Assessment of Hepatocellular Carcinoma Vascularity: Comparison of Contrast-enhanced Coded Harmonic Ultrasound with Harmonic Power Doppler Ultrasound

Jae-Young Lee, Byung-Ihn Choi, Ah-Young Kim, Joon-Koo Han, Shang-Hun Shin and Chang-Min Park

Background: The aim of this study was to evaluate contrast-enhanced coded harmonic ultrasound (CHUS) in the depiction of the vascularity of hypervascular hepatocellular carcinomas (HCCs) by comparing it with that of contrast-enhanced harmonic power Doppler ultrasound (HPDUS).

Materials and Methods: Contrast-enhanced CHUS was prospectively performed in 17 consecutively collected hypervascular HCCs (mean diameter, 3.4 cm; range, 1.8–7.8 cm) using the Coded Harmonic Angio mode of a LOGIQ 700 Expert unit and a 2 to 4 MHz curved linear-array probe. This was conducted using a microbubble contrast agent (Levovist®) and interval-delay scanning (scan interval, 20–30 s; scanning time, 2–5 s). All patients also underwent contrast-enhanced HPDUS, and the results were compared in terms of the depiction and degree of enhancement of tumor vascularity (feeding vessels, intratumoral macrovessels, intratumoral microvessels, and tumor staining), and the presence of artifacts.

Results: There was no significant difference between CHUS and HPDUS in depiction of tumor vascularity in terms of feeding vessels, intratumoral macrovessels and intratumoral microvessels. CHUS, however, was superior to HPDUS in terms of tumor staining ($p = 0.008$). The degree of tumor vascularity enhancement was superior with CHUS in depicting tumor staining ($p = 0.001$), but HPDUS was better in depicting intratumoral macrovessels ($p = 0.039$). CHUS was artifact-free, while several artifacts were seen in all HCCs examined with HPDUS.

Conclusions: Our results suggest that CHUS is capable of depicting tumor vascularity of hypervascular HCCs and is superior to HPDUS. Contrast-enhanced CHUS may be useful, therefore, in evaluating tumor vascularity of HCCs.

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KEY WORDS: • hepatocellular carcinoma • contrast-enhanced ultrasound
**INTRODUCTION**

Hepatocellular carcinoma (HCC) is typically a very hypervascular tumor. Demonstration of vascularity is necessary for the diagnosis of HCC, choice of treatment method, and the assessment of therapeutic response after non-surgical treatment, such as chemotherapeutic embolization, percutaneous ethanol injection therapy, and radiofrequency (RF) ablation.

The value of conventional Doppler ultrasound (US) in demonstrating the vascularity of HCC has been described by many investigators [1–6]. Since microbubble contrast agents for US have become available, many researchers have reported the usefulness of contrast-enhanced Doppler US in demonstrating tumor vascularity of hepatic tumors [7–16]. Kim et al reported that contrast-enhanced power Doppler US was superior to unenhanced power Doppler US in the demonstration and characterization of tumor vascularity in HCC [8]. Furthermore, the high diagnostic agreement of contrast-enhanced power Doppler US with contrast-enhanced computed tomography (CT) suggested it as an alternative to immediate follow-up CT for the evaluation of the therapeutic effect after treatment of HCCs with RF ablation [17]. However, contrast-enhanced power Doppler US is highly susceptible to tissue motion artifact, which limits the use of this technique in patients with hepatic masses near the heart or the great vessels [8]. By combining it with harmonic technique, contrast-enhanced power Doppler US has been shown to be more effective in evaluating tumor vascularity of HCCs because harmonic power Doppler US (HPDUS) generates fewer power Doppler artifacts [14]. Nevertheless, this limitation was thought to have been overcome after the advent of the gray-scale harmonic US technique. According to some early reports of gray-scale US, contrast-enhanced gray-scale harmonic US imaging appeared superior to unenhanced conventional Doppler US for the characterization of hepatic tumors [13]. Moreover, tumor vascularity of HCCs was successfully demonstrated by using contrast-enhanced pulse-inversion harmonic US [16].

Recently, coded harmonic US (CHUS) has been introduced as a new real-time gray-scale second harmonic US imaging technique, and the system is equipped with the recently developed coded excitation mode (Coded Harmonic Angio, GE Medical Systems, Milwaukee, WI, USA). In a recent study of CHUS, it was suggested that contrast-enhanced CHUS could depict tumor vascularity and tumor parenchymal flow with increased sensitivity and specificity in evaluating post-treatment response of HCCs treated with chemotherapeutic embolization, even when compared with dynamic contrast-enhanced CT [18]. It was also suggested that contrast-enhanced CHUS was comparable to magnetic resonance imaging in its ability to show peripheral nodular enhancement with centripetal progression, even in small hemangiomas [19]. However, to our knowledge, there has been no report comparing contrast-enhanced CHUS with contrast-enhanced Doppler US.

This study was carried out, therefore, to determine the ability of contrast-enhanced CHUS to depict vascularity in HCCs by comparing it with that of contrast-enhanced HPDUS.

**MATERIALS AND METHODS**

**Subjects**

From June to July 2000, 17 patients with clinically or histopathologically diagnosed hypervascular HCC were evaluated with contrast-enhanced CHUS. All patients gave fully informed consent for the study, which had been approved by our institutional review board.

There were 13 men and four women (mean age, 57 years; range, 39–81 years). Six patients had histologic confirmation of HCC: one from a percutaneous biopsy and five from surgery. A clinical diagnosis had been made in the remaining 11 patients from the results of hepatic angiography or CT and an α-fetoprotein level > 500 ng/mL. Tumor diameter on US was as follows: less than 3 cm ($n = 9$), 3 to 5 cm ($n = 5$), and more than 5 cm ($n = 3$). The mean diameter of the 17 HCCs was 3.4 cm (range, 1.8–7.8 cm).

**Imaging methods**

The contrast agent used was SH U 508 A (Levovist®; Schering, Berlin, Germany); it is a suspension of monosaccharide microparticles (galactose) in sterile water. The agent was prepared for injection by shaking it with 11 mL of water for 5 to 10 seconds. After standing for 2 minutes for equilibration, 6.5 mL of the suspension (concentration 300 mg/mL) was injected manually through a 20 to 22 gauge cannula (Cath-S; Boin Medica, Seoul, South Korea) placed in an antecubital vein. This was followed by...
3 to 5 mL of physiologic saline to flush the cannula at the same injection rate. Bolus injection techniques were used, and injections given at a rate of approximately 0.5 mL/second for both CHUS and HPDUS.

US was performed by one radiologist using a LOGIQ 700 Expert unit (GE Medical Systems) and a 2 to 4 MHz curved linear-array probe. The acoustic power of CHUS was set at the default (maximum) setting. When performing HPDUS, the pulse repetition frequency was set at a constant 1,700 Hz in all patients. The color gain was manipulated until color noise first became apparent in the region of interest of the image background. The resultant power Doppler US gains ranged from 51% to 61% for HPDUS. The color-write priority was set at the maximum.

For CHUS, we chose a scanning plane that included the tumor before injection of the contrast agent. Sector width was manipulated to as narrow as possible to minimize the disruption of microbubbles out of the region of interest. With these predetermined settings, we obtained the first series of CHUS images 20 to 30 seconds after the first bolus injection of contrast agent. We then obtained each series of CHUS images by interval-delay scanning at intervals of 10 to 20 seconds until contrast agent signals had completely disappeared from within the tumor. We also waited until the contrast agent signals completely disappeared from within the liver. Serial contrast-enhanced HPDUS was then performed using interval-delay scanning at intervals of 10 to 20 seconds, beginning from 20 to 30 seconds after the bolus injection of contrast agent. The scanning time during interval-delay scanning was 2 to 5 seconds for both CHUS and HPDUS. All images obtained by both techniques were recorded on videotape and stored in the hardware of the imaging unit. Reviewing cine loop images, one or two static images depicting tumor vascularity were stored in the hardware between each scanning time.

Two-phase spiral CT examinations were performed using various spiral CT scanners to obtain a diagnosis of hypervascular HCC. Each patient received 120 mL of non-ionic contrast material – iopromide (Ultravist 370; Schering) – intravenously at a rate of 3 mL/second. Hepatic arterial phase and portal venous phase scans were obtained 30 and 65 seconds, respectively, after the first injection of contrast material.

**Analysis**

To enable comparison of CHUS and HPDUS in terms of tumor vascularity depiction, vascularity was categorized into four types: feeding vessel, intratumoral macrovessel, intratumoral microvessel, and tumor staining (Fig. 1). Feeding vessels were defined as peritumoral vessels that supplied a tumor. Intratumoral macrovessels were defined as intratumoral vessels that were the first or second order branch of a feeding vessel, and vessels that were smaller than intratumoral macrovessels were classified as intratumoral microvessels. Tumor staining was defined as diffuse contrast enhancement without definable vascular structure. Intratumoral microvessels were subdivided into branching and linear types according to the presence or absence of a branching pattern of macrovascular signals. Intratumoral microvessels were subdivided into branching, reticular, and spotty types according to their predominant feature. Tumor staining was subdivided into diffuse, central, peripheral, and multifocal types according to what was predominant. The time when each type of tumor vascularity was optimally depicted (optimal depiction time) was recorded.

To compare the degree of enhancement of tumor vascularity, the CHUS and HPDUS images that best depicted each type of tumor vascularity were selected.

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**Fig. 1.** Types of tumor vascularity. A = feeding vessel; B = intratumoral macrovessel (branching type); C = intratumoral macrovessel (linear type); D = intratumoral microvessel (branching type); E = intratumoral microvessel (reticular type); F = intratumoral microvessel (spotty type); G = tumor staining.
and compared in terms of the number and extent of each type. In addition, the frequency of artifact occurrence in both US techniques was compared. US signals that were observed inconsistently outside the vascular structure were regarded as artifacts.

Image analysis was conducted using the static images obtained on CHUS and HPDUS, and a consensus arrived at by three abdominal radiologists. Statistical comparison was performed using the McNemar Chi-squared test and Wilcoxon signed rank test. A p value of less than 0.05 indicated a statistically significant difference.

RESULTS

Table 1 shows a comparison of tumor vascularity depiction between CHUS and HPDUS. Feeding vessels were demonstrated in 14 of 17 HCCs (82%) with both CHUS and HPDUS. Intratumoral macrovessels were depicted in 15 of 17 HCCs (88%) with both CHUS and HPDUS. However, the branching type of macrovessel was more frequently depicted with CHUS than with HPDUS, although this was not statistically significant (p = 0.289). Intratumoral microvessels were demonstrated in nine of 17 HCCs (53%) with CHUS and 10 of 17 HCCs (59%) with HPDUS (p = 1.000). CHUS showed microvessels of either the branching or the reticular type in eight HCCs, while HPDUS revealed the spotty type in all 10 HCCs (p < 0.05) (Fig. 2). In tumor staining, CHUS demonstrated various patterns in 12 of 17 HCCs (71%), while HPDUS did so in only four of 17 HCCs (24%) (p < 0.05).

The optimal depiction times for each type of tumor vascularity, using CHUS and HPDUS, are shown in Table 2. Neither CHUS nor HPDUS showed a significant difference in optimal depiction time of tumor vasculature (p > 0.05).

A comparison of the degree of enhancement between CHUS and HPDUS (Table 3) showed that CHUS was superior to HPDUS in depicting tumor staining (p < 0.05), while HPDUS was superior to CHUS in depicting intratumoral macrovessels (p < 0.05).

US artifacts were not seen on any CHUS images. However, two types of artifact signals were seen to a variable degree in all HCCs with HPDUS (Figs. 2–4). The first type of power Doppler artifact appeared to be diffuse (Fig. 2), linear, or spotty (Fig. 3), and resembled tumor staining, macrovessel or microvessel, respectively. In all four HCCs that occurred in the left hepatic lobe, artifacts were detected on HPDUS because of the effects of respiration and heart movement. In the second type of

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<th>Table 1. Comparison of tumor vascularity depiction between coded harmonic US (CHUS) and harmonic power Doppler US (HPDUS) in 17 hepatocellular carcinomas</th>
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<td>Linear</td>
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*McNemar Chi-squared test.
artifact, blooming artifacts began to appear at a range of 90 to 99 seconds post-injection (mean, 92 s) (Fig. 3). Three of four HCCs showing tumor staining with HPDUS showed blooming artifacts around the tumor. These artifacts caused deterioration of tumor conspicuity and vascularity.

**DISCUSSION**

CHUS has been introduced recently as a new grayscale second harmonic US imaging technique employing contrast agents based on digitally encoded ultrasound technology [19]. CHUS uses a special code sequence to tag the fundamental transmit frequency band. When this coded pulse is transmitted into the body, a second harmonic frequency band is generated inside the body; the decoder processes the total received signal to identify the tagged fundamental frequency band and then removes it without affecting the second harmonic frequency band. From these received harmonic signals, any signals from large and slow-moving tissue-clutter components are subtracted by a specialized decoding technique. This filter mechanism makes it possible to effectively

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**Fig. 2.** A 3 cm hepatocellular carcinoma in the right hepatic lobe of a 63-year-old man. (A) Coded harmonic US images. The image obtained before injection of the contrast agent, at 0 seconds, shows a slightly hypoechoic mass. The images obtained at 31 seconds and 50 seconds after injection show feeding vessels (arrowheads) and intratumoral microvessels of branching (arrow) and reticular (open arrow) types. Diffuse tumor staining is seen 93 seconds after injection. (B) Harmonic power Doppler US images. The image obtained at 27 seconds after injection shows feeding vessels (arrowheads) and linear type of intratumoral macrovessels (arrows). A spotty intratumoral microvessel is demonstrated in the image obtained at 63 seconds after injection. Diffuse tumor staining appears in the image obtained at 192 seconds after injection. However, parenchymal staining (open arrow) also appears in the adjacent liver. This can make identification of true tumor staining from diffuse signals in the tumor difficult. Artifacts induced by respiration and heart motion were also observed (not shown).
suppress any stationary tissue-clutter component relative to any moving microbubble or blood echo component among the harmonic signals. The CHUS technique, therefore, has the potential to provide high sensitivity to contrast-agent echo by high contrast resolution, as well as preservation of wideband resolution of harmonic signals.

As expected, our results showed that these advantages enabled CHUS to depict tumor vascularity as well as or even better than HPDUS. In addition, branching and reticular types of intratumoral microvessels were detected only with CHUS, while the spotty type was mostly found with HPDUS. It might be said that CHUS can provide more detailed intratumoral vascular information on HCCs than HPDUS, although verification of this suggestion would require further study.

In this study, we used an easily breakable microbubble contrast agent. Nevertheless, our results indicate that CHUS is potentially useful for detailed evaluation of tumor vascularity. It is expected that this ability of CHUS to assess tumor vascularity will be very useful in determining the presence of residual viable tumor after local treatment for malignant tumor as well as in characterizing hepatic tumors.

With contrast-enhanced power Doppler US, exact evaluation of the intratumoral vasculature is difficult because of a considerable blooming artifact produced during the early phase of contrast agent enhancement [8]. Furthermore, its susceptibility to tissue motion limits the use of this technique in patients who have difficulty in breath-holding and in patients with hepatic masses near the heart or great vessels [8, 20]. Another limitation of power Doppler US is that the size or extent of a vasculature within a lesion can be overestimated [21]. Contrast-enhanced HPDUS has similar limitations, although HPDUS is known to generate less power Doppler or blooming artifacts when compared with conventional power Doppler US [14]. In contrast, use of CHUS overcomes these problematic artifacts, as our results show. CHUS can thus be used with lesions near the

Table 2. Comparison of the optimal depiction times between coded harmonic US (CHUS) and harmonic power Doppler US (HPDUS) in 17 hepatocellular carcinomas

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<th>CHUS (mean, range)</th>
<th>HPDUS (mean, range)</th>
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<tr>
<td>Feeding vessel</td>
<td>43 (20–67)</td>
<td>41 (20–86)</td>
<td>&gt; 0.05</td>
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<tr>
<td>Macro vessel</td>
<td>47 (21–115)</td>
<td>42 (20–86)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Micro vessel</td>
<td>57 (30–118)</td>
<td>62 (21–146)</td>
<td>&gt; 0.05</td>
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<tr>
<td>Tumor staining</td>
<td>59 (21–119)</td>
<td>98 (33–192)</td>
<td>&gt; 0.05</td>
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*Wilcoxon signed rank test.

Table 3. Comparison of the degree of enhancement between coded harmonic US (CHUS) and harmonic power Doppler US (HPDUS) in 17 hepatocellular carcinomas

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<tr>
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<th>CHUS &gt; HPDUS</th>
<th>CHUS = HPDUS</th>
<th>HPDUS &gt; CHUS</th>
<th>p*</th>
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<tbody>
<tr>
<td>Feeding vessel</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>1.000</td>
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<tr>
<td>Macro vessel</td>
<td>1</td>
<td>7</td>
<td>8</td>
<td>0.039</td>
</tr>
<tr>
<td>Micro vessel</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>0.065</td>
</tr>
<tr>
<td>Tumor staining</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>0.001</td>
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*McNemar Chi-squared test. Data are presented as the number of cases.
heart or great vessels. CHUS, however, has the disadvantage that its imaging resolution is considered inferior to conventional gray-scale imaging. This is because CHUS suppresses both the fundamental and harmonic signals from the stationary background tissue. Due to this disadvantage, CHUS sometimes obscures the contour of deep-seated lesions and its use is, thus, limited in these lesions.

This study had several limitations. First, most of the HCCs were not pathologically proven and, therefore, their tumor vascularity could not be pathologically correlated. Second, there was no gold standard of imaging method available to compare tumor vascularity with CHUS and HPDUS. This meant that we could not obtain diagnostic values from CHUS, but only indicate the ability of CHUS to detect each type of tumor vascularity. Third, we did not evaluate whether CHUS could demonstrate serial contrast-enhancement change in HCCs during the hepatic arterial and portal venous phases; this study focused only on the comparison of two techniques for detecting tumor vascularity.

Despite these limitations, our results suggest that CHUS can adequately depict vascularity of hyper-

**Fig. 3.** A 2.7 cm hepatocellular carcinoma in the right hepatic lobe of a 51-year-old woman. (A) Coded harmonic US images. Feeding vessels (arrows) are demonstrated in the image at 35 seconds after injection of contrast agent. A branching type of intratumoral macrovessel (arrow) is well visualized on the image obtained at 39 seconds after injection; reticular type of intratumoral microvessels (open arrows) are also depicted within the tumor. The tumor is diffusely stained on the images obtained at 40 and 64 seconds after injection. (B) Harmonic power Doppler US images. Feeding vessels (arrows) surrounding the tumor were seen 30 seconds after contrast-agent injection. At 32 seconds, spotty signals (arrows) from the diffusely stained tumor are seen. Such signals can cause confusion due to the similarity in appearance to intratumoral spotty microvessel signals. Intratumoral spotty microvessel signals (open arrows) are seen on the images at 70 and 96 seconds after injection of contrast agent. A blooming artifact (black arrow) around the portal vein is noted on the image obtained at 96 seconds.
vascular HCCs, and is superior in this respect to HPDUS. Contrast-enhanced CHUS, therefore, may offer potential in illustrating HCC vascularity.

REFERENCES


Fig. 4. A 4 cm hepatocellular carcinoma in the right hepatic lobe of a 64-year-old man. (A) Coded harmonic US images. The image obtained before injection of the contrast agent, at 0 seconds, shows a slightly hypoechoic, ovoid tumor (arrowheads). Feeding vessels (long arrows) are well depicted with a branching type of intratumoral macrovessel (short arrow) on the images obtained at 29, 30, and 31 seconds after injection of the contrast agent. A reticular type of microvessel (small open arrow) is depicted on the image obtained at 30 seconds after injection. In the left portion of the tumor, diffuse staining (large open arrow) is seen on the image obtained at 31 seconds after injection. (B) Harmonic power Doppler images. A feeding vessel (arrowhead), branching type intratumoral macrovessels (long arrows), and spotty type microvessels (open arrows) are depicted on the images obtained at 29, 35, and 58 seconds after injection. Tumor staining is not shown in the left portion of the tumor. The short arrows indicate the left margin of the tumor.