A SIMPLIFIED SPIN AND GRADIENT ECHO (SAGE) APPROACH FOR BRAIN TUMOR PERFUSION IMAGING

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

Purpose: A compromised blood-brain barrier (BBB) in tumors leads to extravasation of Gd-DTPA and can severely reduce the reliability of dynamic susceptibility contrast MRI (DSC-MRI) perfusion measures due to competing T_1 effects.[1] Dual gradient-echo (GE) sequences provide a simple analytical method to obtain both T_1-insensitive ΔR_2^* measures and T_1-weighted signals for Dynamic Contrast Enhanced (DCE) MRI analysis.[2] While dual-echo sequences have been shown to provide robust T_1-insensitive GE hemodynamic measures[1], no analogous method exists to obtain T_1-insensitive spin-echo (SE) hemodynamic measures. Towards this end, a combined spin- and gradient-echo (SAGE) EPI method was previously proposed to simultaneously obtain T_1-insensitive ΔR_2 and ΔR_2^* dynamic time-courses.[3,4] This method relies upon the acquisition of multiple echoes (typically 5 echoes) and non-linear fitting of each dynamic to compute ΔR_2 and ΔR_2^* time courses. Here, we propose a simplified SAGE (sSAGE) approach that utilizes a combined dual GE and SE pulse sequence and an analytical solution for computing T_1-insensitive ΔR_2^* and ΔR_2 time series. As this approach only requires the acquisition and storage of three echoes and does not rely upon computationally demanding non-linear fitting algorithms, it could facilitate the more rapid clinical translation and adoption of SAGE-based DSC-MRI.

Methods: C6 glioma cells were implanted in Wistar rats (n=7), and MRI was performed at 4.7T (Agilent) after 14 days. A combined spin- and gradient-echo (SAGE) DSC sequence (TR = 1s, 2 GE, 2 ASE, 1 SE, TEs = 8.6/35/60/87/95ms, 1000 repetitions) was used. After 80s of baseline images, 0.4 mmol/kg Gd-DTPA was injected via jugular catheter. The SAGE-derived ΔR_2 and ΔR_2^* curves were obtained using least squares fitting of a piecewise function as previously described.[3] The sSAGE-derived ΔR_2 and ΔR_2^* were obtained analytically from TEs 1, 2, and 5 using the simplified SAGE Equations 1-3. The simplified SAGE DSC parameters are compared to the full fit SAGE parameters and conventional DSC parameters using TE2 and TE5. The derived hemodynamic parameters include CBF, CBV, and mean vessel diameter (mVD).

$$\Delta R_2^*(t) = \frac{1}{TE_2 - TE_1}\left(\ln\left(\frac{S_{TE_2,pre}}{S_{TE_2}(t)}\right) - \ln\left(\frac{S_{TE_1,pre}}{S_{TE_1}(t)}\right)\right) \quad (1)$$

$$S_{TE=0} = S_{TE_1} \cdot \left(\frac{S_{TE_1}}{S_{TE_2}}\right)^{TE_1/(TE_2 - TE_1)} \quad (2)$$

$$\Delta R_2(t) = \frac{1}{TE_{SE}}\left(\ln\left(\frac{S_{TE_{SE},pre}}{S_{TE_{SE}}(t)}\right) - \ln\left(\frac{S_{TE=0,pre}}{S_{TE=0}(t)}\right)\right) \quad (3)$$

Equations 1-3: Analytical solutions for simplified SAGE ΔR_2^* and ΔR_2.

Results: Figure 1 shows example DSC data in a C6 rat brain tumor ROI (a,c) and normal brain ROI (b,d). In tumor, T_1-shortening effects due to Gd-DTPA extravasation manifest as lower post-bolus ΔR_2^* and ΔR_2 for single echo data (TE2 and TE5, respectively). The SAGE and sSAGE ΔR_2^* curves, both corrected for T_1 leakage effects, do not exhibit reduced post-bolus ΔR_2^* and are in close agreement. In normal tissue (b,d) impervious to CA extravasation, the various ΔR_2^* and ΔR_2 measures are similar. The bar plots in Figure 2 show the mean CBF, CBV, and mVD in tumor relative to normal tissue using the single-echo, sSAGE, and SAGE ΔR_2^* and ΔR_2 (n=7). The GE CBF in tumor was slightly higher than normal tissue, while the SE CBF was slightly lower than normal tissue. None of the GE or SE CBF measures were significantly different. T_1-leakage effects led to significantly reduced single-echo CBV for both GE and SE compared to the sSAGE and SAGE measures ($p<0.0005$), while the sSAGE and SAGE CBV were not significantly different from each other. All three mVD measures were similarly increased in tumors, and the sSAGE and SAGE mVD were not significantly different. The single-echo mVD was significantly different from sSAGE and SAGE mVD ($p<0.05$).

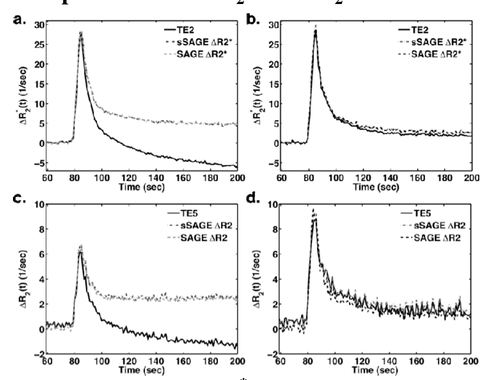

Figure 1: Dynamic ΔR_2^* (a,b) and ΔR_2 (c,d) for tumor (a,c) and normal (b,d) ROIs.

Discussion: The proposed simplified SAGE technique leverages the known insensitivity of dual GE DSC-MRI data to T_1 leakage effects and provides a simple, computationally efficient analytical solution for T_1-correction of SE data, thereby yielding T_1-insensitive GE and SE hemodynamic parameters and measures of vessel size. While SAGE and sSAGE address the more obvious T_1 leakage effects, T_2^* leakage effects would undoubtedly affect the ΔR_2^* curves and derived perfusion parameters. As such, future investigations will focus on obtaining quantitative hemodynamic measures by removing the T_1 leakage effects and then correcting for T_2^* leakage effects.

Conclusions: T_1-insensitive GE and SE hemodynamic parameters can be obtained using a simplified spin-and gradient-echo sequence with three total echoes (two gradient-echoes and one spin-echo). The T1-insensitive ΔR_2^* and ΔR_2 time courses can be calculated using the previously proposed dual-echo equation and the spin-echo correction presented here. As this method does not require time-consuming nonlinear fitting, it is an efficient and clinically feasible method. In addition to T_1-insensitive CBF, CBV, and MTT with both GE (total vasculature) and SE (microvasculature) contrast, this sequence provides measures of mVD and potential for DCE analysis, thereby providing simultaneous measures of perfusion and permeability.[2]

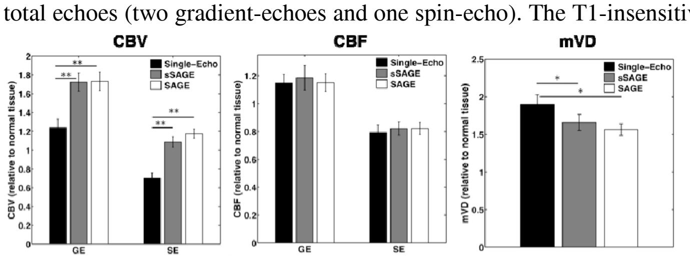

Figure 2: GE and SE CBV and CBF and mVD relative to normal tissue for single-echo, sSAGE, and SAGE. **p<0.01 and *p<0.05.

References: 1. Paulson ES, et al. Radiology (2008) 249(2):601. 2. Quarles CC, et al. Magn Reson Imaging (2012) 30(7):944. 3. Schmiedeskamp H, et al. Magn Reson Med (2012) 68(1):30. 4. Stokes AM, et al. Magnetic Resonance Imaging (2014) (0).