Transcranial Ultrasound Brain Perfusion Assessment With a Contrast Agent-Specific Imaging Mode
Results of a Two-Center Trial

Thilo Hölscher, MD; Wilko Wilkening, PhD; Bogdan Draganski, MD; Saskia H. Meves, MD; Jens Eyding, MD; Heinz Voit, MD; Ulrich Bogdahn, MD; Horst Przuntek, MD; Thomas Postert, MD

Background and Purpose—The purpose of this study was to assess brain perfusion with an ultrasound contrast-specific imaging mode and to prove if the results are comparable between 2 centers using a standardized study protocol.

Methods—A total of 32 individuals without known cerebrovascular disease were included in the study. Perfusion studies were performed ipsilaterally in an axial diencephalic plane after intravenous administration of 0.75 mL of Optison. Offline time intensity curves (TIC) were generated in different anatomic regions. Both centers used identical study protocols, ultrasound machines, and contrast agent.

Results—In both centers, the comparison of the parameter time to peak intensity (TPI) revealed significantly shorter TPIs in the main vessel structures compared with any parenchymal region of interest (ROI), whereas no significant differences were seen between the parenchymal ROIs. The parameter peak intensity (PI) varied widely interindividually in both centers, whereas the inter-ROI comparison revealed statistical significance (P<0.05) in most of the cases according to the following pattern: (1) lentiforme nucleus > thalamus and white matter region, (2) thalamus > white matter region, and (3) main vessel > any parenchymal structure. Similar results were achieved in both centers independently.

Conclusion—The study demonstrates that brain perfusion assessment with an ultrasound contrast-specific imaging mode is comparable between different centers using the same study protocol. (Stroke. 2005;36:2283-2285.)

Key Words: brain imaging ■ contrast imaging ■ transcranial ultrasound

Since the introduction of echo contrast agents in ultrasound diagnostics, the specific acoustic properties of microbubbles have been a focus of research interest. The nonlinear backscattering effect and the generation of harmonic frequencies, respectively, yielded the opportunity to image low-flow or even stationary microbubbles.

Insonation through the intact skull is mainly characterized by imaging with higher mechanical indices and lower fundamental frequencies. The effect of insonation with high acoustic power leads to the destruction, splitting, or fusion of microbubbles. Acoustic signals are generated, which are independent of blood flow. Based on these acoustic properties, contrast agent-specific imaging modes have been developed to improve the visualization and quantification of the microvasculature. Contrast burst imaging (CBI) represents one of these new imaging modes and was used for this study.

The purpose of this study was to assess brain perfusion with CBI in a 2-center trial, using a standard protocol, and to prove if the results of both centers are comparable.

Materials and Methods

Population and Study Protocol
Fifteen healthy volunteers in center 1 (mean age: 25 y) and 17 patients in center 2 (mean age: 46 y) without known cerebrovascular diseases were included in the study. The ipsilateral hemisphere was insonated through the temporal bone window in an axial diencephalic scanning plane. Each proband was studied from both sides of the head. Offline parameter images were generated and rectangular regions of interest (ROIs) (Figure 1) were placed in the following anatomic areas: thalamus anterior (ROI\(_{TA}\)), thalamus posterior (ROI\(_{TP}\)), lentiform nucleus (ROI\(_{LN}\)), white matter (ROI\(_{WM}\), and one of the main vessels (ROI\(_{MV}\)). For each ROI, time intensity curves (TIC) were generated and the parameters time to peak intensity (TPI) and peak intensity (PI) were calculated.

Technical Equipment and Ultrasound Contrast Agent
In both centers, a Sonoline Elegra (Siemens), equipped with a phased-array transducer (2.5 PL 20), was used. After acquisition (36 to 40 frames), the radiofrequency (RF) data were transferred to a PC for further offline analysis.

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From the Department of Radiology (T.H.), University of California–San Diego, San Diego, Calif; the Department of Neurology (B.D., H.V., U.B.), University of Regensburg; the Department of Neurology (S.H.M., H.P.), University of Bochum, Bochum, Germany; the Department of Neurology, St Vincenz KH Paderborn (T.P.); the Department of Neurology (J.E.); St Josef Hospital, Ruhr University, Bochum, Germany; and the Department of Electrical Engineering (W.W.), University of Bochum, Bochum, Germany.

Correspondence to Thilo Hölscher, MD, Assistant Adjunct Professor, University of California San Diego, Medical Center, Department of Radiology, 212 West Dickinson St. B-412, San Diego, CA 92103-8756. E-mail thoelscher@ucsd.edu

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2283
As an ultrasound contrast agent (UCA), FS 069 (Optison; Mallinckrodt) was used.

**Contrast Burst Imaging**

CBI is derived from Power Doppler and is based on the fact that microbubbles undergo destruction, splitting, and fusion at higher acoustic pressures. These broadband noises, partially passing the wall filters, are interpreted as flow signals independent of microbubble movement. The generated broadband noise, typical for microbubble destruction, is detected by CBI.4

**Statistical Analysis**

The Friedman test compared the distribution of coherent variables between different ROIs, whereas the Wilcoxon test was used to prove statistical significance (P<0.05).

**Results**

**Peak Intensity**

In center 1, the absolute parenchymal PIs ranged between 532.2 arbitrary units (AU) in ROI_WM and 2236.5 AU in ROI_LN. Accordingly, the values in center 2 were 1410.0 AU in ROI_WM and 2673.1 AU in ROI_LN. The highest PIs were seen in the vascular ROIs (center 1: 3505.4 AU, center 2: 3792.2 AU).

After overall comparison between parenchymal ROIs, statistically significant differences were seen in both centers as shown in Table 1. With regard to ROI_MV, a probability value of P≤0.001 was seen in comparison with any parenchymal ROIs.

**Time to Peak Intensity**

In center 1, the absolute parenchymal TPIs ranged between 6.5 s (ROI_TP) and 31.0 s (ROI_TA) and in center 2 between 15.2 s (ROI_TP) and 56.3 s (ROI_TA). For each center separately, the mean TPIs (±SD) were similar in all parenchymal ROIs. However, the mean TPIs in center 2 were noticeably prolonged compared with center 1 (Table 2). In both centers, statistical significance was reached between ROI_MV compared with any parenchymal ROIs (P≤0.001).

**Discussion**

As a result of the acoustic properties of UCA microbubbles, innovative ultrasonic imaging modalities to assess the cerebral microvasculature have been introduced in recent years, particularly with regard to the nonlinearity of the UCA backscatter.5–8 However, it has not been shown whether different centers could achieve comparable results using a standardized study protocol. In both centers, reasonable TICs could be generated to a high extent. Statistically significant differences of TPI (P≤0.001) could be shown between main vessel structures and parenchymal ROIs. Focusing on the inter-ROI comparison, no statistical significance could be reached for TPI in either center. However, the mean TPI values were approximately 2-fold higher in the center 2 population compared with center 1. This could be explained by the different age groups (center 1: mean 25 y, center 2: mean 46 y) and progressive osseous calcification with increasing age. Calcification impairs the insonation through the bone, leading to lower acoustic power in the brain tissue. Less acoustic power means less bubble destruction, which impacts the sensitivity of CBI.

The parameter PI varied widely within both study populations, which is most likely the result of the fact that CBI is based on the nonlinear effects of UCA microbubbles. This nonlinearity leads to a nonproportional relation between optic intensities and the concentration of the UCA. However, the intra-individual comparison between different parenchymal ROIs reached statistical significance to a high extent in both centers. Because of the higher physiological microvascularization in gray matter regions, higher PI values were assessed in basal ganglia areas (ie, lentiforme nucleus, thalamus) compared with white matter regions.

**Table 1. Significant Differences (Wilcoxon test) of PI Comparisons Between All ROIs for Both Centers**

<table>
<thead>
<tr>
<th></th>
<th>Center 1</th>
<th>Center 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI_TA &gt; ROI_TA</td>
<td>P&lt;0.001</td>
<td>P&lt;0.004</td>
</tr>
<tr>
<td>ROI_TA &gt; ROI_TP</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>ROI_LA &gt; ROI_LA</td>
<td>P&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>ROI_LA &gt; ROI_LN</td>
<td>P&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>ROI_TP &gt; ROI_TA</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>ROI_TP &gt; ROI_LN</td>
<td>P&lt;0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

ROI_ROA indicates parenchymal ROIs; NS, not significant.

**Table 2. Mean Values±SD for the Parameter Time to Peak Intensity for Both Centers**

<table>
<thead>
<tr>
<th></th>
<th>ROI_TA</th>
<th>ROI_TP</th>
<th>ROI_LA</th>
<th>ROI_LN</th>
<th>ROI_MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center 1</td>
<td>15.9±6.3</td>
<td>15.6±5.9</td>
<td>15.7±5.9</td>
<td>16.6±5.4</td>
<td>11.8±3.9</td>
</tr>
<tr>
<td>Center 2</td>
<td>30.1±12</td>
<td>30.0±12</td>
<td>30.1±12</td>
<td>29.9±11</td>
<td>21.7±11</td>
</tr>
</tbody>
</table>

*All values are measured in seconds.*
In conclusion, we demonstrated that CBI enables assessment of brain perfusion semiquantitatively and achieves comparable results in different centers using the same scanning protocol.

References
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