Tumor Vasculature & Perfusion: Metabolic MRI

Charles S. Springer, Jr.

Oregon Health & Science University

The vascular properties of *in situ* tumors are widely studied using (Dynamic-Contrast-Enhanced) DCE-MRI.[1] This involves acquisition of serial T_1-weighted ^1H_2O images before, during, and after bolus injection of a paramagnetic contrast reagent (CR). Several hydrophilic, monomeric Gd(III) chelates are approved as clinical CRs. As the CR passes through a tissue ROI or voxel, the ^1H_2O signal intensity increases and decreases [CR affects T_1], and its time-course can be analyzed for pharmacokinetic parameters. [The time-course of the blood ^1H_2O signal is also required.] An understandable initial step was to employ very mature pharmacokinetic paradigms developed for tracers.[2] The major parameters extracted included a CR extravasation rate constant (K^{trans}) and distribution volume – thought to be the extracellular volume fraction (v_e). However, an inherent aspect of the classical tracer is that compartmentalization is not intrinsic to the signal: one can tell only that tracer molecules are in a voxel but not their compartments. However, though CR plays a tracer-like role, the ^1H_2O signal is detected in DCE-MRI: water is the signal molecule. Water and tracer molecules are never identically compartmentalized: most water is intracellular. Furthermore, the MRI "knows" the water and CR compartmentalization. The blood, interstitial, and intracellular ^1H_2O magnetizations have fixed amplitudes, and their T_1 values change differently during the CR bolus passage. DCE-MRI in fact keeps separate track of how much CR is in blood plasma and interstitium – even within a single voxel. The only way the MRI can reconcile this with the tracer limitation of not knowing compartmentalization is to assume equilibrium inter-compartmental water exchange is effectively infinitely fast: this "short-circuits" CR compartmentalization.[3-6] Thus, imposition of a tracer paradigm on DCE-MRI data requires the fast-exchange-limit [FXL] assumption for water compartmental interchange.[3-6] Infinitely fast water exchange is physically impossible, and actual kinetics have been known for almost 70 years. A DCE-MRI "shutter-speed" pharmacokinetic paradigm (SSP) accounts for these facts.[3-6]

There are two general, and important, consequences of using the tracer paradigm for DCE-MRI data. First, it systematically underestimates K^{trans} and v_e values, especially for tissues with angiogenic capillaries. The SSP allows very high specificity in discriminating benign from malignant breast[4,5,7] and prostate[6,8] tissues. In each of these diseases ~70% of biopsies find no cancer: most can be avoided with SSP DCE-MRI. The inherently larger K^{trans} values for malignant tumors are particularly suppressed by the tracer analysis. Shutter-speed relief of significant human myocardial v_e underestimation by the tracer approach is also important in the diagnosis of cardiovascular disease.[9] Second, the tracer paradigm denies access to the inter-compartmental water exchange kinetics themselves, which are measured by the mean intracellular water molecule lifetime (τ_i). A recent exciting discovery is that τ_i is a reciprocal measure of active trans-membrane water cycling, which is driven by the on-going activities of osmolyte cycling membrane transporters.[10] Thus, it is quite possible that high-resolution τ_i maps provided by SSP analyses[6,8] represent reciprocal maps of the activity of one of biology's most important, and ubiquitous, enzymes, the Na^+/K^+ATPase. This would be high-resolution MRI metabolic imaging.

References: [1]O'Conner, Jackson, Parker, Jayson, *Nat. Revs. Clin. Oncol.* **9:**167-177(2012). [2]Tofts, *JMRI* **7:**91-101(1997). [3]Li, Rooney, Springer, *MRM* **54:**1351-1359(2005) [erratum, **55:**1217(2006)]. [4]Li, Huang, Morris, Tudorica, Seshan, Rooney, Tagge, Wang, Xu, Springer, *PNAS* **105:**17937-17942(2008). [5]Huang, Li, Morris, Tudorica, Seshan, Wang, Xu, Springer, *PNAS* **105:**17943-17948(2008). [6]Li, Priest, Woodward, Siddiqui, Beer, Garzotto, Rooney, Springer, *JMR* **218:**77-85(2012). [7]Huang, Tudorica, Li, Thakur, Chen, Morris, Tagge, Korenblit, Rooney, Koutcher, Springer, *Radiology* **261:**394-403(2011). [8]Li, Priest, Woodward, Tagge, Siddiqui, Huang, Rooney, Beer, Garzotto, Springer, *MRM* **69:**171-178(2013). [9]Coelho-Filho, Mongeon, Mitchell, Moreno, Nadruz, Kwong, Jerosch-Herold, *Circ. Cardiovas. Imag.* **6:**000-000(2013). [10]Zhang, Poirier-Quinot, Springer, Balschi, *Biophys. J.* **101:**2833-2842(2011).