Estimation of R1 changes from Dual bolus DCE-MRI in Vestibular Schwannomas and Meningiomas of Patients Undergoing Treatment of Bevacizumab

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Target audience: Investigators using DCE-MRI in tumor studies

Purpose: Mapping 3D tissue T1 relaxation rate, R1 (≡ 1/T1) is essential in converting DCE-MRI to 4D contrast concentration images. The purpose of this study was 1) to test reliability of R1 mapping methods; 2) to estimate R1 changes between two bolus injections of contrast agent (CA), the prebolus and the main dose, with the use of dual temporal resolution approach (DTR)[1]. A group of patients with brain tumors undergoing antiangiogenic were used for the validation.

Methods: In DTR, the spatial distribution of R1 needs to be estimated twice. The first is to map the tissue native $R1_N$ before the administration of contrast media (CA). The second $R1_{init}$ is estimated immediately before administration of the main dose of CA. $R1_{init}$ might be higher than $R1_N$ if CA from the prebolus was not entirely eliminated from the brain tissue and lesions. Alternatively, the changes of R1 from $R1_N$ to. $R1_{init}$ can be estimated from fitting the prebolous CA concentration time curve[2] with a pharmacokinetic model. e.g the Kety model, then extending the theoretical curve to the start of the 2nd injection:

$$C(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(\tau) \exp\left(-\frac{K^{trans}}{v_e}(t-\tau)\right) d\tau \qquad [1]$$

and

$$R1_{init} = R1_N + C(t_{init}) r1$$

where t_{init} is the time between the injections of first and second bolus. $r1$ is the longitudinal relaxivity of gadoterate meglumine (Gd-DOTA: Dotarem), which has a elimination half-life of 90 minutes.

DTR-DCE data were acquired from five patients with type 2 neurofibromatosis (NF2) with vestibular schwannomas (VS) and meningiomas (Me). They underwent 3 scans: baseline, 2 and 90 days post-treatment with the anti-vascular endothelial growth factor antibody, bevacizumab. Large volume high temporal resolution (HT, Δt = 1s) DCE MRI followed a small dose (0.02 mM/kg body weight) prebolus and high spatial resolution (HS, voxel size = 1x1x2 mm) series was acquired following a standard dose (0.1 mM/kg). Two sets of variable flip angle (VFA) GRE images were acquired for R1 mapping. $R1_{HT}$ (≡$R1_N$) and $R1_{HS}$ (≡$R1'_{init}$) maps were calculated (Fig 1). Three longitudinal HT and HS DCE series and associated R1 maps, (baseline, 2 days, 3 months) were spatially (4D) co-registered to baseline HS DCE-MRI images acquired on day0. 3D parametric maps of the transfer constant (K^{trans}), the fractional plasma volume (v_p) and the fractional volume of extravascular extracellular space (v_e) were calculated. WM, GM and tumors were automatically segmented for voxel-by-voxel analysis in a region of interest, i.e. tumor, GM and WM (Fig. 2).

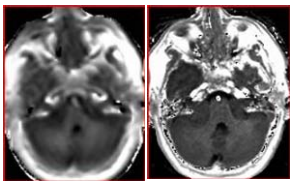

Figure 1. Central slice of coregistered 3D HT $R1_N$ (left) and HS $R1'_{init}$ (right) maps.

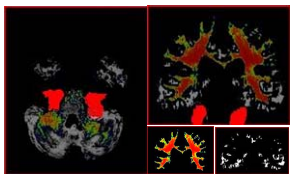

Figure 2. Combined images from segmented probability maps of GM WM and masks of VS.

Results: $R1_N$, $R1'_{init}$ of WM, GM, and brain tumors at first visit (day0) are shown in Table 1. $R1'_{init}$ calculated from the VFA GRE was compared to the one estimated using EQs 1 and 2 ($R1_{init}$). Increases of $R1'_{init}$ from $R1_N$ were 1.0%, 6.7%, 33.3% and 12.5% in GM, WM, VS and Me, respectively. The $R1_{init}$ in VS and Me overestimated by1.0% and 3.7% compared with measured $R1_{HS}$.

Figure 3 shows K^{trans} images calculated from two DCE-MRI series following prebolus and main dose, K_{HT} and K_{HS}, in a patient who had 5 scans from day0 to day450. Visual inspection shows the similar features of change of K^{trans} intensity on the low dose maps following treatment of bevacizumab. Both show earlier response to bevacizumab treatment in VS (2 days onwards) and late response in Me (7 month onwards).

Table 1. Day0, $R1_N$ ($R1_{HT}$) and $R1'_{init}$ ($R1_{HS}$) of tumor, WM and GM

Tissues	$R1_N$	$R1_{HS}$
VS	.66±.03	.88±.03*
Me	.88±.10	.99±.06†
GM	.83±.04	.82±.04
WM	1.18±.05	1.26±.05

*p < 0.0001, †p = 0.07

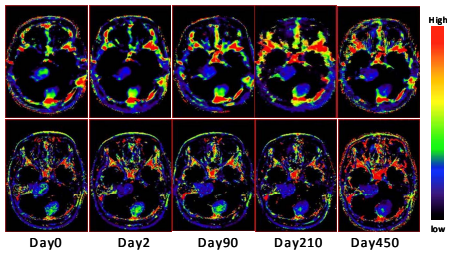

Figure 3. Coregistered 3D KHT (top) and KHS (bottom) images, showing earlier response of VS and late response of Me to antiangiogenic.

Table 2 $R1_N$, $R1'_{init}$, K_{HT} and K_{HS} of tumor under treatment

	Visit	$R1_{HT}$	$R1_{HS}$	K_{HT}	K_{HS}
VS	Day0	.66±.03	.88±.03	.13±.03	.12±.01
	Day2	.68±.05	.89±.04	.07±.01*	.09±.01*
	Day90	.70±.04	.87±.08	.08±.02†	.09±.02†
Me	Day0	.88±.10	.99±.06	.10±.05	.10±.04
	Day2	.90±.09	1.05±.05	.12±.04	.10±.05
	Day90	.88±.07	.10±.06	.10±.06	.10±.04

*p < 0.0001 and † p< 0.01

Table 2 shows K_{HT} and K_{HS} on day0, day2 and day90. In agreement with the visual inspection, there is significant early reduction (day0 onwards) of both K_{HT} and K_{HS} in the progressive VS, but not in Me. There is no significant change of mean values of R1 in brain tissue or tumors in the repeated studies.

Discussions: We have demonstrated significant R1 increase from $R1_N$ to $R1_{init}$ resulting from Gd-DOTA retained in the interstitial space in VS and Me. The amount of increase can be estimated using the Kety model. As expected R1 increase in WM and GM were much less than tumors since little contrast diffuses across capillary endothelium in normal brain tissues[3]. This study also shows that the variable flip angle (VFA) method provides fast and robust measurement of R1, which is the key step in converting DCE-MRI to 4D concentration images. Finally, we present 3D maps of K_{HT} from one-fifth dose of Gd-DOTA. The maps were comparable to the 3D K_{HS} maps where a full dose of CA was injected so that the K_{HT} achieved the same detection of changes in VS and Me induced by VEGF blockade. In conclusion, The VFA is a fast 3D T1 mapping technique. Although the $R1_{init}$ can be estimated in theory, we still recommend acquiring two VFA R1 series, one for $R1_N$ and the other for $R1_{init}$, instead of one[2], especially when different scan sequences or scan parameters were used for the prebolus and main dose DCE.

References: 1. Li et al: MRM 2012, 68:452. 2. Garpebring et al MRM 69:992, 2013. 3. Larsson et al, MRM 2009, 62:1270.