

Quantification of Volumetric Breast Density Using MR Images

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Objective: To determine whether volumetric breast density (VBD) measured from 3 representative slices correlate with the VBD measured from the all slices of breast MR imaging.

Materials and Methods: Precontrast, T1-weighted, sagittal images of the normal breast obtained in 151 women (29–78 years; mean, 45 years) were used for VBD measurement. The borders of the breasts were outlined manually and fibroglandular tissue was segmented from the fat tissue using fuzzy c-means algorithm. VBD (fibroglandular volume/ total breast volume $\times$ 100) was measured from the all slices as well as from 3 representative slices [the middle (n), (n+15)th and (n-15)th slices] for each patient. The results were compared using t-test, intraclass correlation coefficient (ICC) and coefficient of variation (CV).

Results: VBDs measured by the two methods showed excellent agreement (ICC = 0.96; 95% CI = 0.95–0.97) and the CV was 9.74%. The mean absolute difference in VBD between the two methods was not different for fatty (< 20% VBD) and dense (> 40% VBD) breasts (2.37% vs. 2.62%; $p = 0.67$). The 3-slice method showed excellent intra- and inter-observer reproducibility (ICC > 0.9). The mean measurement time for the 3 slice method was significantly lower than that for whole breast measurement (133 sec vs. 572 sec; $p < 0.0001$).

Conclusion: The VBD measured from the 3 representative slices is in excellent agreement with the VBD measured from the all slices and can serve as an efficient tool for measuring VBD in breast MR imaging.

Index words: Breast density; MR imaging; fuzzy c-means algorithm

Introduction

Breast density defined as the proportion of fibroglandular tissue in the breast is an independent risk factor for development of breast cancer (1–4). High breast density at mammography assessed by using the

American College of Radiology (ACR) breast imaging reporting and data system (BI-RADS) classification or computer-assisted semi-quantitative method has been associated with a four- to five-fold increase in breast cancer risk compared to low breast density (1, 2). Changes in breast density over time have been correlated to changes in cancer risk (5). Dense breast tissue can also obscure small cancer and decrease the sensitivity of mammography (6). It is becoming increasingly important to measure the breast density of women since breast density can serve as an additional biomarker for

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breast cancer surveillance and the development of a method for cancer prevention (7–12). However, some concerns about the accuracy of breast density determined by using mammography are raised (13). Since a mammogram is a projection image, different body position, level of compression, and the x-ray intensity may lead to a large variability in the density measurement (14). Breast magnetic resonance (MR) imaging provides strong soft tissue contrast between fibroglandular and fatty tissues, and three-dimensional coverage of the entire breast, thus making it suitable for the breast density quantification (15–17). MR imaging, however, produces hundreds of slices for each breast pair.

Volumetric breast density (VBD) measured from MR imaging has been used to assess the association of breast density with other breast cancer risks in young women with familial history of breast cancer (18) or the change of breast density in the contralateral breast after neoadjuvant chemotherapy or adjuvant tamoxifen in the breast cancer patients (19, 20). The computer-assisted algorithm was used to segment the breast and the fibroglandular tissue from the fat. VBD was calculated from fibroglandular volume and total breast volume obtained in all the slices of the breast. Such measurement, however, has a few drawbacks such as (1) requirement of a certain level of user interaction to demarcate the breast boundaries and apply threshold values and (2) the long duration of time it takes to make the measurements for a single case, making it extremely time consuming and impractical to apply for large breast MR imaging databases (17, 21). One of the ways to reduce the time taken for measurement is to make the measurements from a limited number of slices. Previous studies which aimed at measuring the VBD from the 5 middle slices, however, have not been successful (17). We aimed to select 3 slices including the middle, lateral, and medial side of the breast which would provide a better representation of the entire volume and the distribution of fibroglandular tissue in the entire breast.

The purpose of this study was to propose the 3-slice method to measure VBD from MR imaging data and to determine whether VBD measured using the 3 representative slices correlates with the VBD measured from the all slices of breast MR imaging.

Materials and Methods

Subjects

The institutional review board approved this retrospective observational study, and the requirement for seeking patient approval or informed consent for the review of medical records was waived. From the breast MR imaging database of our institute, we selected a total of 164 breast cancer patients who had undergone preoperative bilateral breast MR imaging during December 2011 to May 2012. Of these, six who had a history of surgical excision and seven who had suspicious lesions on MR imaging in the contralateral breasts were excluded and 151 were included. The age of these patients ranged between 29 to 78 years (mean, 47.6; median = 48). Only the MR imaging data from the contralateral normal breasts were used for VBD measurements.

MR Imaging Protocol

MR examinations were performed using a 1.5-T scanner (Signa; General Electric Medical Systems, Milwaukee, WI) with a dedicated bilateral breast coil (8-channel HD breast array, General Electric Medical Systems). Dynamic contrast-enhanced examinations were performed which included one pre-contrast and five post-contrast bilateral sagittal image acquisitions using a fat-suppressed T1-weighted three-dimensional fast spoiled gradient echo sequence (TR/TE, 6.2 sec/2.2 sec; 320 mm × 256 mm matrix; flip angle, 10°; field of view, 200 mm × 200 mm; 1.5-mm slice thickness, no gap). In average, 168 slices are acquired covering bilateral breasts.

The MR imaging used for the study were precontrast, T1-weighted, fat suppressed, sagittal section images. Only the images from the contralateral normal breast of each patient were used for the analysis.

Measurement

The measurements were done by a single researcher (JJX) with more than two years' experience in measuring VBD using the MIPAV (Medical Image Processing, Analysis and Visualization) software package (Version 5.3.3, NIH, USA) (Fig. 1). The total breast volume

(TBV) and the fibroglandular tissue volume (FGV) were measured separately and volume breast density (VBD) of the breast was calculated as follows;

$$\text{VBD} = (\text{FGV} / \text{TBV}) \times 100$$

The overall method is similar to that described in previously published articles using different software packages (17, 22).

For whole breast VBD measurement, the outline of the breast (defined as region of interest, ROI) was

drawn manually in the MR imaging slice showing the highest projection (23). The ROI was then copied to all the slices of interest in the sagittal stack of images. Since the shape of the breast does not change considerably between contiguous slices, minor manual adjustments were made as necessary so as to separate the breast from the chest wall. The total volume of the breast was then measured from the ROIs in all the slices of interest. The number of the slices ranged from 32–72 (mean, 43) for each breast.

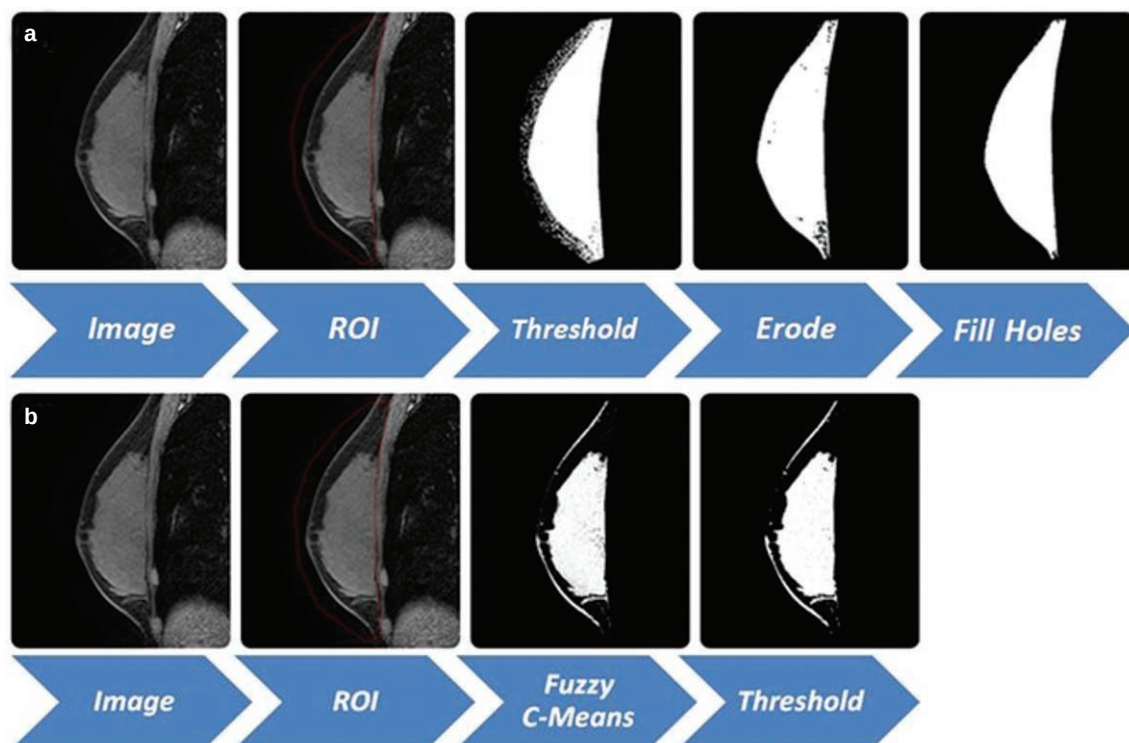


Fig. 1. The measurement of the total breast volume (a) and the fibroglandular tissue volume (b) using the MIPAV (Medical Image Processing, Analysis and Visualization) software.

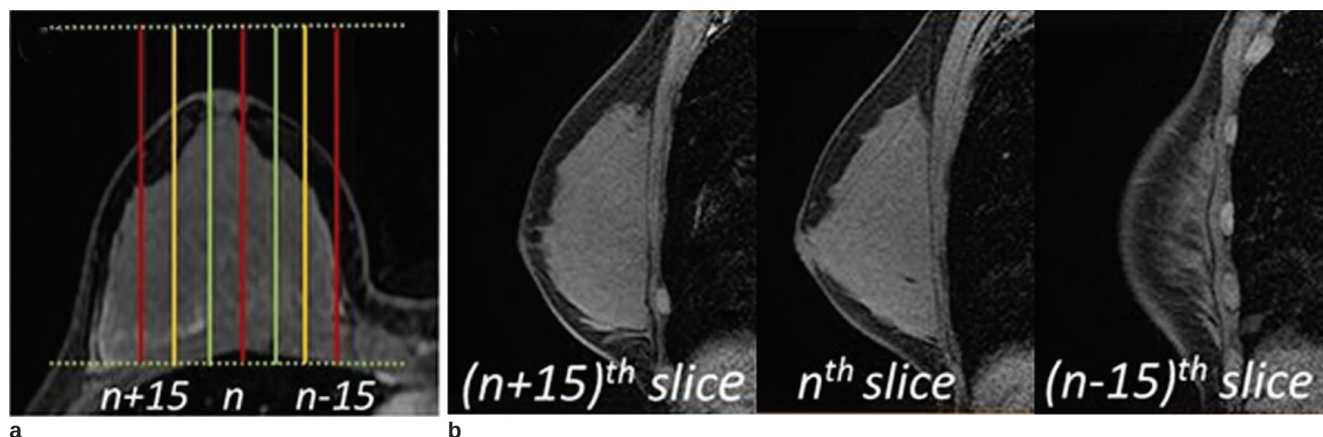


Fig. 2. Selection of the 3 slices of interest (a) and MR images of the 3 representative slices (b) in right breast.

To measure the fibroglandular tissue volume, the same ROIs were used. Fuzzy c-means (FCM) algorithm was applied to segment the fibroglandular tissue from the surrounding fat (17, 21). Three breast tissue regions or classes (fibroglandular tissue, fat and skin) were defined for each breast under study depending on the MR imaging volume and its content when applying FCM algorithm, to segment the whole breast volume into three tissue groups. A suitable threshold was then applied and the fibroglandular tissue volume was calculated. In our analysis, we found a threshold value of 0.4 to be suitable for most images with adequate fat suppression.

For the 3-slice method, VBD was calculated from 3 representative slices for each breast. The slice in the middle in the sagittal stack of images in a MR imaging study of one breast was considered as the middle slice (n). We did not select the middle slice in relation to the nipple as the slice through the nipple is not always the middle slice in MR imaging studies. For the selection of the suitable slices on either side of the middle slice, we considered the 5th, 10th and 15th slices on either side of the middle slice (Fig. 2). We measured the VBD values from 10 selected cases with different breast volume and a broad range of breast densities. From our measurements, the VBD values measured from the ($n \pm 15$)th slices were more closely correlated with the VBD measured from the all slices than the measurements done with the ($n \pm 5$)th and ($n \pm 10$)th slices (Table 1). Therefore, we chose the middle slice (n) and the 15th slice medial ($n-15$)th to and lateral ($n+15$)th to the middle slice as the 3 representative slices for each breast. The measurement of breast density was done in the same way as the whole breast measurement using the same ROIs but only for the 3 selected slices. To assess intraobserver agreement, a random sample of 30 cases was selected and the VPD was reanalyzed using the 2 methods 2 months after the initial assessment.

Data and Statistical Analysis

The mean VBD from the 3-slice method and the whole breast measurement was compared with t-test. The level of agreement between the measurements from the 3-slice method and the whole breast measurement was assessed by performing the intraclass correlation (ICC) test and also by measuring the coefficient of variation (CV). Bland-Altman plot was used to show the agreement between the two methods. To assess whether the agreement between the two methods varied depending on the VBD of the breast, the patients were classified in to three groups based on the obtained VBD values from the whole breast measurement into three categories, < 20%, 20–40% and > 40% and the correlation between the two methods was compared.

In addition, we selected 50 cases at random and measured the VBD by selecting the 3 slices including the slice as that showing the nipple, to determine whether measurements made by selecting the slice showing the nipple have stronger or weaker correlation with the whole breast measurements compared with the 3-slice measurements with the middle slice. Correlation coefficient (r) was calculated.

To assess the interobserver reproducibility of the VBD measurements by the 3-slice method, a random sample of 30 cases was selected and the VBD measurements were done by two breasts radiologists (KWH and SM) with prior experience in using the MIPAV software. From the original and their measurements, the interobserver reproducibility was assessed by calculating the ICC, CV and the kappa statistic. A kappa value (k) of 0.20 or less was interpreted as indicating slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement (24).

The measurement time for each breast by 2 methods was obtained and the mean time was calculated for each method and the results compared with t-test. All statistical analyses were done using SPSS software

Table 1. Comparison of VBD Measurements with Different Representative Slices

Parameter	($n \pm 5$) th	($n \pm 10$) th	($n \pm 15$) th
Correlation coefficient (r)	0.9321 (0.732 – 0.984)	0.9532 (0.809 – 0.989)	0.977 (0.906 – 0.995)
Coefficient of variation	18.02%	14.40%	8.81%
Intraclass coefficient	0.8854 (0.377 – 0.974)	0.931 (0.639 – 0.984)	0.976 (0.908 – 0.994)

(Version 19.0, Chicago, IL) and MedCalc (Version 12.1.4.0, Mariakerke, Belgium). P values less than 0.05 were considered statistically significant.

Results

The mean VBD measured from 3 representative slices was not significantly different from that measured from the all slices of the breast (24.32% vs. 24.55%, $p = 0.39$) (Table 2). The mean absolute difference of VBD values between the two methods was 2.45%. The two methods showed excellent agreement (ICC = 0.9617; 95% CI = 0.9476–0.9721) (Fig. 3). The coefficient of variation was 9.74%. For intraobserver agreement, ICC

Table 2. Comparison of 3-Slice Method with Whole Breast Measurement

Parameter	3-slice	All slices
Mean VBD	24.55%	24.32%
Intraobserver agreement (intraclass coefficient)	0.913 (0.753 – 0.967)	0.929 (0.816 – 0.972)
Mean measurement time	133 sec	572 sec

was 0.9131 (0.7530–0.9672) for the whole breast measurement and 0.9294 (0.8159–0.9724) for the 3-slice method, respectively. The VBD values measured from the all slices of the breast were < 20% in 63 cases, 20–40% in 72 cases and > 40% in 16 cases and the two methods showed better agreement for denser breasts (> 40% VBD; ICC = 0.8183) than for fatty breasts (< 20% VBD, ICC = 0.7048) (Table 3).

When the results were compared with the whole breast VBD, the 3-slice VBD measurements made with the middle slice showed a slightly better correlation than the 3-slice VBD measurements made with the slice of the nipple (correlation coefficient $r = 0.9620$ vs. 0.9441).

For interobserver reproducibility, the ICC coefficients for the 3-slice method ranged between 0.94 and 0.98. The CV ranged between 5.1% and 9.6%. The k values ranged from 0.81 and 0.83, which suggest almost perfect agreement.

The mean measurement time for the 3 slice method was significantly lower than that for whole breast measurement (133 sec vs. 572 sec; $p < 0.0001$).

Table 3. Difference in Measurement between the 2 Methods according to VBD

Parameter	0 – 20% (n = 63)	20 – 40% (n = 72)	> 40% (n = 16)
Mean absolute difference	2.37	3.06	2.62
Coefficient of variation	15.33%	9.06%	5.11%
Standard deviation	3.02%	3.49%	3.61%

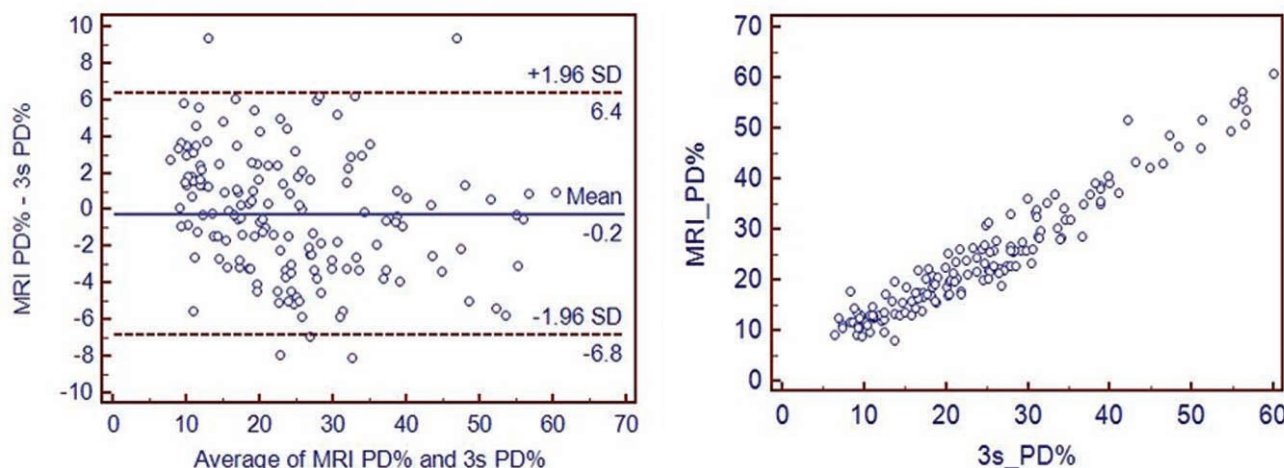


Fig. 3. Bland-Altman plot to show difference (a) and correlation (b) of VBD values between the two methods. Note ; PD% = volumetric breast density measured from the all slices, 3s PD% = volumetric breast density measured from 3 representative slices, SD= Standard deviation

Discussion

In this study, we proposed a new method of VBD measurement using the 3 representative slices from the breast MR images. After segmentation of the breast and fibroglandular tissue, we compared VBD measured by the 3 representative slices and by the all slices of the breast. The two methods of measurement of VBD were not significantly different from each other. However, the 3-slice method reduced the measurement time. In previous studies, measurement of VBD from limited slices from the center of the breast led to overestimation of breast density owing to the normal distribution of fibroglandular tissue within the breast, which is concentrated more in the middle of the breast than at the peripheries (17). Taking this into account, we selected 3 slices including the middle, lateral, and medial side of the breast which would provide a better representation of the entire volume and the distribution of fibroglandular tissue in the entire breast. Compared to the whole breast measurement, the 3-slice method is quicker and makes measurement of VBD from MR imaging data more feasible in large population. Our technique is also highly reproducible in both fatty and dense breasts.

Breast density in MR imaging can be assessed by using either qualitative or quantitative methods. For qualitative (visual) assessment, a four-level categorical scale has been introduced to depict the amount of fibroglandular tissue in the breast (25). In new BI-RADS lexicon, the amount of fibroglandular tissue has been categorized as almost entirely fatty, scattered fibroglandular, heterogeneously fibroglandular tissue, or extremely fibroglandular tissue (26). For quantitative assessment, computer-assisted semi-automatic methods with the adaptive FCM algorithm have been applied for segmentation of fibroglandular tissue from the surrounding fatty tissue and to calculate VBD (21). We also used the FCM algorithm in this study and found two types of error arose in this method. First, in the case of extremely fatty breasts, on application of FCM algorithm, the pixel count is overestimated and the threshold had to be altered depending on the quality of each image. Second, in some MR imaging studies, the fat suppression is not complete especially in the upper regions of the breast

and this would again lead to overestimation of VBD measurements, although still the final results were within acceptable limits. By selecting just 3 representative slices, we may reduce the possibility of errors that would occur if we had the measure the VBD from all the slices of the breast MR imaging.

At present, breast MR imaging is recommended as an adjunct breast screening tool for high-risk women with familial history or personal history of breast cancers and BRCA1, 2 mutation carriers (27, 28). With the advent of less expensive MR imaging techniques and more studies for screening purposes, density assessments at MR imaging should become routine (29). Changes in breast density at MR imaging can be used to monitor the treatment response after tamoxifen or preventive intervention in women at high-risk (25). Unlike mammography, however, MR imaging produces hundreds of slices for each breast pair. Therefore, it is critical to develop a fully automated algorithm for VPD quantification (30–32). Until an automated method and software of measurement of breast is commercialized, our method would be a useful tool in measuring VBD from breast MR imaging. This concept can also be applied to automated studies to limit the number of slices measured and therefore save time and increase reliability.

Our study had some limitations. First, the participants were all Korean women and relatively small breasts; thus, some of the results may not be generalized to other populations. Second, the selection of appropriate threshold value during the measurement of fibroglandular volume was subjective and could be a probable cause for observer variation. Our method is semiautomatic and full automatic method has to be introduced. Third, we did not provide the correlate of total breast volume obtained by 2 methods. It is, however, possible to calculate the volume of the entire breast from the 3-slice volume with acceptable accuracy using the following equation; $\text{TOTAL BREAST VOLUME (cm}^3\text{)} = (3\text{-Slice Volume} \times 21.567) - 89700$ [unpublished data]. Lastly, we did not exclude the skin during measurements. The VBD of the breast excluding the skin, however, can be calculated as performed by other researchers (33).

In conclusion, our proposed a method for measuring the VBD using the 3 representative slices instead of the

all slices of the breast can help us in saving measuring time and thus make it more practical and possible to apply to large databases of breast MR imaging.

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