Spin- and Gradient-echo PWI with correction for T1- and T2(*)-related contrast agent extravasation effects

Heiko Schmiedeskamp[1], Matus Straka[1], Thomas Christen[1], Jalal B. Andre[2], Seema Nagpal[3], Laurence Recht[3], Reena P. Thomas[3], Michael E. Moseley[1], Greg Zaharchuk[1], and Roland Bammer[1]

[1]*Department of Radiology, Stanford University, Stanford, CA, United States,* [2]*Department of Radiology, University of Washington, Seattle, WA, United States,* [3]*Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, United States*

INTRODUCTION – It has been shown that multiecho DSC-PWI is insensitive to T_1-shortening effects that are caused by the leakage of Gadolinium-based contrast agent (CA) into the extravascular-extracellular space (EES) [1-3]. However, CA leakage into the EES also affects R_2* and R_2 [4,5], resulting in a violation of the central volume principle used in $R_2^{(*)}$-weighted DSC-PWI. Thus, estimation errors in CBV and other perfusion parameters could arise from altered CA distribution volumes. The purpose of this study was to correct multiecho spin- and gradient-echo (SAGE) EPI-based perfusion data [6,7] for R_2*- and R_2-related CA extravasation effects. Simultaneously, an additional parameter k_i was determined, which characterizes CA transfer between the intravascular plasma space (IPS) and the EES.

THEORY & METHODS – The relationship between changes in CA concentration and $\Delta R_2^{(*)}$ is shown in Eq. 1. Here, $\Delta R_{2,m}^{(*)}$ is the measured total change in $R_2^{(*)}$, $\Delta R_{2,p}^{(*)}$ is the IPS component, and $\Delta R_{2,e}^{(*)}$ is the EES component. The parameters v_p and v_e represent the volume fractions of the IPS and the EES, respectively; C_p and C_e denote the corresponding CA concentrations. In this work, we applied a simplified model that separates susceptibility effects emanating from CA within the IPS and CA within the EES, as used in [4,8] (cf. Eq. 1). In contrast to previous work, we assumed different transversal relaxivities $r_{2,p}^{(*)}$ and $r_{2,e}^{(*)}$ for the two compartments because of profound structural differences between the IPS and the EES. Eq. 2 can be derived from Eq. 1 under the assumption of unidirectional flow from the IPS to the EES and $C_e << C_p$ for the duration of the acquisition [9,10]. In Eq. 2, K^{trans} is the volume transfer constant between the IPS and the EES that cannot be directly determined using our approach. Instead, a proportional parameter $k_i = K^{trans}/v_p \cdot r_{2,e}^{(*)}/r_{2,p}^{(*)}$ results. According to Ref. [11], a two-step approach to leakage correction can be applied, which first assumes a linear relationship between $\Delta R_{2,p}^{(*)}$ and total CA concentration C_t within each voxel, as well as a linear relationship between the integral of $\Delta R_{2,p}^{(*)}$ and the integral of the arterial input function C_a, which leads to Eq. 3. The residue function R can be derived using deconvolution of Eq. 3 via singular-value decomposition [11,12]; R is then used to determine $\Delta R_{2,est}^{(*)}$, an estimate for $\Delta R_{2,p}^{(*)}$. Subsequently, a least-squares approach can be applied to determine the relative contributions of $\Delta R_{2,est}^{(*)}$ and its integral to measured $\Delta R_{2,m}^{(*)}$, resulting in k and k_i. Finally, $\Delta R_{2,est}^{(*)}$ and k_i are used to determine the leakage-corrected $\Delta R_{2,corr}^{(*)}$ (cf. Eq. 4).

$$\Delta R_{2,m}^{(*)} = \Delta R_{2,p}^{(*)} + \Delta R_{2,e}^{(*)} = r_{2,p}^{(*)} \cdot C_p \cdot v_p + r_{2,e}^{(*)} \cdot C_e \cdot v_e \quad (1)$$

$$\Delta R_{2,m}^{(*)} = \Delta R_{2,p}^{(*)} + r_{2,e}^{(*)} \cdot K^{trans} \cdot \int_0^t C_p(\tau)d\tau = \Delta R_{2,p}^{(*)} + \frac{r_{2,e}^{(*)}}{r_{2,p}^{(*)}} \cdot \frac{1}{v_p} \cdot K^{trans} \cdot \int_0^t \Delta R_{2,p}^{(*)}(\tau)d\tau \quad (2)$$

$$\Delta R_{2,m}^{(*)}(t) \approx a_1 \cdot C_t(t) + a_2 \cdot \int_0^t C_a(\tau)d\tau = \int_0^t a_1 R(t-\tau) \cdot C_a(\tau)d\tau + a_2 \cdot \int_0^t C_a(\tau)d\tau \quad (3)$$

$$\Delta R_{2,m}^{(*)} = k \cdot \Delta R_{2,est}^{(*)} + k_i \cdot \int_0^t \Delta R_{2,est}^{(*)}(\tau)d\tau \quad \text{and} \quad \Delta R_{2,corr}^{(*)} = \Delta R_{2,m}^{(*)} - k_i \cdot \int_0^t \Delta R_{2,est}^{(*)}(\tau)d\tau \quad (4)$$

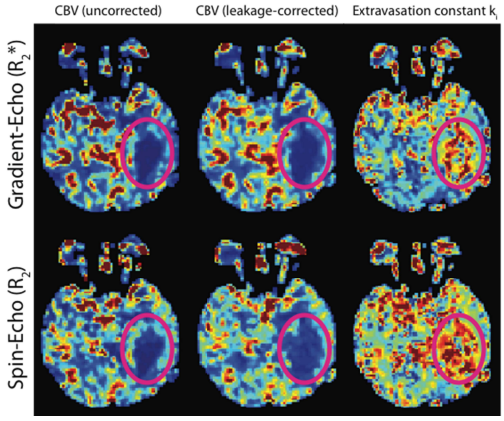

Fig.1: *Patient with confirmed GBM, treated with chemorad. therapy and bevacizumab. Uncorrected and corr. R_2*-&R_2-weighted CBV and k_i are shown.*

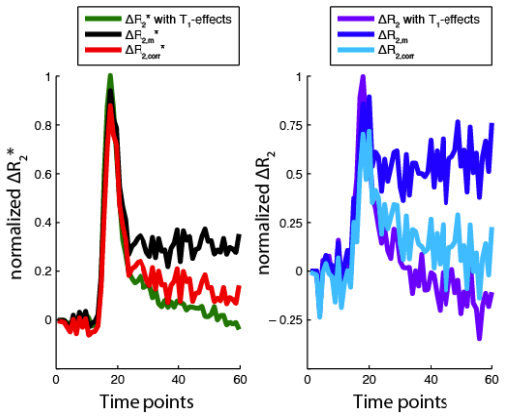

Fig.2: *ROI showing differences between $\Delta R_{2,T1\text{-}effects}$ (uncorrected single-echo PWI), $\Delta R_{2,m}^{(*)}$ (multiecho PWI), and $\Delta R_{2,corr}^{(*)}$ (leakage-corr. multiecho PWI)*

Perfusion maps were computed using a Matlab implementation of the RAPID software package [13]. Hereby, both $\Delta R_{2,m}^{(*)}$ and $\Delta R_{2,corr}^{(*)}$ were used to determine uncorrected and leakage-corrected perfusion parameters. Perfusion data were acquired in 5 patients with glioblastoma multiforme (GBM) using parameters listed in [7].

RESULTS – Fig. 1 shows a selected patient with biopsy-confirmed GBM, following chemoradiation therapy and administration of bevacizumab, a drug used for anti-angiogenic treatment. Both uncorrected and leakage-corrected CBV revealed comparable results in regions not affected by CA extravasation. Within the tumor, altered CBV values account for leakage. Specifically, the maps demonstrated differences in uncorrected vs. leakage-corrected CBV at the rim of the tumor, originating from CA extravasation. The low CBV within the tumor shown here was caused by the anti-angiogenic effect of bevacizumab. The plots in Fig. 2 illustrate ΔR_2* and ΔR_2 in a selected ROI within the tumor. With the suggested correction method, lower post-contrast values of both $\Delta R_{2,corr}$* and $\Delta R_{2,corr}$ resulted. CA leakage was verified in a post-contrast T_1-weighted image (cf. Fig. 3). The extravasation constant k_i (Fig. 1) showed elevated leakage within the tumor. Averaged over all 5 subject, k_i within a tumor ROI was 105% and 29% larger relative to the whole-brain average using R_2*- and R_2-based processing, respectively. Average tumor CBV in all 5 patients was 15% (11%) lower when using leakage-corrected R_2* (R_2) processing.

DISCUSSION – We were able to correct SAGE DSC-PWI acquisitions for R_2*- and R_2-related leakage effects. Although multiecho sequences are insensitive to T_1-related CA extravasation effects, PWI processing can be biased by R_2*- and R_2-effects. In this study, an approach used to correct for T_1-effects [11] was adjusted to account for R_2*- and R_2-related leakage effects. To our knowledge, this is the first approach presenting a correction for T_1- and $R_2^{(*)}$-related extravasation effects in combined GE and SE DSC-PWI. Separation of $\Delta R_{2,e}^{(*)}$ from $\Delta R_{2,p}^{(*)}$ was achieved through pharmacokinetic modeling of CA passage. Hereby, a leakage constant k_i was derived, facilitating improved assessment of brain tumors with DSC-PWI. In 5 patients, CA extravasation in tumor resulted in elevated k_i and altered CBV using the presented correction method.

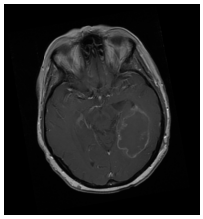

Fig.3: *T_1-w post CA image of patient 1.*

REFERENCES – [1] Miyati, et al. JMRI 1997;7:230-35, [2] Vonken, et al. JMRI 1999;10:109-17, [3] Uematsu, et al. Radiol 2000;214:912-17, [4] Vonken, et al. MRM 2000;43:820-27, [5] Paulson, et al. Radiol 2008;249:601-13, [6] Newbould, et al. Proc. ISMRM 2007, p1451, [7] Schmiedeskamp, et al. Proc. ISMRM 2011, p788, [8] Liu, et al. Med Phys 2011;38:802-9, [9] Patlak, et al. J Cereb Blood Flow Metab 1983;3:1-7, [10] Tofts, et al. JMRI 1999:10:223-32, [11] Quarles, et al. Magn Reson Med 2005;53:1307-16, [12] Ostergaard, et al. MRM 1996;36:715-25, [13] Straka, et al. JMRI 2010;32:1024-37.

ACKNOWLEDGEMENTS – NIH (R01EB002711, R01EB008706, R01EB006526, R21EB006860, P41RR009784), Lucas & Oak Foundations.