Implications of unequal interstitium and plasma contrast reagent relaxivities in pharmacokinetic analysis of DCE-MRI

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Purpose: Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) indirectly detects contrast reagent (CR) concentration through water proton R_1 relaxation rate constant [$\equiv T_1^{-1}$] changes. Within a single tissue compartment, a linear relationship is assumed, $\Delta R_1 = r_1 \cdot [CR]$. The slope r_1, the longitudinal relaxivity, quantifies the CR potency to change water proton T_1. It is current practice to assume that r_1 is the same in blood plasma and all interstitial compartments. However, there is evidence suggesting a potential increases in the interstitium r_1 (1, 2). Based on human prostate data, we demonstrate the implications of differences of r_{1o} (interstitium relaxivity) to r_{1p} (plasma relaxivity) values on DCE-MRI pharmacokinetic parameters.

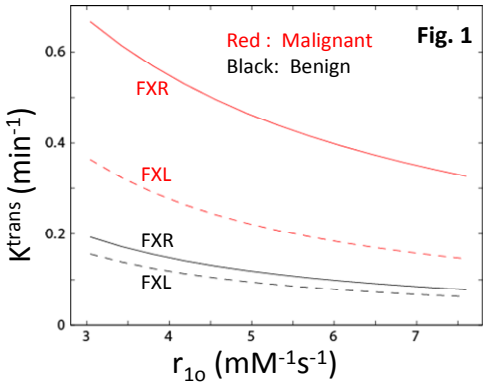
Methods: Prostate DCE-MRI data were acquired on 13 subjects with a Siemens TIM Trio (3T) system under an IRB-approved protocol. RF transmitting was through the whole body coil and RF receiving was with a combination of Spin Matrix and flexible Body Matrix coil arrays. The DCE-MRI acquisition employed a 3D TurboFLASH pulse sequence with a 256*144*16 matrix size and a 360*203 mm^2 FOV, resulting in $(1.4)^2$ mm^2 in-plane resolution. Other parameters are: slice thickness: 3 or 3.2 mm; TR/TE/FA: 5.0 ms/1.57 ms/15º, image frame sampling interval: 6.3 s. A 0.1 mmol/kg CR (ProHance; Bracco) bolus was administered starting ~38 s after initiation of the DCE-MRI sequence. In general, the protocol of (3) was used. All subjects subsequently underwent standard ten-core prostate biopsies with ultrasound guidance. Malignancies were found in 5 subjects and the remaining were benign cases. One region of interest (ROI) was selected for each subject, resulting in 5 malignant and 8 benign ROI time-courses. Simulations were performed on ROI data from the subjects (one ROI per subject). r_{1p} is assumed to be 3.8 $mM^{-1}s^{-1}$. Eq. (1) describes the interstitial CR concentration time-course, $[CR_o](T)$. Ignoring the blood contribution, the associated tissue concentration, $[CR_t](t) = \Delta R_1(t)/r_{1o} = [CR_o](t) \cdot v_e$, is related to the DCE-MRI time-course. Here, $\Delta R_{1t}(t)$ is the time-course of tissue R_1 change [$=R_{1t}(t) - R_{1t}(0)$], and v_e is the extravascular, extracellular volume fraction. Thus, $\Delta R_{1t}(t) = r_{1o} \cdot [CR_o](t) \cdot v_e$. Based on this expression and the expression for $[CR_o]$ given by Eq. (1), it is obvious that simultaneously fitting r_{1o}, v_e, and K^{trans} (CR extravasation transfer constant) to the measured DCE-MRI time-course is not feasible. Thus, simulations were carried out by fitting pharmacokinetic parameters with r_{1o} fixed at 13 different values (from $0.8 \cdot r_{1p}$ to $2.0 \cdot r_{1p}$ with a step-size of $0.1 \cdot r_{1p}$). The standard fast-exchange-limit (FXL) Tofts model (4) was used to obtain K^{trans} and v_e values, and the fast-exchange-regime (FXR) Shutter-Speed approach (3,5) was used to obtain K^{trans}, v_e, and τ_i (mean intracellular water lifetime) values. To avoid local minima in each optimization procedure, 20 different initial guess parameter value sets were used for each r_{1o} step and each model. Parameters from the best fit of the 20 trials for each combination were then selected as the fitted results.

$$[CR_0](T) = K^{trans} \cdot v_e^{-1} \cdot \int_0^T [CR_p](t) \cdot \exp\left(-K^{trans} \cdot v_e^{-1} \cdot (T-t)\right) \cdot dt \qquad (1),$$

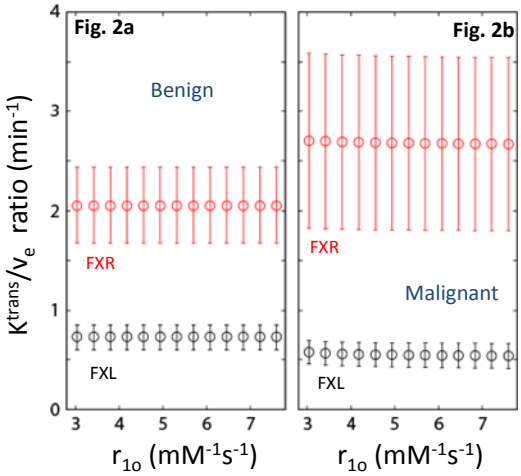
where the plasma CR concentration, $[CR_p] = \{R_{1b}(t) - R_{1b}(0)\}/\{(1 - h_v) \cdot r_{1p}\}$:

$R_{1b}(t)$ is the blood R_1 time-course, $R_{1b}(0)$ is blood R_1 before CR, and h_v is the microvascular hematocrit. Inserting the $[CR_p]$ expression into the $\Delta R_{1t}(t)$ equation (using Eq. (1) for $[CR_o]$), it is easy to see the r_{1o}/r_{1p} ratio (5) in the $\Delta R_{1t}(t)$ equation. r_{1o}/r_{1p} has been assumed to be 1 in kinetic modeling of DCE-MRI data.

Results: **Fig. 1**. shows representative malignant (red) and benign (black) K^{trans} changes with increasing r_{1o} (r_{1p} fixed at 3.8 $mM^{-1}s^{-1}$ for 3T). Each ROI data set was fitted with FXR (solid curve) and FXL (dashed curve). The best fitted values from the 20 different initial guesses are plotted. The K^{trans} values decrease with r_{1o} increase. The averaged K^{trans}/v_e ratios (with standard errors) of the 8 benign ROIs are plotted against r_{1o} in **Fig. 2a**. The ratios from FXR are plotted in red and those from FXL in black. The **2a** equivalents for the 5 malignant ROIs are plotted in **2b**. Regardless of the model and tissue characteristics, the K^{trans}/v_e ratio within each approach remains constant, indicating the $[CR_o]$ time-course is the same regardless of r_{1o}.



Discussion: The key finding from this work is that the K^{trans}/v_e ratio remains the same regardless of the r_{1o}/r_{1p} ratio, which indicates that the same $[CR_o]$ time-course is observed regardless of r_{1o} and r_{1p} difference. Even though it is intuitive that an r_{1o} increase could lead to a decrease of K^{trans}, unchanged K^{trans}/v_e ratio is a numerical outcome rather than a pharmacokinetic implication. By differentiating $\Delta R_{1t}(t)$ {Eq. (1) multiplied by $(r_{1o} \cdot v_e)$} with respect to K^{trans} and v_e, respectively, one will see changes from that of K^{trans} is much greater. Thus the numerical fittings will first adjust K^{trans} to compensate any r_{1o} deviation from r_{1p}, then v_e is adjusted accordingly. When in the FXL, this $r_{1o} \neq r_{1p}$ situation is similar to an error in the AIF scaling (an AIF uncertainty). However, AIF uncertainty can be managed. A 30% or greater r_{1o} change (1) will likely be out of AIF uncertainty and thus noticeably affects K^{trans} and v_e values. For FXR, if $[CR_o]$ remains the same, higher r_{1o} will significantly increase the data sensitivity to water exchange, and the precision of mean intracellular water lifetime can be improved. Interestingly, compared to the Fig. 1 K^{trans} change, the τ_i change (not shown) is much smaller. This is quite reasonable since τ_i measures water exchange kinetics while K^{trans} measures plasma/interstitium CR transfer kinetics. Results from this simulation study may partially explain the observations that DCE-MRI often obtains larger v_e values than one would normally expect. In addition, $K^{trans}/v_e = k_{ep}$, the CR intravasation rate constant (3-5). These results also suggest that k_{ep} could be a more reliable imaging biomarker in certain *in vivo* applications. Current work underscores the importance of quantifying r_{1o} independently.



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