Dynamic contrast-enhanced MRI for breast cancer detection

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Purpose: Magnetic resonance mammography is a promising technique for breast cancer imaging. Because it is known to have very high sensitivity, it is recommended for screening in women who are at high risk for development of breast cancer due to genetic mutation or family history. However, its application in a wider screening context is limited at present by the unacceptably high rate of false positives. We have investigated the use of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in conjunction with a two-compartment contrast kinetics model for breast screening in an attempt to determine the extent to which using quantitative kinetic parameters can improve the sensitivity and/or specificity of this technique for detection of breast cancers.

Methods: Dynamic contrast enhanced MRI mammography was performed on 25 women who had been referred to biopsy based on suspicious (BIRADS category 4) lesions on mammography and/or ultrasonography. Informed consent under an IRB-approved protocol was obtained from all study participants. Study enrollment criteria were i) no older than 55 years old, ii) no silicone breast implants, iii) no biopsy or surgery on the breasts within the past 6 weeks, and iv) no contraindications to MRI. Each patient was scanned once prior to the stereotactic or ultrasound-guided biopsy procedure. Scans were performed on a 1.5T Siemens TIM Avanto with an MRI

$$S = S_0 \frac{\sin\alpha\left(1-e^{-T_R/T_1}\right)e^{-T_E/T_2^*}}{1-\cos\alpha e^{-T_R/T_1}} \quad (1) \qquad \sigma = \frac{S(T_1,T_2^*)-S(T_{1,0},T_{2,0}^*)}{S(T_{1,0},T_{2,0}^*)} = \frac{e^{-r_2^* C T_E}\left(e^{(r_1C+1/T_{1,0})T_R}-1\right)\left(\cos\alpha-e^{T_R/T_{1,0}}\right)}{\left(e^{T_R/T_{1,0}}-1\right)\left(\cos\alpha-e^{(r_1C+1/T_{1,0})T_R}\right)}-1 \quad (2)$$

Devices 7-channel breast imaging coil. After localization, a bilateral axial T1-weighted scan, and unilateral sagittal T1-weighted and T2-weighted fat saturated non-contrast images were obtained at an in-plane resolution of approximately 0.6 x 0.8 mm and a slice thickness of 3 mm using a 2D turbo spin echo sequence. Pre-contrast T1 was determined using a multiple flip angle spoiled gradient echo measurement with flip angles of 5, 10, 20, and 30 degrees. High-resolution (1 mm isotropic resolution) pre- and post-contrast images were obtained using a 3D FLASH sequence. Dynamic imaging was performed at 1.5 mm isotropic resolution over the full volume of both breasts using a 3D FLASH sequence with TR = 2.54 ms, TE = 1.09 ms, and a flip angle of 10 degrees using 6/8 partial Fourier phase encoding. 64-120 slices were acquired, depending on breast size, corresponding to temporal resolution of 12-22 seconds per scan; scans were acquired for 7-10 minutes, including 5-10 pre-contrast baseline images prior to contrast injection. 20 ml of Gd-DTPA contrast was injected using a MedRad autoinjector into the antecubital vein at 4 ml/s, followed by 20 ml of saline at 2 ml/s, giving a contrast dose of 0.1-0.2 mmol/kg. An arterial input function based on measurements made in non-breast DCE-MRI exams was used, scaled for blood volume estimated using a statistical algorithm. Contrast concentration in the breast tissue was computed by solving the full SPGR signal equation (1) for relative signal enhancement, σ (2) using a nonlinear root-finding algorithm (MATLAB's `fzero`). Contrast relaxivity values of r1 = 4/mM/s and r2 = 5/mM/s were used for all calculations. Contrast kinetic parameters were computed on a voxel-by-voxel basis by regression of the measured tissue time courses of concentration to a modified Kety model including a blood volume term.[1] Because AIF was not measured, arrival time was estimated by regressing for multiple lag times and minimizing the fit chi-square value. The input function used is plotted in Figure 1 along with a typical tissue enhancement curve showing noise in concentration measurements of approximately +/-0.05 mM.

Results: Three-dimensional maps of the kinetic parameters K_{trans} and k_{ep} were compared with regions of suspicious enhancement in the post-contrast subtracted images as determined by a trained radiologist specializing in breast MRI (GM). Regions of interest corresponding to these areas were automatically determined by region-growing on Ktrans with a threshold of 0.05/min. Occasionally, manual pruning of ROIs was necessary to restrict them to the suspect lesion. Mean values and standard deviations of each 3D ROI were computed with no further quality control. To account for the effect of partial-volume averaging, which tends to decrease kinetic parameter estimates, we used the mean+1σ value as an estimator. 28 candidate lesions were identified in 22 patients. This included one patient with three distinct lesions, two of which were mammographically occult, two patients with an occult lesion in the contralateral breast, and two patients with disconnected satellite lesions in the ipsilateral breast. There were three screen failures; one due to incorrect protocol settings, the second due to excessive patient motion, and the third due to post-surgical inflammatory changes in the region of interest. Figure 2 shows a plot of K_{trans} vs. k_{ep} for the 28 lesions measured; biopsy-proven cancers are indicated by red asterisks and biopsy-proven benign lesions by green circles, with the specific diagnosis from histopathology adjacent to the marker. Benign diagnoses include mammary fibrosis (MF), fibroadenoma (FA), normal fibroglandular tissue (FT), hemangioma/lymphangioma (HA/LA), intraductal hyperplasia (non atypical, IDH). Malignancies include atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), mucinous carcinoma (MC), and invasive ductal carcinoma (IDC). Of interest is the fact that k_{ep} appears to be a much better independent predictor of malignancy than K_{trans}; a simple threshold estimator at k_{ep} = 0.12/min is shown by the dashed gray line. If we use this criterion to assess individual lesions, we find 16 true positives, 9 true negatives, 3 false positives, and 0 false negatives, giving a sensitivity of 100%, a specificity of 75.0%, a PPV of 84.2%, and an NPV of 100.0%. For comparison, a much larger study of a similar patient population (pre-biopsy) reported an aggregate sensitivity of 88.1%, specificity of 67.4%, a PPV of 72.4%, and a NPV of 85.4%.[2] It is important to note that the latter study incorporated all diagnostic information including morphology, contrast enhancement, and qualitative dynamics, while here we consider only the use of the two quantitative kinetic parameters. Our results suggest that contrast kinetic modeling may be a powerful adjunct to conventional interpretation strategies for breast cancer imaging, potentially leading to significant improvements in sensitivity and specificity of MR mammography.

	Biopsy+	Biopsy-
DCE+	16	3
DCE-	0	9

Table. 1. Confusion matrix for DCE-MRI results relative to bi-

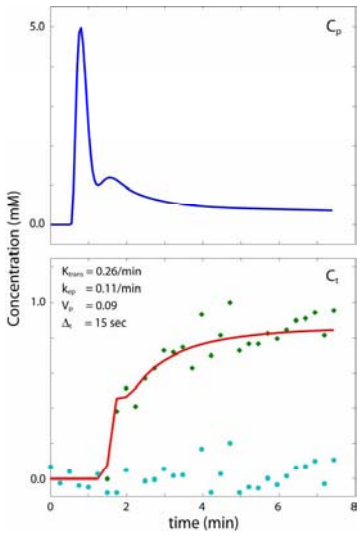

Fig. 1. Model AIF and measured tissue contrast concentration curves.

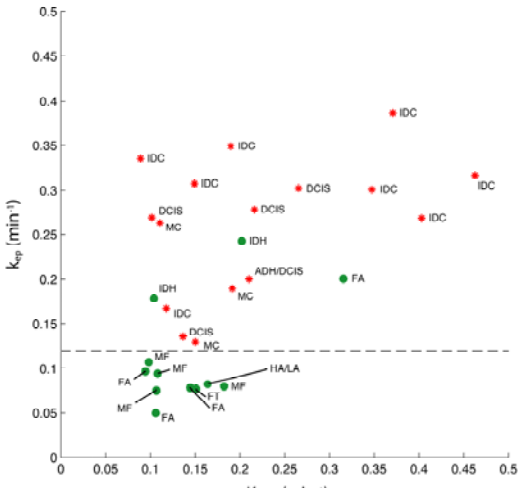

Fig. 2. ROI averaged kinetic parameters vs. biopsy diagnosis

References: [1] Tofts PS JMRI **7**:91-101 (1997). [2] Bluemke DA, et. al JAMA **292**:2735-2742 (2004). **Support:** NIH K25EB005077-03, Benning Foundation