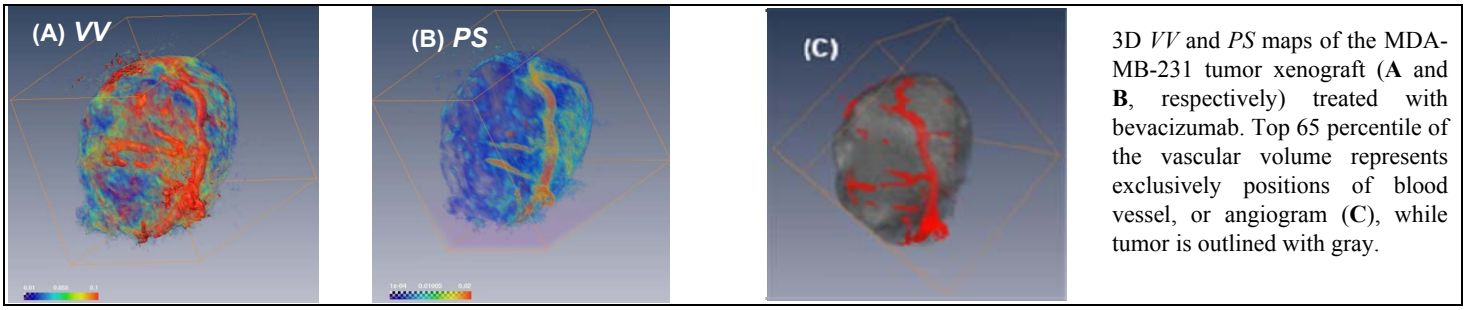
Assessment of Tumor Microvasculature by a Kinetic Model Independent DCE-MRI Method Using a High Molecular Weight Contrast Agent

W. Zhu[1], Y. Kato[1], S. Shankar[1], Z. Bhujwalla[1], and D. Artemov[1]
[1]ICMIC Program, Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, MD, United States

Introduction: Dynamic contrast enhanced MRI is the imaging technique of choice to characterize tumor microvasculature, and to monitor therapeutic response of antiangiogenic and antivascular agents. Microvasculature parameters such as tumor permeability and vascular volume are derived from the time dependent contrast agent concentration profile. However, MR signal intensity is also affected by the water exchange rate and blood flow, in addition to the contrast agent concentration. Therefore, the purpose of this study is to develop a DCE-MRI method that can minimize the effect of water exchange and blood flow to obtain a more reliable assessment of the tumor microvasculature, and to use this method to monitor the tumor vascular parameters in a preclinical mouse model of human breast cancer treated with bevacizumab.

Materials and Methods: MDA-MB-231 human breast carcinoma cells were orthotopically inoculated in the mammary fat pad of female SCID mice. These mice were treated with an intraperitoneal bevacizumab injection at a dose of 10 mg/kg every 4th day. T1-weighted images were acquired at a 9.4T Bruker MR scanner using a saturation-recovery 3D FLASH sequence with the following parameters: a progressive saturation block consisting of hard RF pulses followed by crusher gradients and recovery time, τ, of 20 ms, flip angle of 90^0, and TE/TR=1.5/8 ms before and for 30 min after intravenous administration of HMWCA albumin-GdDTPA at 0.1 mmol Gd/kg. 3D M_0 map was determined by acquiring an M^I_0 map with intensities proportional to M_0 prior to the administration of the contrast with a 3D FLASH, TE/TR=1.5/8ms and a nominal flip angle of 3^0. Quantitative M_0 map was derived from M^I_0 using a calibration constant determined from the ratio of amplitudes of echoes acquired with 4 central phase encoding steps of the same FLASH sequence with parameters TE/TR =1.5/10,000 ms and a 90^0 flip angle to the corresponding $M_O{}^I$ echoes.

Results and Discussions: It has been shown that with a short recovery delay and flip angle of ~90^0, relaxation rate measurements became independent of the water exchange model used, and the effect of inflow was minimized by using a short recovery delay and a 3D acquisition sequence (1). This is in part due to the fact that under these conditions the exponential relaxation behavior of the MR signal can be approximated by a linear term (2). Inflow of the non-saturated protons into the selected slice due to blood flow can be further minimized by the use of a saturation block with 3 nonselective RF pulses followed by crusher gradients. Under these conditions, the contrast agent concentration, *C(t)*, can be determined from the difference between pre- and post-contrast images normalized to M_0 and the T1 relaxivity of the contrast agent, *k*, as $C(t)=(M^{post} - M^{pre})/k\tau M_0$. A linear regression of *C(t)* produced vascular volume (VV) and vascular permeability surface area product (PS) (3) as shown below in Figure A and B. As expected, voxels in the top 65 percentile of the vascular volume map provides angiography information that helps us visualize the tumor vasculature (Figure. C).



3D *VV* and *PS* maps of the MDA-MB-231 tumor xenograft (**A** and **B**, respectively) treated with bevacizumab. Top 65 percentile of the vascular volume represents exclusively positions of blood vessel, or angiogram (**C**), while tumor is outlined with gray.

Conclusion: The new DCE-MRI method that can minimize the effect of water exchange and blood flow on the assessment of tumor microvasculature provides a reliable determination of vascular volume and vascular permeability parameters both in highly permeable tumor areas with conceivably fast water exchange and in mature blood vessels that contain slowly exchangeable water. This method can enable the monitoring the effects of vascular interventions that modulate permeable tumor neovasculature as well as established blood vessels.

References: 1. Kim YR, Rebro KJ, Schmainda KM. Water exchange and inflow affect the accuracy of T1-GRE blood volume measurements:implications for the evaluation of tumor angiogenesis. Magn Reson Med 2002;47(6):1110-1120. 2. Schwickert HC, Roberts TP, Shames DM, van Dijke CF, Disston A, Muhler A, Mann JS, Brasch RC. Quantification of liver blood volume: comparison of ultra short TI inversion recovery echo planar imaging (ULSTIR-EPI), with dynamic 3D-gradient recalled echo imaging. Magn Reson Med 1995;34(6):845-852. 3. Bhujwalla ZM, Artemov D, Glockner J. Tumor angiogenesis, vascularization, and contrast-enhanced magnetic resonance imaging. Top Magn Reson Imaging 1999;10(2):92-103.

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