Parametric Perfusion Imaging With Contrast-Enhanced Ultrasound in Acute Ischemic Stroke

Martin Wiesmann, MD; Karsten Meyer, MD; Thomas Albers; Günter Seidel, MD

Background and Purpose—Color-coded perfusion maps can be calculated from ultrasound harmonic gray-scale imaging data after ultrasound contrast agent bolus injection to analyze brain tissue perfusion. First reports indicate that this method can display cerebral perfusion deficits in acute ischemic stroke. We performed a prospective patient study to evaluate this approach.

Methods—Thirty consecutive patients suffering from acute middle cerebral artery infarction who presented to our department within 12 hours after symptom onset were investigated with ultrasound perfusion harmonic imaging (PHI) after Levovist bolus injection. Color-coded perfusion maps were calculated from the ultrasound data. In addition, the original grayscale images were analyzed in cine mode. Findings were compared with those of cranial CT.

Results—All 30 patients suffered from acute ischemic stroke of the middle cerebral artery territory (median National Institutes of Health Stroke Scale score, 16 points). Twenty-three of the 30 patients (76.7%) had sufficient PHI insonation conditions. In 19 of these 23 patients (82.6%), a marked deficit in contrast enhancement could be visualized by initial PHI with the color-coded parameter images and cine-mode images. In 17 of the 23 (73.9%), the perfusion deficit was found on the parameter images. The area of hypoperfusion in the initial PHI investigation corresponded to the definite area of infarction in follow-up cranial CT. In 3 of 23 patients (13.0%), a perfusion deficit could be demonstrated in PHI, although the supplying artery was found patent by transcranial color-coded duplex sonography.

Conclusions—With PHI, it is possible to display cerebral perfusion deficits in acute ischemic stroke. PHI yields additional information on the perfusion state of the human brain compared with extracranial and transcranial color-coded duplex sonography. (Stroke. 2004;35:508-513.)

Key Words: contrast media ■ diagnostic imaging ■ perfusion ■ stroke ■ ultrasonography

Brain perfusion in patients with acute brain infarctions can be evaluated by several diagnostic methods, including SPECT, PET, CT, and MRI. Compared with ultrasound, these methods are time consuming, require radioactive tracers, or cannot be tolerated by critically ill or restless patients. It is possible to visualize human cerebral perfusion by means of transtemporal gray-scale harmonic imaging.1–4 This technology is called perfusion harmonic imaging (PHI). First reports indicate that PHI can be used to assess pathological brain perfusion.5–7 However, all approaches to analysis of these PHI data have been time consuming and/or have required interactive region-of-interest analyses. In a previous study on healthy subjects, we introduced an automated color-coded evaluation method of harmonic gray-scale imaging.4 The aim of our study was to evaluate the diagnostic potential of this new bedside imaging tool in acute stroke.

Patients and Methods
Inclusion criteria were acute middle cerebral artery (MCA) infarction with symptom onset ≥12 hours before the initial investigation and a sufficient acoustic bone window for transtemporal color-coded duplex sonography (TCCS). Exclusion criteria for ultrasound contrast agent administration (Levovist) were pregnancy, severe cardiac or pulmonary disease, and galactosemia. All patients gave informed consent.

The initial investigation consisted of extracranial duplex sonography, TCCS, and transcranial PHI with Levovist. The cranial CT (CCT) scans (Somatom Plus S, Siemens) being evaluated in this study were performed as part of our routine protocol for stroke patients. Routinely, 1 CCT scan was done as baseline before sonography. A repeated CCT was performed on the second day to confirm localization and size of the infarction. No contrast agent was administered for CCT.

Ultrasound Contrast Agent
The ultrasound contrast agent Levovist (Schering) is an air-containing aqueous suspension of microparticles consisting of 99.9% galactose and 0.1% palmitic acid, which have the capability to pass the pulmonary circulation. It was approved for neurosonology purposes by the German authorities in 1996 and is being administered routinely for the assessment of the basal cerebral arteries in patients with insufficient insonation conditions.

Ultrasound Examination
We performed PHI with a SONOS 5500 ultrasound system (Philips Medical Systems) and a 1.8/3.6-MHz sector transducer (S4 probe,
The ultrasound pulses were triggered by ECG with 1 pulse every 4 cardiac cycles. The investigation was performed in axial midhilaric planes (landmarks: third ventricle, thalamus, anterior horn of the ipsilateral ventricle) with a maximum depth of 10 cm (focus on 8 cm). Gain and transmit power settings were optimized for each patient at the beginning of the investigation and were not changed throughout the procedure. Each hemisphere was investigated after bolus injection of 5 mL Levovist at a concentration of 400 mg/mL following manufacturer’s instructions. The time between the investigation of the 2 hemispheres was 5 to 10 minutes. Levovist injection was followed immediately by a 10-mL saline bolus to flush the injection line. After each injection of Levovist 62, digitized gray-scale imaging data of the brain were stored in the continuous-loop review memory and were then recorded on an optical disk for later offline analysis. The entire investigation was recorded on videotape. The sonographers (G.S., T.A., K.M.) were blinded to the results of the initial CCT scans. They merely had the clinical information of a suspected ischemic stroke in the MCA territory.

Extracranial duplex sonography of the brain-supplying arteries (carotid and vertebral arteries in all segments) was performed with the SONOS 5500 ultrasound system (Philips) in connection with a 7.5-MHz linear transducer (L7540, Philips). For conventional TCCS of the basal cerebral arteries, we used a sector transducer (S4 probe, Philips) with the fundamental frequency of 2 to 4 MHz in the frequency-based mode.

Image Data Postprocessing

Image data were read from the optical disk and transferred to a portable personal computer (Macintosh PowerBook G3, Apple Computer). The software tool for automated color-coded analysis of harmonic gray-scale imaging data was written with a public-domain graphics software tool (NIH Image 1.62, National Institutes of Health).

The software algorithm has been described elsewhere. In short, image data postprocessing consists of 5 steps. First, by evaluating the intensities of the 62 images within 1 loop, we determine the onset and peak of contrast enhancement. Second, from the images obtained before the onset of contrast enhancement, an averaged image (background image) is calculated. Third, the background image is subtracted from the original images. Fourth, the series of 5 consecutive images that shows the highest contrast enhancement as defined by intensity is selected. From various algorithms, 2 have been determined to yield the most promising results and were selected to calculate parameter images for analysis in this study. The first is pixelwise peak intensity (PPI). In a pixel-by-pixel evaluation, an image is calculated in which every pixel is set to the peak intensity found within this series. The second is time-to-peak (TTP). In a pixel-by-pixel evaluation, an image is calculated in which every pixel is set to a value that codes the delay between onset and peak of the contrast enhancement. Finally, the background, PPI, and TTP images are converted to color scale. Gray-scale and color images are stored on hard disk and printed on an ink jet printer for further analysis. Except for initial selection of the ultrasound image series, no user interaction is required during data postprocessing. Data postprocessing is performed in ~90 seconds.

Data Analysis

Two investigators blinded to the diagnosis of the patients evaluated the ultrasound data. First, the anonymous paper prints of the background and parameter images were presented to the investigators in random order. The investigators graded the image quality using an arbitrary scale with scores of 3 (good image quality), 2 (moderately reduced image quality/sufficient for diagnostic evaluation), 1 (reduced image quality/probably sufficient for diagnostic evaluation), or 0 (insufficient for diagnostic evaluation). If diagnostic evaluation was possible (scores of 1 to 3), they then stated whether they detected an area of hypoperfusion on the PPI image, TTP image, or both. The investigators had to decide if they found the perfusion study unremarkable or pathological. If uncertain, they were allowed to review the original 62 digitized gray-scale images in cine mode.

Results

In 7 of the 30 consecutive patients (23.3%) suffering from acute MCA infarction who presented to our department, the temporal bone window was not sufficient for PHI investigation. Twenty-three patients (76.7%) had adequate insonation conditions for PHI and were investigated in the study (10 women, 13 men; age, 30 to 76 years; median National Institutes of Health Stroke Scale score, 16 points). No adverse events related to the PHI investigation were observed during or after the study. Lesion patterns of the 23 patients as found on the repeated CCT scans were as follows: 8 corticosubcortical, 8 cortical, and 7 subcortical infarctions in the MCA territory (Table 1).

Image Quality and Artifacts

Sufficient image quality for diagnostic evaluation (scores of 1 to 3) was found in all 23 studies of the ipsilateral hemispheres and in 22 of the 23 contralateral hemispheres examined. In 1 of the contralateral hemispheres, the transtemporal bone window did not permit diagnostic evaluation. In total, good image quality (score of 3) was found in 15 studies, moderately reduced image quality (score of 2) in 23 studies, reduced image quality in 7 studies, and insufficient image quality for diagnostic evaluation (score of 0) in 1 study. Reduced image quality was caused mainly by artifacts resulting from limitations of the acoustic bone window. In 5 cases, motion artifacts also were observed. Limitations of the transtemporal bone window were encountered in all 46 studies. We observed either low-signal sections at the anterior or posterior border of the ultrasound section or thin low-signal streaks orientated from the ultrasound probe toward the midline.

Analysis of Brain Perfusion

No false-positive findings were observed in the 22 perfusion studies of the contralateral hemispheres. In 19 of 23 patients (82.6%) with MCA infarctions, a perfusion deficit could be identified in PHI. In 10 of these 19 studies, the perfusion deficit was seen on both TTP and PPI parameter images. In 2 studies, the perfusion deficit was identified only on the TTP image; in 5 studies, it was detected only on the PPI image. In 2 studies, the perfusion deficit could be identified only by reviewing the original gray-scale images in cine mode (Table 1). For calculated sensitivities of the evaluation methods, see Table 2.

After evaluation of the parameter images, the readers asked for additional review of the original gray-scale images in cine mode in 11 cases. In 5 of these 11 cases, a perfusion deficit had been detected on either the TTP image (n=1) or PPI images (n=4) only. Review of the gray-scale images was requested for confirmation of these diagnoses and was considered helpful by the evaluators in all cases. In the remaining 6 of 11 cases, no definite perfusion deficit had been detected.
on the parameter images, although the evaluators stated that they were uncertain. In 4 of these 6 cases, the gray-scale images were found to be unremarkable. In the remaining 2 cases, a perfusion deficit was identified on the original gray-scale images but not on the parameter images. Thus, in 2 of the 23 cases, the diagnosis was changed by additional evaluation of the gray-scale images in cine mode.

In 4 of 23 patients (17.4%) with MCA infarctions, the PHI studies were considered unremarkable. In 2 of the 4 cases, the patients suffering from acute stroke. Pos indicates hypoperfusion detected.

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<td>M1 occlusion [r] ICA occlusion [r]</td>
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Overview on patients with sufficient insonation conditions (n=23) suffering from acute middle cerebral artery infarction. Results of perfusion harmonic imaging (PHI), follow-up cranial computed tomography (CCT), initial clinical status (NIHSS: National Institutes of Health Stroke Scale on day 1), and vascular sonographic imaging (TCSS: transcranial color coded duplex sonography, ECCS: extracranial color coded duplex sonography) on the symptomatic cerebral hemisphere.

PI indicates parameter images; CM, cine-mode; TTP pos, area of time delay in the time-to-peak image; PPI pos, area with intensity decrease in the pixelwise-peak intensity image; C, cortical; s, subcortical; cs, corticosubcortical; Area [cm²], area of infarction in the midthalamic plane; CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; M1, M1 segment of the MCA; M2, M2 segment of the MCA; ACA, anterior cerebral artery; r, right side; l, left side; ne, not evaluated.

*Data missing decompressive craniectomy.

MCA was not occluded by the time of the PHI investigation, as demonstrated by TCCS. In these patients, despite good insonation conditions, no area of hypoperfusion could be identified by PHI, but follow-up CCT revealed territorial infarctions of the MCA territory. In a third patient, secondary hemorrhagic transformation as demonstrated by CCT obscured the contrast signal. In the fourth patient, no perfusion deficit was demonstrated by PHI, although the M1 segment of the MCA was found to be occluded in TCCS. However, it cannot be excluded that between the TCCS and PHI examinations, the artery may have been recanalized spontaneously. On the contrary, in 3 cases, the MCA was found to be patent with TCCS, but a perfusion deficit could be demonstrated in PHI.

**CCT Studies**

Whereas the initial CCT scans (mean, 2.4±1.5 hours after symptom onset) showed only early signs of infarction, the areas of hypoperfusion displayed by PHI (mean, 7.4±2.5 hours after symptom onset) corresponded with the demarca-
A 68-year-old man suffering from acute ischemic stroke caused by occlusion of right-sided distal internal carotid artery demonstrated by TCCS. A through D, Color-coded parameter images of the initial ultrasound perfusion study (120 minutes after symptom onset). A, TTP parameter image of right hemisphere depicting delay between onset and peak of contrast enhancement. Large area in the territory of the right MCA shows increased TTP (compare with C). Because acquisition of ultrasound images was performed ECG triggered, time scale reflects heartbeats. B, PPI parameter image of right hemisphere depicting maximum intensity of perfusion. Severely decreased intensity of perfusion is noted in large area in the territory of the right MCA. C, TTP parameter image of left hemisphere is shown for comparison. D, PPI parameter image of left hemisphere is shown for comparison. E: Initial CCT scan (90 minutes after symptom onset) depicts early stroke signs (swelling and obscuration of basal ganglia). For comparison, area covered by right-side ultrasound perfusion study (A) is indicated. F, Repeated CT scan (24 hours after symptom onset) clearly depicts area of infarction in the territory of the right MCA.

Discussion

As demonstrated before, normal and pathological perfusion of the human brain can be visualized by means of contrast-enhanced transcranial gray-scale PHI. In a previous eval-
ulation, we analyzed the time-intensity curves to quantitatively describe the perfusion deficit and were able to show a diminished signal increase in a considerable number of patients suffering from acute cerebral infarction (data not published). These data were in accordance with the results of Federlein et al., who first described the visualization of perfusion deficits by means of transcranial harmonic imaging in a considerable number of cases. In 21 patients (84% of investigated stroke patients), they found a sensitivity and specificity of transcranial harmonic imaging for predicting size and localization of the infarction of 75% and 100%, respectively. However, so far, all approaches to analysis of these PHI data have been time consuming and/or required interactive region-of-interest analyses.

In a previous study on healthy subjects, we introduced an automated color-coded evaluation method of harmonic gray-scale imaging that does not require any user interaction. Instead of displaying the area under the time-intensity curve, which is related to the cerebral blood volume, 2 color-coded parameter images are calculated. First, for calculation of the PPI image, the peak intensity increase from baseline image after administration of the contrast agent is analyzed. This parameter is related to the maximum amount of contrast agent in the tissue. Under the methodological settings of our study, PPI values do not show a significant dose–peak intensity relation and therefore just indicate the presence of contrast agent in the microcirculation as a result of perfusion of this area. Second, the TTP image visualizes the delay between onset and peak of contrast enhancement of brain parenchyma. This parameter can be used to detect cerebral tissue supplied by collateral blood flow. TTP images have been shown to be highly sensitive for cerebral infarction.

The aim of our study was to evaluate the diagnostic potential of these parameter images in acute stroke. To improve reliability, diagnostic algorithms should require as little user interaction as possible, and the design of our study reflects this intention. The investigators had to make a decision based on the parameter images only. Then, in a second stage, interactive analysis of the original gray-scale images in cine mode was possible to see if it would improve the results.

Our results demonstrate that cerebral perfusion deficits can be detected sensitively and reliably in the acute phase of ischemic stroke by PHI through the intact skull. Given adequate insonation conditions, we found cerebral perfusion deficits in 82.6% of the affected hemispheres, whereas no false-positive findings were reported on the contralateral hemispheres. The true sensitivity of the method for detection of perfusion deficits may even be higher. From studies using other perfusion imaging techniques such as CT or MRI, we know that at the time of examination perfectly normal perfusion conditions may have been restored, although ischemic damage to the brain tissue had become irreversible already. The validity of the method, however, is indicated by the fact that the perfusion deficits detected by PHI corresponded well to the definite area of infarction shown by follow-up CCT.

A comparison between PHI and perfusion CT or MRI of the brain has not yet been performed in stroke patients. CT and MRI have fewer artifacts but are more expensive and cannot be performed at the patient’s bedside. However, using MRI or multislice CT scanners allows a larger volume of the brain to be examined. Future studies using both PHI and perfusion CT or MRI will enable us to compare the sensitivity of the methods and the validity of calculated parameter images.

Our data show that color-coded parameter images have a high sensitivity for detection of acute cerebral infarction in the territory of the MCA in the selected cohort of our study. The “real-life diagnostic value” of the method was not measured in this small preliminary study. One inclusion criterion was a sufficient acoustic bone window for native TCCS. This proportion is (with the ultrasound system used in the study) ~80% of all ischemic stroke patients. Therefore, the rate of successful application of the method in real life is ~62%. TTP and PPI images both should be analyzed. This improved the sensitivity from 52.2% and 65.2%, respectively, to 73.9% in our study. However, in 2 cases, perfusion deficits were detected not on the parameter images but in a review of the original gray-scale images in cine mode. We attribute this mainly to motion artifacts, although the algorithm for calculation of the parameter images reduces the influence of motion to a certain degree. One of the 2 studies showed severe motion artifacts. In the other study, motion artifacts were not as severe, but the area of the perfusion deficit was very small. On parameter images, motion artifacts lead to volume averaging and edge artifacts, which may obscure pathological signal changes. Further improvements in the fixation device of the ultrasound probe and higher frame rates of data acquisition may reduce motion artifacts. The frame rate used in this study, ie, 1 ultrasound image every 4 cardiac cycles, is rather low for calculation of TTP images. An increase in frame rate will probably also have a beneficial effect on the diagnostic quality of the TTP images and will therefore be a subject of further studies.

All evaluators stated that color-coding of the parameter images greatly enhanced the visualization of perfusion effects in an easy-to-interpret way. In addition, the diagnostic evaluation of the color-coded paper prints takes considerably less time than evaluation in cine mode, and demonstration to other physicians and archiving of the images are much easier. However, our data indicate that additional evaluation of the original gray-scale images in cine mode may increase the sensitivity of the method. Therefore, it should be performed if motion artifacts are encountered or investigators are uncertain.

The 4 patients with adequate insonation conditions and without depiction of a perfusion deficit characterize the principle and limits of our study. First, if only 1 single standardized insonation plane is used, territorial infarctions can be overlooked because they are out of plane, and artifacts resulting inhomogeneities of the temporal bone are common. However, to obtain a qualitative impression of perfused areas in PHI, it is possible to scan the whole hemisphere with 1 contrast bolus injected. Second, hemorrhagic infarction is a problem for the detection of brain perfusion. Because of the primarily hyperechogenic sonographic appearance of blood, changes in brightness (perfusion) may not be detected.
Third, PHI is a functional measure that does not reveal structural damage of the brain parenchyma but displays perfusion deficits within the microcirculation. As known from other diagnostic modalities of perfusion imaging, despite irreversible ischemic damage to the cerebral parenchyma, cerebral perfusion at the site of infarction may be reduced at the time of examination but can also be normal or even increased after recanalization of the supplying artery.\textsuperscript{10,11} Additionally, a patent MCA main stem in transcranial Doppler gives minor information of the status of the distal branches of the artery. A main diagnostic goal of PHI is the evaluation of more distal parts of the vascular bed of the MCA. Fourth, the major limitation of the method is its impairment by insufficient insonation conditions, i.e., by an insufficient transtemporal bone window. With 5-mL Levovist bolus injections, only 76.7\% (23 of 30) of the investigated patients was sufficient contrast effect detected. In the study of Federlein and coworkers,\textsuperscript{7} 84\% of patients could be investigated with a bolus of 10 mL Levovist. Some increase in detection rate may be achieved by administration of a higher contrast agent dose. Nevertheless, our results indicate that better insonation conditions are required for PHI than for contrast-enhanced TCCS. This limitation could be partly overcome by innovative ultrasound contrast agents with more favorable enhancement properties in the parenchyma.\textsuperscript{3}

Extracranial and duplex sonography and TCCS are well-established ultrasound techniques that render valuable clinical information in acute stroke patients. However, our results show that PHI is able to supply additional information on the perfusion state of the human brain. In 3 of 23 cases, a perfusion deficit could be demonstrated in PHI, although the supplying artery was found to be patent with TCCS.

In conclusion, PHI expands the diagnostic potential of ultrasound techniques from macrocirculation to microcirculation of the brain. A bedside method, PHI can be easily performed and may be a valuable tool for monitoring thrombolytic therapy in a stroke unit setting.

Acknowledgment
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References