Parameter Fits Using Measured Population AIF vs. Literature AIF in DCE-MRI of Pancreatic Cancer Xenograft Model

A. C. Yung[1], S. Ng[1,2], J. Flexman[1], J. C. Tso[1], D. Yapp[1,3], and P. Kozlowski[1]

[1]University of British Columbia, Vancouver, BC, Canada, [2]British Columbia Cancer Research Centre, [3]British Columbia Cancer Research Centre, Vancouver, BC, Canada

Introduction. Dynamic contrast-enhanced MRI (DCE-MRI) has become an important tool in measuring tumour perfusion in animal models of cancer. Standard Kety model analysis of tumour perfusion [1] requires knowledge of the contrast agent concentration in the blood plasma, known as the arterial input function (AIF). Many DCE-MRI studies in mice use an assumed AIF taken from the literature (e.g. Lyng et al. [2], Checkley et al. [3]), even though the mouse strain and cancer model are different. In DCE-MRI of a murine xenograft model of pancreatic cancer, it is possible to extract AIF estimates by measuring concentration time courses in the abdominal aorta. We show here that Kety model parameter fits are improved when a population-averaged AIF is measured from the DCE data in the current study, as opposed to using an assumed AIF from the literature.

Methods. CB-17 SCID mice were implanted with human pancreatic adenocarcinoma via direct surgical suture onto the mouse pancreas [4]. DCE-MRI experiments were performed under isoflurane anesthesia on seven mice, 21 days after tumour implantation on a 7T 30-cm bore Bruker MRI scanner. An actively decoupled rectangular surface coil was used for reception (1.7x1.4cm) and a Bruker quadrature birdcage coil was used for transmission (i.d. = 7cm). 3D-FLASH was used to acquire the data for gadodiamide (Omniscan) concentration estimates (FOV=3.84x21.6x2.4 cm, voxel size=0.3x0.3x1mm): three scans with different flip angles were used to calculate in vivo flip angle maps [5] in order to correct the T1 estimates (α_{nom} = 145°, 180°, 215°; TE/TR=3.5/460 ms, 2x zero-filling for 0.3x0.3x1mm voxel); a three-scan variable flip angle (VFA) method was used to calculate native T_1 in the tumour [6] (α_{nom} = 10°, 20°, 50°, TE/TR=2.7/144ms), and a rapid T_1-weighted scan series (TE/TR=2.7/9ms, α_{nom}=25°, 15.6 sec per scan) was performed before and after bolus injection of 30 mM gadodiamide (20 pre-contrast scans, 150 post-contrast scans). Concentration was derived assuming linearity between contrast concentration and T_1 according to equations given in [7]. Concentration data in the abdominal aorta were selected for the population-averaged AIF if the concentration peak occurred by the second post-contrast scan at a level of 5 mM or more, subjectively rejecting voxels with partial volume effects from adjacent locations. A blood plasma volume fraction of 0.6 was used to convert the measured arterial concentration into the AIF. K^{trans}, v_e and v_p were estimated by Levenberg-Marquardt fitting of the concentration courses, using either the literature AIF from Lyng et al. [2], or with a biexponential function that was fit to this study's population-averaged AIF. Chi square was calculated for each voxel's time course, representing how closely the model fits the data ($\chi^2 = \Sigma\{O-E\}^2 / \sigma^2$, where O=observed concentration, E=expected concentration, σ = standard deviation of O). A model fit was rejected if the standard deviation of normalized residuals was greater than 0.5, or if the fit resulted in v_e or v_p less than zero or greater than 1 (i.e. non-physical values).

Results. 15 individual AIF time courses were selected from a pool of four tumour-bearing mice for inclusion into the population-averaged AIF (see Figure 1, which shows the Lyng AIF for comparison). A biexponential fit to the population average resulted in the following functional form in mM: AIF(t) = 2.94exp(-0.0233t) + 24.9exp(-2.7734t). Figure 2 shows a typical T1-weighted contrast scan, and compares K^{trans} and v_e maps using the measured population AIF versus the literature AIF (white pixels denote rejected model fits). Across this representative tumour, the literature AIF produced 16% more rejected model fits and produced similar K^{trans} values and markedly higher v_e values (median v_e = 0.40 vs. 0.16, median K^{trans} = 0.028 vs. 0.024 min^{-1} for measured AIF vs. literature AIF, respectively). Chi square was smaller using the measured AIF than with the literature AIF in 85% of the tumour voxels. Figure 3 shows the ratio of chi square values from fits using the literature AIF versus the measured population AIF for a typical slice (median chi square ratio across representative tumour = 1.38).

Figure 1. AIF time courses

Discussion and Conclusions. Accurate simultaneous measurement of the AIF and tissue perfusion is notoriously difficult in DCE-MRI, as evident in the presented study: a higher temporal resolution is desired (ideally 2 seconds or less [8]), extraction of vascular concentration is hindered by partial volume and flow artifacts, and the selection process was subjective and prone to interobserver variability. However, despite the uncertainty in this study's AIF estimates, the improved model fits may be indirect evidence that using a population-averaged AIF derived from the same experimental data is more accurate than using a literature value derived for a different mouse strain and tumour model.
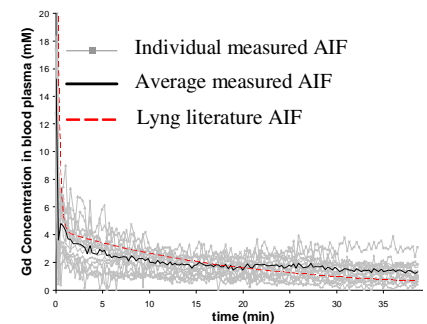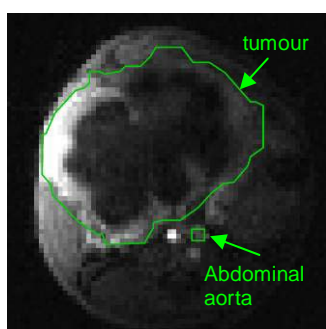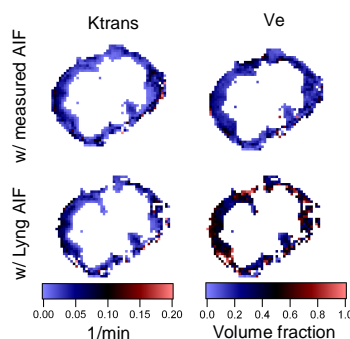

Figure 2: T1-weighted contrast scan **Figure 3: Ktrans and Ve comparison** **Figure 4: Chi square ratio and fit comparison in example voxel (white arrow)**