Received:
15 December 2015

Revised:
24 April 2016

Accepted:
3 May 2016

<http://dx.doi.org/10.1259/bjr.20151050>

Cite this article as:

Wang Y-M, Fan W, Zhang K, Zhang L, Tan Z, Ma R. Comparison of transducers with different frequencies in breast contrast-enhanced ultrasound (CEUS) using SonoVue as contrast agent. *Br J Radiol* 2016; **89**: 20151050.

SHORT COMMUNICATION

Comparison of transducers with different frequencies in breast contrast-enhanced ultrasound (CEUS) using SonoVue as contrast agent

¹YONG-MEI WANG, MD, ²WEI FAN, MD, ¹KAI ZHANG, MD, ³LI ZHANG, BS, ⁴ZHEN TAN, MS and ¹RONG MA, PhD, MD

¹Department of Breast Surgery, Qilu Hospital of Shandong University, Jinan, China

²Department of Gastroenterology, Qilu Hospital of Shandong University, Jinan, China

³Department of Health Care Ultrasound, Qilu Hospital of Shandong University, Jinan, China

⁴Department of Health Science Technology and Management, Stony Brook University, Stony Brook, NY, USA

Address correspondence to: Mr Rong Ma

E-mail: marongw2000@163.com

Objective: To explore the effectiveness of different transducers in breast contrast-enhanced ultrasound (CEUS) using SonoVue® (Bracco, Plan-Les-Quates, Switzerland) as the contrast agent.

Methods: Breast CEUS was performed in 51 patients with 51 breast lesions using a low-frequency transducer (probe C5-1) and a high-frequency transducer (probe L12-5) separately. All image processes were reviewed for the presence of local blood perfusion defects and surrounding vessels. McNemar's test was conducted to compare the detection effectiveness between these two transducers.

Results: Pathological results revealed 38 malignant and 13 benign lesions. The two transducers showed no difference in detecting benign lesions. Among malignant lesions, CEUS conducted by probe C5-1 (frequency range from 1 to 5 MHz) presented 23 (60.5%) lesions with local blood perfusion defects and 26 (68.4%) lesions with

surrounding vessels. Meanwhile, probe L12-5 (frequency range from 5 to 12 MHz) showed only 12 (31.6%) lesions with local blood perfusion defects and 12 (31.6%) lesions with surrounding vessel. Probe C5-1 was more sensitive than probe L12-5 in detecting malignant CEUS characteristics (p -value < 0.05).

Conclusion: The low-frequency transducer was more sensitive than the high-frequency transducer in breast CEUS using SonoVue as the contrast agent. A new contrast agent with a higher resonance frequency, specially designed for high-frequency transducers, may be helpful in improving the clinical value of breast CEUS.

Advances in knowledge: The first study comparing different frequency transducers in breast CEUS of the same patient lesions. We brought out the requirement for CEUS contrast agents which are more suitable for high-frequency examinations.

INTRODUCTION

Nowadays, contrast-enhanced ultrasound (CEUS) has become widely applied in diverse organs for its ability to gather microvascular information.^{1,2} Contrast agents could enhance vascular signals by resonating under the ultrasonic waves of a particular frequency. SonoVue® (Bracco, Plan-Les-Quates, Switzerland), which consists of phospholipid-stabilized microbubbles filled with sulfur hexafluoride, is the most widely used ultrasound contrast agent.^{3,4} CEUS was originally developed for the differential diagnosis of focal lesions in the liver and has been successfully applied in clinical practice. Previous studies^{5,6} have proved that CEUS could improve the diagnostic accuracy of breast lesions. Many CEUS characteristics are correlated with the prognostic factors of breast cancer including the presence of local blood perfusion defects and surrounding vessels.⁷ However, the performance of breast CEUS is not as

satisfactory as that of liver CEUS, which blocks its routine clinical application.²

Generally speaking, convex array transducers with low frequencies are more commonly used in liver examination than linear-array transducers with high frequencies, which are used for breast examination. Nevertheless, the most adequate resonance frequency for contrast agents used in CEUS is around 3 MHz. *In vitro* studies have shown that 80% of the echogenicity is provided by bubbles with a diameter range from 3 to 9 µm in CEUS using SonoVue as the contrast agent. The corresponding resonance frequency of these bubbles is around 3 MHz.⁸ Under this condition, the common use of high-frequency transducers in breast examination might reduce the diagnostic effectiveness of CEUS. We also found that transducers used for conventional breast ultrasound are different from transducers for breast CEUS.^{9,10}

Figure 1. (a) A 51-year-old female with invasive ductal carcinoma revealing a blood perfusion defect (arrow) in contrast-enhanced ultrasound (CEUS). (b) A 43-year-old female with invasive ductal carcinoma revealing surrounding vessels (arrows) in CEUS.

The aim of this study was to compare the effectiveness of transducers with different frequencies in detecting local blood perfusion defects and surrounding vessels in the same breast lesions of the same patients. This study will assess the influence of different transducers on the detection outcomes of breast CEUS and try to find a way to improve the diagnostic efficacy of breast CEUS.

METHODS AND MATERIALS

Patients

Approval was obtained from the Ethics Committee of Qilu Hospital for this study. Informed consent was obtained from all individual participants included in the study. From March 2014 to January 2015, a total of 51 patients (age range, 26–70 years; mean $\pm$ standard deviation, 47.1 ± 8.7 years) went through CEUS of the breast. All patients were prospectively selected on the basis of suspicion of breast lesions classified as breast imaging reporting and data system 3–5, according to the breast imaging reporting and data system of the American College of Radiology, on conventional ultrasound or mammography. Exclusion criteria: patients with contraindications to the contrast

medium, such as a history of cardiac failure, respiratory disorders and hypersensitivity. Pregnant or nursing females were also excluded. When a patient had >1 lesion in the same breast, only the largest one or most suspicious one on conventional ultrasound was evaluated. Thus, 51 lesions (diameter range, 0.6–3.7 cm; mean $\pm$ standard deviation, 1.95 ± 0.77 cm) were included.

Image analysis

A Philips iU22 Color Ultrasound system (Philips, Seattle, WA) with Philips C5-1 and L12-5 probes was used in this study. Previous studies have proven that these two transducers are effective in the CEUS of the liver and breast, respectively.^{11,12} Images were collected with a non-linear imaging technique (power modulation) at a low mechanical index (mechanical index = 0.06) to avoid bubble destruction. SonoVue (Bracco) was reconstituted by the addition of 5-ml sterile normal saline and 25 mg of lyophilized powder. Before contrast imaging, we selected the plane with the maximum tumour diameter based on the conventional ultrasound for CEUS. All patients went through CEUS twice: once by probe C5-1 (low-frequency

Table 1. Comparison of probe C5-1 and probe L12-5 in evaluating malignant breast lesions

Probe	Blood perfusion defects	Surrounding vessels
C5-1	23 (60.5%)	26 (68.4%)
L12-5	12 (31.6%)	12 (31.6%)

Figure 2. Time-intensity curve analysis of contrast-enhanced ultrasound (CEUS) for a 42-year-old female with invasive carcinoma. (a) At the peak of enhancement of CEUS applied by probe C5-1, hyperenhancement and a clear local blood perfusion defect could be seen inside the breast lesion (arrow). (b) At the peak of enhancement of CEUS applied by probe L12-5, only hypoenhancement could be seen in the same lesion.

convex array transducer) and once by probe L12-5 (high-frequency linear array transducer). Each patient received a bolus of 2.4-ml SonoVue followed by a flush with 5-ml saline solution through a 21-G catheter *via* the antecubital vein before every examination. There was an interval of 10 min between the two examinations in every patient.⁹ To eradicate contrast bubbles within the lesion, high-mechanical index (MI) waves were used during this interval. Every CEUS process was recorded for 180 s until no apparent contrast agent could be observed. All CEUS records were evaluated by two sonographers with more than 3 years' experience in CEUS. These two transducers were compared in detecting local blood perfusion defects (a local area within the lesions which shows no

apparent enhancement throughout CEUS) (Figure 1a) and surrounding vessels (the presence of surrounding or penetrating vessels) (Figure 1b). McNemar's test was conducted by SPSS® v. 20.0 software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) for statistical analysis.

RESULTS

The diagnoses for all 51 lesions were confirmed by histopathological examination, with specimens obtained by surgical resections or biopsies. The pathological analysis revealed 38 malignant breast lesions (32 invasive ductal carcinoma, 4 ductal carcinoma *in situ*, 1 invasive micropapillary carcinoma and 1 mucinous carcinoma) and 13 benign breast lesions

Figure 3. Ultrasound images for a 51-year-old female with invasive carcinoma. (a) Colour Doppler ultrasound revealing blood flow inside the breast lesions. (b) Contrast-enhanced ultrasound (CEUS) applied by probe C5-1 revealing a penetrating vessel through the lesion, which coincided with the blood flow seen in colour Doppler imaging (arrow). (c) CEUS applied by probe L12-5 showing no signs of penetrating vessels in the same lesion.

(7 fibroadenoma, 2 adenosis, 2 intraductal papilloma and 2 benign phyllodes tumour).

Local blood perfusion defect was observed in only one benign lesion and the pathological result of this lesion is benign phyllodes tumour. No surrounding vessels were observed in all 13 benign lesions. When evaluating the benign lesions, there was no obvious difference between the low-frequency transducer and the high-frequency transducer. On the contrary, they showed a significant difference when evaluating malignant lesions (Table 1). Probe C5-1 was more sensitive in detecting blood perfusion defects (p -value = 0.003) and surrounding vessels (p -value = 0.000) than probe L12-5.

DISCUSSION

In accordance with previous research, our study showed that both local blood perfusion defects and surrounding vessels are important characteristics in the differential diagnosis of breast lesions. The presence of local blood perfusion defects was reported to be the most accurate enhancement criterion for higher histological grade, negative oestrogen receptor expression and positive c-erb-B2 expression. The appearance of surrounding vessels was reported to be associated with lymph node status.¹³ Thus, effective detection of these two characteristics could improve the diagnostic efficacy of CEUS in breast lesions and increase the accuracy of this procedure in predicting the biological behaviour of breast cancers non-invasively.

Among malignant lesions, CEUS conducted by probe C5-1 presented 23 (60.5%) lesions with local blood perfusion defects and 26 (68.4%) lesions with surrounding vessels, while probe L12-5 showed only 12 (31.6%) lesions with local blood

perfusion defects and 12 (31.6%) lesions with surrounding vessels, respectively. Usage of the low-frequency transducer helped increase the incidence of detecting local blood perfusion defects and surrounding vessels in malignant lesions (Figures 2 and 3). It implied that low-frequency transducers might be more suitable for SonoVue in CEUS. However, as a superficial organ, the breast should be examined by a high-frequency transducer in conventional ultrasound examination. Here in lies the conflict between a suitable transducer for CEUS and a suitable transducer for conventional ultrasound examination. Ignorance of either would definitely decrease the diagnostic effectiveness of breast CEUS.

In conclusion, the results reported in this study imply that the detection effectiveness of breast CEUS might be influenced by the low-resonance-frequency contrast agent in an examination taken by a high-frequency transducer. This could decrease the diagnostic value of breast CEUS. The invention of new contrast agents with high corresponding resonance frequency might greatly improve the clinical value of breast CEUS and promote its clinical application.

There were some limitations in our present study. First, this pilot study enrolled only 51 patients, and no difference in the detection of benign lesions was shown. Further studies with more patients are mandatory to verify the results presented in this study. Second, the order of the two transducers used to detect the same lesion might have caused bias in the image evaluation. However, we minimized the bias by giving a 10-min interval and by not evaluating the images until both examinations were completed. In addition, we did not investigate any quantitative CEUS characteristics owing to the relatively small number of cases. Our preliminary results thus have to be verified by future studies.

REFERENCES

1. Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver—update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol* 2013; **39**: 187–210. doi: <http://dx.doi.org/10.1016/j.ultrasmedbio.2012.09.002>
2. Piscaglia F, Nolsøe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med* 2012; **33**: 33–59. doi: <http://dx.doi.org/10.1055/s-0031-1281676>
3. Westwood M, Joore M, Grutters J, Redekop K, Armstrong N, Lee K, et al. Contrast-enhanced ultrasound using SonoVue® (sulphur hexafluoride microbubbles) compared with contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging for the characterisation of focal liver lesions and detection of liver metastases: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2013; **17**: 1–243.
4. Pei XQ, Liu LZ, Xiong YH, Zou RH, Chen MS, Li AH, et al. Quantitative analysis of contrast-enhanced ultrasonography: differentiating focal nodular hyperplasia from hepatocellular carcinoma. *Br J Radiol* 2013; **86**: 20120536. doi: <http://dx.doi.org/10.1259/bjr.20120536>
5. Du J, Wang L, Wan CF, Hua J, Fang H, Chen J, et al. Differentiating benign from malignant solid breast lesions: combined utility of conventional ultrasound and contrast-enhanced ultrasound in comparison with magnetic resonance imaging. *Eur J Radiol* 2012; **81**: 3890–9. doi: <http://dx.doi.org/10.1016/j.ejrad.2012.09.004>
6. Wan C, Du J, Fang H, Li F, Wang L. Evaluation of breast lesions by contrast enhanced ultrasound: qualitative and quantitative analysis. *Eur J Radiol* 2012; **81**: e444–50. doi: <http://dx.doi.org/10.1016/j.ejrad.2011.03.094>
7. Cao XL, Bao W, Zhu SG, Wang LH, Sun MH, Wang L, et al. Contrast-enhanced ultrasound characteristics of breast cancer: correlation with prognostic factors. *Ultrasound Med Biol* 2014; **40**: 11–17. doi: <http://dx.doi.org/10.1016/j.ultrasmedbio.2013.08.014>
8. Gorce JM, Arditi M, Schneider M. Influence of bubble size distribution on the echogenicity of ultrasound contrast agents: a study of SonoVue. *Invest Radiol* 2000; **35**: 661–71.

- doi: <http://dx.doi.org/10.1097/00004424-200011000-00003>
9. Saracco A, Szabó BK, Aspelin P, Leifland K, Tánzos E, Wilczek B, et al. Contrast-enhanced ultrasound using real-time contrast harmonic imaging in invasive breast cancer: comparison of enhancement dynamics with three different doses of contrast agent. *Acta Radiol* 2015; **56**: 34–41. doi: <http://dx.doi.org/10.1177/0284185114520860>
10. Szabó BK, Saracco A, Tánzos E, Aspelin P, Leifland K, Wilczek B, et al. Correlation of contrast-enhanced ultrasound kinetics with prognostic factors in invasive breast cancer. *Eur Radiol* 2013; **23**: 3228–36. doi: <http://dx.doi.org/10.1007/s00330-013-2960-5>
11. Orlacchio A, Bolacchi F, Petrella MC, Pastorelli D, Bazzocchi G, Angelico M, et al. Liver contrast enhanced ultrasound perfusion imaging in the evaluation of chronic hepatitis C fibrosis: preliminary results. *Ultrasound Med Biol* 2011; **37**: 1–6. doi: <http://dx.doi.org/10.1016/j.ultrasmedbio.2010.10.012>
12. Wenhua D, Lijia L, Hui W, Wei Y, Li T. The clinical significance of real-time contrast-enhanced ultrasonography in the differential diagnosis of breast tumor. *Cell Biochem Biophys* 2012; **63**: 117–20. doi: <http://dx.doi.org/10.1007/s12013-012-9346-1>
13. Wan CF, Du J, Fang H, Li FH, Zhu JS, Liu Q. Enhancement patterns and parameters of breast cancers at contrast-enhanced US: correlation with prognostic factors. *Radiology* 2012; **262**: 450–9. doi: <http://dx.doi.org/10.1148/radiol.11110789>