Quantitative assessment of tumor perfusion and K^{trans} using dual-echo DSC-MRI signals compensated for extravascular tissue T_1 and T_2 relaxation

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INTRODUCTION: A potential difficulty with dynamic susceptibility contrast (DSC) MRI methods to study human tumors results from the fact that the Gadolinium (Gd) agents can leak out of the vasculature into the extravascular extracellular space (EES) and result in unreliable blood volume (BV) and blood flow (BF) measurements (1,2). The leakage of contrast agent results in a simultaneous change in the EES T_1 and T_2, which compete with the susceptibility-induced signal decreases. Typically, loading doses of contrast agent prior to the first pass study, low flip angles, dual-echo pulse sequences, or post-processing techniques are used to minimize or remove the T_1 changes (1,2). However, such approaches could result in enhanced EES T_2 sensitivity. The purpose of this study is to theoretically demonstrate how dual-echo MR signals can be used to calculate tumor BF and BV compensated for T_1 and T_2 relaxation changes while also providing a measure of the EES concentration of contrast agent (C_e) from which the volume transfer constant, K^{trans}, and the volume of the EES, v_e, can be calculated.

THEORY and METHODS: The gradient-echo signal after contrast injection can be written as shown in Eqn. 1, where TR is the repetition time, TE is the echo time, T_1 is the pre-contrast tissue T_1 relaxation time, T_2^* is the pre-contrast gradient-echo relaxation time, α is the flip angle, R1 and R2 are the T_1 and T_2 relaxivities of the contrast agent, $C_e(t)$ is the concentration of contrast agent in the EES, and $\Delta R2^*(t)$ is the susceptibility-induced T_2^* relaxation rate change and is proportional to concentration of contrast agent in the blood plasma (Cp(t)). Equation 1 takes into account the contrast extravasation-induced T_1 and T_2 relaxation changes in the EES in addition to the expected susceptibility-induced T_2^* relaxation changes. In a typical dual echo experiment the T_1 effects are removed by taking the ratio of the two signals and solving for $\Delta R2^*(t)$. However, as shown below the ratio (and therefore the calculated $\Delta R2^*(t)$) still retains the T_2 leakage effects ($R2 \cdot C_e(t)$):

$$S(t) = \frac{\left(1 - e^{-TR/T1} e^{-TR \cdot R1 \cdot Ce(t)}\right) e^{-TE/T2^*} e^{-TE \cdot R2 \cdot Ce(t)} e^{-TE \Delta R2^*(t)} \sin(\alpha)}{\left(1 - e^{-TR/T1} e^{-TR \cdot R1 \cdot Ce(t)} \cos(\alpha)\right)} \quad [1]$$

$$\frac{S_{TE1}(t)}{S_{TE2}(t)} = \frac{e^{-TE1/T2^*} e^{-TE1(R2C_e(t))} e^{-TE1 \Delta R2^*(t)}}{e^{-TE2/T2^*} e^{-TE2(R2C_e(t))} e^{-TE2 \Delta R2^*(t)}} = e^{(TE2-TE1)(1/T2^* + R2 \cdot Ce(t) + \Delta R2^*(t))} \quad \text{or} \quad \Delta R2^*(t) + R2 \cdot C_e(t) = \frac{\log(S_{TE1}(t)/S_{TE2}(t))}{TE2 - TE1} - 1/T2^* \quad [2]$$

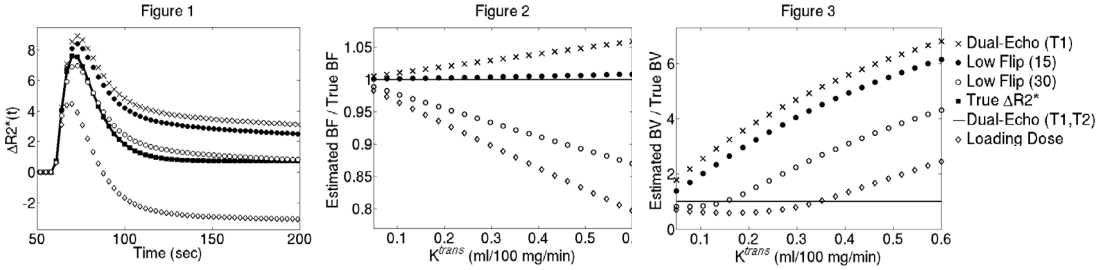
To remove the T_2 leakage effects we must first calculate $C_e(t)$. Equations 1 and 2 can then be used to separate the T_2 and T_1 leakage effects using a new function, S_{T1}, defined below (β = TE1/(TE2-TE1))(3). Using S_{T1} an analytical expression for $C_e(t)$ can be derived:

$$S_{T1}(t) = S_{TE1}(t) \cdot \left(\frac{S_{TE1}(t)}{S_{TE2}(t)}\right)^{\beta} = \frac{(1 - e^{-TR/T1} e^{-TR \cdot R1 \cdot Ce(t)}) \sin(\alpha)}{1 - e^{-TR/T1} e^{-TR \cdot R1 \cdot Ce(t)} \cos(\alpha)}, \quad \Rightarrow \quad C_e(t) = \frac{1}{R1 \cdot TR \cdot T1} \left[T1 \cdot \log\left(\frac{\sin(\alpha) - S_{T1}(t)\cos(\alpha)}{\sin(\alpha) - S_{T1}(t)}\right) - TR \right] \quad [3]$$

Once $C_e(t)$ has been calculated, a $\Delta R2^*(t)$ free of EES T_1 and T_2 leakage effects can be computed by subtracting $R2 \cdot C_e(t)$ from the $\Delta R2^*(t)$ calculated in Eqn. 2. The $\Delta R2^*(t)$ can then be used to calculate tumor blood volume and blood flow free of the influence of contrast extravasation. In addition, $C_e(t)$ can be fit to the tracer kinetic models typically used to describe DCE-MRI signals so that measures of K^{trans} and v_e, can be calculated (4).

Simulations were used to compare the signals and the calculated tumor BF and BV for the new proposed approach (labeled Dual-Echo (T_1,T_2-compensated)) to loading doses of contrast agent, low flip angles, and the standard dual-echo approach (Dual-Echo (T_1-compensated)) Concentration time curves, Ct(t), were generated by convolving a simulated arterial input function with exponential residue functions (R(t) = exp(-t·BF/BV)). The BV was held constant at 6 ml/100 mg, while the BF was set to either 30, 60, or 120 ml/100mg/min (low-high BF). Contrast agent leakage was simulated using the standard Kety-equation with K^{trans} and v_e ranging from 0.05-0.6 ml/100mg/min and 0.6-1.0%, respectively. The MRI signals were computed for each Ct(t) using Eqn. 1 with a 1 sec TR, a 1 sec pre-contrast tissue T1, 90° flip angle, and TE1/TE2 set to 20ms/30 ms. For the loading dose approach the tissue T1 was assumed to be 500 ms. 30° and 15° flip angles were used for the low flip angle approach. The BF and BV were calculated as the maximum (BF) and area (BV) under the flow residue function product derived from SVD approach (5).

RESULTS Figure 1 shows examples of the $\Delta R2^*(t)$ for each method. The $\Delta R2^*(t)$ for the new dual-echo approach (Dual-Echo (T1,T2)) and the true one were identical for all values of K^{trans}. The $\Delta R2^*(t)$ acquired with the standard dual-echo and the 15 degree low flip angle always substantially overestimated the true $\Delta R2^*(t)$ indicating enhanced EES T_2 sensitivity. The $\Delta R2^*(t)$ calculated from the 30 degree flip angle and the loading dose signals resulted in $\Delta R2^*(t)$s that varied both above and below the true $\Delta R2^*(t)$ depending on K^{trans} indicating a mixture of EES T_1 and T_2 sensitivity. Figures 2 and 3 show the ratio of the estimated to true BF (30 ml/100 mg/min case) (Fig. 2) and BV (Fig. 3) for each method as a function of K^{trans}. The new dual-echo approach exactly reproduced the true BF and BV. The standard dual-echo and the 15-degree flip angle approaches slightly overestimated BF and greatly overestimated BV. The BF for the 30-degree flip angle and the loading dose approaches were always lower than the true values. The BV calculated from these latter methods was slightly lower than the true value for low K^{trans} and substantially higher for larger values of K^{trans}.



DISCUSSION Under these simulated conditions the pulse sequences commonly used to minimize EES relaxation effects provided unreliable estimates of BF and BV. Using the new dual-echo approach we were able to exactly reproduce the true $\Delta R2^*(t)$, BF, and BV while simultaneously computing the $C_e(t)$ from which K^{trans} can be calculated. Future studies will include simulations to determine the influence of the fast-exchange assumption and EES/cellular exchange, experimental validation, and a comparison of K^{trans} values acquired with both DSC-MRI and DCE-MRI.

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