Incorporating the Effects of Transcytolemmal Water Exchange in the Reference Region Model for DCE-MRI Analysis

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INTRODUCTION Models have been developed for analysis of dynamic contrast enhanced MRI (DCE-MRI) data that do not require direct measurement of the arterial input function (AIF); such methods are referred to as reference region (RR) models (1,2,3). Additionally, the effects of water exchange at different time scales have been incorporated into the Kety analysis of DCE-MRI data (4,5). Here we combine these two approaches to build a RR model which incorporates the effects of transcytolemmal water exchange.

THEORY The RR method establishes a relationship between C_{TOI} and C_{RR} (contrast agent (CA) concentration in the tissue of interest (TOI) and RR, respectively) yielding a model that is independent of the concentration in the blood plasma, C_p. The result is Eq. [1]:

$$C_{TOI}(T) = R \bullet C_{RR}(T) + R \bullet [(K^{trans,RR}/v_{e,RR}) - (K^{trans,TOI}/v_{e,TOI})] \bullet \int_0^T C_{RR}(t) \cdot (\exp(-K^{Trans,TOI}/v_{e,TOI}) \cdot (T-t))dt, \quad [1]$$

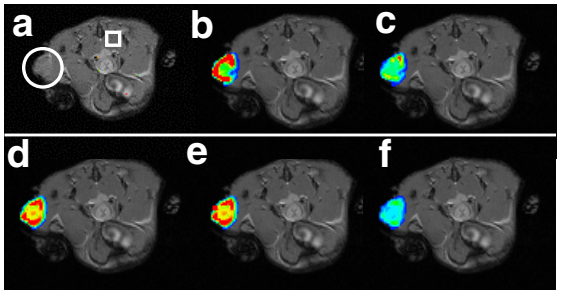
where $K^{trans,RR}$ and $K^{trans,TOI}$ are K^{trans} for the RR and TOI, respectively; $v_{e,RR}$ and $v_{e,TOI}$ are v_e for the RR and TOI, respectively; and $R \equiv K^{trans,TOI}/K^{trans,RR}$. An equation that calibrates C_{TOI} to the measured longitudinal relaxation rate constant (T_1, or its inverse R_1) is also required. This is typically taken as Eq. [2]:

$$R_1(t) = r_1 C_{TOI}(t) + R_{10}, \quad [2]$$

where r_1 is the longitudinal relaxivity of the CA, and R_{10} is the native longitudinal relaxation rate of the tissue before CA administration. Eq. [2] is a fast exchange limit (FXL) model; thus, by inserting Eq. [1] into Eq. [2] a FXL-RR model is obtained. Equations accounting for transcytolemmal water exchange in the calibration between CA concentration and ($\equiv 1/T_1$) have been developed (4, 5); the result is Eq. [2]:

$$R_1(t) = (1/2)\{(2R_{1i} + r_1 C_{TOI}(t) + (R_{10} - R_{1i} + 1/\tau_i)(v_e/f_w) - [(2/\tau_i - r_1 C_{TOI}(t) - (R_{10} - R_{1i} + 1/\tau_i)/v_e/f_w)^2 + 4(1 - v_e/f_w)/\tau_i^2 (v_e/f_w)^{1/2}]\}, \quad [3]$$

where R_{1i} is the intracellular R_1, τ_i is the average intracellular water lifetime of a water molecule, and f_w is the fraction of water that is accessible to a mobile CA. Eq. [3] is a fast exchange regime (FXR) model; thus, by inserting Eq. [1] into Eq. [3] a FXR-RR model is obtained. To peform a fit to data with the FXR-RR model, a C_{RR} time course is required and this should also include the effects of transcytolemmal water exchange. To do this a gamma variate form of C_{RR} is assumed and incorporated into Eq. [3] with $\tau_{i,RR}$ = 1.0s, $f_{w,RR}$=0.8, and $v_{e,RR}$=0.08 (reasonable values for muscle (4)). Eq. [3] is then fit to a R_1 time course obtained from a RR (muscle) and the C_{RR} time course that yields a best fit of the data is used in all subsequent fits.



METHODS Eight female mice were injected s.c. in the hind limb with 10^6 4T1 mammary carcinoma cells and imaged using a Varian 7.0 T scanner equipped with a 38 mm quadrature birdcage coil 16 days post injection. A variable flip angle gradient echo (GRE) approach produced a T_1 map. The DCE-MRI protocol employed a T_1-weighted, GRE sequence to obtain 35 serial images for each of 8 axial planes in 40 min of imaging. The parameters were: TR\TE\α = 100ms\3.1ms\30°, FOV = (30 mm)^2, slice thickness = 1.0 mm, matrix = 128^2, NEX = 4. A bolus of 0.2 mmol/kg Magnevist was delivered within 30 s *via* a jugular catheter. In each mouse thirty voxels within the perivertebral muscle were selected as the RR. In each case, $R_{1i} = R_{10}$, f_w = 0.8, and $v_{e,RR}$ was set to 0.08 (4) and $K^{trans,RR}$, $K^{trans,TOI}$, and $v_{e,TOI}$ were varied. A 40 voxel ROI was fit with each model to obtain a value for $K^{trans,RR}$ which was then fixed so that a subsequent two-parameter ($K^{trans,TOI}$ and $v_{e,TOI}$) FXL-RR and a three-parameter ($K^{trans,TOI}$, $v_{e,TOI}$, and $\tau_{i,TOI}$) FXR-RR voxel-by-voxel analysis could be performed.

RESULTS $K^{trans,RR}$ returned by the FXR and FXL models were 0.056min^{-1} and 0.045min^{-1}, respectively. The Figure depicts results of one mouse from this study. Panel a is a post-contrast T_1-weighted image displaying both the tumor (circle) and RR (square). Panels b and c depict the K^{trans} and v_e maps, respectively, obtained from the FXL-RR analysis. Panels d, e, and f depict the τ_i, K^{trans}, and v_e maps, respectively, obtained from the FXR-RR method. The FXR-RR K^{trans} map indicates increased values throughout the tumor and along the periphery of the lesion as well as a pronounced central region that does not appear on the FXL-RR map. The τ_i map (d) indicates larger values along the rim and within the center of the tumor which correlates with the FXR-RR K^{trans} map and agrees with previous FXR analyses; i.e., when τ_i is significant, the system is driven out of fast exchange limit and the greater the differences between the FXR and FXL. However, the FXL v_e map yields significantly higher values than the FXR model.

DISCUSSION The differences between K^{trans} for the FXR-RR and FXL-RR models, as well as the correlation between τ_i and K^{trans}, parallel those described previously by non-reference region FXR model analyses of DCE-MRI data. The fact that the FXL-RR model reported higher $v_{e,TOI}$ values that the FXR-RR has not been seen in previous FXR models and this requires further investigation.

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