Effects of arterial input functions on dynamic MRI kinetic parameters estimates: an analysis of parameter variability and model fitting in breast cancer patients

N. J. Taylor[1], N. Tunariu[1], M-L. W. Ah-See[2], J. J. Stirling[1], M. J. Beresford[2], A. Makris[2], J. A. d'Arcy[3], D. J. Collins[3], and A. R. Padhani[1]

[1]Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [2]Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [3]CRUK Clinical MR Research Group, Royal Marsden NHS Foundation Trust, Sutton, Surrey SM2 5PT, United Kingdom

Introduction: Estimations of the variability of dynamic contrast enhanced MRI (DCE-MRI) kinetic parameters are essential requirements for phase I antiangiogenesis and vascular targeting drug trials. By enabling investigators to define the degree of change that would be statistically significant, reproducibility estimates help design clinical studies by enabling appropriate power calculations. Kinetic parameters are calculated by fitting enhancement curves to pharmacokinetic, usually 2 compartment models (e.g. those described by Tofts[1] and Brix[2]), after deconvolution of the arterial input function (AIF). There is controversy about whether AIF should be explicitly measured in individual patients or if population AIFs should be used in kinetic analyses. Recent data suggests that measured AIFs do not in themselves lead to more reliable kinetic parameter estimates[3]; moreover, accurately measuring AIFs in clinical trials is technically challenging. The main pooled input functions used are biexponential in shape and include those described by Weinmann[4] (W) and Fritz-Hansen[5] (FH); these have been recently combined[6] (Modified Fritz-Hansen, MFH) and pooled femoral artery (FA) AIF has also been measured[7]. In this study, these four AIFs were used with the Tofts model[1] to calculate kinetic parameters (K^{trans} - transfer constant (min^{-1}), v_e - leakage space (%), k_{ep} - rate constant (min^{-1}) and initial area under Gd curve ($IAUGC_{60}$ in mmol.s) in order to assess their effects on fitting accuracy and reproducibility.

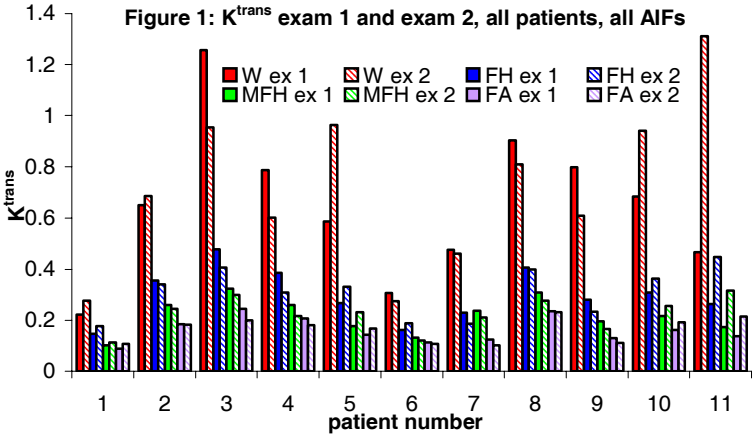
Methods: Eleven patients with primary breast cancers underwent two DCE-MRI scans in one week, receiving 0.1mmol/kg Gd-DTPA during the T_1W dynamic series. Three 8mm slices were acquired in the oblique sagittal plane covering the tumour and axillae. Tumour ROIs were drawn on all slices by an experienced radiologist, and the data processed using MRIW software[8] (ICR, London). Data from all slices were analysed pixel-by-pixel using the four AIFs (W, FH, MFH & FA) in turn keeping all other variables constant. Pixels (% of all pixels) which failed to fit were counted for each AIF and removed from any further analyses. Kinetic parameter values for each tumour pixel were obtained including χ^2 (goodness-of-fit) values. Reproducibility calculations used the methods of Galbraith[9] and the following statistics were use to compare the four AIFs: mean parameter value, repeatability coefficient (r) in % which represents the range beyond which differences are considered statistically significant, and within-patient coefficient of variability (wCV). A Kruskal-Wallis analysis of the differences between AIFs for each kinetic parameter was carried out.

Results: Figure 1 shows the effect of AIF on median tumour K^{trans} values and Table 1 gives reproducibility statistics for each quantitative parameter, together with the overall mean χ^2 values for goodness-of-fit, the overall fit-fail percentages and the semi-quantitative IAUGC reproducibility statistics. Significant differences ($p<0.01$) in the Kruskal-Wallis analysis are shown in Table 2.

Discussion: The magnitude of K^{trans} and k_{ep} values is greatest with the Weinmann AIF with v_e remaining unchanged; this is directly related to the low maximal amplitude and slower rate of decay of the Weinmann AIF. Deconvolution of higher amplitude FH/MFH and FA AIFs reduces the magnitude of the remaining tissue enhancement curve and thereby reduces the value of the calculated K^{trans} values (this also had the effect of reducing heterogeneity of pixel maps). $IAUGC_{60}$ is not a modelled parameter, but as the onset time calculation is affected by the AIF, small but non-significant differences were seen between the AIFs. χ^2 values tended to be lowest for the FH AIF indicating that it is probably the better fit for breast cancer data sets. However the FH AIF also had a high percentage of fit failures. Parameter variability is greatest for the Weinmann input function, with the other AIF results being very similar for most kinetic parameters. In conclusion, using different modelled AIFs has profound effects on the model fitting and parameter variability; the MFH seems to be best in this regard. However, it is possible that using AIFs other than Weinmann's will not change the sensitivity to treatment-related change[10] because mean values are also reduced, thus reducing the dynamic range.

K^{trans}	W	FH	MFH	FA
r%	-53.7 to 116.2	-35.8 to 55.8	-36.0 to 56.3	-31.5 to 46.0
wCV%	32.1	17.4	17.5	14.6
mean	0.683	0.303	0.220	0.163
v_e				
r%	±21.7	±13.2	±14.6	±16.5
WCV%	7.8	4.7	5.3	6.0
mean	0.519	0.604	0.382	0.601
k_{ep}				
r%	-49.5 to 97.9	-28.9 to 40.6	-30.2 to 43.2	-28.9 to 40.7
WCV%	27.9	13.1	13.9	13.1
mean	1.493	0.556	0.605	0.296
Mean χ^2	0.035	0.025	0.030	0.027
Fit fail %	6.8	16.6	4.9	28.4
$IAUGC_{60}$				
r%	±49.5	±39.1	±40.1	±39.4
WCV%	17.9	14.1	14.5	14.2
mean	12.77	13.77	13.72	14.53

Table 1: Summary statistical data



p<0.01	W	FH	MFH	FA
W	-	*	*	*
FH	K^{trans}, k_{ep}, χ^2	-	*	*
MFH	K^{trans}, k_{ep}, v_e	v_e	-	*
FA	K^{trans}, k_{ep}	K^{trans}, k_{ep}	k_{ep}, v_e	-

Table 2: Kruskal-Wallis data: only differences with p<0.01

References:

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