Ultrasound Perfusion Imaging in Acute Middle Cerebral Artery Infarction Predicts Outcome

Günter Seidel, MD; Karsten Meyer-Wiethe, MD; Grit Berdien; Dirk Hollstein; Daniel Toth, Dipl-Phys; Til Aach, Prof. Dr.-Ing.

Background and Purpose—Initial reports indicate that transcranial harmonic imaging after ultrasound contrast agent bolus injection (BHI) can detect cerebral perfusion deficits in acute ischemic stroke. We evaluated parametric images of the bolus washout kinetics.

Methods—Twenty-three patients with acute internal carotid artery infarction were investigated with perfusion harmonic imaging after SonoVue bolus injection ≤40 hour after the onset of symptoms. The findings were compared with those of cranial computed tomography (CCT) and clinical course 4 months after stroke.

Results—Images of pixel-wise peak intensity (PPI) and time to peak intensity could be calculated for all patients. Spearman rank correlations of \( r = 0.772 \) (\( P < 0.001 \)) and \( r = 0.572 \) (\( P = 0.008 \)) between area of PPI signal decrease and area of infarction in the follow-up CCT as well as outcome after 4 months were obtained, respectively.

Conclusions—In the early phase of acute ischemic stroke, BHI after SonoVue bolus injection is a useful ultrasound tool for analyzing cerebral perfusion deficits at the patient’s bedside. BHI data correlate with the definite area of infarction and outcome after 4 months. (Stroke. 2004;35:1107-1111.)

Key Words: ultrasonography ■ stroke ■ contrast media

In patients with acute cerebral ischemia, brain perfusion can be analyzed by several diagnostic methods, such as computed tomography (CT), magnetic resonance tomography, single-photon emission computed tomography, and positron emission tomography. Ultrasound, as a less time-consuming, inexpensive, and well-tolerated bedside method for critically ill patients, has been introduced for the evaluation of brain perfusion. 1-4 By using transcranial harmonic imaging, it is possible to track an ultrasound contrast agent bolus within the human cerebral microcirculation. This technology is called bolus perfusion harmonic imaging (BHI). Initial reports have indicated that this harmonic imaging technique may be useful in assessing pathologic brain perfusion. 5-9

The purpose of our study was to evaluate the diagnostic and prognostic potential of this new imaging tool after processing of the image loops in patients with acute ischemic stroke.

Subjects and Methods

Patients
Inclusion criteria were as follows: acute onset of sensorimotor hemiparesis, neglect or incomplete aphasia ≤40 hours before the initial investigation, and early stroke signs on cranial computed tomography (CCT) (focal hypoattenuation or focal brain swelling in the territory of the internal carotid artery, obscuration of basal ganglia, or hyperdense middle cerebral artery sign 10 ), as well as a sufficient acoustic bone window for conventional transcranial color-coded sonography (TCCS). Exclusion criteria were as follows: intracranial hemorrhage detected by CCT and complete aphasia, pregnancy, and severe cardiac, pulmonary, or renal disease. All patients gave informed consent.

By using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Score (mRS), the clinical status of the patients was assessed before the investigation. The mRS was reevaluated after 4 months by a telephone interview to evaluate functional outcome. The initial ultrasound investigation consisted of extracranial and transcranial color-coded duplex sonography as well as transcranial perfusion harmonic imaging using the bolus kinetics with SonoVue (Bracco/Altana Pharma). Two CCT scans (Aquilion; Toshiba Medical Systems Europe) were performed as part of our routine protocol for stroke patients. Routinely, one CCT scan was performed as first-line diagnostic approach before sonography (mean 3.3 [SD 3.3] hours, median 2 [interquartile range 2.5] hours after symptom onset). A repeat CCT (mean 83.7 [SD 79.3] hours, median 52 [interquartile range 101.5] hours) was performed to confirm localization and size of the infarction. No contrast agent was administered for CCT.

Ultrasound Contrast Agent
The ultrasound contrast agent SonoVue is a sulfurhexafluoride-containing aqueous suspension of phospholipid microbubbles, which is capable of passing the pulmonary circulation (1 to 5×10⁶ microbubbles/mL; diameter was <8 μm in >90% of microbubbles). The agent has been approved for neurosonology purposes by the German authorities and is routinely administered for the assessment of the images.
of basal cerebral arteries in patients with insufficient insonation conditions.\textsuperscript{11}

**Ultrasound Examination**

We performed BHI with a SONOS 5500 ultrasound system (Philips Medical Systems) and a 1.8/3.6-MHz sector transducer (S4 probe; Philips). The ultrasound pulses were triggered with 1 pulse every 1.5 seconds, as described previously.\textsuperscript{12} The investigation was performed in a standardized axial midthalamic plane (landmarks: third ventricle, thalamus, and the anterior horn of the ipsilateral ventricle), with a maximum depth of 10 cm (focus on 8 cm) on the symptomatic hemisphere in each patient. Gain and transmit power settings were optimized for each patient at the beginning of the initial investigation. The digitized gray-scale images of the brain were stored in a continuous-loop review memory and were then recorded on an optical disc for later off-line analysis. The entire investigation was recorded on videotape. The symptomatic hemisphere was investigated after a bolus injection of 2.4 mL of SonoVue. The SonoVue injection was followed immediately by a 10-mL saline bolus to flush the injection line. The sonographers (G.S. and K.M.), who were blinded to the results of the initial CCT scans, were provided with only the clinical information of an ischemic stroke in the middle cerebral artery (MCA) territory (exclusion of hemorrhage).

Extracranial color-coded duplex sonography of the brain-supplying arteries (carotid and vertebral arteries in all segments) was performed with the SONOS 5500 ultrasound system (Philips) connected to a 7.5-MHz linear array scanner (L7540; Philips) and a 12-MHz sector scanner (S12 probe; Philips). For conventional TCCS of the basal cerebral arteries, we used a sector transducer (S4 probe; Philips) with a fundamental frequency of 2 to 4 MHz in the frequency-based mode.\textsuperscript{13} We classified the Doppler flow in the middle cerebral artery of the symptomatic hemisphere by the thombolysis in brain ischemia (TIBI) score.\textsuperscript{14} The TIBI waveforms are graded as follows: 0 indicates absent; 1, minimal; 2, blunted; 3, dampened; 4, stenotic; and 5, normal.

**Data Analysis**

For further analysis, we calculated parametric images displaying the peak signal increase in each pixel (pixel-wise peak intensity [PPI]) and the time to peak intensity (TTP) from the start of the contrast enhancement. We used a custom-made PC software (BHI-View), which is a Linux command-line tool implemented in C language using the TIFF library to stack-process image data and create color-coded parametric images.\textsuperscript{15} The user controls the program with a smtexf file. In a bolus kinetics image series, the program identifies the maximum at each pixel localization, which is then normalized to the maximum signal increase and color-encoded into the PPI image. The time corresponding to the frame number of the image containing a certain pixel’s maximum is represented by color and is set into the TTP image. Pixels that remain black in the whole series represent regions without any recognizable blood flow and are displayed as gray.

A perfusion disturbance was defined as significant when a decrease of >50% of normalized intensity in the PPI image was visible and/or a delay of >3 seconds in a region compared with the surrounding brain tissue was seen. The area of perfusion disturbance (area of pathological pixel-wise peak intensity [APPPI] for PPI images and area of pathologic time to peak intensity [ATTP] for the TTP images) was manually calculated by a public domain graphics software tool (Scion Image, Release 4.02; Scion Corporation) and statistically compared with clinical and CCT parameters. The definitive location and area of infarction in the midthalamic plane (area of infarction in the follow-up CCT [ACCT]) were displayed by CCT follow-up investigations and manually calculated by a graphics software tool (Scion Image).

**Statistical Analysis**

We used mean and median values as well as standard deviations and interquartile ranges (between 1 and 3 quartiles) for the description of the data. Calculation of correlation between the different variables was performed using nonparametric Spearman rank correlations. Correlation coefficients and two-sided \( P \) values are shown (SPSS 11.5). A significant correlation was assumed for \( P<0.05 \).

**Results**

Twenty-three patients with acute infarction in the anterior circulation (MCA or anterior cerebral artery [ACA] infarction) were investigated in this study (10 women, 13 men; mean age 63.8 [SD 8.4] years; median NIHSS before the ultrasound investigation 11.0 [interquartile range 14] points; median mRS before the ultrasound investigation 4.0 [interquartile range 1]). Lesion patterns were as follows: 15 cortico-subcortical, 5 subcortical, and 2 lacunar MCA infarctions. One patient had an infarction in the ACA territory.

All BHI investigations (mean 11.3 [SD 10.9] hours, median 6.5 [interquartile range 9.5] hours after symptom onset) showed contrast enhancement and were of sufficient quality for further analysis. In 19 of 22 patients with MCA infarctions (86.4%), an area of significant decrease in the PPI image could be identified (Figure 1 and 2). In a single patient with ACA infarction, no perfusion deficit could be displayed in the midthalamic insonation plane. At the site of the PPI value decrease, the TTP image showed an area of contrast delay of >3 seconds in 7 of 19 patients (36.8%). None of the patients showed an isolated delay in the TTP image without a decrease in the PPI image.

Follow-up CCT was performed (mean 83.7 [SD 79.3] hours, median 52 [interquartile range 101.5] hours after symptom onset). We calculated the correlation between the area of infarction in the follow-up CCT and several covaribles (Table). We found a highly significant positive correlation between the area of infarction in the follow-up CCT and the severity of stroke symptoms (mRS before the ultrasound investigation and after 4 months, NIHSS before the ultrasound investigation), as well as the area of amplitude decrease in the BHI study. The presence of a severe stenosis or occlusion of the ipsilateral internal carotid artery and ACCT were significantly positively correlated. A highly significant negative correlation could be calculated between ACCT and the Doppler blood flow in the middle cerebral artery (TIBI score: in 13 patients no flow signal, in 4 patients each a dampened or a stenotic flow signal and 2 normal findings).

These associations are clinically important because they show the relationship between area of infarction in the midthalamic plane and the clinical and vascular status of the patient. The statistical evaluation of the ultrasound variables (TIBI score, stenosis >70%, or occlusion of the ipsilateral internal carotid artery, APPPI, and ATTP) revealed only one highly significant negative correlation between the area of amplitude decrease in BHI and the TIBI score \((r=-0.535, \ P=0.009)\). This indicates that a low TIBI score with absent or reduced blood flow in the middle cerebral artery is associated with a large area of signal decrease in BHI.

Twenty patients could be reevaluated by telephone interview 4 months (mean 121.7 [SD 38.8] days, median 103 [interquartile range 56.75] days) after symptom onset. Three patients were lost to follow-up. Three patients died from space-occupying infarction. The median mRS of the
follow-up investigation was 2.5 [interquartile range 4.75] points (n=20). The statistical analysis (Table 1) revealed a highly significant positive correlation between the mRS after 4 months and the clinical scores before the ultrasound investigation (modified Rankin Score and NIHSS), the area of amplitude decrease in BHI, and the area of infarction in the follow-up CCT (Table 1). The early vascular status (TIBI score, stenosis >70%, or occlusion of the ipsilateral internal carotid artery) of the patient failed to show a significant association with the outcome of the patient. No adverse effects attributed to the contrast agent application were observed during the study.

Discussion
The purpose of our prospective study was to evaluate patients with acute ischemia in the carotid territory by analyzing brain perfusion with harmonic imaging. As we demonstrated, the area of significant amplitude decrease detected by BHI in the early phase of ischemic stroke correlates significantly with the definite area of infarction shown by follow-up CCT and the outcome of the patient after 4 months. Parametric imaging with BHI technology increases the diagnostic impact of neurosonology by providing additional information on the distal vascular bed of the brain in the early phase of ischemic stroke at the patient’s bedside.

In several studies, very early vascular findings after symptom onset were found to be a strong predictor for further outcome of acute ischemic stroke patients.16,17 This was also confirmed by our present study. A significant correlation could be found only for APPI; the other vascular variables (TIBI score, stenosis >70%, or occlusion...
perfusion disturbance. Until now, a comparison between BHI and perfusion CT or MRI of the brain has not been performed in a considerable number of stroke patients. The advantage of BHI is that it can provide qualitative information regarding brain perfusion at the patient’s bedside. It may prove to be a helpful extension of the conventional ultrasound examination of the basal cerebral arteries with TCSS.

The foremost limitation of BHI to date is that one contrast agent bolus must be applied for each set of parametric images. A technical solution is the so-called matrix probe, which scans multiple insonation planes within one investigation and one bolus applied.

Insonation artifacts occur in every BHI investigation, mainly at the edges of the insonation field. Because of their characteristic shape, these artifacts can be distinguished from perfusion deficits, but they minimize the area of proper BHI investigation.

In conclusion, this preliminary study is particularly encouraging as a basis for further efforts in the field of minimally invasive bedside analysis of brain perfusion. The combination of extracranial and transcranial color-coded sonography, as well as BHI parametric imaging, expands the diagnostic potential of ultrasound techniques from macrocirculation to microcirculation of the brain. Therefore, determining the value of BHI in displaying cerebral perfusion deficits has become essential. Future assessment of BHI will include more advanced ultrasound contrast agents and ultrasound systems and comparison with perfusion-weighted MRI.

Acknowledgments

This study was supported by a grant from the European Commission (UMEDS QLG1-CT-2002-01518) and sponsored by Bracco-Byk Gulden. For technical support, we are grateful to Johanna Lahmann, Department of Neurology, University Hospital Schleswig-Holstein, Campus Lübeck. We thank Inke R. König, PhD, from the Institute of Medical Biometry and Statistics, University Hospital Schleswig-Holstein, Campus Lübeck, for excellent statistical advice.

References


Spearman Rank Correlations

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACCT</th>
<th>mRS After 4 Months</th>
<th>Variable Coefficient</th>
<th>P</th>
<th>Variable Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.299</td>
<td>0.187</td>
<td>0.402</td>
<td>0.079</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS before ultrasound</td>
<td>0.689</td>
<td>0.001</td>
<td>0.634</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS before ultrasound</td>
<td>0.546</td>
<td>0.010</td>
<td>0.564</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.315</td>
<td>0.165</td>
<td>−0.030</td>
<td>0.902</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIBI-score</td>
<td>−0.734</td>
<td>&lt;0.001</td>
<td>−0.416</td>
<td>0.068</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis or occlusion of ICA</td>
<td>0.453</td>
<td>0.039</td>
<td>0.436</td>
<td>0.054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS after 4 months</td>
<td>0.650</td>
<td>0.006</td>
<td>1.0</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APPI</td>
<td>0.772</td>
<td>&lt;0.001</td>
<td>0.572</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTP</td>
<td>0.402</td>
<td>0.071</td>
<td>0.125</td>
<td>0.599</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCT</td>
<td>1.0</td>
<td>—</td>
<td>0.605</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Scatter plot of area of infarction in the follow-up CCT (ACCT) and the area of pathological contrast enhancement displayed in the pixel-wise peak intensity image (APPI). The linear regression (3.026×ACCT−0.27×APPI) shows a highly significant correlation (P<0.001).


Ultrasound Perfusion Imaging in Acute Middle Cerebral Artery Infarction Predicts Outcome

Günter Seidel, Karsten Meyer-Wiethe, Grit Berdien, Dirk Hollstein, Daniel Toth and Til Aach

Stroke. 2004;35:1107-1111; originally published online March 18, 2004; doi: 10.1161/01.STR.0000124125.19773.40

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/5/1107