Using DCE-MRI to Determine Vascular Properties of Female Rhesus Macaque Reproductive Tissue: Pharmacokinetic Model Considerations

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Introduction. The female uterus and ovary are among the few normal tissues to undergo periodic angiogenic changes [1]. Using a primate model (rhesus macaque), we investigate the feasibility of DCE-MRI to quantify blood volume fraction (v_b) and contrast reagent (CR) transendothelial permeability. The standard model with v_b (SM2) [2] and the second generation "shutter-speed" model (SSM2) [3], are used in parallel for this effort.

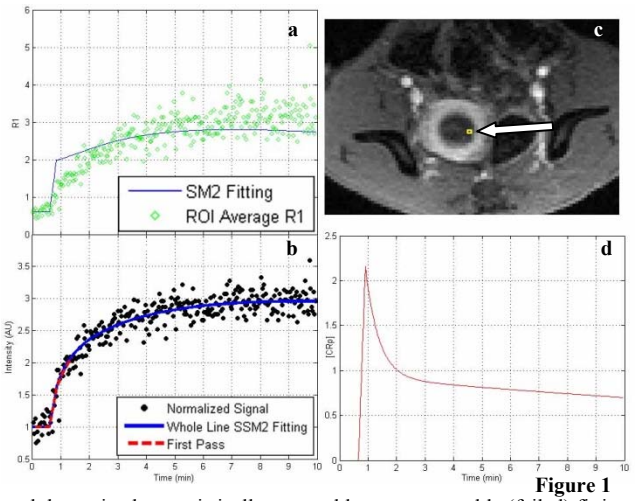

Figure 1

Methods. Dynamic-Contrast-Enhanced (DCE) MRI data were obtained from each of 4 adult female macaques undergoing controlled ovarian stimulation, once before (pre) and once after (post) an injection of recombinant human chorionic gonadotropin (hCG) [4] (8 DCE sessions). A CR bolus (Prohance, 0.05 to 0.15 mmol/kg I.V. at 0.5 mL/s) was administered ~40 s after MRI acquisition initiation. Each DCE series acquired 300 images with intersampling intervals of 2.14 or 2.38 s with a Trio 3T (Siemens). Images were acquired by a 3D gradient echo sequence with the following parameters: TR/TE = 3.6/1.77 ms, 8° Flip Angle, 2 mm slice thickness. Regions-of-interest (ROIs) were selected to include the entire *uterine basalis* zone and *endometrium*. Time-course data were fitted to estimate pharmacokinetic parameters K^{trans} (volume CR transfer constant), v_b, and v_e (the extracellular, extravascular volume fraction) for each ROI pixel. The mean intracapillary and intracellular water lifetimes (τ_b and τ_i, respectively) are effectively zero for the SM2 and were fixed at 300 ms for the SSM2 analyses. A generalized arterial input function (AIF), [amplitude-adjusted, using as reference tissue [5] pelvic skeletal muscle], was applied for each subject. Fitting-returned curves were manually reviewed pixel-by-pixel and determined as statistically acceptable or unacceptable (failed) fittings based on residual chi-square calculations and subjectively as to how well the curve agreed with all data points. Three-dimensional parametric grid searches (not shown) were performed on selected individual pixel data to evaluate accuracy and stability of the parameter values returned.

Results. In 4 out of 8 data sets, SM2 experienced higher pixel fitting failure rates than SSM2. Both models successfully fitted all pixel data in the other 4 sets. A representative example of a single uterine pixel time-course data set, and corresponding fitted curves, is shown in **Fig. 1**. SM2 significantly overshoots the data points during contrast uptake and trends toward undershooting thereafter (panel a). This is almost certainly due to its assumption that equilibrium transendothelial water exchange is effectively infinitely fast [6]. For the same data, SSM2 (fitted successively, as in [7]) manages to match the data points quite well throughout the entire time-course (panel b). Figure 1c shows an axial DCE image with the uterine pixel-of-interest outlined in yellow; Figure 1d presents the AIF used in analysis. **Fig. 2** shows parameter values for three post-hCG data sets for which both models successfully fitted all pixels in the respective ROIs. Each large bar represents the ROI mean parameter value (K^{trans}, in min^{-1}) with the error bar representing one SD. Absolute values vary slightly across subjects, but consistent trends are evident. SM2 overestimates K^{trans} and v_e relative to SSM2, and the opposite is true for v_b. The relative shutter-speed effect is particularly large for v_b (34% mean SM2 underestimation for those shown), the crucial angiogenic biomarker. However, this SSM2 realization likely has suboptimal exchange-sensitivity [8], and the differences may be even greater. **Fig. 3a** shows an axial DCE image with the *basalis* zone ROI circumscribed in yellow for one subject (#3, pre-hCG) yielding incomplete fittings. False-color axial *uterine basalis* zone parametric maps are shown of the SM2 (panels b-d) and SSM2 (panels e-g) fittings. Pixels with unacceptable fittings were omitted during mapping, and thus are black. Here SM2 fitted less than 68% of the pixels while SSM2 provided acceptable fittings for better than 96% of the 103 ROI pixels.

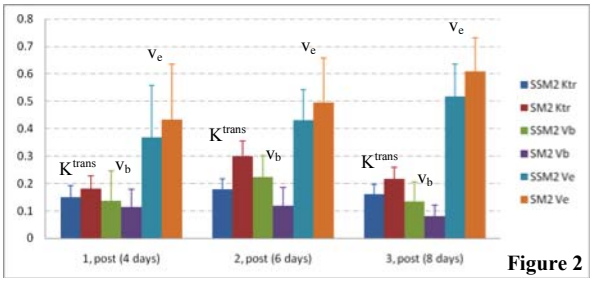

Figure 2

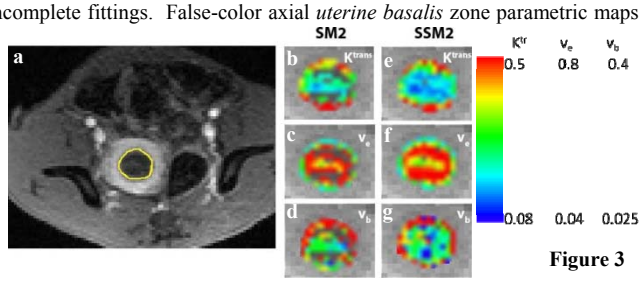

Figure 3

Discussion. Probably because it more realistically accounts for water exchange effects in DCE data modeling, the SSM2 exhibits a better ability to match the current data (Figs. 1a,b). Given the generally small CR doses used in this study, SM2 and SSM2 differences are expected to be small [8]. Still, advantages of SSM2 over SM2 can be seen. The SM2 experienced failures in nearly 10% of all pixels fitted while the SSM2 failed less than 1%. Only 4 data sets were completely fitted by SM2, while SSM2 completely fitted 7. A fitting mismatch such as that shown in Fig. 1a may indicate a poorly defined parametric space for SM2 in this application [6]. Also, the globally-defined AIF cannot be equally suitable for four different subjects.

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Reference: 1. Reynolds, Redmer, Fed Amer Soc Exp Biol J, 1992. **6**(3): p. 886-892. **2.** Tofts, J Magn Reson Imaging, 1997. **7**(1): p. 91-101. **3.** Li, Rooney, Springer, Magn Reson Med, 2005. **54**(6): p. 1351-9. [Erratum: Magn Reson Med 2006;55:1217.]. **4.** Wolf, Ramsey, Yeoman, Fanton, Mitalipov, Biol Reprod, 2004. **71**(2): p. 486-493. **5.** Kovar, Lewis, Karczmar, J Magn Reson Imaging, 1998. **8**(5): p. 1126-34. **6.** Li, Springer, and Jerosch-Herold, NMR Biomed, 2009. **22**(2): p. 148-57. **7.** Li, Rooney, Varallyay, Goodman, Selzer, Tagge, Pike, Neuwelt, Springer, *Int Soc Magn Reson Med*. 2008. Proc of the 16th Annual Mtg ISMRM, Toronto, Canada. **8.** Li, et al., Proc Natl Acad Sci USA, 2008. **105**(46): p. 17937-42.