Comparison of Analysis Methods for DCE-MRI Data Via Impact on Sensitivity to Treatment Effect

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Introduction: Dynamic contrast enhanced MRI (DCE-MRI) has demonstrated utility in both diagnosing and evaluating the progression and response to treatment of malignant tumors [1]. It is commonly assumed that precise tracking of changes in vascular parameters measurable using DCE-MRI requires conversion of the observed signal intensity changes seen in various tissues post-injection to Gd concentration values [2,3]. Recent studies, however, have indicated that such conversion may be unnecessary using certain protocols [4,5] and may in some cases increase the apparent measurement noise. Questions have also been raised regarding the advisability of attempting to measure a data-derived arterial input function (AIF) [6] from DCE-MRI data as opposed to assuming a single generalized population AIF for all subjects in a given study [7]. In this work we have attempted to assess the impact of each of these decisions on the statistical confidence in study outcome using data from a Phase I clinical study of the effects of a compound with expected anti-angiogenic effects on solid tumors.

Methods: This analysis makes use of data from a single dose cohort (n=6) imaged at two centers at baseline and 8 weeks post-treatment. DCE-MRI data were acquired using a 3D SPGR sequence acquired with an oblique coronal prescription and TE/TR/FA = 1.1/5.3/30. 12 slices were acquired per volume, with 8 retained. All data were acquired using 1.5T systems. The primary parameters of interest were the volume transfer constant K^{trans} and the blood-normalized area under the tumor time-concentration curve (IAUCBN(90)). Both K^{trans} and IAUCBN(90) were calculated independently at each voxel within the tumor ROI, with statistical analysis carried out on the median resulting values. Parameters were calculated using four methods: using calculated gadolinium concentration ([CA]) with a data-derived AIF; using calculated [CA] with a generalized population AIF; using signal difference with a data-derived AIF; and using signal difference with a generalized population AIF. The ability to detect drug effects within a given cohort is determined primarily by the size of the biological effect (in this case a reduction in blood flow and vascular permeability) and the inter-patient coefficient of variability (CoV) in observed change. The size of biological effect is in theory independent of the measurement method. Inter-patient CoV is dependent on both the inherent biological variability of the response to treatment and on the scan-rescan variability of the measurement. This last factor is the only one that should be affected by choice of method. The methods were evaluated for effectiveness based on their relative inter-patient CoV.

Results: Table 1 below shows the analysis results for this cohort using all combinations of AIF method, signal type, and parameter. Mean baseline absolute values for both K^{trans} and IAUCBN(90) were nearly identical for all methods other than data-derived AIF using signal difference. Values for both K^{trans} and IAUCBN(90) using this method were roughly double those obtained using the other three methods. This difference was statistically significant in all cases ($p<0.01$).

Table 1: Results for change from Baseline to Week 8 DCE-MRI scans for all combinations of method and parameter

AIF Method	Signal Type	Parameter	Mean Delta	Lower 95% CI	Upper 95% CI	Inter-Subject CoV
Data-Derived	Calculated Gd Concentration	K^{trans}	-31%	-99%	+36%	2.74
Data-Derived	Calculated Gd Concentration	IAUCBN(90)	-42%	-100%	+18%	1.83
Data-Derived	Signal Difference	K^{trans}	-36%	-56%	-16%	0.63
Data-Derived	Signal Difference	IAUCBN(90)	-36%	-55%	-16%	0.71
Generalized	Calculated Gd Concentration	K^{trans}	-27%	-72%	+18%	2.15
Generalized	Calculated Gd Concentration	IAUCBN(90)	-35%	-76%	+6%	1.47
Generalized	Signal Difference	K^{trans}	-23%	-38%	-7%	0.94
Generalized	Signal Difference	IAUCBN(90)	-24%	-42%	-6%	1.05

Discussion: Several interesting observations can be made regarding the results of this experiment. First, the results for Mean Delta support the assumption that measured biological effect should be independent of analysis method. The mean measured change from baseline is remarkably similar across the eight combinations of method and parameter. The only modest outliers are the two Generalized AIF – Signal Difference parameters. However, an examination of the confidence interval data shows clearly that these are not in fact significantly different from the other six methods. It is also interesting to note that the absolute values of both parameters measured using the Data Derived AIF – Signal Difference method are biased high with respect to the other six methods. This is reflective of the fact that the relationship between signal difference and [CA] is linear using these acquisition parameters only up to roughly 1mM [4], while the peak [CA] in arterial plasma following a rapid bolus injection of 0.1 mmol/kg may exceed 3mM. Therefore the signal difference method under-estimates the AIF during the first bolus passage, leading to an over-estimation of both K^{trans} and IAUCBN(90). This bias will not be important in applications where the critical parameter is change following treatment, but may be important in cases where the absolute values of the measured vascular parameters are used to assess degree of malignancy. In cases where the main interest is in measuring change from baseline, the most critical parameter is Inter-Subject CoV. As expected, there are clear differences in this parameter among the methods. In particular, the Signal Difference methods show clear advantage over the Calculated [CA] methods. This is reflective of the fact that the process of conversion from signal difference to calculated [CA] involves the calculation of a pre-contrast T1 map, the registration of that T1 map to the DCE-MRI data, and finally the calculation of [CA] values at each voxel based on pre-contrast T1 and signal change post-injection. Each of these steps introduces random noise to the parameter estimation process. This advantage is shown most critically by the fact that while the mean change in both K^{trans} and IAUCBN(90) from baseline is similar for all four methods, these changes are statistically significant only for the Signal Difference methods. It is also interesting to note that the use of a data-derived AIF provides a significant advantage when using signal difference, but a significant disadvantage when using calculated [CA]. This is due to primarily to the difficulty of calculating accurate T1 values within the large arteries which are used to derive the AIF, which leads to extreme inaccuracies in estimation of [CA] in some cases. This experiment indicates that when the acquisition parameters are such that a linear relationship can be defined between signal difference and [CA], attempts to estimate [CA] in the analysis process may produce less reliable results than those obtained directly from signal difference. There also appears to be some advantage to the use of a data-derived AIF in cases where bias in the absolute parameter values is not critical. In other cases, the use of a generalized population AIF may be advisable.

References: [1] Tofts P, Brix G, *et al*., JMRI, 10:223 – 232, 1999. [2] Evelhoch J, JMRI 10:254–259, 1999. [3] Leach M, Brindle K, *et al.*, Brit J Cancer 92:1599-1610, 2005. [4] Ashton E, Durkin E, *et al.,* Proc. ISMRM 2007. [5] Walker-Samuel S, Leach M, Collins D, Phys Med Biol 52:589 – 601, 2007. [6] Ashton E, McShane T, Evelhoch J, LNCS 3749:451 – 458, 2005. [7] Galbraith S, Lodge M, *et al.,* NMR Biomed, pp. 132 – 142, 2002.