In vivo measurement of pharmacokinetic parameters in small animal DCE-MRI using cardiac sampling of the vascular input function

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Introduction Dynamic contrast enhanced MRI (DCE-MRI) allows non-invasive investigation of tumor function through its sensitivity to the characteristics of the tumor microvasculature; this sensitivity permits monitoring the response of the tumor to therapy. DCE-MRI exploits the principle that a bolus of injected contrast agent extravasates into tissue from the bloodstream at a rate dependent upon the structure of the tissue microvasculature. The contrast agent dynamics can then be measured by observing the signal changes in rapidly acquired images.

The resulting contrast agent concentration curves may be quantitatively analyzed to evaluate microvascular changes. Parametric models, such as the widely used two-compartment model (1), describes the microvasculature in terms of two or three parameters: K^{Trans} and k_{ep}, which describe the flow and permeability of the tissue microvasculature, and the optional parameter v_p that accounts for the volume of blood vessels in the tissue voxel. These models describe the exchange of contrast agent between blood and tissue, and thus require measurement of both. The measurement in blood, known as the vascular input function (VIF), is subject to substantial measurement uncertainties, particularly when measured in small animal models of cancer (2). Partial volume effects and inflow enhancement can severely distort VIFs (3). Additionally, the low blood volumes and rapid heart rates of mice suggest a need for sampling of the VIF faster than the 1 s rate desired in humans (4).

We have developed an approach to VIF sampling which is insensitive to partial volume artifacts, while also achieving very high temporal resolution. Sampling is performed in an interleaved slice traversing the heart, exploiting the relatively large size of the left ventricle to avoid partial volume artifacts. High temporal resolution sampling of the VIF is achieved through the CACTUS (Cardiac Anatomy Constrained, Temporally Unrestricted Sampling) algorithm that uses fully-encoded images and manual segmentation to guide measurement of the signal via constrained reconstruction of undersampled data(5). Measurements in a tumor model were performed to investigate the differences in pharmacokinetic parameters produced by cardiac VIF sampling with local vessel sampling.

Methods All experiments and procedures were approved by our Institutional Animal Care and Use Committee, which is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. All data was acquired on a Biospec 4.7T small animal MR scanner (Bruker Biospin MRI, Billerica, MA).

The effects of the developed VIF measurement strategy on pharmacokinetic parameters was measured by comparing parameters resulting from cardiac and local vessel VIF measurements in three mice bearing orthotopic Uth83 anaplastic thyroid tumors. Acquisition parameters were: TE = 1.55 ms, TR = 41 ms, flip angle = 30º, slice thickness = 1 mm. One trans-cardiac slice was acquired using a radial acquisition scheme while seven slices were acquired of the tumor with Cartesian encoding. The acquisition matrix for the tumor slices was 256x96 over a 4 cm x 3 cm FOV. The acquisition matrix for the radial encoded cardiac slice was 256 points over 4 cm with 384 spokes and an angular increment of 120.5º over 30 repetitions (120 repetitions of the Cartesian slices). A 5 mm presaturation band was applied around the trans-cardiac slice to suppress inflow enhancement during excitation (6). Manual segmentation was performed to use with the constrained reconstruction algorithm. VIFs were taken both from the LV using CACTUS and from an artery near the tumor via manual VIF selection. Pharmacokinetic parameter maps were calculated by fitting the extended Toft's model to the concentration time courses. The mean and standard deviation of K^{Trans}, k_{ep}, and v_p were calculated, as well as the inter-subject variance of the parameters.

Results VIFs from each technique are shown in Fig 1. The cardiac VIF features a larger amplitude and sharper initial rise, which is consistent with a reduction in partial volume and inflow enhancement artifacts and improved temporal resolution. The resulting pharmacokinetic parameter maps are shown in Fig 2. Mean parameter values for each mouse are given in Table 1. The inter-subject coefficient of variation was reduced for all three pharmacokinetic parameters: the CVs between mice of K^{Trans}, k_{ep}, and v_p from the cardiac measurement are 36%, 25%, and 28%, respectively. For the local vessel measurement, these quantities are 71%, 79%, and 61%. The values of v_b derived from the cardiac measurements displayed structure more similar to the other parameters than the noise-like measurements of v_b derived from the local vessel. A blood vessel included in the displayed slice produced a large pseudopermeability artifact that is visible in the maps of K^{Trans} and k_{ep} for the local vessel measurement. This artifact does not appear in the K^{Trans} and k_{ep} maps created from the cardiac VIF, but rather it manifests in the measurement of v_b, as is physiologically appropriate.

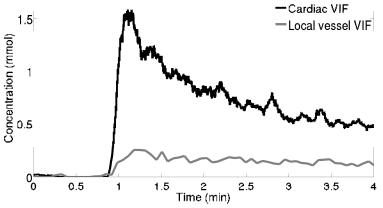

Figure 1 VIFs measured in the heart and in a local vessel

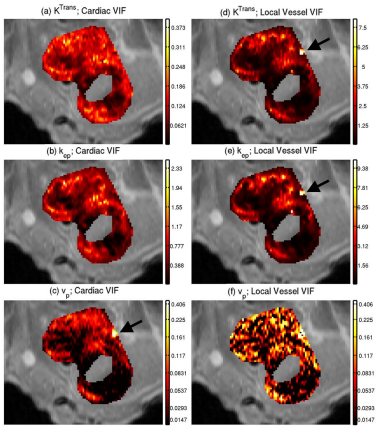

Figure 2 Pharmacokinetic parameters calculated from each VIF
Arrows highlight the pseudopermeability artifact

Discussion A substantial reduction in the variation of pharmacokinetic parameters across subjects was observed; this change in relative variation would decrease the number of mice needed for an experiment by a factor of four, assuming similarly proportional effects. Additionally, the measured parameter maps calculated from the cardiac VIF show resistance to pseudopermeability artifacts and improved measurements of v_p, compared to a conventional local vessel VIF.

The improvements in VIF measurement will provide substantial benefits to the measurement of pharmacokinetic parameters in small animal DCE-MRI. High temporal resolution decreases sampling distortions, and cardiac sampling provides a reduction in partial volume artifacts, decreasing errors in the VIF. This in turn leads to greater precision of measured pharmacokinetic parameters, which will improve the sensitivity and power of preclinical DCE-MRI involving small animal models of cancer.

	Head/Neck Mouse 1	Heart Mouse 1	Head/Neck Mouse 2	Heart Mouse 2	Head/Neck Mouse 3	Heart Mouse 3
K^{Trans} (min^{-1})	0.286 ± 94%	0.052 ± 34%	1.099 ± 94%	0.112 ± 49%	0.438 ± 37%	0.086 ± 47%
k_{ep} (min^{-1})	2.251 ± 91%	0.775 ± 43%	1.332 ± 98%	0.509 ± 76%	0.247 ± 35%	0.526 ± 46%
v_p	0.041 ± 86%	0.017 ± 72%	0.091 ± 122%	0.030 ± 102%	0.158 ± 89%	0.026 ± 99%

Table 1 Measured kinetic parameter values

Acknowledgements The authors would like to express their thanks to Valen E. Johnson, Ph. D., for helpful enlightenment on statistical matters. They further thank Charles Kingsley, Jorge DeLacerda and Yunyun Chen for their assistance in animal handling and preparation. Financial assistance was provided by NIH Grants P30 CA16672 and P50 CA83639, as well as institutional start-up funds.

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