

Evaluation of the Kinetic Properties of background Parenchymal Enhancement Across Phases of the Menstrual Cycle

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Introduction: The sensitivity of dynamic contrast enhanced (DCE) - MRI for detecting early stage invasive breast cancer is well established, but the specificity of DCE-MRI is highly variable [1]. One potentially confounding, yet intriguing variable in breast cancer risk stratification is background parenchymal enhancement (BPE) – an entity that has recently been shown to have a strong association with breast cancer risk [2]. BPE is generally referred to as the enhancement of the normal appearing fibroglandular parenchyma after contrast administration and presumed to be bilateral, symmetric, and diffuse [2,3]. However, not only is this finding often focal, regional and/or asymmetric, but it is also temporally dependent on hormonal status. Considering that breast pathology may have overlapping distribution and appearance, effectively limiting the specificity as well as sensitivity of breast DCE-MRI [4], delineating parenchymal enhancement from true pathology and characterization of its kinetic parameters is of utmost importance. Furthermore, it is widely understood that the milieu of hormonal activity within the breast has implications not only on the delayed enhancement of fibroglandular tissue, but also the kinetics of parenchymal enhancement [5,6]. For this reason, the purpose of our study was to investigate the kinetic properties of background parenchymal enhancement between phases of the menstrual cycle.

Materials and Methods:

Subsequent to institutional review board approval, a retrospective review of 144 subjects who underwent MRI guided breast biopsies for suspicious lesions was performed. MRI data were acquired using a whole body Siemens 3T Tim Trio system and a 7-element breast coil. DCE-MRI using a 3D VIBE sequence (resolution 1.4 x 0.9 x 1.5 mm) with fat suppression was acquired for these patients with at least five consecutive frames (duration 40 sec each) and administration of Gd-DTPA contrast agent after the first frame. Included in the study were women who were pre-menopausal, who completed a questionnaire specifically indicating their last menstrual period (LMP), and who had pathologically proven benign disease (n = 41). Cases were stratified into 4 categories corresponding to the weeks of the menstrual cycle, assuming a 28-day cycle with day 0 the first day of menses: Week 1: Days 0-6 (n = 9); Week 2: Days 7-13 (n = 13); Week 3: Days 14-20 (n = 7); Week 4: Days 21-27 (n = 12). Post-image processing was performed using custom-made IDL software. A single reader, blinded to menstrual phase data, manually drew regions of interest for the entire breast on a single sagittal image approximately within the center of each suspicious lesion. A linear principal component analysis (PCA) transformation was then applied in accordance with a recently published study [7] which effectively decomposed datasets into eigenvalues, eigenvectors (Fig.1b), and projection coefficient maps (Fig.1a). The first principal component (Fig.1 top row) captured the major source of variance, which was the signal change between pre- and post-contrast images corresponding to the enhancing substance of the breast excluding the suspicious lesion. The second component (Fig.1 bottom row) captured the next major source of variance, which in all cases, corresponded to the suspicious lesion. Minor sources of variance within the remainder of principal components corresponded essentially to noise within non-enhancing regions of the breast and were excluded from analysis. Signal enhancement percent was calculated as $(S_{post} - S_{pre})/S_{pre}$, where S_{pre} and S_{post} are the signal intensity before (i.e. 1st time point) and after (i.e., 5th time point) administration of contrast respectively. For kinetic analysis, eigenvectors were normalized between 0 and 1. The difference between the 2nd and 3rd time points was measured as the early enhancement rate, Percent signal enhancement and early enhancement rate were compared between weeks of the menstrual cycle using a 2-tail t-test.

Results and Discussion:

Figure 1(a) demonstrates a representative image used in this study; an ROI was drawn around the entirety of a single sagittal image centered on a pathologically proven benign breast finding. Figure 1(b) is a schematic of the normalized time intensity curves for the first two eigenvectors, the first of which corresponds to BPE, and the second corresponding to the enhancing lesion. The mean percentage signal enhancements for weeks 1-4 were 42.1±17.3%, 33.7±13.6 %, 39.9±11.3 %, and 52.7±25.6 % respectively. The p-values for differences between Week 1, Week 2, and Week 3 vs. Week 4 were 0.138, 0.012, and 0.152, respectively (figure 2a).

The mean, normalized slopes of increasing intensity between the 2nd and 3rd time points of imaging (figure 2b) were 0.45 ± 0.09 (Week 1), 0.46 ± 0.10 (Week 2), 0.48 ± 0.12 (Week 3), and 0.54 ± 0.06 (Week 4). P-values were 0.020, 0.018, and 0.302 for Weeks 1, 2, and 3 respectively vs. Week 4. The results of this study are in keeping with a previous study by Delille et al [6]. It stands to reason that the finding of increased parenchymal enhancement during the late luteal phase coincides with elevated levels of both progesterone and estrogen during the luteal phase of the menstrual cycle as it has been suggested that estrogen has a histamine-like effect, inducing vasodilation and an increase in microvascular permeability [8]. Mitotic activity, proliferation of breast epithelial cells, stromal edema and myoepithelial vacuolization have also been shown to increase in the late luteal phase [5]. To our knowledge, the present study is the first work to use a semi-automated segmentation technique to measure BPE in patients with pathology proven benign lesions and to compare the kinetic pattern of background enhancement across menstrual phases.

References: 1. Saslow et al., CA Cancer J Clin 2007;57(2):75-89. 2. King et al, Radiology 2011; 260(1): 50-60. 3. Morris, EA. Magn Reson Imaging Clin N Am 2010;18: 57-74. 4. Takayoshi et al, Breast Cancer 2011 (ahead of print) 5. Ramakrishnan et al Modern Pathology 2002; 15(12):1348-1356. 6. Delille et al, The Breast Journal, 2005(11): 236-241. 7. Eyal et al, J Magn Reson Imaging 2009; 30:989-998. 8. Zeppa R. J Clin Endocrinol Metab 1969;29: 695-700.

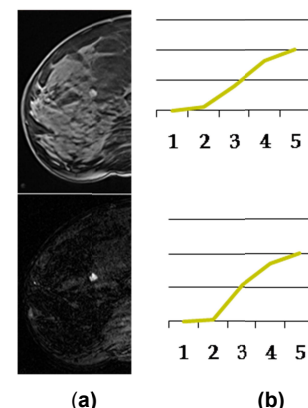


Figure 1 PCA applied to the entire breast centered on a benign fibroadenoma. (a) Projections coefficient maps. (b) Plots of the eigenvectors corresponding to the projection coefficient maps in (a). The top row corresponds to the 1st principal component generated (i.e. BPE); the bottom row corresponds to the 2nd principal component (i.e. lesion).

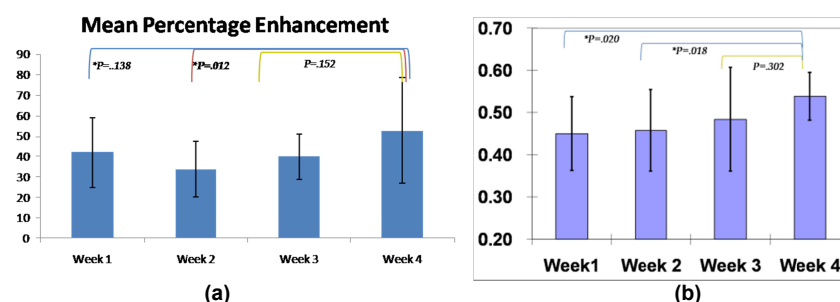


Figure 2 (a) Mean percentage enhancement. (b) Mean slopes of increasing intensity between the 2nd and 3rd time points of imaging.