maximum amplitude and remains constant (= "steady state", cf. Figure 1) for approximately one minute. The CA being confined to the vascular space, S_{norm} equals the BVf during the steady state [3,4]. In tissues with permeability limited CA leakage [8], the signal increase during this steady state time interval is modeled according to: $S_{norm}(t) = S_{iv} + S_{ev}[1 - \exp(-\kappa^*(t-t_0))]$, where t_0 is the time of CA injection, S_{iv} is the extrapolated BVf, S_{ev} is the volume fraction of the leakage compartment and κ is a parameter related to the endothelial permeability [6].
The BVf was obtained from the ΔR_2* steady state technique according to $BVf = 0.03\,\Delta R_2/(4\pi^*\gamma^*B_0^*\Delta\chi)$ [7] with $\Delta R_2^* = 1/T_2^*_{post} - 1/T_2^*_{pre}$, B_0 = 4.7 T, γ = 26.75 10^7 rad s^{-1} $T^{-1}$and $\Delta\chi$ = 0.28 10^{-6} CGS. T_2* maps pre and post MoldayION injection were fitted using a monoexponential decay function. The vascular area fraction A_A = Σvessel area/tumor area was used as histological BVf.

Results and discussion: Figure 1 illustrates how S_{norm} reaches a steady state for voxels in large vessels (BVf = 1).and in contralateral brain tissue (BVf ≈ 0.025) for about one minute, During this time interval the exponential model is fitted to the signal from tumor tissue. The histogram in Figure 2 shows regional BVf averaged over all eight rats. The contralateral BVf and the tumoral BVf are in accordance with values obtained in previous studies [9]. BVf obtained with the different techniques are not significantly different ($p \geq 0.2$), corroborating the $RSST_1$ technique and the pharmacokinetic model.

Conclusion: The $RSST_1$ technique using a pharmacokinetic model for tumor BVf quantification is validated with a different MRI technique using a blood pool CA and by histology. The $RSST_1$ technique is powerful because, despite leakage from tumor vasculature, it can be used with gadolinium-based CA that are routinely used in clinical practice. In contrast to conventional dynamic contrast enhanced MRI techniques the $RSST_1$ technique in combination with the pharmacokinetic model does not require determination of the arterial input function making BVf quantification straightforward. The $RSST_1$ technique is easy to implement on clinical MRI scanners.

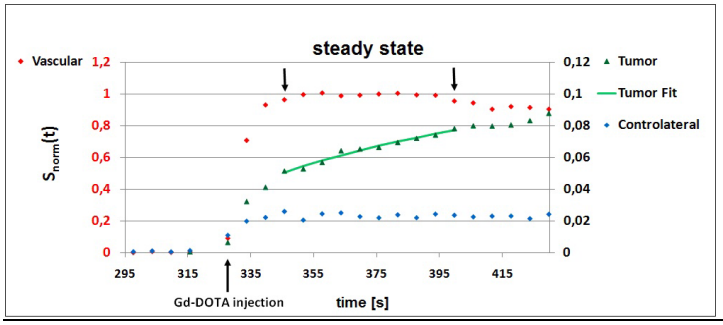

Fig. 1: Normalized $RSST_1$ signal in a representative rat. Time of Gd-DOTA injection and duration of steady state interval are marked with arrows.

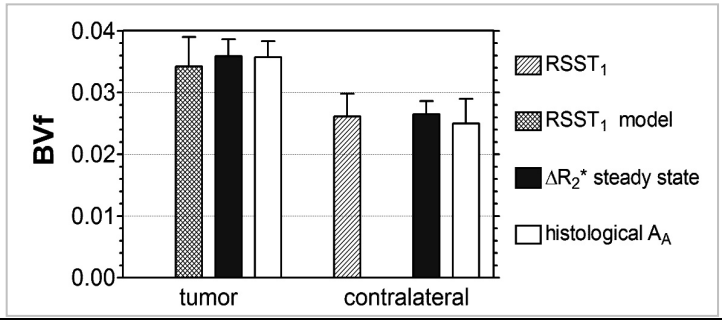

Fig. 2: Regional BVf obtained with these techniques are not significantly different. A_A = vascular area fraction

[1] Aronen et al, Radiology 1994; [2] Akella et al, J Magn Reson Imaging 2004; [3] Perles-Barbacaru and Lahrech, J Cereb Blood Flow Metab 2007; [4] Lahrech et al, J Cereb Blood Flow Metab 2008; [5] Perles-Barbacaru et al, J Cereb Blood Flow Metab 2011; [6] Perles-Barbacaru et al, ESMRMB 2008; [7] Tropres et al, MRM 2004; [8] Tofts et al, J Magn Reson Imaging 1999; [9] Julien et al, Br J Cancer. 2004;