Comparison of Manually Selected Arterial Input Function and Standard Radiological Arterial Input Function in MR Estimation of Permeability Parameters Using Model Selection Approach

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Target Audience: Scientists and experts working in the field of Dynamic Contrast Enhanced MRI and permeability studies

Purpose: The purpose of this study is to compare the results of using a Standard Radiological Arterial Input Function (SRAIF) vs. the Manually Selected Arterial Input Function (MSAIF) in Dynamic Contrast Enhanced (DCE)-MR image analysis. The AIF is one of the key elements in pharmacokinetic models and plays a crucial role in calculating permeability and perfusion parameters in DCE-MRI studies. In this study these two AIFs are recruited in pharmacokinetic analysis of DCE-MR images of rat brain to compare the estimated permeability parameters such as extracellular-extravascular space volume (v_e), plasma volume (v_p) and forward vascular transfer constant (K^{trans}). Two contrast agents (Gd-DTPA and Gadofosveset) with different molecular sizes are used in this study.

Methods: Nine Fisher 344 female rats were inoculated intra-cerebrally with 9L Gliosarcoma cells that were cultured in Dulbecco's modified eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS). Cells were harvested and re-suspended and 5 µl of the cell suspension with a concentration of 8×10^7/ml was implanted into the rat brain. Imaging was done using two contrast agents, once on the 13th and once on 14th day after inoculation. The two contrast agents were gadofosveset and gadolinium-diethylenetriaminepentaacetic acid or Gd-DTPA. The animals were scanned on a GE-3T clinical system (Signa Excite, GE health) using a 50mm(diameter)×108mm RF rung length small animal imaging coil (Litzcage small animal imaging system, Doty Scientific Inc., Columbia, SC). One set of T1-pre followed by a set of DCE-T1 weighted images and a set of T1-post images were acquired in each experiment. For creating the resting (pre-contrast) T1 maps, multiple flip angle (2°, 5°, 10°, 15°, 20° and 25°) fast 3D Spoiled Gradient Echo (3D SPGRE) images were obtained using the following MR specifications: TR/TE=500/12 ms, 256×256 matrix, 13 slices, 1 mm thick, 40×30 mm FOV, NEX=4. A series of 3D SPGRE (flip angle = 30°) image packs were acquired every 11.7 sec for a total scan time of 15 minutes. Contrast agents were administered as a bolus through the tail vein of animal over 10 seconds. Gadofosveset was administered at 0.12 ml/kg (0.03 mmol/kg) and Gd-DTPA was administered at 0.2 ml/kg (0.1 mmol/kg). A Nested Model Selection (NMS) approach[1] was recruited to estimate permeability parameters from DCE-MR experiments. There are four physiologically nested conditions (Model 0 to 3) relevant to the presence of CA at different tissue compartments as follows: No evidence of vascular filling, evidence of filling with no leakage, evidence of filling with leakage without backflux to the vascular compartment, and leakage with re-entry of CA in the vascular space. Using an analytical method[1], resting T1 map along with the baseline (before CA administration) of the dynamic signal were used to calculate the relaxivity change (ΔR_1), which is assumed to be proportional to the CA concentration. Toft's extended model[3] and its reduced forms were used to explain the behavior of the time trace of CA concentration of each voxel for estimating permeability parameters relevant to the models stated above (0, 1, 2, and 3)[1]. F-Statistic was used to select the best model for each voxel. Model 3 was the focus of this study due to the fact that it allows us to measure three permeability parameters (v_p, v_e, and K^{trans}). All analyses were done using SRAIF and MSAIF. The MSAIFs were selected by an expert radiologist for each animal. The SRAIF is the result of a previously reported study[2]. For each animal and for each CA, two AIF profiles were used for the analysis: Both AIFs were calibrated to blood relaxivity and normalized to the CA concentration of the white matter. Also, the SRAIF profile was shifted in time so that its rising point matched that of the AIF in the same animal (see Figure 1).

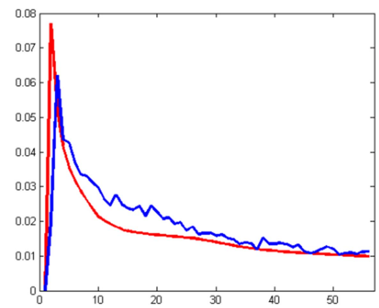

Figure 1. The normalized and rise-time corrected SRAIF and MSAIF from of one of the rats after intravenous bolus injection of GD-DTPA

Results: Figure 1 shows both SRAIF and MSAIF for one of the rats for GD-DTPA. Table I shows the mean and standard deviation of v_p, K^{trans} and v_e that have been measured for the whole lesion (only Model 3 areas) in all nine animals using the two contrast agents. For assessment of the significance of the difference of the mean values of each of the parameters between the two groups, paired T-test was performed along with calculation of the Intra-class Correlation (ICC) between the results from using the two AIFs.

Table 1. Mean and standard deviation of the permeability parameters, estimated using the SRAIF and MSAIF for the two contrast agents. For each contrast agent, the P-value of the Paired T-test and the Inter-Class-Correlation were calculated between the estimated values of the permeability parameters calculated using the two AIFs.

	Gadofosveset			GD-DTPA		
	SRAIF	MSAIF	P-value/ICC	SRAIF	MSAIF	P-value/ICC
Ktrans [min^{-1}]	0.025±0.008	0.023±0.008	0.1289/0.9538	0.046±0.011	0.048±0.010	0.3008/0.9382
v_e [%×100]	0.227±0.047	0.203± .031	0.2031/0.3902	0.236± .056	0.202± .031	0.1289/0.4203
v_p [%×100]	0.016±0.006	0.015±0.005	0.7344/0.0077	0.016±0.004	0.016± .006	0.9102/0.5620

Discussion: The results show high correlation between the K^{trans} values calculated for each contrast agent, using the two AIF profiles (ICC = 0.95 and 0.94 for Gadofosveset and Gd-DTPA respectively) which shows perfect agreement; however, the mean K^{trans} for the two contrast agents are considerably different which is due to their different molecular size which affects the transvascular transfer rate. Even though the mean values of v_e and v_p when using the same AIF for the calculations are in strong agreement for both contrast agents, these values have a lower correlation when they are calculated for the two different AIFs (for v_e , ICC = 0.39 and 0.42 for for Gadofosveset and GD-DTPA respectively and for v_p, ICC = 0.0077 and 0.56). It should also be noted that the MSAIF profiles for the Gadofosveset were much closer to the SRAIF compared to Gd-DTPA.

Conclusion: In this study, we did an assessment of the variations of the values of the permeability parameters (v_e, v_p and K^{trans}) when estimated using two different AIF profiles (MSAIF and SRAIF). For each CA, the results show less variation in the estimated values of K^{trans}, compared to v_e, v_p. Thus using MSAIF compared to SRAIF would not significantly affect K^{trans} due to the fact that this parameter is relevant to the trend of the time trace of CA concentration in both AIFs. However, v_e and v_p are more susceptible to the AIF profile change. These results show the importance, sensitivity and biasing level of each estimated permeability parameter against different AIF profiles. As a continuation of this study, Quantitative Auto-Radiography (QAR) and histology measurements of the vascular physiology parameters would allow to investigate the accuracy and biasing effect of each AIF on the estimated parameters.

References:

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