Association of breast density and region of interest size with apparent diffusion coefficient value of normal fibroglandular tissue at MRI

Poster No.: B-0441
Congress: ECR 2017
Type: Scientific Paper
Authors: N. Radovic, G. Ivanac, M. Crnogorac, E. Divjak, T. Cicvara-Pecina, J. Petrovic, B. Brkljacic; Zagreb/HR
Keywords: Breast, Oncology, MR, MR-Diffusion/Perfusion, Imaging sequences, Normal variants, Cancer
DOI: 10.1594/ecr2017/B-0441
Purpose

Introduction:

Diffusion-weighted imaging (DWI) is garnering an increasingly important role in diagnostic evaluation of breast cancer as an adjunct to dynamic contrast enhanced (DCE) magnetic resonance (MR). DWI depicts random thermal motion of water molecules which is affected by presence of barriers such as cell membranes and therefore reflects histologic structure of breast tissue while providing a contrast mechanism different from what is observed on conventional T1- and T2-weighted images. A quantitative measurement of diffusion is provided by calculating apparent diffusion coefficient (ADC), which may be more specific than signal intensity change at DWI alone [1]. Over the past 15 - 20 years numerous studies have demonstrated high sensitivity and specificity of ADC to discriminate between benign and malignant lesions as malignancies have shown low ADC values due to higher cellular density [2-6]. Furthermore, DWI accompanied by measurement of ADC values and combined with DCE MR yielded 13.5% increased specificity compared to DCE MR alone [6].

Clinical implementation of DWI continues to be affected by drawbacks and limitations in spite of a plethora of published research. Absence of consensus on optimal technical parameters and ADC value thresholds for discrimination between benign and malignant lesions impairs standardisation of imaging protocols and diagnostic interpretation. Additionally, ADC values of normal fibroglandular breast tissue may vary significantly between individuals, which may affect conspicuity of cancer, especially considering that malignant non mass lesions show an overlap in values with benign lesions and normal parenchyma [4,7,8].

The purpose of this study was to determine whether ADC value of normal fibroglandular tissue at 1.5T is associated with breast density on MR and the size of region of interest (ROI) used to calculate it.
Methods and materials

Patients:

This retrospective study was approved by the Ethics Committee of University Hospital Dubrava, Zagreb, Croatia, and included 27 women referred for clinical breast MRI at our institution from April to June 2016. All participating individuals signed the informed consent form after having received oral and written information regarding the study. Eligible patients were those who were not pregnant or breastfeeding at the time of exam, had no history of breast surgery and had not undergone nor were undertaking radiation therapy, chemotherapy, or hormonal therapy. Additionally, patients whose breasts showed no areas of fibroglandular tissue large enough to encompass the larger region of interest on the ADC map were excluded so as to avoid miscalculation due to partial volume averaging with surrounding fat. The mean patient age was 50 ± 13 years.

Magnetic resonance imaging acquisition:

All images were obtained as part of the standard clinical examination on a Philips Ingenia 1.5T MRI system (Philips Healthcare, Best, The Netherlands) using a 7-channel breast coil. The imaging protocol included a T2-weighted fast spin echo sequence, DWI, a pre-contrast T1-weighted sequence and 6 dynamic contrast enhanced T1-weighted sequences in the aforementioned chronological order.

Diffusion-weighted images were acquired in the transverse plane using the single-shot echo planar imaging technique with parallel imaging and spectrally selected suppression of fat.

DWI scan parameters were as follows: TR/TE = 9400/86 ms, flip angle = 90°, slice thickness = 3 mm, interslice gap = 0.6 mm, acquisition matrix = 136 x 136, FOV = 33.5 cm, and reduction factor = 3. Diffusion gradients were applied in three directions with b = 0, 400, and 800 s/mm². The DWI acquisition time was circa 3 minutes.

Pre-contrast T1-weighted images used to evaluate breast density was acquired using the 3D gradient echo technique with spectrally selected suppression of fat and scan parameters as follows: TR/TE = 5.1/2.5 ms, flip angle = 10°, slice thickness = 2 mm, interslice gap = 1 mm, acquisition matrix = 340 x 280, and reduction factor = 3.

Image analysis:
All MR images were archived using INFINITT PACS (INFINITT Healthcare, Seoul, Republic of Korea) and analyzed by fellowship trained radiologists.

ADC maps of diffusion-weighted images were constructed automatically on a pixel-by-pixel basis by the Philips Ingenia software that calculated ADC within the manually drawn ROIs with the following logarithmic equation:

\[
\ln (S_i) = \# b_i \times ADC + \ln (S_0)
\]

where \( S_i \) is signal intensity measured on the \( i \)-th \( b \) value, \( b_i \) is the corresponding \( b \) value and \( S_0 \) is signal intensity for \( b = 0 \) s/mm\(^2\).

ADC of normal fibroglandular tissue of each breast was measured by manually drawing two sets of five circular ROIs of sizes equaling 15 mm\(^2\) and 30 mm\(^2\), and averages were calculated for each set. ROIs were placed on parametric map images inside the largest areas consisting solely of fibroglandular tissue signal intensity, while care was taken to exclude regions where signs of either benign or malignant disease were detected on any of the pre- or postcontrast MR images. Areas of fibroglandular tissue signal intensity not large enough to fully encompass the larger ROI were excluded from measurements so as to avoid partial volume averaging with fat. The radiologist who measured ADC was blinded to assigned breast density categories.
Fig. 3: T2-weighted fat-suppressed image of a patient's left breast (A) and the corresponding DWI image at $b = 800$ s/mm$^2$ (B) and ADC map image with an ROI drawn inside fibroglandular tissue (C).

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Pre-contrast T1-weighted images were retrospectively analyzed by a fellowship trained radiologist who was blinded to ADC measurements. Each breast was given a density assessment corresponding to ACR BI-RADS® Atlas breast density classification (Breast Imaging Reporting and Data System, Reston, VA, American College of Radiology; 2013.) and added to low or high density group, the former including 12 patients and containing 23 breasts that were interpreted as being fatty or having scattered fibroglandular tissue, and the latter including 15 patients and containing 23 heterogeneously dense and dense breasts.
Fig. 1: Pre-contrast T1-weighted fat-suppressed image (A) and the corresponding ADC map image (B) in a patient whose breasts were interpreted as having scattered fibroglandular tissue.

References: Department of Diagnostic and Interventional Radiology, University Hospital Dubrava - Zagreb/HR

Fig. 2: Pre-contrast T1-weighted fat-suppressed image (A) and the corresponding ADC map image (B) in a patient whose breasts were interpreted as being dense.

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**Statistical analysis:**

Mean ADC values for the two ROI sizes in each breast were compared by Pearson's correlation coefficient. Association between mean ADC and breast density level (low vs high density group) was assessed using Student's t-test.
Images for this section:

**Fig. 1:** Pre-contrast T1-weighted fat-suppressed image (A) and the corresponding ADC map image (B) in a patient whose breasts were interpreted as having scattered fibroglandular tissue.

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**Fig. 2:** Pre-contrast T1-weighted fat-suppressed image (A) and the corresponding ADC map image (B) in a patient whose breasts were interpreted as being dense.
Fig. 3: T2-weighted fat-suppressed image of a patient's left breast (A) and the corresponding DWI image at $b = 800$ s/mm$^2$ (B) and ADC map image with an ROI drawn inside fibroglandular tissue (C).
Mean ADC of fibroglandular tissue was $1.79 \pm 0.18 \times 10^{-3}$ mm$^2$/s and $1.8 \pm 0.2 \times 10^{-3}$ mm$^2$/s on smaller and larger ROI respectively. Intrasubject ADC measurements for the two ROI sizes were highly correlated ($r^2 = 0.9101$ $r = 0.954$, $p < 0.001$).

**Fig. 4**: Scatter plot showing intrasubject fibroglandular tissue ADC correlation between smaller and larger ROI.

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ADC was not associated with breast density level: mean values for low vs high density group were $1.781 \pm 0.165 \times 10^{-3}$ mm$^2$/s vs $1.794 \pm 0.2 \times 10^{-3}$mm$^2$/s ($p > 0.5$) on smaller ROI and $1.785 \pm 0.2 \times 10^{-3}$mm$^2$/s vs $1.814 \pm 0.206 \times 10^{-3}$mm$^2$/s ($p > 0.5$) on larger ROI.
Fig. 5: Chart, comparing mean fibroglandular tissue ADC and standard deviation between low and high density group as measured on smaller ROI.

References: Department of Diagnostic and Interventional Radiolog, University Hospital Dubrava - Zagreb/HR
**Fig. 6:** Chart, comparing mean fibroglandular tissue ADC and standard deviation between low and high density group as measured on larger ROI.

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Fig. 3: T2-weighted fat-suppressed image of a patient’s left breast (A) and the corresponding DWI image at b = 800 s/mm² (B) and ADC map image with an ROI drawn inside fibroglandular tissue (C).

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Fig. 5: Chart, comparing mean fibroglandular tissue ADC and standard deviation between low and high density group as measured on smaller ROI.

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Fig. 6: Chart, comparing mean fibroglandular tissue ADC and standard deviation between low and high density group as measured on larger ROI.

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Conclusion

Quantification of DWI through measurement of ADC has shown value in improving the accuracy of MRI for diagnosis of breast cancer. A multitude of previous studies have measured normal fibroglandular tissue ADC and demonstrated that values can vary widely between individuals [3, 5, 8, 9, 11-13]. Two studies suggested the need for comparison between ADC of lesions and normal tissue to increase reproducibility and compensate for discrepancies in reported values casued by difference in strength of diffusion gradients applied during imaging in various centres [3, 10]. Therefore, diffusion quantification for tumor differentiation and evaluation of treatment response should account for normal variability. Unfortunately, only a small number of studies tried to establish association between normal tissue ADC and factors potentially influencing measurement, such as background parenchymal enhcancement on MR, menstrual cycle variation, age and mammographic density. Two of these earlier studies reported a positive correlation between ADC and mammographic density [14, 15].

To our knowledge this is the first study evaluating ADC in correlation with breast density on MRI and the first to correlate ADC with ROI size. Our data suggest no association between ADC of normal fibroglandular tissue and breast density, which contradicts results from previously published work. Decreased values observed in earlier studies in breasts showing low mammographic density may have been caused by intravoxel partial-volume averaging with fat leading to lower measurements compared to dense breasts [14]. Instead of measuring ADC of entire breast parenchyma depicted on selected images, our measurements included only the most central and homogeneous areas of fibroglandular tissue intensity so as to achieve most representative values. Our finding suggests contrast between lesions and fibroglandular tissue on quantitative DWI will not be affected by breast density, with the possible exception of fatty breasts in which the signal from minimal residual fibroglandular tissue will be partially obscured by fat or intraductal secretions on most or all ADC map pixels. Consequently, comparison of ADC between lesions and parenchyma should be omitted in patients with high degree of breast involution as representative fibroglandular tissue values cannot be measured. According to our data no association exists between ADC and ROI size, thus proposing that intrasubject breast tissue ADC variability will not affect observation of intersubject variability.

Future research should be directed towards determining of yet unknown factors influencing ADC measurements of normal breast parenchyma, whether related to histologic structure or physiologic state. This would allow for better understanding of observed interindividual variability and lead to development of a standardized quantitative methodology that would improve diagnostic accuracy of DWI MR and broaden its clinical application.
Our study has certain limitations. Firstly, the breast density stratification method we applied was based on subjective interpretation and it is possible that an association between ADC and fibroglandular tissue density was missed due to incorrect density assessment. However, we believe the average difference in breast structure between the two groups was high enough to disallow such possibility. Secondly, both sets of ROIs were of relatively small size and placed in a somewhat arbitrary manner, thus putting into question the degree to which our data reflect the ADC means of entire fibroglandular tissue. However, drawing of multiple ROIs compensated for potential compromising effects on results consequential to choice of ROI size and placement. Furthermore, significant increase of ROI size would lead to an additional number of subjects with low breast density being excluded from the study, thus increasing the likelihood of missing an association between ADC and fibroglandular tissue density due to reduced difference in breast structure between two groups of eligible subjects.

In summary, our results demonstrate that normal breast parenchymal ADC values reflect microstructural characteristics unrelated to breast density or ROI size. Adequately measurable contrast between lesions and normal tissue on quantitative DWI will not be affected by breast density. This knowledge should facilitate development of a standardized approach to breast DWI interpretation in clinical practice.


