Pulse Inversion Imaging of Liver with Microbubble Contrast: Improved Characterization of Tumoral Vasculature in Focal Hepatic Lesions

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Introduction
The challenge presented to ultrasound imaging technology by the advent of microbubble contrast agents is to create a method that detects the echoes from bubbles in preference to the echoes from tissue. Recent progress in ultrasonography is represented by the development of harmonic and pulse inversion imaging (Fig. 1, 2). Pulse inversion imaging is a newly developed one, which uses the full bandwidth image of nonlinear echoes from bubbles in real time, thus overcomes that the conflict between the requirement of contrast and resolution in harmonic imaging (1). At higher acoustic pressures, resonant signals at second, and other, harmonic frequencies start to appear. As sound pressures increase further, phenomena related to microbubble destruction or disruption occur. These include the production of transit ultrasonic signals, an effect referred to as stimulated acoustic emission (SAE) (2, 3). SAE can be visualized as intense transit enhancement on color or gray-scale images (Fig.3).

We studied the value of gray-scale SAE using a microbubble contrast agent for improved demonstration and characterization of various focal hepatic lesions.

Fig. 1. Principles of conventional (a) and harmonic (b) imaging. Microbubbles oscillate nonlinearly in the acoustic field, emitting echoes at double the transmitted frequency. Harmonic imaging suppresses echoes detected from solid tissue (Modified according to Burns).

Fig. 2. Principles of pulse inversion imaging. A pulse of sound and inverted pulse are transmitted in the same direction. Linear echoes from tissue will cancel to zero. The microbubble echoes are distorted and the nonlinear components will reinforce each other, and produce a strong harmonic signal (from Ref. 1).

Materials and Methods
Patients
47 Hepatocellular carcinoma (n=42)
42 Metastatic adenocarcinoma (n=20)
13 Hemangioma (n=13)
2 Focal nodular hyperplasia (n=2)

Contrast Agents / Instrumentation
Levovist (SH U 508A; Schering, Germany)
2.5g, 300mg/mL, bolus injection
HDI-5000 scanner (ATL Inc., Bothell, WA)
C5-2 curvilinear array transducer

Techniques
During and immediately after contrast injection, the liver was scanned continuously at low mechanical index (MI) to visualize resolvable vessel. Next, interval delay high MI imaging was performed. Scanning was resumed, producing a characteristic echogenic veil (SAE), which was caused by microbubble destruction.

Analysis
The each images were assessed for vascularity and characteristics of lesional signals in the focal hepatic lesion. The presence or absence of stimulated echo signals in lesional and perilesional area of the tumor, and appearance of tumoral border were analyzed for the characterization of the tumor.

Results
In the 77 patients, enhancement of large vessels of the liver was seen at pulse inversion with low-MI imaging. In all patients, the veil was imaged in parenchymal and/or tumoral lesions at interval delay high MI images.

Hepatocellular Carcinoma
Pulse inversion continuous low-MI imaging showed profuse lesional and perilesional vessels with a long, branching and tortuous architecture. On interval delay scan with high-MI, hepatocellular carcinoma was seen as a SAE defect with lesional or perilesional bright signals in all patients (Fig. 4). At the peak of the veil, the tumor appeared frequently as white ball with irregular border against less echogenic liver.

Fig. 3. SAE effect in the liver of healthy volunteer. (a) Color Doppler US produces a strong, mosaic pattern of color signals of the liver. (b) Gray-scale US shows transit white flash SAE effect of intense parenchymal enhancement (Veil) at interval delayed image.

Fig. 4. SAE effect in the liver of a patient with hepatocellular carcinoma. (a) Color Doppler US shows profuse lesional and perilesional vessels. (b) Gray-scale US shows SAE defect with lesional bright signals of the tumor. (c) B-mode US shows hypoechoic mass with irregular border.
Metastases

On SAE images, hepatic metastases showed less echogenicity than normal liver (SAE defect), whereas the margin of the tumor participated in the veil. The result was that the lesions appeared more well defined than on baseline images in all patients (Fig. 6). Eleven (26%) of 42 metastases were seen on SAE but undetectable on baseline images.

Hemangioma

After injection, no intranodal vessels with sparse marginal vascularity was shown in continuous low-MI imaging. This lead to a reversal of echogenicity of the hemangioma on interval delay image (Fig. 7).

In two patients, progressive increased lesional enhancement were seen on continuous scans (Fig. 8). The SAE appearance of hemangioma may be dependent on intratumoral vascularity.

**Focal Nodular Hyperplasia**

Because focal nodular hyperplasia involves normal liver cells, it would show the same acoustic emission characteristics as normal hepatic tissue while it manifests as a mass (Fig. 9).

**Echogeticity of Hepatic masses on Pulse Inversion Imaging**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Vessels at low-MI image</th>
<th>Interval Delay</th>
<th>Image (SAE)</th>
<th>Border Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Profuse</td>
<td>Irregular</td>
<td>White ball</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>Marginal</td>
<td>Sharp</td>
<td>SAE defect</td>
<td></td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Filling in</td>
<td>Sharp</td>
<td>Reversal echo</td>
<td></td>
</tr>
<tr>
<td>FNH</td>
<td>Profuse</td>
<td>Sharp</td>
<td>Same SAE</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion**

Hepatic harmonic US with microbubble contrast agent can be used to assess both tumor vessel morphology with low-MI continuous imaging and the relative microvascular volume of the tumor with high-MI interval delay imaging. The results of this study are promising and suggest the potential to differentiate hepatic tumors.

**References**