Robust Quantification of Background Parenchymal Enhancement (BPE) in Dynamic Contrast-Enhanced (DCE) MRI Breast Examinations

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Introduction: Background Parenchymal Enhancement (BPE) following administration of contrast agent (CA) in DCE-MRI breast examinations may be a potential indicator of breast cancer risk [1]. However, BPE is typically evaluated *via* visual assessment of subtracted images [2] where signal intensity (SI) may be affected within and between patient examinations by variations in the B_1 field and by fat suppression performance [3]. SI changes are also dependent on native T_1 relaxation times and do not simply reflect CA uptake. Instead, the difference in relaxivity (ΔR_1) can provide a BPE measure which is directly proportional to the change in CA concentration within the parenchyma. The purpose of this study was to develop objective measures of BPE, including ΔR_1 and a normalized parenchymal enhancement coefficient (PEC) to compare against relative signal enhancement.

Materials & Methods:

Patient Selection: Retrospective evaluation was approved by the local Research Ethics Committee and did not require informed consent. MRI examinations were performed between days 6-16 of the menstrual cycle in line with recommendations [4]. 20 patients with at least one normal breast on clinical reports were selected. MRI indications included high-risk screening for BRCA1/2 mutation or post-mantle radiotherapy, disease staging and assessment of treatment response.

Data Acquisition: Routine clinical DCE-MRI breast examinations were undertaken at 1.5T (MAGNETOM Aera, Siemens) using 3D fat-suppressed spoiled gradient-echo sequences (TR/TE=4.5/2.0 ms, voxel size=1.3×1.3×1.0 mm^3, flip angle (FA)=18°), with standardized administration of a single CA dose (Dotarem, Guerbet) at 2 mL/s (MedRad, USA). One pre-contrast and eight post-contrast axial images were acquired followed by a further matched post-contrast dataset at a lower FA (4°) (each ~1 min in length). Measurements were performed on the right or contralateral breast. Breast segmentation was performed using in-house software (IDL 8.3, ITTVIS). MR breast density (%FGT) was defined as the volume of fibroglandular tissue relative to the total breast volume.

BPE Analysis: For each patient, three methods to measure BPE were applied to the segmented parenchyma encompassed within a 20 mm transaxial slab bisecting the nipple. The final dynamic frame (8 mins post-contrast) exhibited maximum parenchymal enhancement for all patients and was used for post-contrast evaluation. A mutual information algorithm registered pre- and post-contrast images [5].

1) ***Relative Enhancement (RE):*** Relative enhancement (RE) was calculated for each voxel as the percentage increase in signal intensity: $[SI_{post\text{-}contrast} - SI_{pre\text{-}contrast}]/SI_{pre\text{-}contrast}$ x 100.
2) ***Relaxivity Difference (ΔR_1):*** Pre- and post-contrast T_1 relaxation times and the difference in R_1 relaxivity (ΔR_1) were calculated for each voxel by using signal intensity calibration curves together with calculation of the equilibrium magnetization.
3) ***Parenchymal Enhancement Coefficient (PEC):*** A branch of the internal mammary artery was located in a standardized position in the upper inner quadrant of the breast, 2-4 cm from the chest wall. A 3.6 cm^3 volume was drawn to encompass the artery on the post-contrast images and arterial voxels were identified from histogram thresholding of the subtraction dataset. The median arterial RE between pre- and post- contrast time-points was then calculated. The median parenchymal RE was normalized against this value to give a Parenchymal Enhancement Coefficient (PEC): $RE_{parenchyma}/RE_{artery}$ x 100.

Table 1: Histogram metric statistics for Relative Enhancement (RE) and Difference in Relaxivity (ΔR_1)

	RE		ΔR_1	
	Median	IQR	Median	IQR
Range/median	18.0	19.3	15.6	17.7
IQR/median	1.7	1.5	1.6	1.4
Skewness	1.4	0.6	0.7	1.1
Kurtosis	4.3	2.5	2.5	2.4

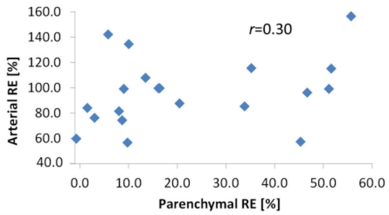

Figure 1: Correlation between parenchymal and arterial RE.

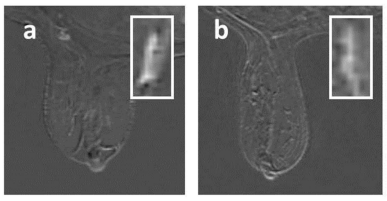

Figure 3: Post-contrast subtraction images with associated arterial ROIs (*inset*). Subjects a and b exhibit similar, low parenchymal RE (10.1% and 9.8%, respectively), but very different arterial RE (134.4% and 56.6%, respectively).

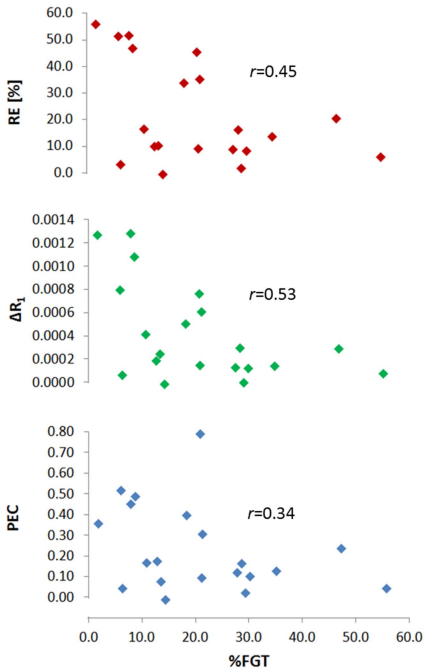

Figure 2: Correlations between BPE measures (Relative Enhancement (RE), Difference in Relaxivity (ΔR_1) and Parenchymal Enhancement Coefficient (PEC)) and %FGT.

Statistical Analysis: Medians, the range and interquartile range (both normalized against the median), skewness and kurtosis were extracted from the RE and ΔR_1 histograms of each patient. The Wilcoxon Signed-Rank Test (two-sided α=0.05) was used to compare these metrics. The Pearson product-moment correlation coefficient was used to assess relationships between PEC, median values of RE, ΔR_1, pre-contrast T_1, and %FGT.

Results: Median values of ΔR_1 and RE were strongly correlated (r=0.96). ΔR_1 histograms had significantly lower values of skew and kurtosis than RE histograms (p<0.001and p=0.003, respectively). Although ΔR_1 histograms had lower values of range/median and IQR/median, this was not significant (p=0.20 and p=0.06, respectively) (*Table 1*). There was no correlation between the level of parenchymal and arterial RE (r=0.30) (*Figure 1*). As expected, PEC was correlated to both RE and ΔR_1 (r=0.89 and 0.80, respectively). Weak correlations were observed between parenchymal RE, ΔR_1 or PEC and %FGT in this pilot cohort (r=0.45, 0.53 and 0.34, respectively) (*Figure 2*). However, correlation was observed between pre-contrast parenchymal T_1 relaxation times and %FGT (r=0.75).

Discussion & Conclusion: If BPE is to have robust predictive value for breast cancer risk, measurements should be as quantitative as possible. The great variability in parenchymal RE with respect to arterial RE in different patients (*Figure 3*) suggests that observed BPE may differ from the actual CA concentration supplied to the breast and underlines the need for quantitative BPE evaluation. Measurement of ΔR_1 accounts for native differences in parenchymal T_1 relaxation times and is directly proportional to parenchymal CA uptake. ΔR_1 calculation may be particularly valuable for longitudinal or multicenter studies – unlike RE, which may not translate between machines and centers. Our results suggest that it is feasible to pursue truly quantitative measurements of breast BPE; objective metrics such as ΔR_1 may help to establish the value of parenchymal enhancement as a risk factor for breast cancer. Baseline parenchymal T_1 measurements may also prove useful, and the correlation with %FGT merits further investigation.

References: [1] King *et al*.; *Radiology* 2011; 260(1): 50-60; [2] ACR BI-RADS Atlas 5th Edition; *American College of Radiology* 2013; [3] Azlan *et al*.; *Magn Reson Med* 2011; 67(2): 531-540; [4] NHS BSP Publication No. 68; 2012; [5] Roulston *et al*.; *Physica D: Nonlinear Phenomena* 1999; 125(3–4):285-294.

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