Relative Enhanced Diffusivity (RED) as a Marker of Breast Tumor Microvasculature

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Introduction: The influence of microcirculation on diffusion weighted imaging (DWI) can be obtained using a bi-exponential decay model known as intravoxel incoherent motion (IVIM)[1]. This two-compartment model accounts for the influence of blood microcirculation in DWI and separates it from true random water diffusion. For breast applications, this model has proven that cancerous lesions exhibit a higher perfusion fraction than the low perfused healthy fibroglandular tissue (FGT)[2-6]. IVIM studies have also shown that the microcirculation influence in diffusion measurements is only observable at the low b-value regime. In this study, we have investigated if a simplified approach based on the relative increase of the apparent diffusion coefficient (ADC) at the low b-value regime (sensitive to blood microcirculation) with respect to the mid b-value regime (non-sensitive) using only two non-zero b-values is correlated with dynamic contrast enhanced MRI (DCE-MRI) and may aid in lesion differentiation. **Methods:** This study included 41 patients with known breast pathology. All patients were imaged on a 3T scanner (Siemens Skyra, Erlangen, Germany) equipped with a dedicated 16-channel bilateral breast coil. The imaging protocol collected fat suppressed unilateral sagittal images using a twice-refocused spin-echo sequence with echo planar imaging (EPI) readout (TR/TE: 9300/85ms; matrix: 90x90; in-plane resolution: 2x2mm; slice thickness: 2.5mm; 60 slices; GRAPPA factor 2) including one or two non-weighted (b=0 s/mm^2) images and two diffusion weights (b=200 and 700 s/mm^2) in 30 directions, with Anterior-Posterior (AP) phase encoding polarity. An additional b=0 s/mm^2 image with reversed phase encoding polarity (PA) was acquired to apply distortion correction as previously reported[7]. T1-weighted DCE-MRI, with the same slice thickness and FOV as the DWI, was acquired with a 3D radiofrequency spoiled gradient-echo sequence without fat suppression (flip angle: 15°; TR/TE: 5.82/2.18ms; in-plane res: 0.7x0.7mm). After the acquisition of one baseline image, a bolus injection of 0.1 mmol/kg body weight gadolinium-based contrast agent Dotarem was given automatically at a rate of 2 ml/s followed by a 20 ml saline flush. Lesions were fully segmented in DCE-MRI and DWI independently. DWI processing: ADC values were obtained imposing a monoexponential decay of the signal intensity (SI) measured between each set of two distinct b-values: $SI_f = SI_i e^{(b_i - b_f)ADC_{i,f}}$, i being the starting b-value and j the final one, thus obtaining $ADC_{0,200}$, $ADC_{0,700}$, $ADC_{200,700}$. Relative enhanced diffusivity (RED) was defined as: $RED\ (\%) = 100\left(\frac{ADC_{0,200} - ADC_{200,700}}{ADC_{200,700}}\right)$. Signal to noise ratios (SNR) were calculated for the b=0 s/mm^2 images using the difference method described in[8]. DCE-MRI processing: The signal enhancement (SE) at each post-contrast image was calculated voxelwise as: $SE(\%) = 100\frac{SI_{postcontrast} - SI_{baseline}}{SI_{baseline}}$. Semi-quantitative parameters were subsequently derived voxel by voxel including the initial area under the curve at 60 seconds after injection ($IAUC_{60}$), the maximum enhancement (ME), and the steepest slope (SS). Statistical analysis: Median values of each parameter calculated for each lesion was used to perform statistical analysis. Pearson correlation (r) was used to evaluate correlations between DWI and DCE-MRI derived parameters. Statistical comparison between different groups was carried out using independent samples Student's t-test with Bonferroni adjustment for multiple testing. Receiver-operating characteristic (ROC) analysis was performed for lesion classification potential. **Results:** 38 lesions out of 52 met the criteria for inclusion. Out of these 38 lesions, 21 were invasive ductal carcinoma (IDC), and 17 were benign (fibroadenoma (n=11), phyllodes (n=4), fibroadenomatosis (n=1), and adenosis (n=1)), proved by histopathology. The correlation between the median values of $IAUC_{60}$ and RED for each lesion is presented in Fig 1. Results from the DWI and DCE-MRI analysis are reported in Table 1. ROC analysis revealed a perfect classification for the sample only when using RED (AUC=1.0). Fig 2 shows an example of the RED parametric map for an invasive ductal carcinoma and a benign phyllodes tumor. Fig 3 shows how the RED parametric map is hyperintense for an IDC compared with surrounded FGT.

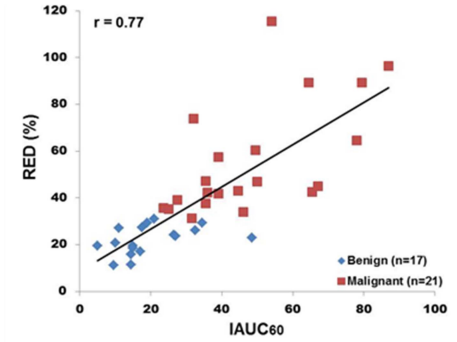

Fig 1. Pearson correlation (r) and linear regression between relative enhanced diffusivity (RED) and initial area under the curve at 60 seconds ($IAUC_{60}$).

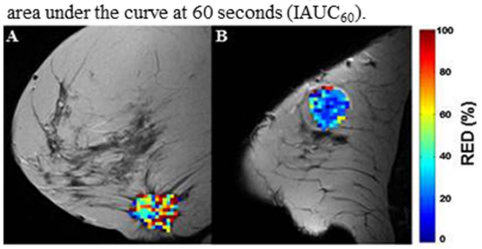

Fig 2. Relative enhanced diffusivity (RED) maps overlaid on T2-weighted images for **(A):** Invasive ductal carcinoma and **(B):** Benign phyllodes tumor.

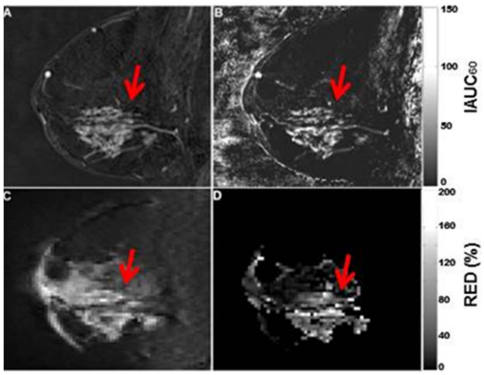

Fig 3. Invasive ductal carcinoma (red arrow). **(A):** DCE-MRI 2 minutes post-contrast subtracted image. **(B):** $IAUC_{60}$ parametric map. **(C):** DWI b=700 s/mm^2 image. **(D):** RED parametric map after filtering out low signal in DWI.

Discussion: Our results suggest that a parameter dependent on the incoherent blood microcirculation can be obtained from DWI with the use of only two non-zero b-vales. This parameter was found to present a strong correlation with $IAUC_{60}$ derived from DCE-MRI. This finding is particularly valuable for potential clinical applications where the time is a key factor. The choice of the b-values was made to enable separation of the regime where microcirculation affects the ADC measurement and the regime that is only dependent on water diffusion. Based on previous studies[2-6] we consider the microcirculation influence in DWI to be negligible over b=200 s/mm^2. Based on its formulation, RED will be dependent on water diffusion and blood microcirculation, so that higher microcirculation or lower water diffusion increases RED values. This fact may explain the higher differentiation potential in comparison with pure ADC parameters. The main limitations of our study include those intrinsic to DWI, in particular the low SNR that poses a difficulty to reliably obtain quantitative parametric maps. The SNR constraint also affects the resolution that can be achieved, preventing an accurate quantification of small lesions. Exclusion criteria included lesions with longest diameter <1cm (n=6), lesions with no contrast enhancement (n=3), and lesions with SNR<5 for DWI b=0 s/mm^2 images (n=5). **Conclusion:** The new parameter described in our study, relative enhanced diffusivity (RED), presented a high correlation with the $IAUC_{60}$ obtained from DCE-MRI. In addition, RED outperformed other DWI parameters for the differentiation of benign and malignant lesions. Furthermore, due to RED dependence on microcirculation, it could potentially be used for further applications as monitoring treatment response.

Table 1	$ADC_{0,700}$*	$ADC_{0,200}$*	$ADC_{200,700}$*	RED*	$IAUC_{60}$*	ME	SS
IDC (n=21)	1.05 ± 0.16	1.45 ± 0.24	0.91 ± 0.15	56 ± 24	48 ± 19	226 ± 37	128 ± 26
Benign (n=17)	1.73 ± 0.24	2.00 ± 0.26	1.62 ± 0.24	22 ± 6	20 ± 11	214 ± 86	95 ± 19

*(p<0.001). ADC (x10^{-3} mm^2/s). RED (%). ME(% of baseline). SS (% of baseline/min). IDC (invasive ductal carcinoma)

References: [1] Le Bihan D, et al. Radiology 1988. [2] Sigmund EE, et al. MRM 2011. [3] Nilsen LB, et al. Eur Radiol 2013. [4] Bokacheva J, et al. JMRI 2014. [5] Iima M, et al. Invest Radiol 2014. [6] Cho GY, et al. MRM 2014. [7] Teruel JR, et al. MRM 2014. [8] Dietrich O, et al. JMRI 2007.