Background—Second harmonic imaging (SHI) is a new ultrasound technique that is able to detect microbubbles in the tissue vascular space. The aim of this pilot study was to prove that this technique may detect focal abnormalities of cerebral echo-contrast enhancement in acute hemispheric stroke.

Case Descriptions—Two male patients (aged 72 and 64 years) were included who presented with acute onset of severe hemiparesis and no established demarcation of the ischemic area in CT scans. After bolus application of galactose-based microbubbles, axial SHI examinations in a diencephalic plane of sections were performed using the transtemporal approach. Ultrasound investigations were recorded and evaluated offline. In both individuals demarcated focal abnormalities of cerebral contrast enhancement were detectable: in patient 1 the region of the lentiform nucleus and the adjacent parts of the temporoparietal lobe was affected, and in patient 2 a large region including the lentiform nucleus and cortical white matter was involved for at least 24 hours. Follow-up CT scans demonstrated a striatocapsular infarct in patient 1 and complete MCA infarction in patient 2, correlating with the presumed ischemic area in acute ultrasound examinations. The patient with complete MCA infarction showed missing contrast enhancement in the entire hemisphere of the affected side in follow-up SHI examinations. He died of malignant space-occupying brain edema. In the patient with the striatocapsular infarction, reappearance of echo-contrast enhancement in the ischemic area was assessable after 1 week.

Conclusions—SHI may identify focal abnormalities of cerebral echo-contrast enhancement in acute hemispheric stroke. Furthermore, this technique helps to determine size, localization, and prognosis of the ischemic region and could be useful for bedside assessment of echo-contrast agent distribution related to brain tissue perfusion. (Stroke. 1999;30:1702-1706.)

Key Words: cerebral ischemia n contrast media n imaging, harmonic n ultrasonography, transcranial

Harmonic imaging (HI) is a novel ultrasound technique that uses the nonlinear properties of gas bubbles by transmitting at 1 frequency and receiving at twice or multiples of the fundamental frequency. The theoretical advantage of the harmonic over the fundamental frequency is that contrast agent microbubbles resonate with harmonic frequencies whereas adjacent tissue hardly does. The resonance at twice the driving frequency, called the second harmonic, is the strongest harmonic and is therefore most appropriate to enhance the backscattered contrast-enhanced signal in comparison with that of tissue and to increase the signal-to-noise ratio. In this way HI may enhance the ability of B-mode scanners to differentiate bubbles in the tissue vascular space from the surrounding avascular tissue.1-3 Recently published studies in echocardiography4-6 have demonstrated that this technique may help to visualize infarct size during acute myocardial infarction. The potential role of this promising technique in cerebrovascular diseases has not been evaluated previously. In 1 preliminary study of healthy individuals,7 it could be demonstrated that HI produces accurate contrast in different brain areas and in this respect may represent an ultrasonic tool related to brain perfusion. We describe 2 patients with acute ischemia in the territory of the MCA with corresponding perfusion abnormalities assessed by second harmonic imaging (SHI).

Subjects and Methods

Harmonic Imaging Examinations

For all HI and transcranial color-coded sonography (TCCS) examinations, a Hewlett Packard SONOS 5500 duplex device capable of SHI in connection with a 2.5-MHz 90° sector transducer was used. To improve spatial resolution a low insonation depth (10 cm) was used. According to previously published studies,8 a diencephalic plane of section through the transtemporal approach with depiction of the third ventricle, the thalamus, and adjacent parenchymal
structures was used. The second harmonic system operated at 1.8-MHz transmit and at the second harmonic frequency of 3.6 MHz. Compared with a previously published SHI study of the brain that used a cardiac cycling frequency of once every 4 heartbeats, we used a lower frame rate (once every 2 cardiac cycles) to be able to rapidly correct the ultrasound probe for patient motions. Four grams of a 400-mg/mL concentrated, galactose-based microbubble suspension (Levovist, Schering AG) was injected into an antecubital vein over a period of 10 seconds. From the start of the injection the examination was stored on magnetic optic disk over a period of 122 cardiac cycles (61 images). Thirty minutes later the examination was repeated on the contralateral side. The perfusion defect was defined as the area without visible contrast effect, as assessed by 2 experienced TCCS investigators (T.P. and J.F.). Quantitative measurements of parenchymal contrast were performed offline by calculating gray scale intensities of the integrated backscatter from digital unprocessed data in defined regions of interest (ROI). According to a previously published study,7 time-intensity curves were created for the following circular ROIs: posterior and anterior parts of the thalamus adjacent to the third ventricle, the region of the lentiform nucleus, cortical white matter, the region of reduced contrast enhancement on the affected side, and corresponding regions on the unaffected side. The region of the white matter or the lentiform nucleus was defined as ischemic in the acute stage, if (1) no visual contrast could be assessed in gray scale images and no characteristic time-intensity curves were demonstrable showing a baseline phase, a phase of increasing optic intensity, and a tiding phase in the affected region, and (2) in the same scanning line at least 1 other region in a different insonation depth exhibited contrast enhancement (exclusion of focal acoustic window failure).

Figure 1. In acute TCCS examinations in patient 1, decreased MCA flow velocities on the affected side (top) compared with the unaffected side (bottom), most likely indicating recanalization of the MCA with persisting branch occlusion.

Case Reports

Case 1
A 72-year-old man was admitted with acute onset of a severe right-sided weakness (upper extremity 0/5 strength, lower extremity 1/5 strength) and global aphasia. First CT scans were performed 5 hours after the onset of symptoms and demonstrated obscuration of the lentiform nucleus; exact size and localization of the infarction were not yet detectable. In CT angiography (CTA) scans, the middle cerebral artery (MCA) mainstem was occluded. TCCS and CTA examinations 5 hours later demonstrated recanalization of the MCA mainstem; MCA flow velocities were decreased on the affected side, which suggested multiple MCA branch occlusions9 (Figure 1). Extracranial duplex examinations were normal. At the first SHI examination, a defined region of reduced contrast enhancement in projection to the lentiform nucleus and adjacent structures of the temporoparietal lobe was detectable in HI images, whereas in the thalamus and the cortical white matter accurate contrast enhancement could be observed (Figure 2). Evaluation of time-intensity curves in the suspected ischemic area on the affected side failed to
demonstrate an increase in acoustic impedance after echo-contrast application. In the other ROIs of the affected side and in all ROIs of the unaffected side, time-intensity curves were normal (Figure 3). One day after admission the clinical, SHI, and TCCS findings were unchanged compared with the initial examination. One week later aphasia had remitted almost completely, but high-grade hemiparesis persisted. On CT scans a sharply demarcated striatocapsular infarction could be visualized (Figure 4). Thalamic and cortical structures of the affected hemisphere were spared. TCCS demonstrated symmetrical flow velocities in the MCA. Contrary to the first SHI examinations, contrast enhancement was detectable in the ischemic area on days 7 and 14 after onset of symptoms. In all other ROIs, contrast enhancement continued to be symmetrical.

Case 2
A 64-year-old male patient was referred to our hospital with acute onset of a left-sided hemiplegia 2 hours before admission. TCCS and digital subtraction angiography demonstrated MCA mainstem occlusion. Local thrombolysis using 66 000 IU urokinase was not successful, and the MCA mainstem remained occluded. In SHI images performed after thrombolysis, a large demarcated area of missing contrast enhancement enclosing the region of the white matter and the area of the lentiform nucleus was detectable, whereas in the thalamus typical contrast enhancement appeared. In CT scans no pathological changes, including early infarction signs, were observable. Two days later CT scans demonstrated a complete space-occupying infarction in the MCA territory that was causing midline shift and compression of the lateral ventricles. At this time, the MCA mainstem was recanalized, as demonstrated by TCCS. In SHI examinations no contrast enhancement in any parenchymal region of the affected side was detectable, whereas the recanalized MCA demonstrated clear increase of gray-scale intensities. On the unaffected side no SHI examinations could be performed because of temporal hyperostosis. Three days after onset of clinical symptoms the patient died of cerebral herniation.

Discussion
The evaluation of perfusion abnormalities may play a key role for therapeutic decisions in the acute stage of stroke victims. Although early CCT signs such as focal hypodensity,
focal swelling, or hyperdense MCA sign can be found in more than half the patients, the precise extent and localization of the ischemic areas is usually not detectable in conventional CT images. The use of contrast-enhanced CT, perfusion-weighted MRI, and PET has been advocated in several studies as a diagnostic tool to evaluate cerebral perfusion-weighted MRI, and PET has been advocated in several studies as a diagnostic tool to evaluate cerebral perfusion in acute stroke. However, the availability of PET and MRI scanners is limited, the running costs are high, and performance of these methods is nearly impracticable in acute stroke patients. In contrast, SHI represents a rapid and easily applicable bedside examination technique. A recently published study has shown that this ultrasound method allows visualization of focal cerebral contrast enhancement in individuals without cerebrovascular diseases. However, the clinical value of this technique in acute stroke patients is undetermined. The present cases show that SHI may identify and localize damaged brain tissue with missing contrast enhancement, most likely due to reduced perfusion in acute hemispheric brain infarction. In acute CT scans of patient 1, obscuration of the basal ganglia indicates ischemic cell damage of this area; white matter appeared to be normal. Acute and follow-up CTA, TCCS, and CT examinations point toward an initial embolic MCA mainstem occlusion with fragmentation of the thrombus in connection with adequate cortical collateral blood supply from the posterior cerebral artery and anterior cerebral artery. Because of the good collateralization, cortical structures were saved from the ischemia and the patient did not develop malignant MCA infarction. Acute SHI examinations showed a defined region of absent contrast enhancement in projection to the lentiform nucleus and adjacent structures of the temporoparietal lobe and a characteristic contrast enhancement in projection to the white matter. In contrast, patient 2 developed a malignant space-occupying brain infarction that included the entire MCA territory. Extensive involvement of both the basal ganglia region and white matter by the ischemic damage could be demonstrated in acute SHI examinations, whereas CT scans were still normal at this time. In both individuals, acute ultrasound investigations could provide important and early prognostic information by allowing estimation of the size and localization of the ischemic area. In patient 1, contrast enhancement reappeared in the region of the striatocapsular infarction. However, reperfusion occurred outside the revival times of ischemic damage and irreversible tissue damage could not be prevented. In patient 2, cytotoxic cerebral ischemia (and possibly reperfusion of the occluded MCA mainstem) caused massive tissue swelling, with secondary compromise of circulation from increasing pressure in the extravascular space. Accordingly, in follow-up SHI examinations no contrast enhancement was detectable in any parenchymal region of the affected hemisphere.

Although our preliminary SHI results are promising, physical properties such as depth-dependent attenuation of the reflected second harmonic ultrasound beam and the nonlinear relationship between microbubble concentration and optic intensity must be taken into account in the evaluation of cerebral perfusion disorders. Because of the distorted anatomy in transcranial real-time images compared with neuroradiological imaging techniques and the similar echogenicity of the white matter, thalamus, and lentiform nucleus, precise anatomic localization of the ischemic region is difficult. A further disadvantage of this method is the nonhomogenous increase in tissue brightness due to focal acoustic window failure. Technical developments of ultrasound equipment and new generations of ultrasound contrast agents may help to overcome this problem.

Previous animal studies have shown that SHI can be used to provide accurate assessment of risk area and infarct size during acute myocardial infarction. The findings in our patients demonstrate that abnormalities of cerebral contrast enhancement can be evaluated and monitored in acute stroke patients by means of SHI. Our data indicate that SHI may provide data about prognosis of ischemic cerebral tissue by allowing estimation of extent and duration of cerebral ischemia. Further clinical studies with more patients are needed to establish this new ultrasound technique as a diagnostic tool in acute stroke.

**References**


Second Harmonic Imaging In Acute Middle Cerebral Artery Infarction: Preliminary Results
Thomas Postert, Jens Federlein, Sepp Weber, Horst Przuntek and Thomas Büttner

Stroke. 1999;30:1702-1706
doi: 10.1161/01.STR.30.8.1702
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/30/8/1702

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/