The DCE-MRI AK\textsuperscript{trans} Parameter Has Diminished Sensitivity to AIF Variation

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Introduction: The DCE-MRI pharmacokinetic parameter (\(AK_{\text{trans}}\)) 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). \(AK_{\text{trans}}\) is defined as \([K_{\text{trans}}(\text{SSM}) - K_{\text{trans}}(\text{SM})]\), where \(K_{\text{trans}}\) is a contrast reagent (CR) extravasation rate constant. Thus, it apprises 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 SM 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 \(AK_{\text{trans}}\) subtraction may mitigate or eliminate many systematic DCE-MRI parameter errors caused by uncertainties in, e.g., AIF and pre-CR T1 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 T1-weighted DCE-MRI images, with 10° flip angle, 2.9 ms TE, 6.1 ms TR, 32 cm FOV, 320×320 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\textsuperscript{®}) 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 T1 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\textsubscript{RR}, method (9,10). The AIF\textsubscript{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\textsubscript{RR}s. Each AIF\textsubscript{RR} has the same shape as <AIF>: one with higher (red) and the other with lower (green) peak amplitude.

Results: Biopsy pathology analyses revealed that 8 of the 24 lesions were malignant. Figure 2 shows lesion ROI \(K_{\text{trans}}(\text{SM})\), \(K_{\text{trans}}(\text{SSM})\), and \(AK_{\text{trans}}\) scatter plots for all 24 lesions. Straight lines connect DCE-MRI data fitting values using the <AIF> and AIF\textsubscript{RR}, respectively, from the same lesion. Note the scale break. Most \(K_{\text{trans}}(\text{SM})\) and \(K_{\text{trans}}(\text{SSM})\) values increase upon going from <AIF> to AIF\textsubscript{RR} – an AIF variation effect. However, the effects on \(AK_{\text{trans}}\) are near zero in most cases. The Table lists the lesion group-averaged [mean±(SD)] AIF effects on ROI \(K_{\text{trans}}(\text{SM})\), \(K_{\text{trans}}(\text{SSM})\), and \(AK_{\text{trans}}\) values: the parameter value obtained using the <AIF> is subtracted from that derived using the AIF\textsubscript{RR}. Paired t tests show that the AIF effects on \(K_{\text{trans}}(\text{SM})\) and \(K_{\text{trans}}(\text{SSM})\) are statistically significant (P<0.01) for both malignant and benign lesion groups [also on \(v_4(\text{SM})\) and \(v_4(\text{SSM})\), not shown: \(v_4\) is the extracellular, extravascular volume fraction], but not on the \(AK_{\text{trans}}\) parameter (P=0.26 and 0.34 for malignant and benign groups, respectively) [nor on \(\Delta V_c\), not shown]. The distributions of AIF effect on \(K_{\text{trans}}(\text{SM})\) and \(K_{\text{trans}}(\text{SSM})\) are broad and centered significantly off zero. The \(AK_{\text{trans}}\) distribution is narrow and centered essentially on zero. Upon going from <AIF> to AIF\textsubscript{RR}, the \(K_{\text{trans}}(\text{SM})\) and \(K_{\text{trans}}(\text{SSM})\) breast cancer diagnostic specificities (at 100% sensitivity) change from 68% and 100% to 75% and 94%, respectively, while the \(AK_{\text{trans}}\) specificity remains 100%.

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 \(K_{\text{trans}}\) 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 \(AK_{\text{trans}}\) (or \(\Delta V_c\)) parameter appears to be much less susceptible to systematic errors caused by AIF variations, presumedly due to similar or equal AIF-induced parameter errors in the SM and SSM analyses being cancelled by the subtraction. Since \(AK_{\text{trans}}\) 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.

Grant Support: NIH: RO1-CA120861, RO1-NS40801, RO1-EB00422.