A NEW REFERENCE AGENT MODEL FOR DCE-MRI THAT EXPLOITS SELECTIVE DETECTION OF TWO 19F MRI CONTRAST AGENTS

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INTRODUCTION: Dynamic Contrast Enhancement (DCE) MRI main limitations are: 1) Identifying the Arterial Input Function (AIF), 2) Interpretation regarding blood flow and permeability, 3) Uncertainty in the value of the hematocrit in the tumor microvasculature (which can vary between 0.40%, and is known as the Fassaeus Effect) [1]. The Reference Region Model has been proposed as an alternative method for evaluating DCE-MRI results without requiring an AIF [2], yet this method cannot account for changes in blood flow and hematocrit that affect the evaluation of vascular permeability. Instead of comparing DCE of a single contrast agent (CA) in two tissues, we propose a new model that compares two contrast agents in a single tissue, termed the Reference Agent Model (RAM). This new model is independent of blood flow and hematocrit because these vascular characteristics are identical for both agents, so that RAM accurately determines the relative permeabilities of the agents, known as relative-Ktrans defined as RktransCA,1/KtransCA,2 = [PSCA,1/Fp(1-Hct)] / [PSCA,2/Fp(1-Hct)]. To implement RAM, two MRI contrast agents must be selectively detected. Because two co-injected T1 or T2 MRI contrast agents are difficult to selectively detect with MRI, we have developed 19F contrast agents and optimized 19F MRI methods to perform simultaneous 19F-DCE-MRI of two agents in a mouse model of breast cancer. METHODS: New Model and Simulations: The operation equation for the Reference Agent Model was derived from the standard DCE-MRI differential equations [2]; computer simulations were used to study the effect of temporal sampling, statistical noise and pharmacokinetic constants on its accuracy and precision. A series of activity curves for each agent were generated using the standard Toft’s model and a range of Ktrans and kep [2]. Animal Model: Five female SCID mice were injected subcutaneously with 10x102 MDA-231 breast cancer cells in the right flank; all tumors were allowed to an average volume of 250 mm3 before initiating 19F-DCE-MRI studies. Contrast Agents: Two sets of 40% v/v nanoemulsions of perfluorinated liquids with different 19F MR frequencies were prepared: 1) Perfluoro-15-crown-5-ether (CE), singlet (20 equivalent 19F atoms) at 0 ppm; 2) Perfluorooctane (OC), triplet at 8 ppm. Both emulsions were extruded through a 50 nm filter and have the following composition: DPPC 85% mol, 16:0 PEG2000 PE 8.0% mol, and 7% DPPA [4]. The size of all nanoemulsions was determined by dynamic light scattering (DLS). H-MRI: Two pre-contrast 2D T1-w and T2-w 1H images were acquired as an anatomical reference (FOV= 35 mm2, matrix=1282, Thickness=4 mm, Total Slices=11). These images were rescaled to serve as an anatomical reference for 19F-MRI 19F-DCE-MRI: A series of dynamic 19F-MRI images were acquired using the same geometry than the 1H MRI anatomical reference, and the following GE pulse sequence: TR=300 msec, TE=3.09 msec, NEX= 8, alfa=42.2 deg. Geometry: FOV= 35 mm2, matrix=642. Slice Thickness=4 mm, Total Slices=11). A total of 20 image sets were acquired for a total acquisition time of 51.2 min and a temporal resolution of 2.5 min/image. Two vials with each emulsion were placed next to the mouse as internal controls for small differences in T1-weighting and spin density. After the first image set was acquired, a 75 µL of each agent (CE=3.5 mM, OC=4.6mM) were injected manually through a tail vein catheter over 35 seconds. Matlab was used to process the data and fit both activity curves to the Reference Agent Model (RAM). RESULTS: Our computer simulations (Figure 1B) showed that: 1) Rktrans can be calculated with only 5% error at SNR > 25, even when the sampling resolution is only 2 minutes. 2) At an SNR > 15 the precision of RAM is independent of temporal resolution (1 sec vs. 120 sec.). 3) Selection of temporal resolution greatly affect the precision of RAM at SNR < 15. 19F-DCE-MRI: The size of both nanoemulsions was 55 ±5 nm. Both fluorinated contrast agents were simultaneously imaged in vivo (Fig. 2A) using a GE selective excitation sequence (Fig. 3). The active curves of both agents were fitted to RAM and yielded Rktrans 2.35. DISCUSSION: To the best of our knowledge, this is the first report describing the selective detection of two 19F CA in a solid tissue under dynamic and multislice conditions [5]; it also opens the possibility of estimating relative permeability of two agents independent of blood flow and hematocrit. REFERENCES: 1) Lipowsky et al. Microvasc. Res., 1980, 19:297. 2) Tofts P., et al. J Magn Reson Imaging 1999, 10:223. 3) Yankeelov TE, et al. Magn Reson Imaging 2005, 23:519. 4) Mulder W. et al. NMR Biomed 2006, 19:142. 5) Ruiz-Cabello J, et al. NMR Biomed 2010, 24:114