Comparison of Patient-Specific and Fixed Arterial Input Functions for Assessing Treatment Response at DCE-MRI

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Introduction Obtaining quantitative DCE-MRI parameters requires the specification of an arterial input function (AIF) – the time-course of contrast concentration in the blood plasma pool. When assessing treatment response, the AIF would ideally be measured during each examination from a vessel feeding the tumour so that any changes to the AIF between examinations are properly accounted for. For DCE-MRI studies it turns out that measuring the AIF in this way is very challenging due to in-flow effects, signal saturation with large concentrations and other confounding factors. For clinical trials looking at treatment response, particularly a cohort response, it is typical to use a fixed AIF which is usually derived by averaging measured AIFs over a suitable population [1]. Whilst the use of a fixed AIF removes a major source of variation, if the treatment has an effect on the AIF then such changes will be erroneously reflected in the tissue parameters, such as K^{trans} and v_e. This is undesirable since changes to the AIF – even if they are caused by the treatment – are reflective of a systemic effect, rather than a localised tumour effect. This abstract compares the repeatability and treatment response effect of K^{trans} obtained using AIFs derived in three ways: i) a fixed AIF, ii) a visit-specific AIF obtained from a suitable vessel appearing in the DCE-MRI data, iii) an AIF obtained on the same day with a dynamic contrast CT examination.

Materials and Methods DCE-MRI data were acquired with the following set-up. 0.2mg/kg Magnevist followed by 20mls saline both at 3mls/sec; 1.5T Siemens Avanto; 3D FFE sequence with TR/TE = 3.05/0.89 ms, FA = 16°, 14x5mm slices NSA = 1, IPAT = 2, FOV = 308x320mm, 208x256 matrix. Dynamic scans were preceded by a calibration scan with the same parameters except FA = 3°, NSA = 8 to enable contrast quantification. Patients were imaged twice at baseline, 7 days apart. For abdominal disease sites, patients were imaged coronally using a sequential breath-hold technique optimised for liver lesions; two image volumes were acquired during each 6 sec breath-hold, followed by a 6 sec breathing gap, 40 volumes were acquired over a 4 minute period. For non-abdominal disease sites patients were imaged axially with a free breathing technique; 80 image volumes acquired continuously at 3.3 sec/vol for 4.3 min. DC-CT data were acquired with the following set-up. GE Lightspeed; Omnipaque 300 0.5ml/kg followed by 20 mls saline both at 3-5mls/sec; 5 second delay followed by breath hold cine covering 4x5mm, at 0.5 sec/volume in centre of lesion of interest over 55 sec at 120 kV, 60 mA; following this, twelve breath-hold acquisitions at 10 sec intervals. MR data were acquired on the same day no more than four hours after the CT data.

Patients included in this study were restricted to those that had a suitable vessel appearing in the DCE-MRI data, which resulted in 16 patients from the original 29. Repeatability results are calculated from repeat baseline measurements and treatment changes are presented from measurements taken after 7 days of treatment with Recentin – a potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases which is known to cause a cohort decrease in K^{trans} [2]. The fixed AIF was based on the population-averaged AIF presented in [1]. The visit-specific DCE-MRI derived AIF was obtained by fitting a cosine-based AIF model [3] to data from a suitable vessel appearing in the field of view. The DC-CT derived AIF was obtained either from the aorta, or another suitable vessel, and a previously published correction method [4] was used to account for the different contrast agent volumes and delivery rates for the DCE-MRI and DC-CT acquisitions. The extended Tofts model was applied to the tumour data from four slices and the median K^{trans} reported for each visit. Repeatability was assessed using the coefficient of variation and a paired t-test was used to assess the significance of treatment changes.

Results The table gives the following statistics for K^{trans} in this sub-group of patients: coefficient of variation, percentage treatment effect over cohort, 95% confidence interval of the treatment effect (variation over cohort) and p-value of t-test.

AIF	K^{trans}	K^{trans} Treatment Effect			
	CoV / %	Cohort change / %	95% confidence interval / %		p-value
Fixed	14.4	-53.1	-87.2	72.6	0.00059
DCE-MRI	46.3	-59.0	-89.6	61.7	0.00022
DC-CT	22.5	-67.5	-91.7	27.0	0.00004

Discussion These results indicate that although the fixed AIF has the smallest CoV, the treatment effects measured by both the visit-specific DCE-MRI and DC-CT AIFs are larger, and have greater statistical significance. The increase in the overall treatment effect of the DC-CT AIF relative to the fixed AIF is dominated by patients whose K^{trans} values increase, as evidenced by the upper bound of the 95% confidence interval going from 72.6% to 27.0% (the lower bounds are similar at -87.2% and -91.7%). This suggests that in patients whose K^{trans} is increased by the treatment, changes in the AIF after treatment may be larger than the repeat measurement AIF variation (before treatment), and so using a fixed AIF may be masking a treatment effect. A similar but less marked comparison is valid for the DCE-MRI visit-specific AIF.

In this study the DC-CT derived AIF is used because the accuracy of such AIFs is typically superior to those derived from DCE-MRI measurements due to the different contrast mechanisms and the much higher temporal sampling rates used with DC-CT. However, it should be noted that the DC-CT derived AIF was obtained four hours prior to the DCE-MRI measurement, and so even if the DC-CT derived AIF (after volume and injection rate correction) was error-free, it would be different from the AIF pertaining to the DCE-MRI measurement due to variations in heart-rate, prandial status or other effects. Whilst the clinical trial from which these data are taken gives a unique opportunity to study the various sources of variation in such measurements, using a DC-CT derived AIF is clearly not a feasible approach for obtaining a visit-specific AIF in general.

The repeatability of the DCE-MRI visit-specific AIF is more than three times higher than for the fixed AIF, and it should be noted that in 45% of patients (13/29) it was not possible to obtain a visit-specific AIF from the DCE-MRI data. A fixed AIF is therefore still the recommended approach, but this study indicates that obtaining a visit-specific arterial input function is still an important unsolved problem hindering the wider application of DCE-MRI for assessing treatment response.

References

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