Contrast-Enhanced Tissue Harmonic Imaging versus Phase Inversion Harmonic Sonographic Imaging for the Delineation of Hepatocellular Carcinomas

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Key Words

Contrast harmonic imaging · Contrast tissue harmonic imaging with low mechanical index · Hepatocellular carcinoma · Sonazoid

Abstract

Objective: To compare contrast tissue harmonic imaging (THI) with low mechanical index (MI) and conventional contrast harmonic imaging (CHI) with respect to lesion visibility of hepatocellular carcinoma (HCC). **Methods:** One hundred and twenty-five patients (84 men and 41 women, age range 39–94 years, mean age 74 years) with 100 naïve HCCs and 30 lesions after radiofrequency ablation (RFA) for HCC were evaluated. One hundred and four patients had liver cirrhosis of Child-Pugh class A, and the remaining 21 had Child-Pugh class B cirrhosis. The lesion conspicuity and intratumoral echogenicity during the postvascular phase were compared using conventional CHI and contrast THI with low MI. **Results:** The MI values ranged from 0.20 to 0.30 on convention-

al CHI and from 0.30 to 0.35 on contrast THI. Regarding HCC lesion conspicuity, contrast THI with low MI was clearer in 79 lesions (60.8%), equal in 34 lesions (26.2%), and less clear in 17 lesions (13.1%) when compared with conventional CHI. The lesion conspicuity with contrast THI was significantly better than that with conventional CHI ($p < 0.01$). All of the postablative lesions were well delineated in patients who received RFA. **Conclusion:** Low-MI contrast THI was superior to conventional CHI with respect to lesion visibility of HCCs and might offer good imaging for the guiding of RFA.

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Introduction

Contrast harmonic sonographic imaging can depict tumor vascularity sensitively and accurately and is able to characterize liver tumors, recognize hepatocellular carcinoma (HCC) dedifferentiation, evaluate treatment efficacy, and guide ablation therapy for unresectable HCC

[1–13]. Several contrast harmonic software applications have been developed for contrast-enhanced ultrasound (CEUS) examination, although the most promising techniques are phase inversion and amplitude modulation [14, 15]. Harmonic imaging techniques, which utilize the nonlinear properties of tissue and contrast agent, can partially reduce some artifacts. Contrast harmonic imaging (CHI) exploits the nonlinear oscillations of microbubbles in contrast agents that produce harmonic overtones of the original sound wave [16, 17]. However, in patients with liver cirrhosis, it is often difficult to identify hepatic lesions on CEUS [18]. This could be due to a decrease in Kupffer cells and/or their function in patients with cirrhosis and tissue background suppression.

Tissue harmonic imaging (THI) is a form of native harmonic imaging that provides a better signal-to-noise ratio and reduced side lobe artifacts, resulting in better performance in scanning obese patients and patients with poor acoustic windows [19–22]. The contrast-to-tissue ratio in harmonic imaging is generally limited by the tissue background signal comprising both the leakage harmonic signal and the tissue harmonic signal. The technique of low-mechanical index (MI) THI using contrast media can offer a better contrast-to-tissue ratio at the cost of blood flow signals from ultrasound contrast agents. Therefore, contrast THI with low MI could offer an overlay view of conventional THI and contrast imaging. Contrast THI with low MI might be good for detail resolution, image quality, focal abnormality margin sharpness, and penetration for hepatic imaging.

The purpose of this study was to conduct a retrospective evaluation of contrast THI with low MI for imaging of cirrhotic liver tissue and HCCs compared with conventional CHI with respect to lesion visibility.

Subjects and Methods

Approval for this retrospective study was obtained from the local ethical review board.

Subjects

Between April 2013 and October 2014, 125 patients with 130 HCCs were enrolled in our study (table 1). A specific tumor diagnosis was made after CEUS and compared with the correct, final diagnosis based on additional imaging techniques or histology. The patient population included 84 men and 41 women (age range 39–94 years, mean $\pm$ SD 74 ± 9.1 years). One hundred and four patients had liver cirrhosis of Child-Pugh class A, and the remaining 21 had Child-Pugh class B cirrhosis. One hundred HCCs were treatment-naïve nodules, and the remaining 30 lesions had received prior therapies 1 day after radiofrequency ablation (RFA) for HCCs.

Table 1. Baseline clinical characteristics of the patients

Number of patients	125
Number of tumors evaluated	130
Sex	
Male	84
Female	41
Age, years	
Mean $\pm$ SD	74 ± 9.1
Range	39–94
Etiology	
HBV	10
HCV	104
NonBNonC	11
Child-Pugh class	
A	104
B	21
C	0
Tumor location	
Left lateral	28
Left medial	17
Right medial	37
Right lateral	45
Segment 1	3
Tumor size, cm	
Mean $\pm$ SD	1.6 ± 1.1
Range	0.5–6.0
Tumor depth, cm	
Mean $\pm$ SD	7.3 ± 2.6
Range	3–14

HBV = Hepatitis B virus; HCV = hepatitis C virus.

Ultrasound Equipment and Examination

All examinations were performed using the same ultrasound unit (LOGIQ E9, GE Healthcare, Chalfont St. Giles, UK) with a 4.0-MHz convex ultrasound probe (C1–6) or a 2- to 8-MHz linear probe (9L). The convex probe was usually used to obtain images, while the linear probe was used to assess nodules on the liver surface. To provide a baseline reference for the examination, a conventional gray-scale sonography was performed first to assess the localization, size, and echogenicity of the lesion in comparison with the surrounding liver tissue.

CHI was performed with the phase inversion method using a convex probe or with the amplitude modulation method using a linear probe at a low MI, automatically defined by the software, and the focus was placed deeper than the nodule plane to avoid rapid destruction of the microbubbles. After the administration of Sonazoid (Daiichi-Sankyo, Tokyo, Japan), the hepatic arteries, the portal veins, and background liver parenchyma were gradually enhanced (vascular phase image). Approximately 10 min after the injection, the liver was scanned again to observe the postvascular image (Kupffer image). After the examination of CHI during the postvascular phase, the contrast-imaging mode was manually changed to conventional THI at a low MI (<0.35).

The lesion conspicuity and intratumoral echogenicity during the postvascular phase were compared with conventional CHI and con-

Fig. 1. Small HCC in segment 8 of the liver in a 91-year-old man. **a** B-mode ultrasound showed a small isoechoic nodule with an indistinct border (circle). **b** Conventional CHI depicted a defect image of the lesion during the postvascular phase. **c** On contrast THI with low MI, the border of the defect image was more sharply demonstrated.

Fig. 2. Post-RFA HCC lesion in segment 2 of the liver in an 86-year-old woman. **a** B-mode ultrasound showed a hypoechoic lesion with an indistinct border (circle). **b** Conventional CHI displayed a defect image of the lesion during the postvascular phase. **c** On contrast THI, the border of the defect image was more sharply demonstrated.

trast THI with low MI. However, the detection of intratumoral vascularity on contrast THI was not assessed in this study. The lesion conspicuities using CHI and contrast THI were evaluated by subjective visual review in terms of lesion border definition, lesion contrast, etc. The lesion echogenicity was divided into hypoechoic, isoechoic, or hyperechoic regions with respect to the background liver.

Contrast Agent

Sonazoid consists of perfluorocarbon-containing microbubbles stabilized by a phospholipid monolayer. The bubble diameter range is approximately 2–3 μm , and the concentration is 10^6 microbubbles per milliliter. This contrast agent was reconstituted with 2 ml sterile water for injection. The anticipated clinical dose for imaging of liver lesions is 0.010 ml encapsulated gas per kilogram of body weight. Each injection of contrast agent was followed immediately by a saline flush (10 ml). In patients with multiple

liver lesions, each lesion was analyzed separately with one bolus injection of contrast medium per lesion.

Statistical Analysis

Data were expressed as means $\pm$ standard deviations. Differences were compared with the χ^2 test and unpaired Student's *t* test. A *p* value <0.05 was considered to be significant.

Results

On baseline ultrasound, 45 (34.6%) of the 130 observed nodules were located in the left lobes of the livers, 82 (63.1%) were in the right lobes, and 3 (2.3%) were in

Table 2. Echo signals in lesions compared with B-mode, CHI, and contrast THI (n = 130)

B-mode		CHI		Contrast THI	
High	49	high	2	high	2
		iso	3	iso	4
		low	44	low	43
Iso	5	high	0	high	0
		iso	0	iso	1
		low	5	low	4
Low	76	high	0	high	0
		iso	3	iso	5
		low	73	low	71

Table 3. Characteristics of ultrasound technologies: CHI vs. contrast THI

	CHI	Contrast THI
MI	0.20–0.30	0.30–0.35
Spatial resolution	○	◎
Frame rate	12–16	15–25
Deep penetration	△	◎
Spatial compound	×	◎
Suppression of tissue background signal	◎	○

◎ = Excellent; ○ = good; △ = fair; × = poor.

segment 1 (table 1). The maximal diameter of the tumors ranged from 0.5 to 6.0 cm (1.6 ± 1.1 cm) on ultrasound. The distance from the skin to the deepest edge of the tumor lesions ranged from 2.0 to 14 cm (6.6 ± 3.1 cm). The MI values ranged from 0.20 to 0.30 on conventional CHI and from 0.30 to 0.35 on contrast THI.

Regarding HCC lesion conspicuity in patients with liver cirrhosis, contrast THI with low MI was clearer in 79 lesions (60.8%), equal in 34 lesions (26.2%), and less clear in 17 lesions (13.1%) when compared with conventional CHI (fig. 1). The lesion conspicuity with contrast THI was significantly better than that with conventional CHI ($p < 0.01$). In patients who had received RFA, all of the postablative lesions were well delineated (fig. 2). The depths of the lesions (the distance from the surface of the skin to the far edge of the lesion) ranged from 4 to 14 cm (7.6 ± 3.1 cm) in the clear conspicuity with contrast THI

group and from 4 to 10 cm (5.4 ± 2.9 cm) in the clear conspicuity with conventional CHI group. There was a significant difference in the depths of lesions between these two groups ($p = 0.03$).

The numbers of lesions that showed hyperechogenicity, isoechogenicity, and hypoechogenicity on B-mode ultrasound were 49 (37.7%), 5 (3.8%), and 76 (58.5%), respectively. On the whole, contrast THI and conventional CHI depicted hypoechogenicity better during the post-vascular phase [90.8% (118/130) vs. 93.8% (122/130), $p = 0.49$] (table 2).

Discussion

Our study investigated whether low-MI contrast THI can obtain clear images of HCC in patients with liver cirrhosis. To the best of our knowledge, this is the first report using contrast THI with low MI for HCC. By controlling the ultrasound power, the destruction of the bubbles could be easily controlled. Our results showed that low-MI contrast THI was superior to conventional CHI in delineating the lesion borders.

Some key factors could be considered in this improvement of lesion conspicuity on low-MI contrast THI (table 3). The first is the limitation of canceling the background signals. Contrast THI demonstrated not only harmonic signals from microbubbles, but also from the fibrous capsule of HCC. The second factor is deeper penetration. Contrast THI could offer deeper ultrasound penetration than conventional CHI, and thus a wide viewing image could be obtained [19, 23–25]. The third is the higher frame rate of THI needed to create a smooth moving image compared with CHI. The fourth factor is the special compound imaging. THI has a special compound imaging mode that uses electronic beam steering of a transducer array to rapidly acquire several overlapping scans of an object from different view angles. Real-time spatial compound imaging can provide improved contrast resolution and tissue differentiation by reducing speckle, clutter, and other acoustic artifacts [26, 27].

Now that we understand the differences between conventional CHI and contrast THI, we can select the most appropriate imaging application for different purposes. Low-MI contrast THI was able to clearly depict the lesion borders in some HCC patients. Thus, contrast THI has the potential to provide better sonographic images for the guidance of RFA because of easy targeting of HCC nodules. When the signals of vascularity should be focused upon for the differential diagnosis of liver tumors, con-

ventional CHI may be more useful. Even though vascular images were not evaluated with contrast THI in this study, the blood flow images could be created by enhancing the signals of microbubble resonance while canceling background echo signals effectively. In THI with contrast agents, intratumoral intensity might be influenced by background intratumoral echo signals.

The principal limitation of this study was its retrospective design. The second was that this study could suffer from selection bias and/or information bias because the HCC patients enrolled received CEUS examinations according to tumor size and/or number. Another limitation is the preliminary nature of this study with a relatively

small number of patients. Further prospective studies of this technique with larger numbers of patients are warranted.

In conclusion, low-MI contrast THI was superior to conventional CHI in the delineation of liver lesions and might have the potential to provide better sonographic images for RFA guidance and early response assessment of RFA.

Disclosure Statement

The authors have no conflict of interest to declare.

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