DCE-MRI Temporal Resolution Requirements for Vascular Permeability Measurements in Rhesus Macaque Reproductive Tissues

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Introduction. The use of Dynamic Contrast Enhanced (DCE) MRI to map vascular properties is growing. At least for malignant tumor imaging, the consensus is that spatial resolution takes precedence over temporal resolution (1,2). Since increased spatial resolution is usually achieved at the expense of temporal resolution, a question is how much can the latter be sacrificed. The female reproductive uterus and ovary are among the few normal tissues to undergo periodic changes in angiogenesis (3). In fact, the high and variable blood volume fraction (v_b) can change many-fold during the menstrual cycle (4). Thus, a vascular term must be included in DCE-MRI pharmacokinetic analysis of data from these tissues. Using a primate model (rhesus macaque), we investigated the effects of temporal resolution on the precision and accuracy of K^{trans} (the CR [contrast reagent] volume transfer rate constant) determination. We use the second-generation three-site water exchange ("shutter-speed") DCE-MRI model (5), which includes the v_b parameter.

Methods. DCE-MRI data were obtained from adult, female macaques (n = 3) undergoing controlled ovarian stimulation (COS) (6). 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 150 images with intersampling intervals of 2.14 or 2.38 s with a Trio 3T (Siemens). Regions of interest (ROIs) representing three different tissues (muscle, ovary and uterine endometrium) were selected. Time-course data were fitted to estimate the parameters K^{trans}, v_b, and v_e (the extracellular, extravascular volume fraction). Each time-course was re-sampled to simulate intersampling intervals from approximately 6 - 40 s. Each simulated time point was generated by averaging the appropriate number of surrounding points to yield the desired time resolution (e.g., contiguous three-point sets were averaged to give a sampling rate 1/3 that of the original acquisition) thereby preserving the signal-to-noise ratio (SNR). Parameter uncertainty was investigated with 200 Monte Carlo simulations at each temporal resolution with proper Gaussian noise (8% of the signal at the actual sampling rate) to be comparable to single pixel SNR. The noise amplitude was reduced for increasing numbers of averaged time points, and added to the actual ROI data, for each simulated temporal resolution evaluated.

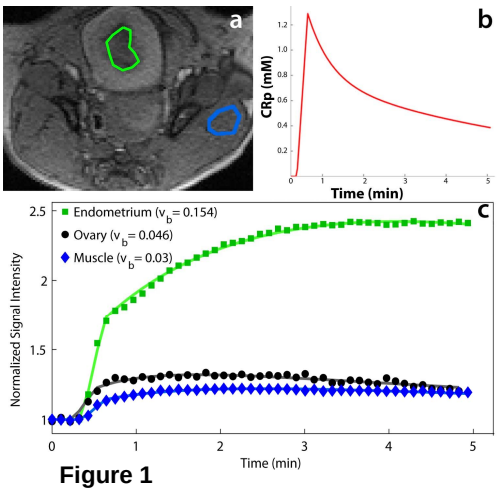

Figure 1

Results. Normalized intensity (S/S_{preCR}) data points from one animal are shown in **Figure 1c**. The color-matched muscle and endometrium ROIs are outlined in **Figure 1a** – an axial pelvic image from the inferior perspective - the ovarian ROI is from another slice not shown. **Figure 1b** shows the biexponentially fitted, adjusted Arterial Input Function (AIF) with a linear uptake used. The color-matched **Figure 1c** curves are the fittings of the 6.44 s interval simulated time-courses (three point averaged ROI data) with first-pass fitted v_b values given next to the defined color-matched symbols. The K^{trans} and v_e parameters were varied (7). **Figure 2** shows the fitted K^{trans} values for different temporal resolution simulations. As the intersampling interval increases, the fitted K^{trans} value remains constant (and thus provisionally accurate), with constant precision (SNR was adjusted to remain the same for a given total acquisition time), up to a point when it starts to decrease. This behavior suggests that any sampling rate smaller than the reciprocal of the cutoff, demarcated by the dotted line onset, diminishes the K^{trans} determination accuracy. It is important to note that when K^{trans} starts to deviate from its high temporal resolution value, the fitted curves (not shown) and the simulated time-courses do not match the well-sampled data time-courses as well. Also, the fitted parameter precision on these smeared time-courses "increases" (decreasing error bars, not shown) with increasing intersampling interval. Thus, fitted parameter precision alone can be misleading. The projected trends (dotted lines) were estimated by linear regressions.

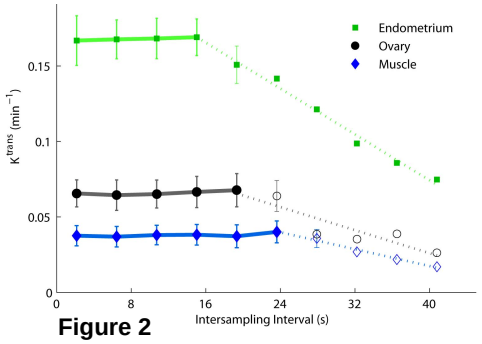

Figure 2

Discussion. These results have clearly shown that, for tissues with non-negligible v_b, high temporal resolution is desired. In our experience with comparable K^{trans} magnitudes, the intersampling interval can be larger than the ~16 s demonstrated here for endometrium with tissues where v_b doesn't appear to be as significant. This allows for temporal resolution sacrifice in favor of spatial resolution, resulting in an intersampling interval of even ~30 s (8). For very large v_b values, as seen in endometrial (**Figure 2**) and myometrial (not shown) tissues, model parameters like v_b and v_e become increasingly coupled and harder to determine. Thus, for the optimal tradeoff of spatial resolution and SNR, simulation may become the only useful way to establish the minimum sampling rate required for best parameter determination. Additionally, the large blood flow values measured by ultrasound in both the uterus and the ovary (3) complicate accurate discriminations between the vascular perfusion and permeation K^{trans} components by MRI alone, though this issue can be addressed (9) to some extent. It is clear that significant parameter underestimation can result from an insufficient DCE-MRI sampling rate. For non-invasive monitoring of the cyclic vascular changes of uterine and ovarian tissues, this becomes even more prominent. The actual sampling rate used here is shown to be much faster than the minimum required by the tissues studied at this stage in the menstrual cycle. However, it is known that uterine tissue undergoes dramatic changes in vascularization and permeability throughout the cycle (3). Though not shown, the myometrium displays extremely high blood volume (almost double that observed in endometrium). Fitting data with such high v_b has proven to be challenging for the current model and calls for extremely fast sampling. Both variable tissue vasculature and potentially extremely high v_b must be considered when determining sampling rate. Accounting for these factors suggests that sampling as fast as possible while maintaining SNR at least 10 (as was simulated in this study) is necessary for accurate K^{trans} determination. The current model does not account for possible T_2^* effects, which is likely to be low given the measured maximum [CR_p] is only ~ 1.2 mM.

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