Does Measurement of the Arterial Input Function Improve the Correlation between Tumor Microvessel Density and MR-Derived Perfusion of Small Molecular Extracellular Gd Chelates?

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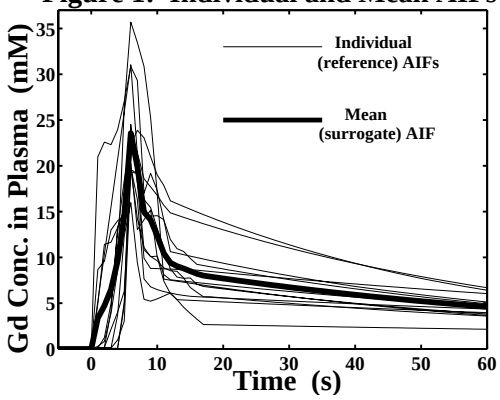
Introduction: Small molecular extracellular Gd chelates (SMEGdC, e.g. Gd-DTPA) are often used for quantitative dynamic contrast-enhanced MR imaging (DCE-MRI) of tumor perfusion (1-10). For such studies, it has often been reported that tracer kinetic parameters (e.g., the perfusion parameter K^{trans}) do not correlate with histological measurements such as microvessel density (MVD) (1-4). This lack of correlation between K^{trans} and MVD probably results from the fact that K^{trans} embodies several factors related to perfusion of SMEGdC (vessel density, vessel geometry, permeability, and flow), whereas MVD relates only to vessel density (1-3). Unfortunately, for most quantitative DCE-MRI tumor studies employing SMEGdC, the arterial input function (AIF) is not measured carefully for each subject, which can lead to significant (>30%) random errors in K^{trans} (2-5). Thus, it is not clear whether the lack of correlation between K^{trans} and MVD is caused by underlying physiology or random measurement errors in K^{trans}. The purpose of this study was to determine if the correlation between K^{trans} and MVD can improve with careful AIF measurements.

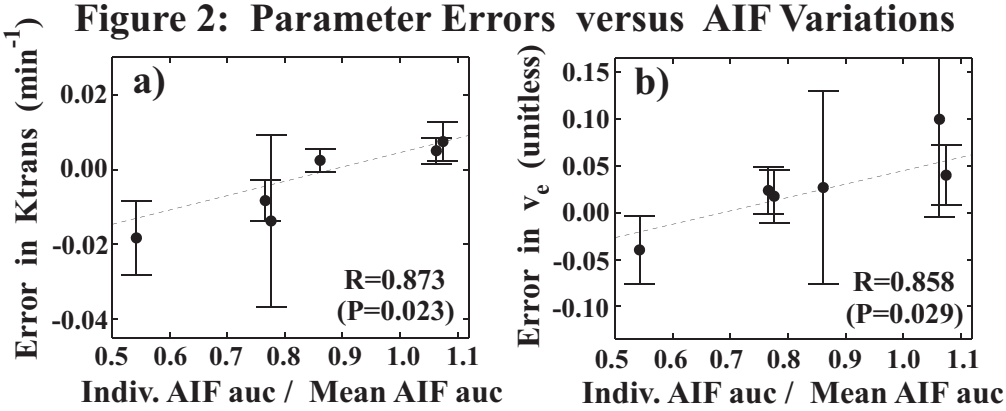
Methods: This study was approved by the Carleton U. Animal Care Committee. About 10^6 R3230 AC cells were injected sub-Q into each of six male ~350 gm Fischer-344 rats, producing tumors which were allowed to grow to ~0.5 to 2.5 cm (3-6 weeks). In vivo quantitative DCE-MRI (1.89 T) experiments (all acute) were then performed on the animals after halothane anesthesia. Following a bolus i.v. injection of 0.3 mmol/kg Omniscan, an RF-spoiled gradient-echo imaging pulse sequence was used for dynamic imaging (5.5 min total) of both tumor (3-10 axial slices) and the aorta (1 axial slice). A specialized interleaved phase encode acquisition strategy allowed for high temporal resolution in the aorta (~0.8 s), despite lower temporal resolution in the tumor (5-17 s). The imaging parameters for the tumor were: 128x64, TR=80-260 ms, TE=4 ms, flip=30-60°, Δz=2 mm. For the aorta: 64x32, TR=26 ms, TE=4 ms, flip=30°, Δz=5 mm. The Gd concentration-versus-time in the tumor tissue ($[C]_t(t)$) was estimated via the Bookend Method (6). The AIF was measured with a combination of aorta phase imaging and arterial blood sampling (7). Six tumor experiments were performed on the six rats. Additional AIF-only experiments were performed on 4 of the 6 tumor rats plus one other non-tumor rat, for a total of 12 AIF measurements. The tumors were then perfused with formalin, sliced, embedded in paraffin, mounted on slides, and stained for factor VIII (for MVD) and Haematoxylin & Eosin (for assessing cellularity). MVD was counted both in a "hot spot" of vessels and in 9 random fields per slide (400x) (1-3). Cellularity, which we hypothesized may correlate with the distribution volume, v_e, was assessed in 10 random fields per slide (400x) (4,8). Tracer kinetic modeling was used to calculate K^{trans} and v_e voxel-by-voxel from the AIF and $[C]_t(t)$ data (2-4). To estimate potential errors caused by not measuring individual AIFs ("surrogate AIF errors"), K^{trans} and v_e were also calculated with a mean (surrogate) AIF obtained by averaging all 12 measured AIF curves (Fig. 1) (5).

Figure 1: Individual and Mean AIFs



Results: The AIF was measured to an accuracy of ~5%. The ranges of values measured for K^{trans} and v_e were ~0.0-0.1 min^{-1} and ~0.0-0.5 respectively, consistent with the literature (9,10). Median fit uncertainties for K^{trans} and v_e were 0.003 min^{-1} and 0.0087, respectively. Each of the data points in Fig. 2 represents, for all voxels of one of the six tumors, the mean and standard deviation of the surrogate AIF error in K^{trans} or v_e. These errors were correlated (P=~0.026) with the areas under the curves (auc) of the individual AIFs, as expected (3). Surrogate AIF errors were also positively correlated with increasing values of K^{trans} or v_e (P<0.0001).

Figure 2: Parameter Errors versus AIF Variations



Combining the data for all 6 tumor rats, the overall surrogate AIF error for all rats was -0.004 ± 0.015 min^{-1} for K^{trans} and 0.027 ± 0.077 for v_e. For each tumor, the MVD and cellularity measurements for the histological slide containing the largest tumor section were compared to the K^{trans} and v_e maps (individual AIFs employed) of the MR slice having the largest tumor section. Regardless of how the two were compared, no quantitative correlation whatsoever was found between histology and MR.

Conclusion: The results of this study show that there is no correlation between histological tumor MVD and tumor K^{trans} measured with small molecular extracellular Gd chelates, even when AIFs are measured carefully.

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