Comparison of Transcranial Brain Tissue Perfusion Images Between Ultraharmonic, Second Harmonic, and Power Harmonic Imaging

Toshiyuki Shiogai, MD; Natsuko Takayasu, MD; Toshiki Mizuno, MD; Masanori Nakagawa, MD; Hiroshi Furuhata, MD, PhD

Background and Purpose—To clarify optimal brain tissue perfusion images visualized by transcranial ultrasound harmonic imaging, we compared gray-scale integrated backscatter (IBS) images of new ultraharmonic imaging (UHI) and conventional second harmonic imaging (SHI) with power harmonic imaging (PHI) (harmonic B-mode with harmonic power Doppler images) in 10 patients with and 4 without a temporal skull.

Methods—Using a SONOS 5500 (Philips), we evaluated transient response images taken after a bolus Levovist injection at a horizontal diencephalic plane via temporal windows. Based on transmitting/receiving frequencies (MHz), 4 imaging procedures using an S3 transducer (SHI2.6 [1.3/2.6], UHI [1.3/3.6], PHI2.6 [1.3/2.6], and PHI3.2 [1.6/3.2]) and 2 imaging procedures using an S4 transducer (SHI3.6 [1.8/3.6] and PHI3.6 [1.8/3.6]) were compared in terms of size and location, peak intensity (PI), contrast area demarcation, and background image quality.

Results—In intact skull cases, gray-scale imaging tended to show larger contrast areas than PHI. A large contrast area was most frequently observed in SHI2.6 images, despite there being more high-PI cases in UHI. No contrast area with unclear background was observed in a few cases. PHI, particularly PHI3.6, demonstrated sharper demarcation and a clearer background than gray-scale imaging.

Conclusions—Transcranial gray-scale SHI using a low receiving frequency of 2.6 MHz is the superior method. PHI identifies contrast area localization better than gray-scale imaging and is particularly suitable for intraoperative and postoperative cases. (Stroke. 2004;35:687-693.)

Key Words: contrast media • perfusion, brain • imaging techniques • ultrasonography, Doppler, color, transcranial

Transcranial ultrasonic imaging using contrast-specific phenomena has been tried clinically in evaluation of brain tissue perfusion.¹⁻³ The usefulness for patients with ischemic stroke⁴⁻⁸ and with cognitive impairments⁹ has been pointed out. The physical properties of microbubbles as echo-contrast agents in an acoustic field depend mainly on acoustic power. At low acoustic emission power, the bubbles act as linear backscatters,¹⁰ and to receive these signals, conventional fundamental imaging such as B-mode images on color velocity (CV) or power Doppler (PD) images have been used. Initial experiments have shown that brain tissue perfusion by the fundamental imaging of B-mode¹¹ and PD¹² with high-frequency transducers was necessary to insonate via a skull defect. However, fundamental imaging using linear backscatter does not sufficiently visualize brain tissue perfusion. With an increase in emission power, microbubbles start to show resonance phenomena and nonlinear stationary scattering where emitted signals have not only the fundamental frequency (same as the transmitting frequency) but also harmonic components (multiples of the transmitting frequency).¹³ When the insonated power level is increased, microbubble destruction results in the production of intense transient nonlinear backscatter, referred to as stimulated acoustic emission (SAE).¹⁰,¹⁴

Using the harmonic or SAE mechanism, visualization of brain tissue perfusion with low-frequency transducers via temporal acoustic windows has been clinically evaluated. Instead of conventional B-mode imaging, gray-scale second harmonic imaging (SHI) using integrated backscatter (IBS),¹,³,⁹ directly integrated radiofrequency signals from brain tissue, or pulse-inversion methods²,⁵ have been used for transcranial harmonic imaging. Fundamental imaging with SAE such as background B-mode with color-coded imaging of CV⁷ or PD¹⁴ and parameter imaging calculated from time-intensity curve, called contrast burst imaging or time variance imaging,² have been introduced.
In echocardiography, SHI combined with PD is the most sensitive technique in terms of contrast-to-tissue ratio (CTR)\(^1\)\(^2\) and microbubble detection at the perfusion level.\(^3\) However, for transcranial application, SHI with PD or power harmonic imaging (PHI) has only been studied experimentally.\(^4\)\(^5\) Clinical studies outside preliminary observations\(^6\) have not been published.

Recently, to increase CTR, new ultraharmonic imaging (UHI) using beyond the second but below the third level of harmonics has been used for contrast echocardiography. UHI produces low precontrast tissue signals, exhibits efficient microbubble destruction with multiple-frame triggering,\(^7\)\(^8\) and optimizes postcontrast myocardial opacification. However, transcranial effectiveness has also yet to be clarified.

Until now, an optimal imaging procedure that considers transmitting and receiving frequencies and the effect of temporal skull has not been fully elucidated for transcranial evaluation of brain tissue perfusion. Therefore, to clarify optimal transcranial images by contrast-enhanced harmonic imaging, we compared the gray-scale IBS images of UHI, SHI, and PHI with different transmitting and receiving frequencies in patients with and without a temporal skull.

Methods

We used a SONOS5500 (Philips Medical Systems) ultrasound system with new S3 and old S4 ultraband transducers that cover frequency ranges from 1.3 to 3.6 and 1.8 to 3.6 MHz, respectively. The transducer was fixed securely on the temporal acoustic window during contrast studies. The investigation depth was 12 cm, and the focus was 6 cm (12 cm in 1 PHI case). The harmonic imaging was performed on the transtemporal axial diencephalic plane (landmarks were the third and anterior horns of lateral ventricles) involving the temporal lobe (TL), basal ganglia (BG), and thalamus (Th) that were confirmed by fundamental B-mode and CV images before and after the contrast studies. Sixty-two transient response images triggered by ECG were acquired at 1 image per 2 cardiac cycles (sampling intervals, 1.7±0.3 seconds) after a bolus 7-mL (300-mg/mL) injection of Levovist (Schering) through an antecubital vein catheter, and the data storing on a magneto-optical disk were verified.

In gray-scale IBS images of UHI and SHI, the mechanical index, system gain, and compression were 1.5 (or 1.6), 75, and 70 (or 75), respectively. In PHI, a harmonic PD image is superimposed on the background harmonic B-mode image with parameters identical to the IBS images. The PD image settings were as follows: color gain, 40%; pulse repetition frequency, 3.9 kHz; and filter, 4. Quantification was performed by T-INT mode and analyzed by acoustic densitometry\(^9\) for IBS images and Quanti-Con (EchoTech Co) for PHI images.

On the basis of transmitting/receiving frequencies (MHz), 6 imaging procedures were compared: the principal study involved 4 imaging procedures using an S3 transducer (IBS images of SHI2.6 [1.3/2.6] and UHI [1.3/3.6], PHI2.6 and PHI3.2 [both B-mode images of 1.6/3.2, PD images 1.3/2.6 and 1.6/3.2]), and the previous pilot study concerned 2 imaging procedures using an S4 transducer (SHI3.6 [1.8/3.6] and PHI3.6 [1.8/3.6]). The 6 imaging techniques were evaluated in terms of maximum size (diameter) and location of contrast area, maximum peak intensity (PI) based on time-intensity curve analysis in the three regions of interest (TL, BG, and Th), sharpness of contrast area demarcation, and background image quality (clarity).

The subjects were fourteen stable patients in rehabilitation wards with open temporal acoustic windows previously confirmed by fundamental CV imaging. The ten patients with an intact temporal skull were compared with four patients who had received temporal craniectomy. The previous pilot study of 2 imaging procedures (SHI3.6 and PHI3.6) was performed on the same day. The following principal study of 4 imaging procedures (SHI2.6, UHI, PHI2.6, and PHI3.2) was performed on the same day 0.5 to 11 months (mean, 3 months) after the pilot study. No differences in patients' neurological conditions and pathologies on imaging studies were confirmed before the principal studies. Patients' demographics are presented in Table 1.

Informed consent was obtained from patients and/or family members before the study. We used Student's \(t\) and \(\chi^2\) tests; statistical significance was set at \(P<0.05\).

Results

Intact Temporal Skull Cases

Size and Location of Contrast Area

A large contrast area (5 to <7 cm in diameter) and wider range of locations involving the TL, BG, and Th were most frequently observed in SHI2.6 images compared with UHI and SHI3.6 images (Table 2). In PHI images, there was a tendency toward smaller contrast areas in PHI3.2 than in PHI2.6 or PHI3.6. Gray-scale imaging tended to have larger \((P<0.01)\) and wider range of location \((P<0.001)\) of contrast areas than PHI.

Contrast Intensity

There were more cases of high PI (>10 dB) in UHI than other images and a tendency toward low PI in PHI3.2 and PHI3.6 \((P<0.05)\).

<table>
<thead>
<tr>
<th>TABLE 1. Patient Demographics</th>
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<tr>
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<tr>
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<tr>
<td>Age, mean (range), y</td>
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<td>Sex, n</td>
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<td>Male</td>
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<tr>
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<td>Primary diagnosis, n</td>
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<tr>
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<tr>
<td>Lacunar</td>
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<tr>
<td>Hemispheric</td>
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<tr>
<td>Moyamoya disease</td>
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<tr>
<td>Cerebral hemorrhage</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Anoxia</td>
</tr>
<tr>
<td>Cerebral contusion</td>
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<tr>
<td>Spinocerebellar degeneration</td>
</tr>
<tr>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Major site of cerebral and/or vascular lesions*</td>
</tr>
<tr>
<td>Right</td>
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<tr>
<td>Left</td>
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<tr>
<td>Diffuse or none</td>
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<tr>
<td>Examined side</td>
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<tr>
<td>Right</td>
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<td>Left</td>
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</tbody>
</table>

*Diagnosed by CT, MRI and angiography, and/or color duplex sonography.
Contrast Area Demarcation and Background Image Clarity

The frequency of sharp demarcation was higher in SHI2.6, UHI, PHI2.6, and PHI3.6 cases than in SHI3.6 and PHI3.2 cases. There was greater difficulty in identifying the anatomical localization of the contrast area caused by unclear background images, particularly in UHI, SHI3.6, and PHI3.2 (Figure 1b, 1c, and 1e). No contrast area associated with extremely unclear background images was observed in SHI2.6 and UHI in 2 cases, SHI3.6 in 3 cases, and PHI3.2 and PHI3.6 in 1 case each, despite small contrast spots in the near field from the transducer being identified in PHI2.6 cases.

Cranietomized Cases

The contrast area of all images in all craniectomized cases but 1 became larger than those in intact skull cases (Table 3). The contrast effects in the near field were more obvious in PHI than in gray-scale imaging (Figure 2). Size and location of contrast areas tended to increase in images using higher receiving frequencies, particularly in PHI3.6 (Figure 2f), but resulted in no significant differences. In all images, high PI (>10 dB) was observed in all but 1 case. Contrast area demarcation was always sharper in PHI and UHI compared with SHI (P<0.01). However, background image was unclear in all UHI and 2 SHI2.6 cases (P=0.06).

### Table 2. Comparison of Harmonic Perfusion Images of Patients With Intact Temporal Skull

<table>
<thead>
<tr>
<th>Images (Transmitting/Receiving Frequencies)</th>
<th>SHI2.6 (1.3/2.6)</th>
<th>UHI (1.3/3.6)</th>
<th>SHI3.6 (1.8/3.6)</th>
<th>PHI2.6 (1.3/2.6)</th>
<th>PHI3.2 (1.6/3.2)</th>
<th>PHI3.6 (1.8/3.6)</th>
<th>P</th>
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</thead>
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<tr>
<td>Maximum diameter, cm</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>5–&lt;7</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3–&lt;5</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>None</td>
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<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>TL/BG/Th</td>
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<td>1</td>
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<tr>
<td>TL/BG</td>
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<td>5</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>TL or BG or Th</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Maximum PI, dB</td>
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<td></td>
<td></td>
<td>&lt;0.05</td>
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<tr>
<td>&gt;10</td>
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<td>6</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<tr>
<td>5–10</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Demarcation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Sharp</td>
<td>6</td>
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<td>3</td>
<td>8</td>
<td>2</td>
<td>7</td>
<td>0.07</td>
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<tr>
<td>Poor</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>7</td>
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<td></td>
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<tr>
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<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Background</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Clear</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Gray-Scale Harmonic Imaging

A clearer distinction between tissue and contrast bubbles, which is expressed by CTR, increases as a function of the harmonic frequency order (second, third, and higher harmonics). Imaging based on higher harmonics shows a higher CTR, which is significantly influenced by precontrast tissue signals, than imaging at a lower or fundamental frequency. UHI rejects tissue signals by receiving signals beyond the second but below the third harmonics. In myocardial contrast echocardiography, UHI produces low precontrast tissue signals and efficient postcontrast myocardial opacification.

In our patients with a temporal skull, transcranial UHI was not always superior to SHI. Although a high PI in UHI was observed more frequently than in SHI, a large contrast area was more frequently identified in SHI2.6 than in UHI. The ultraharmonics scattered from bubbles are usually low-energy components compared with second harmonics. Attenuation of ultrasonic signals by temporal skull depends on both the transmitting and receiving frequencies. Higher-frequency signals are more attenuated than lower-frequency signals. Therefore, ultraharmonic signals of a higher receiving frequency of 3.6 MHz are more attenuated than second harmonic signals of 2.6 MHz. Furthermore, the tissue signal rejection itself in increased...
CTR resulted in a further drawback in UHI, whereby the background image was always unclear in patients both with and without a temporal skull.

In transcranial harmonic gray-scale imaging, aside from the pulse-inversion method,\textsuperscript{2,5} harmonic IBS\textsuperscript{1,3,4,9,18} has been used more frequently than harmonic B-mode.\textsuperscript{6} In terms of background image, harmonic B-mode in PHI tended to identify anatomical localization more easily than harmonic IBS in gray-scale imaging, particularly in skull defect cases (Table 3 and Figure 2). However, myocardial contrast enhancement using open-chest dogs increased equally with either B-mode or IBS imaging.\textsuperscript{22} Further clarifications are necessary to determine superiority.

Figure 1. Comparison of harmonic perfusion imaging via intact temporal skull of a patient whose MRI showed a few lacunar infarctions on corona radiata. Six different images based on transmitting/receiving frequencies were taken before (top) and after (bottom) contrast injection: SHI2.6 (a), UHI (b), SHI3.6 (c), PHI2.6 (d), PHI3.2 (e), and PHI3.6 (f). Background images are clear in a, d, and f, where the anterior horn (AH) of lateral ventricles is visualized. Contrast area demarcation was sharp in all but e.
Gray-Scale Harmonic Imaging and PHI

In echocardiography, SHI with PD (or PHI) is the most sensitive technique.\textsuperscript{13,15} In our intact skull cases, however, the contrast areas of PHI images using Levovist were of a smaller size and lower PI than gray-scale imaging of UHI and SHI. The same superiority of transcranial gray-scale SHI was reported in serial experiments using dogs with 2 different echo-contrast agents, Optizon\textsuperscript{16} and Sonazoid.\textsuperscript{17} This inferiority of PHI is probably due to acoustic pressure attenuation by the skull. PHI requires destruction of bubbles in the microcirculation to generate signals. Bubble destruction requires application of a higher ultrasound power compared with the harmonic response. However, harmonic gray-scale imaging will display bubbles if they have significant harmonic response without destruction.\textsuperscript{16}

The distribution of acoustic pressures in sector scans is inhomogeneous, so microbubbles are barely detectable in the near field. In transcranial harmonic PD, there were no signal increases in the posterior part of the brain.\textsuperscript{16,17} Despite the use of parameter imaging derived from transcranial gray-scale SHI,\textsuperscript{3,8} it was difficult to delineate contrast areas in the anterior and posterior borders of the ultrasound section. However, in our craniectomized cases, the contrast effects in the near field were more obvious in PHI than in gray-scale IBS imaging (Figure 2). Furthermore, there was sharp contrast area demarcation in all cases and clear background in all cases but 1. These results indicate that PHI would be suitable for skull defect cases. However, the relationship between high acoustic pressure with microbubble contrast agents and local microvascular damage should be taken into consideration.\textsuperscript{23}

Contrast-specific SAE signals are detectable by transcranial CV or PD imaging without the use of harmonic technology.\textsuperscript{14} Contrast burst imaging and time variance imaging using the SAE mechanism improved diagnostic sensitivity compared with gray-scale pulse-inversion SHI with transmitting and receiving frequencies of 1.3 and 2.6 MHz.\textsuperscript{2} The contrast signals are display color coded, but the tissue signal is suppressed. Therefore, it is necessary to change from contrast burst imaging image to harmonic B-mode image to decide anatomical localization before contrast infusion and repositioning of the transducer as a result of patient movement.\textsuperscript{2} In addition, parameter images relating to PI were introduced, although the information from the background anatomical localization proved unsatisfactory. To overcome this problem, color-coded parameter imaging derived from gray-scale SHI overlaid on MRI has been introduced.\textsuperscript{3} However, this offline analysis would not be suitable for acute stroke patients. In contrast, conventional or pulse-inversion SHI and background harmonic B-mode of PHI display tissue harmonic images and facilitate permanent anatomic orientation. In PHI additionally, contrast PD images on the background harmonic B-mode image can immediately be switched on and off.

\begin{table}[h]
\centering
\caption{Comparison of Harmonic Perfusion Images of Patients With Temporal Skull Defect} 
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
 & SHI2.6 & UHI & SHI3.6 & PHI2.6 & PHI3.2 & PHI3.6 & \textit{P} \\
(1.3/2.6) & (1.3/3.6) & (1.8/3.6) & (1.3/2.6) & (1.6/3.2) & (1.8/3.6) & & \\
\hline n & 4 & 4 & 2 & 4 & 4 & 3 & \\
\hline
\text{Maximum diameter, cm} & & & & & & & \\
\geq 7 & 2 & 2 & 1 & 1 & 1 & 2 & \\
5–<7 & 1 & 1 & 0 & 2 & 2 & 0 & \\
3–<5 & 1 & 1 & 1 & 1 & 0 & 1 & \\
<3 & 0 & 0 & 0 & 0 & 1 & 0 & \\
None & 0 & 0 & 0 & 0 & 0 & 0 & \\
\hline
\text{Location} & & & & & & & \\
TL/BG/Th & 3 & 3 & 1 & 1 & 2 & 2 & \\
TL/BG & 1 & 1 & 0 & 2 & 1 & 1 & \\
TL or BG or Th & 0 & 0 & 1 & 1 & 1 & 0 & \\
None & 0 & 0 & 0 & 0 & 0 & 0 & \\
\hline
\text{Maximum PI, dB} & & & & & & & \\
>10 & 4 & 4 & 1 & 3 & 3 & 2 & \\
5–10 & 0 & 0 & 1 & 1 & 0 & 1 & \\
<5 & 0 & 0 & 0 & 0 & 1 & 0 & \\
\hline
\text{Demarcation} & & & & & & & \\
Sharp & 1 & 4 & 0 & 4 & 4 & 3 & \\
Poor & 3 & 0 & 2 & 0 & 0 & 0 & \\
\hline
\text{Background} & & & & & & & \\
Clear & 2 & 0 & 2 & 3 & 3 & 3 & (0.06) \\
Unclear & 2 & 4 & 0 & 1 & 1 & 0 & \\
\hline
\end{tabular}
\end{table}
Despite the use of low receiving frequencies, images with no transcranial contrast were almost always associated with an unclear background and were more frequently identified in gray-scale imaging than PHI. The probable reason is that color-coded imaging such as PHI identifies even a small contrast area more easily than gray-scale imaging.

For Optimal Perfusion Imaging
To overcome the major drawback of transcranial ultrasound attenuation, further developments in ultrasound equipment and contrast agents are essential. However, the importance of appropriate frequency selection and beam configuration for transcranial imaging has been pointed out. Furthermore,

Figure 2. Comparison of harmonic perfusion imaging via temporal skull defect of persistent-vegetative patient with moyamoya disease. Six different images were taken before (top) and after (bottom) contrast as in Figure 1. Background images were clear in all 6 images where third ventricle (III), anterior horn (AH), and inferior horn (IH) of lateral ventricles were visualized. Contrast area demarcation is sharp in UHI (b), PHI2.6 (d), PHI3.2 (e), and PHI3.6 (f) and poor in SHI2.6 (a) and SHI3.6 (c).
microbubble destruction is more evident at lower frequencies and higher acoustic powers. Therefore, subharmonic imaging using a frequency range of around 0.5 to 1 MHz would probably be suitable for transcranial perfusion imaging because of the much smaller attenuation of scattered subharmonic signals and the high CTR. Finally, for intact temporal skull cases, gray-scale SHI using a low receiving frequency of 2.6 MHz is the superior method. Therefore, clinical application for acute stroke cases, particularly interventional occlusion and recanalization of major arteries, is recommended. Compared with gray-scale imaging, PHI can more easily identify contrast area localization, especially in skull defect cases, and therefore is more suitable for intraoperative and postoperative follow-up.

References

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