

OPEN

The Diagnostic Value of Superb Microvascular Imaging (SMI) in Detecting Blood Flow Signals of Breast Lesions

A Preliminary Study Comparing SMI to Color Doppler Flow Imaging

Yan Ma, MD, Gang Li, MD, Jing Li, MD, and Wei-dong Ren, MD

Abstract: The correlation between color Doppler flow imaging (CDFI) and Superb Microvascular Imaging (SMI) for detecting blood flow in breast lesions was investigated, as was the diagnostic value of SMI in differentiating benign from malignant breast lesions.

These lesions were evaluated using both CDFI and SMI according to Adler's method. Pathologic examination showed 57 malignant lesions and 66 benign lesions. The number of blood vessels in a single mass was detected by 2 techniques (SMI and CDFI), and the difference between the 2 values (SMI-CDFI) was calculated. The optimal threshold for the diagnosis of malignant neoplasms and the diagnostic performances of SMI, CDFI, and SMI-CDFI were calculated.

For the total lesions and malignant lesions alone, the difference between SMI and CDFI for detecting blood flow was significant ($P < 0.01$), but the difference was not significant for benign lesions ($P = 0.15$). The area under the receiver operating characteristic curve was 0.73 (95% confidence interval [CI]: 0.64–0.82) for CDFI; 0.81 (95% CI: 0.74–0.89) for SMI; and 0.89 (95% CI: 0.82–0.95) for SMI-CDFI. Furthermore, the modality of “SMI-CDFI” showed the best diagnostic performance.

SMI provides further microvessel information in breast lesions. The diagnostic modality of “SMI-CDFI” can improve the diagnostic performance of ultrasound in the differentiation between benign and malignant masses.

(*Medicine* 94(36):e1502)

Abbreviations: CDFI = color Doppler flow imaging, CEUS = contrast-enhanced ultrasound, DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging, MVD = microvessel density, ROC = receiver operating characteristic, ROI = region of interest, SMI = Superb Microvascular Imaging.

Editor: Xiaowen Hu.

Received: March 31, 2015; revised: July 23, 2015; accepted: August 11, 2015.

From the Department of Ultrasound, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China.

Correspondence: Wei-dong Ren MD, Department of Ultrasound, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, China (e-mail: cmurdw@126.com).

This work was supported in part by the Fundamental Research Funds of Shengjing Hospital, China Medical University (MD63).

The study design and protocol were approved by the ethics committee of Shengjing Hospital of China Medical University, and written informed consent was obtained. All patients were notified of the detailed research profile and provided written informed consent before the beginning of the study.

The authors have no conflicts of interest to disclose.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NonCommercial License, where it is permissible to download, share and reproduce the work in any medium, provided it is properly cited. The work cannot be used commercially.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001502

INTRODUCTION

A major cause of morbidity and mortality in women, breast cancers, has been found to be highly dependent on angiogenesis of microvessels for their growth, invasion, and survival. Furthermore, there is a significant difference in microvascular architecture between benign and malignant tumors.¹ Therefore, the characteristics of tumor microvessels are of paramount importance in differentiating between benign and malignant lesions.² Currently, breast tumor vascularity can be assessed by noncontrast-enhanced ultrasonography, such as color Doppler flow imaging (CDFI), and contrast-enhanced imaging techniques, such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), contrast-enhanced ultrasound (CEUS), and dynamic contrast-enhanced computed tomography.^{3–5} CDFI can provide information on tumor vascularity associated with breast malignancy; however, it has been proven to be unreliable in differentiating benign from malignant breast lesions when compared with the invasive imaging modalities listed above.^{6,7} The number of vessels seen with CDFI often indicates the macrovascularity of breast cancers, but not the microvasculature. The vessels which can be observable by pathology such as microvessel density (MVD) but cannot be measured by CDFI are known as microvascularity.⁸ Imaging technologies with contrast media have been used as an additional imaging modality when the combination of x-ray mammography and conventional ultrasonography could neither provide sufficient information nor be appropriately applied. However, all of these invasive imaging modalities require a higher cost and operating skill level.^{9,10}

Therefore, clinically significant challenges exist in detecting small or micro blood flow states without contrast media. Superb Microvascular Imaging (SMI) is an innovative Doppler ultrasound technique, specifically for imaging very low flow states, which can use a unique algorithm that allows visualization of minute vessels with slow velocity without using a contrast agent. To date, no clinical research with SMI technology for microvascular evaluation has been reported.¹¹ The purpose of this study was to elucidate the application of SMI in evaluating breast tumor vascularity and evaluate the diagnostic performance of SMI in differentiating benign from malignant breast lesions. Furthermore, if a significant difference exists between CDFI and SMI in diagnostic performance for breast lesions, it will be determined whether the integration of SMI into CDFI can improve the diagnostic performance.

MATERIALS AND METHODS

The prospective study design and protocol were approved by the ethics committee of our institution, and written informed consent was obtained. All patients were notified of the detailed research profile and provided written informed consent before the beginning of the study.

Patients

From August 2014 to December 2014, 128 women with 145 breast masses who were referred for routine breast ultrasound examinations and had ultrasound-visible solid breast masses were initially recruited in our institution. Nineteen women who declined pathologic examination and 1 woman with breast implants were excluded. In total, 108 women with 123 breast masses were finally included. Histopathology of the 123 breast masses was confirmed via ultrasound-guided core needle biopsy and/or surgical biopsy after needle localization according to standard clinical protocols. The procedures were consecutively performed after obtaining ultrasound images. These 108 patients with breast masses were divided into 2 groups according to the pathologic classification: the benign lesion group and the malignant lesion group. The benign lesion group included 52 women (age range 15–54 years, average 34.3 ± 11.7 years) with 66 lesions, whereas the malignant lesion group included 56 women (age range 31–69 years, average 52.4 ± 10.2 years) with 57 lesions. Histologic classification of the breast tumor tissue and diagnostic standards followed the World Health Organization histologic classification of breast tumors (2012 edition).¹²

Ultrasound Examination

All ultrasound examinations were performed with a high-frequency transducer (L14-5 Aplio400; Toshiba Medical Systems Corporation, Tochigi, Japan). To avoid interobserver variability, all sonographic scanning was performed by 2 radiologists (with >5 years of experience in breast sonography and CDFI, and 2 months of experience in SMI). A third radiologist served as a blinded expert (with >10 years of experience in breast sonography and CDFI, and 3 months of experience in SMI) in cases of disagreement. Grayscale, CDFI, and SMI images were obtained during the standard ultrasound appointment. The combined CDFI, SMI, and grayscale ultrasound examination time was between 10 and 20 minutes.

A minimum of 2 orthogonal grayscale images of each solid lesion was obtained. The radiologists who performed the breast ultrasound recorded the conventional ultrasound features of the lesion, including the lesion shape, orientation, margin, boundary, echo pattern, posterior features, effect on surrounding tissue, calcifications, and special cases.

Then, 2 orthogonal images of each lesion were scanned slowly with CDFI. The following settings were used for the CDFI examination: the color velocity scale was adjusted at <5 cm/s, the wall filter was adjusted at 50 to 100 Hz, the color gain was adjusted adequately such that the background color was suppressed and small vessels could be detected, and the region of interest (ROI) was adjusted to include the lesion and normal breast tissue adjacent to the lesion. If the patients were breathing heavily, they were asked to hold their breath during acquisition. During acquisition, no pressure was applied through the transducer to prevent the vessels from collapsing.^{13,14} The signal was considered 1 real blood flow signal on ultrasonography (CDFI or SMI) if pulsed Doppler showed an arterial flow pattern. The vascularity of the lesion with the richest vascular images was recorded. Moreover, similar to CDFI, the standard procedure of SMI was performed. SMI was available in 2 modes: monochrome (grayscale) and color. The following settings were used for SMI examination: the color velocity scale of SMI was adjusted to 1.0 to 2.0 cm/s, the color frequency was adjusted to 5 to 7 MHz, and the vascular information was enhanced by adjusting the time smooth.

Evaluation Indicators

The vascularity of the breast lesion was observed and recorded using CDFI and SMI, respectively. According to Adler's method, the vascularity was subjectively determined to be absent (grade 0), minimal (grade 1), moderate (grade 2), or marked (grade 3). The amount of blood flow visualized in ROI was determined according to the image. In general, if 1 or 2 pixels contained flow (usually <1 mm in diameter), it was considered minimal flow. If a main vessel was seen in the area and/or several small vessels were visualized, the blood flow was judged to be moderate. Breast tissue was classified as having marked vascularity when 4 or more vessels were visualized.¹⁵

Statistical Analysis

For the statistical analysis, to assess the difference between CDFI and SMI in evaluating vascularity for the same breast lesion, the degree of blood flow detected by these 2 techniques according to Adler's classification was graded and compared using Redit analysis. If there was a significant difference between CDFI and SMI in either the benign lesion or the malignant lesion group, then the number of vessels detected by SMI subtracted by the number of vessels detected by CDFI for the same breast mass would be calculated and thus termed "SMI-CDFI." Furthermore, a *t* test was applied to determine whether the SMI-CDFI was different in the benign versus malignant groups. A receiver operating characteristic (ROC) curve was constructed to observe the diagnostic performance of CDFI, SMI, and SMI-CDFI for differentiating between benign and malignant breast lesions, using histologic findings as reference standards and thus providing a breakthrough in the clinical application of SMI. The optimum threshold value of the above 3 diagnostic modalities was used as a reference standard, which was calculated by a ROC plot. The area under the ROC curve as well as the diagnostic sensitivity and specificity was calculated after determining a cutoff value by analyzing the ROC curve for CDFI, SMI, and SMI-CDFI. A pathological diagnosis was used as the "gold standard" for evaluating the diagnostic performance of SMI-CDFI. The sensitivity was calculated as $TP/(TP+FN)$ and the specificity as $TN/(TN+FP)$, where TP represented the number of true-positive findings, TN represented the number of true-negative findings, FP represented the number of false-positive findings, and FN represented the number of false-negative findings.

In a subset of 30 patients, an additional observer produced a further set of CDFI and SMI images by 2 independent radiologists. These 2 radiologists were blind to the data generated by each other. To assess the reproducibility of the determined vascularity between the 2 observers, the κ -coefficient and intraclass correlation coefficient were calculated.

The software package SPSS for Windows 13.0 (SPSS Inc, Chicago, IL) was used for the statistical data analysis. Continuous data were expressed as the mean \pm standard deviation. A *P* value of <0.05 was considered statistically significant.

RESULTS

Reproducibility

The intraobserver reproducibility in a subset of 30 lesions between Adler's grade of CDFI or SMI acquired by 2 independent operators was assessed. The κ -coefficients of CDFI and SMI were 0.76 and 0.82. The intraclass correlation coefficients of the number of blood flow signals detected by SMI and CDFI between 2 independent operators were 0.86 and 0.87. In the

subgroup, there was good agreement between 2 independent operators. Compared with the entire study population, this subset showed no significant difference in terms of origin (symptomatic or screening), lesion size, or whether the lesions were benign or malignant.

Adler’s Classification

Of the 123 studied breast lesions, histopathological analysis revealed 66 (53.7%) benign lesions and 57 (46.3%) malignant lesions. The benign lesions included fibroadenoma (n = 26), mammary adenosis (n = 18), adenomatous hyperplasia (n = 10), papilloma (n = 5), mastitis (n = 5), and benign phyllodes tumor (n = 2). The malignant lesions included invasive ductal carcinoma (n = 47), ductal carcinoma in situ (n = 4), invasive lobular carcinoma (n = 3), malignant phyllodes tumor (n = 2), and tubular carcinoma (n = 1). The mean diameter of the benign lesions was 2.1 ± 1.4 cm (range 0.6–5.4 cm). The mean diameter of the malignant lesions was 2.4 ± 1.4 cm (range 0.9–6.0 cm). The histopathological features and the diagnosis of the breast lesions are listed in Table 1. The degrees of blood flow of all the lesions were graded from 0 to 3 according to Adler’s method, and the results are shown in Table 2. Redit analysis indicated that the difference between SMI and CDFI in detecting the blood flow of all lesions was statistically significant ($R_{SMI} = 0.55, R_{CDFI} = 0.45, u = 2.89, P < 0.01$), suggesting that compared with CDFI, SMI was more sensitive in detecting levels of blood flow that were higher than grade 1. Likewise, for the malignant lesions, the difference between SMI and CDFI was also significantly different ($R_{SMI} = 0.58, R_{CDFI} = 0.41, u = 3.71, P < 0.01$), and the results are indicated in Table 4. In other words, when compared with CDFI, SMI was more sensitive in detecting higher-level blood flow (grade 3). However, for the benign lesions, there was not a significant difference between SMI and CDFI in detecting the blood flow ($R_{SMI} = 0.53, R_{CDFI} = 0.47, u = 1.43, P = 0.15$), and the results are provided in Table 3.

The Number of Blood Flow Signals Detected by SMI and CDFI

For all of the breast lesions, the number of blood flow signals detected by SMI was equal or greater than the number detected by CDFI, regardless of the pathological type. For the benign lesion group, the mean number of vessels detected by CDFI was 1.65 ± 1.79 (range 0–6), and that by SMI was 2.73 ± 2.63 (range 0–9); the mean value of SMI-CDFI in the benign lesion group was 1.08 ± 0.98 (range 0–3) (Figure 1). In contrast, for the malignant lesion group, the mean number of vessels detected by CDFI was 3.30 ± 2.16 (range 0–9), whereas that by SMI was 6.79 ± 3.75 (range 0–15); the mean value of

TABLE 2. The Degree of Blood Flow of 123 Lesions, According to Adler’s Method [No. (%)]

All Masses	Grade 0	Grade I	Grade II	Grade III
SMI	20 (16.26)	25 (20.33)	23 (18.70)	55 (44.71)
CDFI	31 (25.20)	33 (26.83)	25 (20.33)	34 (27.64)

CDFI = color Doppler flow imaging, SMI = Superb Microvascular Imaging.

Redit analysis revealed there was a significant difference between SMI and CDFI on detecting blood flow of all breast lesions ($P < 0.01$).

TABLE 3. The Degree of Blood Flow of 66 Benign Lesions, According to Adler’s Method [No. (%)]

Benign Masses	Grade 0	Grade I	Grade II	Grade III
SMI	18 (27.27)	21 (31.82)	14 (21.21)	13 (19.70)
CDFI	26 (39.39)	19 (28.79)	11 (16.67)	10 (15.15)

CDFI = color Doppler flow imaging, SMI = Superb Microvascular Imaging.

Redit analysis revealed there was no significant difference between SMI and CDFI on detecting blood flow of breast benign lesions ($P = 0.15$).

SMI-CDFI in the malignant lesion group was 3.50 ± 1.90 (range 0–9) (Figure 2). There was a significant difference between the benign lesion group and the malignant lesion group in the value of SMI-CDFI ($t = 9.03, P < 0.01$). The above results indicate that compared with CDFI, SMI was more sensitive in detecting the vascular flow of malignant lesions. The insufficient vascularity of benign breast tumor may account for the lack of significant difference between SMI and CDFI in detecting the blood flow according to Adler’s method.

Comparison of Diagnostic Performance: CDFI, SMI, and SMI-CDFI

ROC curve analysis was used to identify the threshold required to differentiate the malignant from benign lesions. The optimum threshold value calculated by constructing the ROC was 2.5 for CDFI, 4.5 for SMI, and 2.5 for SMI-CDFI, which were rounded to 3 for CDFI, 5 for SMI, and 3 for SMI-CDFI as the cutoff values to differentiate malignant lesions from benign

TABLE 1. Histopathological Analysis

Benign Lesions	No. (%)	Malignant Lesions	No. (%)
Fibroadenoma	26 (39.39)	Invasive ductal carcinoma	47 (82.46)
Mammary adenosis	18 (27.27)	Ductal carcinoma in situ	4 (7.02)
Adenomatous Hyperplasia	10 (15.15)	Invasive lobular carcinoma	3 (5.26)
Papilloma	5 (7.58)	Malignant phyllodes tumor	2 (3.51)
Mastitis	5 (7.58)	Tubular carcinoma	1 (1.75)
Benign phyllodes tumor	2 (3.03)		
Total	66		57

TABLE 4. The Degree of Blood Flow of 57 Malignant Lesions, According to Adler's Method [No. (%)]

Malignant Masses	Grade 0	Grade I	Grade II	Grade III
SMI	2 (3.51)	4 (7.02)	9 (15.79)	42 (73.68)
CDFI	5 (8.77)	14 (24.56)	14 (24.56)	24 (42.11)

CDFI = color Doppler flow imaging, SMI = Superb Microvascular Imaging.

Ridit analysis revealed there was a significant difference between SMI and CDFI on detecting blood flow of breast malignant lesions ($P < 0.01$).

lesions. Thus, the area under the ROC curve for CDFI was 0.73 ± 0.05 (SE), (95% confidence interval [CI]: 0.64–0.82), providing 66.7% sensitivity and 68.2% specificity, and the area under the ROC curve for SMI was 0.81 ± 0.04 (SE), (95% CI: 0.74–0.89), providing 73.7% sensitivity and 80.3% specificity. Regarding SMI-CDFI, the area under the ROC curve was 0.89 ± 0.03 (SE), (95% CI: 0.82–0.95), providing 86.0% sensitivity and 86.4% specificity. The diagnostic modality of “SMI-CDFI” showed the best diagnostic performance among the 3 modalities.

DISCUSSION

The topic of the vascularity of breast tumors is always a focus in the field of breast cancer research. As an easy, effective imaging modality that has been widely applied in clinical practice, the vascular assessment of CDFI can provide information on the degree of vascularization, which correlates with the biological behavior of the breast tumor. However, a variety of enhanced imaging techniques for breast tumor vasculature including DCE-MRI and CEUS have been proven to be more sensitive than CDFI. DCE-MRI and CEUS most likely improve the sensitivity and specificity for detecting breast cancer by

focusing on the consequences of tumor angiogenesis: the increased MVD with altered vascular characteristics. Tumor angiogenesis is a basis for discriminating between benign and malignant tumors. The detection of vascularization in the lesions has shown a significant association with malignancy.^{16,17} However, CDFI is limited by its angular dependency and poor signal-to-noise ratios, and it is often unable to evaluate flow signals from small vessels (<1 mm) in which the flow is low (3–5 cm/s)¹⁸; however, the microvessels could usually be observable by pathologic examination. This flow approximately equals the tissue motion velocity, making the technique difficult to distinguish real blood flow from motion artifacts caused by, for example, patient breathing. As a result, some authors found that vascularity detection via CDFI was not useful as the main sign for malignancy.¹⁷ Moreover, there could be considerable overlap with benign lesions. The vessel which can be measured by SMI but not by CDFI is regarded as microvessels in our study.

With the improvement of ultrasound technology, the SMI mode allows radiologists to visualize the microvascular patterns of lesions in detail without the additional use of a contrast agent.¹⁹ As a novel imaging technology, SMI is different from conventional CDFI in assessing microvessels of breast tumors. SMI focuses on detecting microvessel blood flow, which is intimately associated with tumor angiogenesis. When using the imaging modality of “SMI-CDFI” with a cutoff value of 3 as a sign of malignancy, SMI-CDFI showed better diagnostic performance than that of SMI or CDFI alone. The above results suggest that as a new diagnostic modality for differentiate breast lesions, SMI-CDFI could represent a favorable discriminator and that SMI could make up the deficiency of CDFI in distinguishing low-velocity blood flow from motion artifacts. It has been demonstrated that the amount of blood flow visualized by SMI was markedly more than (≥ 3) that visualized by CDFI in microvessels that are highly suggestive of malignancy.

Blood flow was better visualized with SMI (83.7%) than with CDFI (74.8%), and some tumor vessels could be detected only with SMI. Moreover, SMI presented higher resolution than CDFI in revealing microvascular flow signals and the vascularization of malignant breast tumors. Therefore, this finding

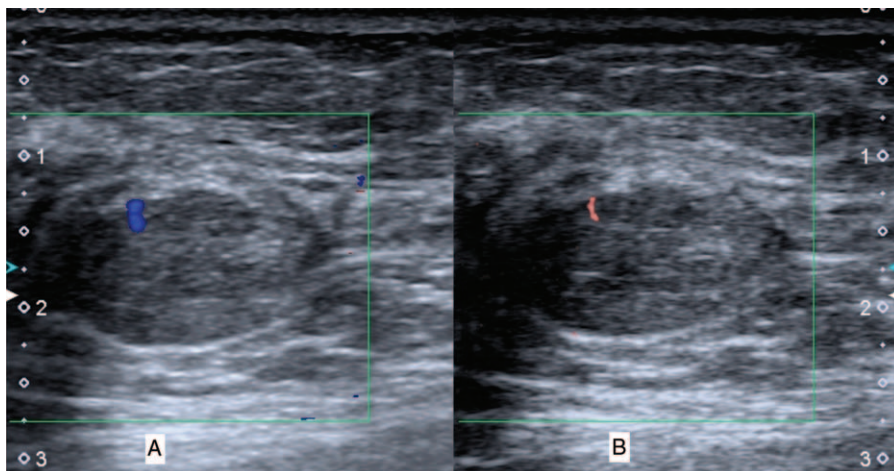


FIGURE 1. A 38-year-old woman with fibroadenoma. The vascularity of the breast mass was investigated using CDFI (A), and the map showed that 1 vessel was detected, which was grade 1 according to Adler's method. The vascularity of the breast mass was investigated using SMI (B), and the map showed that 1 vessel was detected, which was grade 1 according to Adler's method. CDFI = color Doppler flow imaging, SMI = Superb Microvascular Imaging.

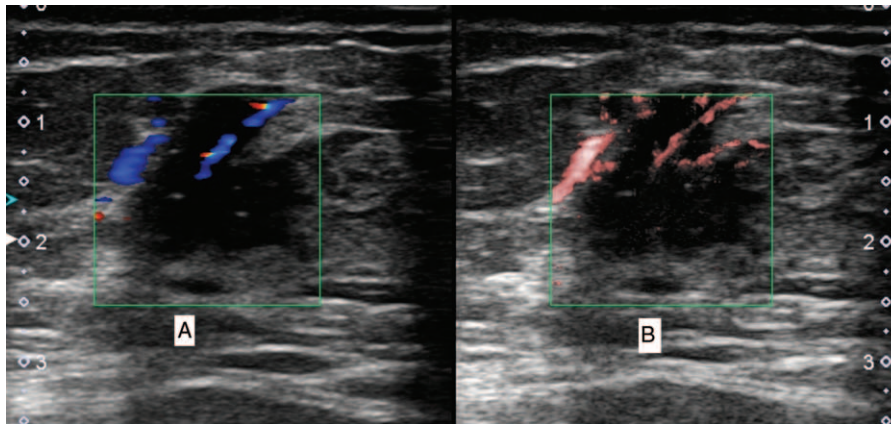


FIGURE 2. A 36-year-old woman with invasive ductal carcinoma. The vascularity of the breast mass was investigated using CDFI (A), and the map showed that 4 vessels were detected, which were grade 3 according to Adler's method. The vascularity of the breast mass was investigated using SMI (B), and the map showed that 7 vessels were detected, which were grade 3 according to Adler's method. CDFI = color Doppler flow imaging, SMI = Superb Microvascular Imaging.

provided us with the important caveat that some malignant lesions may also be in a high-functioning metabolic state in which detection is not possible by CDFI. It was presumed that this phenomenon was caused by the different imaging principles on which the 2 techniques are based. CDFI applies a wall filter to remove clutter and motion artifacts, resulting in a loss of low-flow components. SMI can analyze clutter motion, and uses a new adaptive algorithm to identify and remove tissue motion and reveal true blood flow. In addition, CDFI was developed with the primary goal of visualizing blood flow at higher resolution. Moving beyond this goal, SMI is able to visualize lower-velocity blood flow as well. The most significant problem in the detection of low-velocity blood flow is the presence of extraneous Doppler signals (motion artifacts) arising from nearby structures; CDFI is unable to distinguish these motion artifacts from actual blood flow. However, we analyzed the characteristics of such motion artifacts and successfully extracted only the clinically relevant information with SMI. In contrast, for benign lesions, the SMI results showed no significant improvement over those of CDFI. This was because benign lesions naturally have much lower vascularity. This finding also agreed with the nature of angiogenesis of tumors.

Our study first proposed the diagnostic modality of SMI-CDFI and applied this modality in preliminary clinical practice. The diagnostic accuracy determined by SMI-CDFI in this study suggests that SMI is a potentially valuable technique for differentiating benign from malignant breast lesions by detecting microvascular signals. However, our results showed 8 false-negative cases, including 3 ductal carcinomas in situ, 3 invasive ductal carcinomas, 1 invasive lobular carcinoma, and 1 tubular carcinoma. These false-negative findings may result from special pathological conditions or limitations of the imaging technique. Doppler imaging is mainly dependent on the presence of posterior acoustic shadowing, the tumor size, and the presence of necrotic areas. As a consequence of rapid growth of malignant parenchyma, some certain areas of breast tumor may be necrosis which result from the absence of vascular supply. It is generally believed that there is no observable CDFI signal in the necrotic areas.²⁰ Similarly, if a hypoechoic area showed little flow on SMI in a breast lesion, it would be highly suggested that the lesion is aggressively malignant. For these false-negative cases, dynamic-enhanced MRI would make up

for the deficiency of the novel Doppler technique, which may show the interstitial enhancement from vessel leakage in the areas of necrosis.²¹ Moreover, the breast is not a homogeneous organ, but is rather composed of fat tissue and glands. Breast tissue can roughly be classified as dense and not dense tissue. The dense gland structure and breast cancers with deep lesions may have unfavorable effects on ultrasound detection of blood flow. In addition, there were 9 false-positive results, including 4 cases of mastitis, 2 cases of benign phyllodes tumor, 2 fibroadenomas, and 1 papilloma. Du et al²² reported that some phyllodes tumors and mastitis were rich in vascularity, which may account for our results. Furthermore, the mean diameter of the 9 "false positive" benign lesions was 3.34 ± 1.33 cm, suggesting that breast benign lesions with higher vascularity generally tended to be larger than the benign lesions with lower vascularity.

The present study had several limitations that should be solved in a future study. First, the study included a relatively small sample size of patients. A prospective clinical study with a larger scale would be needed to more accurately quantify the optimal threshold of SMI-CDFI for differentiating benign from malignant breast lesions. Second, the gold standard for measuring vascularity is currently a histological estimation of the MVD²³; however, evaluations of the MVD were not available for all lesions, but this measure could be considered in our future study for a more rigorous analysis. Third, Power Doppler sonography, which is based on the total integrated Doppler power spectrum, may be more sensitive for detecting low-velocity blood flow than CDFI.²⁴ However, Power Doppler was not evaluated. In practice, grayscale ultrasound can clearly show the echo, shape, and boundary of breast lesions, providing preliminary diagnostic information for differentiating the malignancy of breast masses. The combined diagnostic performance of grayscale ultrasound and SMI may improve the diagnostic accuracy of malignancy. Therefore, a specific guideline for the combination of BI-RADS category in grayscale ultrasound and SMI features should be provided in the future.

In conclusion, although CDFI and SMI were capable of evaluating breast tumor angiogenesis, our study revealed that SMI was more sensitive than CDFI for revealing microvascular blood flow and vascularization of malignant breast tumors. Owing to their native differences in detecting resolution,

SMI can provide detailed microvascular information that is completely invisible in CDFI images. Therefore, as a non-enhanced imaging technique, SMI provided important information on tumor vascularity; moreover, the diagnostic modality “SMI-CDFI” drawn from our study is a promising option for differentiating breast tumors. The application of SMI in monitoring the dynamic changes in angiogenesis under neoadjuvant chemotherapy for breast cancers could also be part of future research.

ACKNOWLEDGMENT

Toshiba Medical Systems (China) provided the technical assistance for this study

REFERENCES

- Liu H, Jiang Y, Dai Q, et al. Peripheral enhancement of breast cancers on contrast-enhanced ultrasound: correlation with microvessel density and vascular endothelial growth factor expression. *Ultrasound Med Biol*. 2014;40:293–299.
- Tozaki M, Toi M, Miyamoto Y, et al. Power Doppler sonography of breast masses: correlation of Doppler spectral parameters with tumor angiogenesis and histologic growth pattern. *J Ultrasound Med*. 2000;19:593–600.
- Bitencourt AG, Lima EN, Chojniak R, et al. Multiparametric evaluation of breast lesions using PET-MRI: initial results and future perspectives. *Medicine (Baltimore)*. 2014;93:e115.
- Shen ZY, Hu B, Wu MF. Correlation between Blood Flow Signal of Color Flow Imaging and Nottingham Prognostic Index in Patients with Breast Carcinoma. *Breast Care (Basel)*. 2012;7:126–130.
- Wang Y, Dan HJ, Fan JH, et al. Evaluation of the correlation between colour power Doppler flow imaging and vascular endothelial growth factor in breast cancer. *J Int Med Res*. 2010;38:1077–1083.
- Heywang-Kobrunner SH, Schreer I, Heindel W, et al. Imaging studies for the early detection of breast cancer. *Dtsch Arztebl Int*. 2008;105:541–547.
- Nothacker M, Duda V, Hahn M, et al. Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review. *BMC Cancer*. 2009;9:335.
- Peters-Engl C, Medl M, Mirau M, et al. Color-coded and spectral Doppler flow in breast carcinomas—relationship with the tumor microvasculature. *Breast Cancer Res Treat*. 1998;47:83–89.
- Heijblom M, Klaase JM, van den Engh FM, et al. Imaging tumor vascularization for detection and diagnosis of breast cancer. *Technol Cancer Res Treat*. 2011;10:607–623.
- Drudi FM, Cantisani V, Gnechi M, et al. Contrast-enhanced ultrasound examination of the breast: a literature review. *Ultraschall Med*. 2012;33:E1–7.
- Machado P, Segal S, Lyschchik A, et al. A novel microvascular flow technique: initial results in thyroids. *Ultrasound Q*. 2015[Epub ahead of print].
- Sinn HP, Kreipe H. A Brief Overview of the WHO Classification of Breast Tumors 4th Edition Focusing on Issues and Updates from the 3rd Edition. *Breast Care (Basel)*. 2013;8:149–154.
- Kumar A, Srivastava V, Singh S, et al. Color Doppler ultrasonography for treatment response prediction and evaluation in breast cancer. *Future Oncol*. 2010;6:1265–1278.
- Browne JE. A review of Doppler ultrasound quality assurance protocols and test devices. *Phys Med*. 2014;30:742–751.
- Adler DD, Carson PL, Rubin JM, et al. Doppler ultrasound color flow imaging in the study of breast cancer: preliminary findings. *Ultrasound Med Biol*. 1990;16:553–559.
- Zhu Q, Cronin EB, Currier AA, et al. Benign versus malignant breast masses: optical differentiation with US-guided optical imaging reconstruction. *Radiology*. 2005;237:57–66.
- del Cura JL, Elizagaray E, Zabala R, et al. The use of unenhanced Doppler sonography in the evaluation of solid breast lesions. *AJR Am J Roentgenol*. 2005;184:1788–1794.
- Schroeder RJ, Bostanjoglo M, Rademaker J, et al. Role of power Doppler techniques and ultrasound contrast enhancement in the differential diagnosis of focal breast lesions. *Eur Radiol*. 2003;13:68–79.
- Wu L, Yen HH, Soon MS. Spoke-wheel sign of focal nodular hyperplasia revealed by superb micro-vascular ultrasound imaging. *QJM*. 2015;108:669–670.
- Lee SW, Choi HY, Baek SY, et al. Role of color and power doppler imaging in differentiating between malignant and benign solid breast masses. *J Clin Ultrasound*. 2002;30:459–464.
- Cheung YC, Lo YF, See LC, et al. Hemodynamic parameters by color Doppler ultrasound and dynamic enhanced magnetic resonance imaging in palpable T1 breast cancers. *Ultrasound Med Biol*. 2003;29:881–886.
- Du J, Li FH, Fang H, et al. Microvascular architecture of breast lesions: evaluation with contrast-enhanced ultrasonographic micro flow imaging. *J Ultrasound Med*. 2008;27:833–842.
- Jiang J, Chen YQ, Xu YZ, et al. Correlation between three-dimensional ultrasound features and pathological prognostic factors in breast cancer. *Eur Radiol*. 2014;24:1186–1196.
- Huang YH, Chen JH, Chang YC, et al. Diagnosis of solid breast tumors using vessel analysis in three-dimensional power Doppler ultrasound images. *J Digit Imaging*. 2013;26:731–739.