SHOULD DSC-MRI BASED BLOOD VOLUME AND VESSEL SIZE MEASURES BE CORRECTED FOR CONTRAST AGENT T2 LEAKAGE EFFECTS?

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Target Audience: Researchers interested in the development of advanced perfusion imaging methods.

Purpose: Cerebral blood volume (CBV) obtained from spin echo (SE) dynamic susceptibility-contrast MRI (DSC-MRI) sequences are maximally sensitive to capillary-sized vascular structures, while gradient echo (GE) derived hemodynamic parameters are sensitive to vessels of all sizes, and the combination of GE and SE imaging permits analysis of mean vessel diameter (mVD).[1] However, quantification of these parameters relies on the assumption that the contrast agent remains confined to the intravascular space, which may not be the case in tumors. Previous studies have shown that GE CBV is adversely affected by contrast agent leakage and must be corrected to obtain reliable CBV measures.[2] However, to date, no studies have systematically considered both T_1 and T_2 contrast agent extravasation effects on SE CBV and mVD. Various leakage correction strategies have been proposed[2-5] for GE CBV, but these have not been applied or validated for SE CBV. Here, we propose a new strategy to correct for T_2 leakage effects on multi-echo derived T_1-insensitive ΔR_2 time series. Using a previously derived biophysical model[6], we can remove T_2 leakage effects from the acquired ΔR_2 time series. This strategy was tested in 9L and C6 rat tumor models known to exhibit a range of both T_1 and T_2 leakage effects. For validation, we compared uncorrected and corrected SE CBV and mVD against reference values obtained with an intravascular iron oxide CA.

$$\Delta R_{2,T_1-corr}(t) = \frac{1}{TE_{SE}}\left(\ln\left(\frac{S_{TE_{SE},pre}}{S_{TE_{SE}}(t)}\right) - \ln\left(\frac{S_{TE=0,pre}}{S_{TE=0}(t)}\right)\right),$$

$$\text{where } S_{TE=0} = S_{TE_1}\cdot\left(\frac{S_{TE_1}}{S_{TE_2}}\right)^{TE_1/(TE_2-TE_1)}$$

$$\Delta R_{2,T_1+T_2-corr}(t) = \Delta R_{2,T_1-corr}(t) - r_{2t,eq}v_eC_e$$

Equations 1-3: Calculation of T_1-corrected and T_1+T_2-corrected ΔR_2.

Methods: 9L gliosarcoma and C6 glioblastoma cells were implanted in Fischer (n=12) and Wistar (n=9) rats, and MRI was performed at 4.7T (Agilent). Intravenous catheters were inserted for contrast administration with Gd-DTPA and MION. Pre-contrast T_1 maps were acquired using an inversion recovery technique (TR=8s, TE=2.9ms, 8 TI from 0.25s to 6s, FA=15º). A combined spin- and gradient-echo (SAGE) DSC sequence (TR = 1s, TE1-3 = 8.6 (GE), 35 (GE), and 95 (SE) ms, 1000 repetitions) was used. After 80s of baseline images, 0.4 mmol/kg Gd-DTPA was injected. Thirty minutes after Gd-DTPA injection, a matched volume of MION at 3 mg Fe/kg was injected. The T_1-corrected ΔR_2 was obtained from simplified SAGE fitting of TEs 1-3 (Equation 1). The T_1- and T_2^*-corrected ΔR_2 was calculated by subtracting the ΔR_1-derived $v_eC_e(t)$, scaled by the equilibrium transverse relaxivity, from the T_1-corrected ΔR_2 (Equation 3). The derived hemodynamic parameters include SE CBV and mVD.

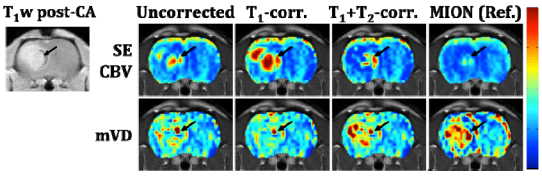

Figure 1: Example SE CBV and mVD images in a 9L tumor comparing uncorrected, T_1-corrected and T_1+T_2-corrected with MION reference values.

Results: Figure 1 shows SE CBV and mVD images from uncorrected, T_1-corrected, and T_1+T_2^*-corrected ΔR_2 curves in a 9L tumor-bearing rat. The uncorrected SE CBV is overestimated and mVD is underestimated compared to the MION images. Similarly, the T_1-corrected SE CBV is strongly overestimated, while mVD is underestimated. Both the T1+T2-corrected SE CBV and mVD are similar to the MION images. The bar plots for SE CBV and mVD are shown in Figure 2, with the MION reference values as the rightmost bar. Significance was determined using a paired t-test with $p<0.05$. In both tumor types, the uncorrected and T_1-corrected SE CBV and mVD were significantly different from the MION values in 9L tumors, while the T_1+T_2-corrected values were not significantly different from MION. In the C6 tumors, the T_1-corrected SE CBV was significantly different from MION, and the T_1+T_2-corrected values most closely matched the reference values.

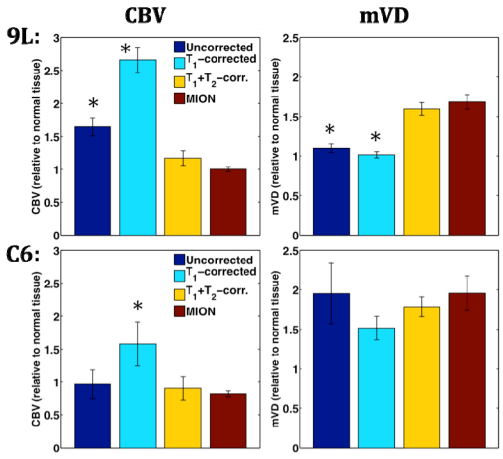

Figure 2: Spin echo (SE) CBV and mVD in 9L and C6 tumors comparing uncorrected, T_1-corrected and T_1+T_2-corrected parameters with MION reference values. *p<0.05.

Discussion: In general, correction of both T_1 and T_2 leakage effects improved the reliability of SE CBV and mVD values in both tumor types. Uncorrected hemodynamic measures may have confounding leakage effects, while T_1-correction can expose underlying T_2 leakage effects. This highlights the need for comprehensive correction of both T_1 and T_2 leakage effects to more accurately represent the non-leaky tumor hemodynamics. The effect of the correction was greater in 9L tumors due to the greater degree of T_2 leakage effects observed in these tumors, as compared to C6.

Conclusions: To date, the reliability of leakage correction strategies for multi-echo DSC-MRI has not been studied in conjunction with a reference standard. In this study we validated a simple and efficient approach that corrects for both T_1 and T_2 leakage effects. The dataset acquired herein also enables a systematic comparison of correction strategies. Ultimately, improved measures of CBV and mVD may enhance understanding of complex tumor hemodynamics, including vascular development and response to treatment.

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