Minimizing the Influence of Blood Volume Fraction on Other Pharmacokinetic Parameters in DCE-MRI

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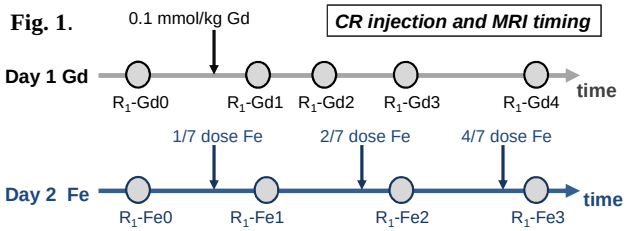
Purpose: Pharmacokinetic modeling of dynamic contrast enhanced (DCE)-MRI data using extravsating contrast reagent (CR) often cannot separate the influence of blood volume fraction (v_b) on fitted K^{trans} (CR transfer constant) and v_e (extracellular, extravascular volume fraction) values. Not surprisingly, the inclusion(1,2) or neglect(3,4) of a v_b contribution results in different K^{trans} and/or v_e values returned in pharmacokinetic modeling and confounds biological interpretation. It is worth noting, however, v_b influence on DCE-MRI time-course with bolus CR injection only dominates during CR first pass and diminishes during most part of the CR washout phase. Here we show that the same K^{trans} and v_e values can be obtained with quantitative DCE-MRIs using R_1 [$\equiv T_1^{-1}$] data that do not include the CR first pass. This could simplify quantitative K^{trans} and v_e interpretation when moderate CR extravasation is expected.



Methods: Five subjects with brain lesions were provided informed consent before participating in this multi-session MRI study. All MRI data were collected using a 3T Siemens TIM Trio instrument equipped with a body RF coil transmitter and a 12-channel matrix head coil receiver. **Figure. 1** shows a simplified schema of the two-day DCE-MRI protocol: *day 1*, 0.1 mmol/kg Gadoteridol (Prohance, Bracco) CR in a single injection; *day 2*, DCE with 510 mg total Ferumoxytol (Feraheme, AMAG Pharmaceuticals) CR in three injections (dosed at 1/7, 2/7, 4/7 of the total injection amount, respectively). Using a thirty-six inversion time (TI) gradient-echo inversion recovery EPI sequence (5) with non-selective adiabatic inversion RF pulse, water proton R_1 data were collected before and up to four times after Prohance (Gd) injection out to 70 min post-injection and at four time points before and after the three Ferumoxytol (Fe) injections. As shown in Fig.1, Gd or Fe R_1 data acquisitions are labeled sequentially with respect to CR injection. Individual Gd or Fe CR R_1 maps were calculated using a single exponential inversion recovery model followed by co-registration to a high resolution T_1-weighted anatomical image. The four co-registered Ferumoxytol R_1 data were modeled voxelwise using a two water compartment (blood – extravascular) model to extract blood volume fraction (v_b) and mean capillary water molecule lifetime (τ_b). Due to its large size, Ferumoxytol does not extravasate to any appreciable extent following IV injection and thus provides a reliable v_b estimation. The five co-registered Gadoteridol R_1 data were modeled voxelwise using i) a two-compartment [v_e, and (1-v_e); i.e. the extravascular, intracellular volume fraction (v_i)] model, and ii) a three-compartment model (v_b, v_e, and v_i). For the latter, voxelwsie v_b values from Fe DCE were incorporated. Since the first R_1 data post Gd injection were acquired *ca.* ~ 140 s post CR injection, CR concentrations in blood and interstitium largely track each other, and therefor diminished transendothelial water exchange effect is expected for these data time-courses.

Results: **Figure 2a** shows a lesion slice R_1 map post Gd CR injection. The colored rectangular border encloses the general lesion area exhibiting noticeable post-CR enhancement. **Fig. 2b** shows the zoomed v_b color map obtained from the Fe DCE modeling. The lesion K^{trans} color map from modeling Gadoteridol extravasation without v_b is shown in **Fig 2c**. The somewhat resemblance of the lesion v_b and K^{trans} maps (independently measured by our two-day MRIs with Fe vs. Gd CRs) demonstrates potential parameter dependence between the two. With a 10X more sensitive color scale, the absolute K^{trans} difference between modeling with and without v_b incorporated into Gadoteridol DCE pharmacokinetic equations is shown in **Fig. 2d**. For most of the lesion, the K^{trans} difference between the two models is small. When all lesion areas are pooled from the subjects, K^{trans} and v_e values from both approaches are almost identical. Linear regression of K^{trans} (no v_b) *vs.* K^{trans} (including v_b) returned a slope of 0.9932, and that of v_e (no v_b) *vs.* v_e (including v_b) to be 0.9996, with either intercept effectively zero. This indicates that with acquisition scheme described here, v_b has minimal impact on the extravasating Gd DCE model parameter values (K^{trans} and v_e).

Discussion: The resemblance of the independently measured lesion v_b (by Fe DCE, **2b**) and K^{trans} (by Gd DCE, **2c**) data demonstrates experimentally some dependence between v_b and K^{trans} (correlation coefficient, 0.44 for Fig. 2 lesion data) model parameters. This could complicate DCE-MRI model approach and results in different numerical K^{trans} and v_e values whether v_b is incorporated into the model. The feasibility of modeling DCE-MRI with R_1 data to achieve consistent K^{trans} and v_e values independent of v_b is presented in this work. The consistency of these pharmacokinetic parameter values will greatly simplify their interpretation and facilitate biological interpretation. During CR bolus passage, the relative influence of pharmacokinetic parameters varies (6) with CR extravasation rate. With a K^{trans} of 0.005 to 0.1 min^{-1}, a diminishing v_b influence on DCE data is expected after the CR bolus first pass (*ca.* 140 s after injection in current study). Compared to the standard gradient echo DCE-MRI approach, the sparse temporally sampled quantitative R_1 mapping approach used here is more tolerant of $\mathbf{B_1}$ and $\mathbf{B_0}$ inhomogeneities which may be beneficial at higher field. Furthermore, quantitative R_1 data provide direct measures of blood R_1 and tissue R_1 time courses, thus simplifies blood volume fraction calculation when intravascular CR (Ferumoxytol in this study) is used. Accurate blood volume fraction measurement is extremely value in brain lesion diagnosis and therapeutic monitoring (7,8). A limitation of the sparse temporally sampled approach is the potential "ceiling" effect in K^{trans}; i.e. sensitivity to measure large K^{trans} values is expected to be reduced. For brain lesions K^{trans} values are often in a range that is well suited to a sparse-temporally sampled approach. Without a fast R_1 map sequence, lesions with fast CR extravasating nature, such as those seen in prostate cancer, may not benefit from this approach. Sparsely sampled data may affect optimization routine during model fitting. Our experience indicates that for commonly applied pharmacokinetic models (1-4), the parameter space often shows a smooth varying nature. Thus, it is often the high signal-to-noise ratio (SNR), not necessarily the high temporal resolution, that helps in reducing local minimums in the parameter space.

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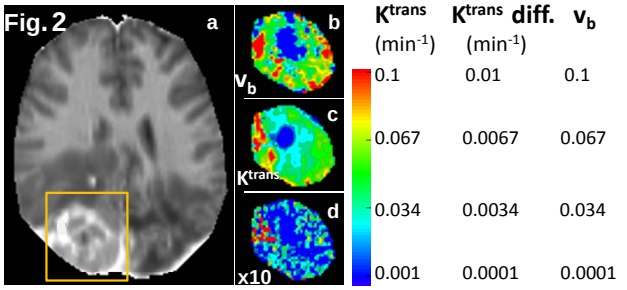

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