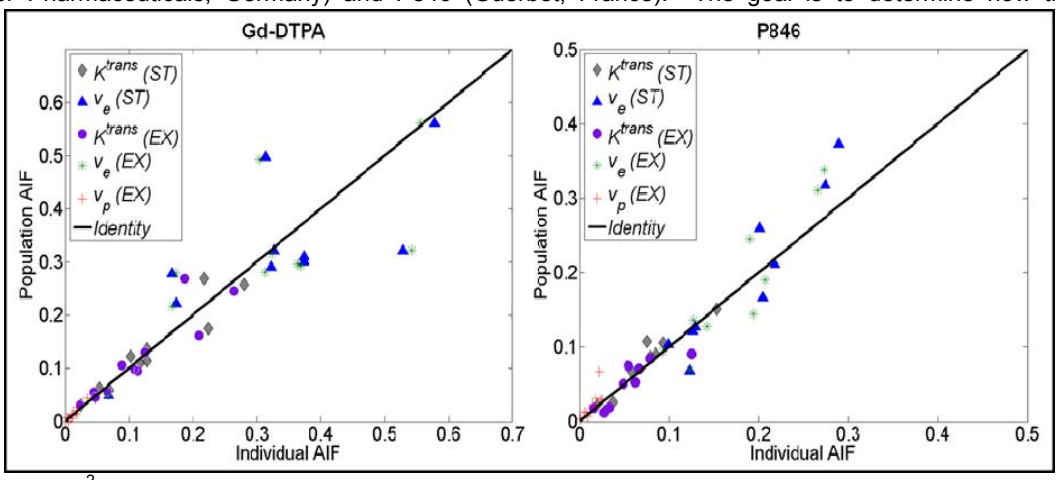
Is it "Safe" to Use a Population Arterial Input Function for DCE-MRI in Mice?

M. E. Loveless[1,2], J. Halliday[3], C. Liess[3], L. Xu[4], R. Dortch[2,5], J. Whisenant[2,6], J. C. Waterton[3], J. C. Gore[2,5], and T. E. Yankeelov[2,5]

[1]Biomedical Engineering, Vanderbilt University, Nashville, TN, United States, [2]Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States, [3]Imaging, Translational Sciences, AstraZeneca, Macclesfield, Cheshire, United Kingdom, [4]Biostatistics, Vanderbilt University, Nashville, TN, United States, [5]Radiology and Radiological Science, Vanderbilt University, Nashville, TN, United States, [6]Chemical & Physical Biology, Vanderbilt University, Nashville, TN, United States

INTRODUCTION

For quantitative analysis of DCE-MRI data, the time course of the concentration of the contrast agent in the blood plasma (C_p, or *AIF)* is required. Because of the difficulty associated with measuring the *AIF*, many studies have used a cohort of similar subjects to obtain a population average *AIF*; however, few studies have gathered these data in mice[1]. In this study we compare parameters resulting from two common models (the standard and extended Tofts[2]) using both individual and population derived *AIF*s in mice for two different contrast agents, Gd-DTPA (Bayer Pharmaceuticals, Germany) and P846 (Guerbet, France). The goal is to determine how the individual and population AIF derived parameters compare and how this affects the number of animals that would be needed in a given study.



MATERIALS and METHODS

Eleven mice were subcutaneously injected with 0.5 x 10^6 4T1 breast cancer cells dorsal to the front flank. After 8-10 days, the mice were imaged at 7T. Pre-contrast T_1 maps were obtained using an IR snapshot FLASH gradient echo sequence over nine inversion times with *TR\TE* \α= 10000 ms\ 3.44 ms\15° and NEX = 4, FOV = 25 mm^2, and matrix = 64^2 for one 2 mm slice. The DCE-MRI protocol employed a FLASH sequence with *TR\TE\α* = 6 ms\2.41 ms\10°, and NEX = 4. A bolus of 0.05 mmol/kg Gd-DTPA or P846 was delivered *via* a jugular catheter using an automated syringe pump at a rate of 2.4 mL/min. Signal data from the left ventricle (LV) of each mouse were converted to C_p time courses (AIF_{ind})[2]. The population averaged AIF was then determined (AIF_{pop}), and both AIF_{ind} *and* AIF_{pop} were used to fit the tissue of interest (TOI) signal data (C_t) for the whole tumor for each mouse to the standard (ST) and extended (EX) Tofts models[2] using the following equations:

$$C_t(t) = K^{trans} \cdot \int_0^t C_p(u) \cdot e^{-(K^{trans}/v_e)(t-u)} du \qquad \text{and} \qquad C_t(t) = K^{trans} \cdot \int_0^t C_p(u) \cdot e^{-(K^{trans}/v_e)(t-u)} du + v_p \cdot C_p(t) .$$

The resulting parameters using both AIF_{ind} and AIF_{pop} were analyzed using linear regression, concordance correlation coefficient (CCC)[3], Pearson correlation coefficient and power analysis to detect a 50% change in the population mean.

RESULTS

The figure above presents the fitted parameters from the two models when driven by AIF_{ind} (x axis) or the AIF_{pop} (y axis) for the average TOI time course per mouse. The table below reports the CCC (lower and upper 95% CI), Pearson correlation coefficient, and the slope and intercept values for regressing the AIF_{ind} data on the AIF_{pop} for each parameter. The median percent increase in sample sizes were calculated using non-parametric bootstrap method.

	CCC (95% CI)		Pearson		Intercept		Slope		Δ% in Pop.Size	
	Gd-DTPA	P846	Gd-DTPA	P846	Gd-DTPA	P846	Gd-DTPA	P846	Gd-DTPA	P846
K^{trans} (ST)	**0.929** (0.809,0.975)	**0.928** (0.734,0.982)	0.954	0.947	-0.021	-0.001	1.197	1.097	35	19
v_e (ST)	**0.824** (0.483,0.948)	**0.837** (0.623,0.935)	0.832	0.935	0.084	-0.077	0.736	1.479	-14	100
K^{trans} (EX)	**0.955** (0.854,0.987)	**0.849** (0.466,0.964)	0.960	0.854	-0.008	0.007	1.062	0.823	16	11
v_e (EX)	**0.796** (0.423,0.938)	**0.822** (0.584,0.930)	0.808	0.915	0.094	-0.074	0.694	1.452	-16	100
v_p (EX)	**0.875** (0.756,0.967)	**0.451** (0.022,0.740)	0.979	0.731	-0.004	0.001	1.538	1.610	58	57

DISCUSSION

As shown by the CCC, parameters reported using AIF_{ind} and AIF_{pop} agree very well. Correlation is the highest for K^{trans} for both agents; in fact, the power analysis shows a minimal change in population when using the AIF_{pop} for both Gd-DTPA and P846 for this parameter. This analysis also illustrates that even fewer animals may be required for v_e using Gd-DTPA (yellow highlights). However, to detect a 50% difference for v_p with Gd-DTPA and P846 (and v_e for only P846), the population must be 50-100% larger when using AIF_{pop} (blue highlights) instead of the AIF_{ind}. While we note that these calculation are specific to imaging protocol and tumor model, the principle is generally applicable and suggests that DCE-MRI analyses using population derived AIFs are appropriate for use in mice. Further analyses will include a voxel-by-voxel parametric analysis of agreement.

REFERENCES [1] Pickup et al; *Acad Radiol* 2003;10:963-68, [2] Tofts et al; *JMRI* 1999;10:223-32., [3] Lin; *Biometrics* 1989;45:255-68.

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