The DCE-MRI ΔK^{trans} Parameter Has Diminished Sensitivity to AIF Variation

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Introduction: The DCE-MRI pharmacokinetic parameter (ΔK^{trans}) shows high diagnostic accuracy in breast cancer detection (1-3). This novel imaging biomarker results from analyzing a DCE-MRI data set twice, once with the Standard Model (SM) (4) and once with the Shutter-Speed Model (SSM) (5). ΔK^{trans} is defined as [K^{trans}(SSM) - K^{trans}(SM)], where K^{trans} is a contrast reagent (CR) extravasation rate constant. Thus, it appraises precisely the only SM/SSM difference - their treatments of inter-compartmental water exchange kinetics. The SM assumes the exchange kinetics are always effectively infinitely fast; all exchange MR systems remain in their fast-exchange-limit [FXL] conditions. The SSM admits these systems can transiently depart their FXLs during bolus CR passage through tissue (1,2).

Currently, there is no widely adopted, standard DCE-MRI protocol for data acquisition and processing. As is the case for the SM, accuracy and reproducibility of parameters derived from SSM analysis of DCE-MRI data may be influenced by data acquisition and processing scheme choices, such as arterial input function (AIF) quantification (6,7). We hypothesize that the ΔK^{trans} subtraction may mitigate or eliminate many systematic DCE-MRI parameter errors caused by uncertainties in, *e.g.*, AIF and pre-CR T_1 determinations. In this study, we investigated the effects of different AIF estimations on breast tumor pharmacokinetic parameters using the SM and SSM analyses.

Methods: 23 patients with 24 mammography-detected suspicious lesions (1 patient presented 2 lesions) consented to research DCE-MRI studies prior to biopsies as standard care. The DCE-MRI acquisitions were performed using a 3T Siemens instrument with the body transmit and 4-channel phased-array bilateral breast receive RF coils. A 3D TWIST gradient-recalled-echo (GRE) sequence (8) was used to acquire axial bilateral T_1-weighted DCE-MRI images, with 10° flip angle, 2.9 ms TE, 6.1 ms TR, 32 cm FOV, 320x320 matrix size, and 1.2 mm slice thickness. TWIST is a k-space undersampling and data sharing GRE sequence delivering near isotropic 1 mm image voxels at 18 s temporal resolution. The total DCE acquisition time was approximately 10 min with Gd CR (Prohance®) IV injection through an antecubital vein (0.1 mmol/kg at 2 mL/s) carried out following acquisition of two baseline image volumes. Prior to DCE-MRI, proton density images were acquired at the same spatial locations - for pre-CR T_1 determination. For SM and SSM pharmacokinetic modeling of lesion ROI DCE-MRI time-course data, each analysis was conducted twice, differing only in the AIF employed. One analysis used the population-averaged AIF, <AIF>, obtained from another patient cohort (with the same CR dose, injection rate and site) by averaging reliable individual AIFs measured from an axillary artery (1-3). The other analysis used the patient-specific reference region AIF, AIF_{RR}, method (9,10). The AIF_{RR} employed for each DCE-MRI data set fitting was derived by adjusting <AIF> peak height using the patient's chest wall muscle as RR (10). **Figure 1** shows the <AIF> (black) and two sample AIF_{RR}s. Each AIF_{RR} has the same shape as <AIF>: one with higher (red) and the other with lower (green) peak amplitude.

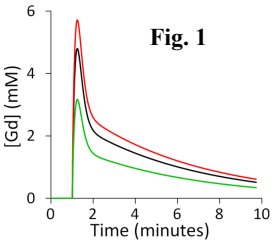

Fig. 1

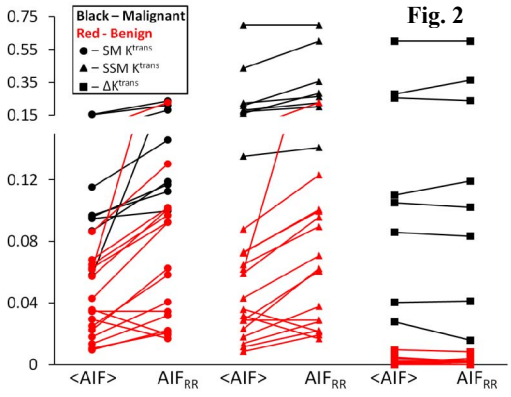

Fig. 2

Results: Biopsy pathology analyses revealed that 8 of the 24 lesions were malignant. **Figure 2** shows lesion ROI K^{trans}(SM), K^{trans}(SSM), and ΔK^{trans} scatter plots for all 24 lesions. Straight lines connect DCE-MRI data fitting values using the <AIF> and AIF_{RR}, respectively, from the same lesion. Note the scale break. Most K^{trans}(SM) and K^{trans}(SSM) values increase upon going from <AIF> to AIF_{RR} – an AIF variation effect. However, the effects on ΔK^{trans} are near zero in most cases. The **Table** lists the lesion group-averaged [mean(±SD)] AIF effects on ROI K^{trans}(SM), K^{trans}(SSM), and ΔK^{trans} values: the parameter value obtained using the <AIF> is subtracted from that derived using the AIF_{RR}. Paired t tests show that the AIF effects on K^{trans}(SM) and K^{trans}(SSM) are statistically significant ($P<0.01$) for both malignant and benign lesion groups [also on v_e(SM) and v_e(SSM), not shown: v_e is the extracellular, extravascular volume fraction], but not on the ΔK^{trans} parameter ($P=0.26$ and 0.34 for malignant and benign groups, respectively) [neither on Δv_e, not shown]. The distributions of AIF effect on K^{trans}(SM) and K^{trans}(SSM) are broad and centered significantly off zero. The ΔK^{trans} distribution is narrow and centered essentially on zero.

Upon going from <AIF> to AIF_{RR}, the K^{trans}(SM) and K^{trans}(SSM) breast cancer diagnostic specificities (at 100% sensitivity) change from 68% and 100% to 75% and 94%, respectively, while the ΔK^{trans} specificity remains 100%.

Table. Lesion Group-Averaged AIF Effects

	K^{trans}(SM) (min^{-1})	K^{trans}(SSM) (min^{-1})	ΔK^{trans} (min^{-1})
M (N=8)	0.046(±0.040)[a]	0.069(±0.065)[b]	0.007(±0.011)*
B (N=16)	0.032(±0.041)[c]	0.028(±0.041)[d]	0.0003(±0.0011)[#]

Mean(±SD); M: malignant; B: benign. Paired t tests (<AIF> *vs.* AIF_{RR}):
[a]$P < 0.01$; [b]$P < 0.01$; [c]$P < 0.004$; [d]$P < 0.008$; *$P = 0.26$; [#]$P = 0.34$.

Discussion: AIF quantification has long been a challenging issue for quantitative DCE-MRI. AIF uncertainty is a major source of systematic pharmacokinetic parameter error. Our results show that no matter which model is used to fit the data, changes in breast tumor K^{trans} values resulting from different AIF choices can be significant. AIF time offset error can also propagate into parameter error. These aspects could be particularly troublesome for multi-site DCE-MRI studies because of difficulty in maintaining AIF quantification consistency (reproducibility). Encouragingly, the new ΔK^{trans} (or Δv_e) parameter appears to be much less susceptible to systematic errors caused by AIF variations, presumably due to similar or equal AIF-induced parameter errors in the SM and SSM analyses being cancelled by the subtraction. Since ΔK^{trans} also is a very sensitive measure of vascular compromise (1,2), the use of this imaging biomarker could be rather advantageous in DCE-MRI studies of cancer detection and therapeutic monitoring.

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References: **1.** Li *et al. PNAS* **105**:17937-17942 (2008). **2.** Huang *et al. PNAS* **105**:17943-17948 (2008). **3.** Huang *et al. PISMRM* **18**:368 (2010). **4.** Tofts *et al. JMRI* **10**:223-32 (1999). **5.** Li *et al. Magn Reson Med* **54**:1351-9 (2005). **6.** Yang *et al. Magn Reson Med* **61**:851-9 (2009). **7.** Yankeelov *et al. Curr Med Imaging Rev* **3**:91-107 (2009). **8.** Song *et al. Magn Reson Med* **61**:1242-8 (2009). **9.** Yang *et al. Magn Reson Med* **52**:1110-7 (2004). **10.** Li *et al. JMR* **206**:190-199 (2010).