Investigating the influence of physiological variation on the form of the arterial input function in DCE-MRI

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Introduction Dynamic contrast-enhanced MRI (DCE-MRI) modelling often requires the use of an arterial input function (AIF). Because this may be difficult to measure directly, alternative approaches have been explored such as the use of population representative AIFs (1). This study considered the variation in the form of the measured AIF as associated with routinely recorded measurements of physiological characteristics. This was to investigate whether the change in form of AIFs between individuals may be solely due to noise or poor measurement techniques and to consider the possibility of refining population representative AIFs with respect to such physiological information.

Materials and Methods 44 AIFs from 27 oncology patients, attending for between one and four scans, were directly measured and transformed into concentration measurements following the procedure in Li *et al* (2). These were acquired on a 1.5 T Philips Intera system (Philips, Best, Netherlands) using a 3D Fast Field Echo (FFE; spoiled gradient echo) volume of 25 slices, matrix size 128 × 128, TR = 4 ms, TE = 0.82 ms with a quadrature body coil. The field of view was 375 mm × 375 mm except where this would lead to wrap-around artefacts obscuring the artery and/or region of interest, in which case it ranged from the above minimum to 400 mm × 400 mm. The slice thickness was 4 mm except where this would not capture at least two slices each side of the tumour, in which case the slice thickness was 8 mm. Variable flip angle FFEs were used for baseline T_1 measurements with flip angles of 2°, 10° and 20°. The dynamic series used the same protocol with a flip angle of 20° and a temporal resolution of 4.97 s. Participants were given an injection of 0.1 mmol/kg of bodyweight Omniscan 0.5 mmol/ml (gadodiamide, GE Healthcare) at a rate of 3 ml/s via the antecubital vein using a Spectris power injector (Medrad Inc, PA, USA). Two sample AIFs from one participant are shown in Figure 1. Data were included where consent and ethical approval were available, the required variables were successfully measured, and the AIF passed the standard in-house quality control procedures. 12 subjects were male, 15 were female with mean age of 63.8 years (range 29.4 to 80.0), mean weight of 73 kg (range 45 to 102) and mean pulse rate immediately prior to contrast agent injection of 76 bpm (range 55 to 111). Forward stepwise multiple linear regression models were applied to the data using the Matlab (Mathworks, MA, USA) *stepwise()* command to identify potential influences of subjects' sexes, ages, mean weights and mean pulse rates on the following characteristics of the measured AIF: the first pass peak height (FPPH), first pass peak full width half maximum (FWHM), second pass peak height (SPPH) and the ratio SPPH / FPPH (the peak ratio), as illustrated in Figure 1. These models were examined further using the StatsDirect (StatsDirect Ltd, UK) biomedical statistics package.

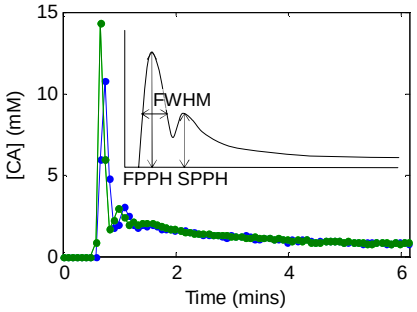

Figure 1: Two example AIFs from a single study subject with inlaid diagram illustrating three of the four parameters of interest in this study.

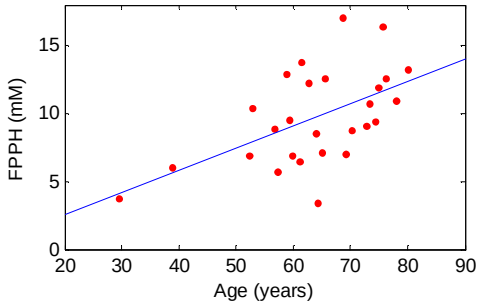

Figure 2: Scatter plot of FPPH against age with least squares regression line indicating a potential linear relationship.

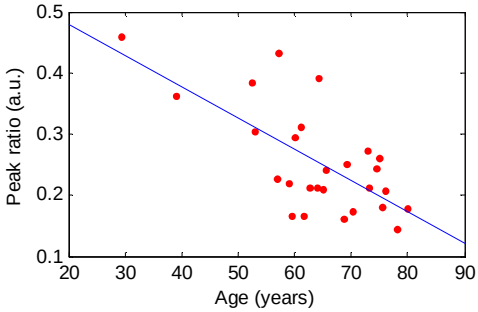

Figure 3: Scatter plot of peak ratio against age with least squares regression line indicating a potential linear relationship.

	Intercept	*Coefficient for Age (95% CI)*	*r^2 (95% CI)*	*2-tailed p*
FPPH	-0.7652	0.1646 (0.0606 to 0.2685)	0.30 (0.04 to 0.59)	0.0032
Peak Ratio	0.5831	-0.005135 (-0.002884 to -0.007386)	0.47 (0.17 to 0.71)	<0.0001

Table 1: Models relating to sex, age, weight and pulse rate. r^2 confidence intervals (Fisher's z transformed) are as given by StatsDirect using a simple linear regression on these data.

Results Scatter plots were made of mean measured FPPH, FWHM, SPPH and peak ratio against each predictor. Residual and normal plots were made for the constructed models. Figures 2 and 3 shows plots for FPPH and peak ratio respectively against age with regression lines indicating potential linear relationships. Our dataset showed some predictive value of subject age with respect to FPPH and peak ratio, as shown in Table 1. No other significant relationships were observed.

Discussion Models were successfully constructed for the FPPH and the peak ratio, both suggesting significant relationships between the age of the subject and the measured AIF variable. The model for the FPPH suggests that 30% of the variance in the measured height of the first pass peak may be due to the influence of age through some physiological mediator. Age could, e.g., be a proxy measurement of the reduction in compliance of the arteries. The coefficient for the predictor variable age in the model is 0.1646, suggesting that an increase in age for this population of 20 years tends to be associated with an increase in the first pass peak height of 3.3 mM which may represent a sizeable error if using a population representative AIF. The model for the peak ratio showed a small coefficient for the change in ratio with age but with a higher significance and r^2 than the FPPH model. This suggests that the ratio measurement may be more robust to measurement error than the FPPH. No associations could be found between our predictor variables and the FWHM although we would expect some to exist if the models above are accurate. For example, if the FPPH does increase with age and is not associated with weight then we would expect the FWHM to increase with weight according to dosing. This study may not reflect this due to the FWHM being a function of the peak height and time of start of uptake, both of which may be prone to sampling error.

Conclusion Relationships have been demonstrated between the age of the subject and both the FPPH and the peak ratio. No other relationships were found. It appears that the form of the AIF as measured in this study does reflect underlying physiological variation and it may be that any future increased sensitivity to such variation may reflect improvements in the acquisition technique. This also cautions against using population models without balancing the challenges of directly measuring an AIF against the information contained therein. Certain measures, such as the second pass peak and the first pass FWHM, may be considered to be currently 'poor' in that they have not been shown to reflect the subject variation as measured in this study, although it does not seem reasonable to suppose that the range of predictor variables in this study could ever fully explain the intrinsic variation in a perfectly measured AIF. It may be possible to utilise this analysis approach to improve the estimation of a population representative AIF in order to more accurately model patient microvascular characteristics.

Acknowledgements We would like to acknowledge the support of AstraZeneca and Cancer Research UK in this work (CRUK grant codes C237/A6295 and C19221/A6086) and to thank Lucy Kershaw for her helpful discussions.

References (1) Parker, G.J.M., *et al.*, *Magn. Reson. Med.*, 56:993-1000, 2006; (2) Li K., *et al.*, *J. Magn. Reson. Imag.*, 12:347-357, 2000.