Use of a high temporal resolution population-averaged arterial input function to improve DCE-MRI reproducibility in phase I clinical trial settings

G. J. Parker[1], C. Roberts[1], A. Macdonald[1], S. Cheung[1], G. A. Buonaccorsi[1], D. L. Buckley[1], A. Jackson[1], Y. Watson[1], K. Davies[1], G. C. Jayson[2]

[1]Imaging Science & Biomedical Engineering, University of Manchester, Manchester, United Kingdom, [2]Cancer Research UK Department of Medical Oncology, Christie Hospital, Manchester, United Kingdom

Introduction Analysis of dynamic contrast-enhanced (DCE)-MRI data using tracer kinetic modeling requires definition of the concentration of contrast agent in the blood – the arterial input function (AIF). Simple kinetic models assume that a simplified functional AIF form may be used, and that it is valid for all individuals[1]. However, it has been shown that using a simplified AIF leads to large systematic errors in model output parameters such as the volume transfer constant K^{trans} and blood plasma volume v_p[2]. It is also generally assumed that inter-patient variability in factors such as cardiac and kidney function will cause AIF differences between individuals. Therefore, the accepted aim for kinetic modeling studies is to measure an AIF in each patient, even if this aim is met in only a minority of studies (e.g.[3-5]). Reliable AIF measurement is often not possible, due to data acquisition constraints or to the lack of a suitable artery in the imaging field of view. In such cases, it would be desirable to use an assumed AIF that has sufficient information content to allow accurate estimation of model parameters. We have previously defined a functional form for a high temporal resolution population-averaged AIF, obtained from 113 individually-measured patient AIFs, and shown that it meets this requirement[5]. Here we show that using this functional form of the population AIF also markedly improves the reproducibility of model parameters over those obtained using individually-measured AIFs. We conclude that it is valid to use a good quality population AIF if it is not possible to acquire AIFs from individual patients, and raise the possibility that this may in many settings be the preferred option.

Patients 31 patients with advanced cancer demonstrating abdominal or pelvic masses were enrolled in a multi-visit study to assess a novel anti-vascular compound. Each patient attended for DCE-MRI at two pre-dosing time points within 1 week to allow assessment of reproducibility. 32 tumours were identified for analysis.

DCE-MRI Protocol All data were acquired on a 1.5 T Philips Intera system using the whole body quadrature coil for transmission and reception. The baseline T_1 measurement consisted of 3 axial spoiled Fast Field Echo (gradient echo) volumes with flip angles 2, 10, 20 degrees, respectively and 4 NSA. The dynamic series consisted of 75 consecutively-acquired axial volumes with a flip angle of 20 degrees, 1 NSA, and a temporal resolution of 4.97 s. All studies maintained the same number of slices (25), field of view (375 mm × 375 mm), matrix size (128 × 128), TR (4.0 ms), and TE (0.82 ms). Elliptical k-space sampling, partial Fourier encoding, overcontiguous slice spacing, and partial echo acquisition were used to improve temporal resolution. Slice thickness was 4 mm for small target lesions or 8 mm for larger lesions, giving volume coverage of 100 mm or 200 mm, respectively.

Contrast Agent Administration 0.2ml/kg of Omniscan 0.5mmol/ml (Gd-DTPA-BMA; gadodiamide) was administered intravenously via the antecubital vein at the beginning of the 6th dynamic volume using a Spectris power injector (Medrad, Inc) at a rate of 3 ml/s, followed by an equal volume saline flush, also at 3 ml/s.

Time Series Parameterisation The kinetic model parameters K^{trans}, v_e, and v_p, determined using a generalised version of the Kety model[6], were measured within a manually-defined 3D tumour region of interest. Analysis was confined to the enhancing proportion of the tumour, and all parameters were determined voxel-by-voxel. A previously described automated AIF extraction method was employed to measure the AIF in each patient[7] in either the descending aorta or iliac arteries, depending on volume location (which was dictated by target tumour location). Signal intensity was converted to concentration of contrast agent by employing the standard relationship between a spoiled gradient echo signal and T_1[8]. A contrast agent relaxivity of 4.5 $s^{-1}mM^{-1}$ was assumed.

Reproducibility Assessment Reproducibility was assessed by calculating the 95 % confidence interval for the observation of genuine change in a single individual (the repeatability)[9,10]. Kendall's tau was used to test for correlation of the absolute value of the difference in the parameters over the two scans against the mean parameter value for the two scans. In the event of a significant correlation, repeatability was investigated in terms of the percentage change in the parameter, following the procedures in[10]. Otherwise, repeatability was investigated in terms of the absolute difference in the parameter between visits, following the procedures in[9].

Figure 1 shows the results of the reproducibility experiments for K^{trans}, v_p, and v_e. A paired, 2 tailed, t test on the effect of using the population AIF, applied individually to each parameter, indicates no systematic change in the values of K^{trans} (p = 0.256). However, due to the use of the population AIF v_p decreased by 0.011 and v_e increased by 0.054 on average (for both parameters $p \leq 0.001$). Only for v_p did the repeat study differences depend on the mean of the two studies (Kendall's tau, 2 tailed: p = 0.002 for measured AIF; p < 0.001 for population AIF). Repeatability is therefore expressed in terms of percentage change for v_p but in measurement units for K^{trans} and v_e (Fig. 2).

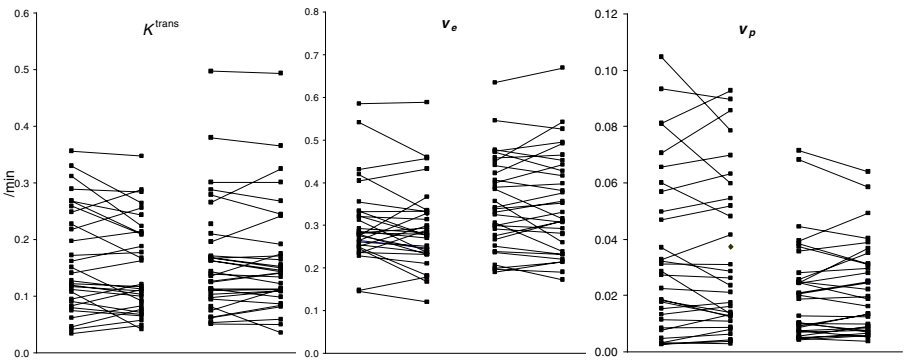

Fig. 1. *K^{trans} v_e, v_p values with measured AIF (left plots in each graph) and population AIF (right plots).*

The repeatability for K^{trans}, v_e, and v_p is seen to improve when using the population AIF (by 41.3 %, 41.1 %, and 22.6 %, respectively). Based on these data, the minimum changes that can be observed with 95 % confidence that they are not due to random fluctuations when using the population AIF are: K^{trans} 0.0451 min^{-1}; v_e 0.0701; v_p 45.3 %.

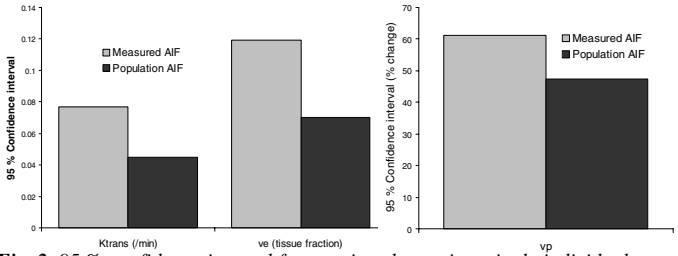

Fig. 2. *95 % confidence interval for genuine change in a single individual.*

Discussion We have shown that a high temporal resolution population-averaged AIF improves the reproducibility of parameters obtained using kinetic modelling of DCE-MRI data and that only small changes in accuracy can in general be expected. The inferior reproducibility when using the measured AIF may be due to temporal under-sampling of the first pass peak, which is a key element in the AIF (and in the tissue concentration time courses, when present) for accurate definition of K^{trans} and v_p. The peak height of measured AIFs varies between visits more than other features[5], with subsequent implications for the precision of these parameters. The improved reproducibility in v_e when using the population AIF may be due to removal of any artefactual inter-visit variability in the washout tail of the AIF or to a knock-on effect on v_e during the modelling process due to the stabilising effect of the population AIF on the measurement of K^{trans} and v_p. In summary, our results indicate that a high temporal resolution population-averaged AIF is likely to be beneficial for many DCE-MRI studies, in particular where reliable AIF measurement is not possible.

References 1. Tofts, P.S. and Kermode, A.G., Magn. Reson. Med., 17, 357, 1991. **2.** Parker, G.J.M., et al., Proc. Int. Soc. Magn. Reson. Med., 1582, 1996. **3.** Fritz-Hansen, T., et al., Magn. Reson. Med., 36, 225, 1996. **4.** Buckley, D.L., et al., Radiology, 233, 709, 2004. **5.** Parker, G.J., et al., Proc. Int. Soc. Magn. Reson. Med., 2101, 2005. **6.** Tofts, P.S., J. Magn. Reson. Imag., 7, 91, 1997. **7.** Parker, G.J., et al., Proc. Int. Soc. Magn. Reson. Med., 1264, 2003. **8.** Haase, A., Magn. Reson. Med., 13, 77, 1990. **9.** Galbraith, S.M., et al., NMR Biomed., 15, 132, 2002. **10.** Roberts, C., et al., Proc. Int. Soc. Magn. Res. Med., 146, 2004.