Ultrasound Perfusion Imaging of the Human Brain

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Background and Purpose—Color-coded perfusion maps can be calculated from ultrasound harmonic gray-scale imaging data to analyze brain tissue perfusion.

Methods—In 13 healthy volunteers, 2 doses (0.5 and 1.5 mL) of Optison, a perfluoropropane-containing ultrasound contrast agent, were injected intravenously, and they produced a strong increase in echo enhancement in the brain parenchyma. The contrast agent was injected twice for ultrasound examination of both hemispheres. A total of 24 hemispheres per dose was available for further analysis. We used harmonic imaging for quantification of echo enhancement. Color-coded perfusion maps were calculated from the ultrasound data. In 1 subject, magnetic resonance images were obtained parallel to the orientation of the ultrasound scans.

Results—After administration of both doses of Optison, it was possible to evaluate brain tissue perfusion in all 24 hemispheres. Subtraction of precontrast images and color coding enhanced the visualization of hemispheric perfusion. The epiphyseal gland, anterior interhemispheric fissure, third ventricle, and lateral fissure can be used as reliable anatomic landmarks. Artifacts caused by abrupt changes in thickness of the temporal bone are observed as signal-void streaks oriented from the ultrasound probe toward the cerebral midline.

Conclusions—Harmonic gray-scale imaging with Optison shows strong echo enhancement in the brain parenchyma. By calculating color-coded perfusion maps, it is possible to visualize human brain tissue perfusion at the patient’s bedside.

Key Words: contrast media ■ perfluorocarbons ■ perfusion ■ ultrasonography

Several methods have been used to attempt to evaluate brain perfusion in patients with acute brain infarctions, including single-proton emission CT, PET, CT, and MRI. Compared with ultrasound, these methods are time-consuming, require radioactive tracers, or are intolerable to critically ill or restless patients. It has been shown that it is possible to visualize and measure changes in ultrasound intensities in perfused areas of the brain through the intact skull with the use of harmonic gray-scale ultrasound imaging.1–4 Harmonic imaging is a new ultrasound method that increases the signal-to-noise ratio in color-coded duplex sonography as well as gray-scale imaging. In 3 studies on healthy human volunteers and 2 case reports of patients suffering from cerebral infarction, the use of harmonic imaging in gray-scale ultrasound produced signal-enhancing effects in different regions of the brain.1–5 However, the extent of contrast enhancement in the parenchyma was highly variable and depth dependent. In the first part of this study, using the new perfluoropropane-based ultrasound contrast agent Optison, we concluded that harmonic gray-scale imaging with Optison produced strong echo enhancement in the brain parenchyma.4 The most robust quantitative parameter for harmonic gray-scale imaging was the area under the time-intensity curve. So far, however, all approaches to analyze these harmonic-imaging perfusion data have been time-consuming and/or have required interactive region-of-interest analyses.

The purpose of this second evaluation of the data was to investigate an automated, color-coded evaluation method of harmonic gray-scale imaging. This analysis is of particular interest for the design of further investigations intending to visualize perfusion defects by ultrasound methods in patients with acute ischemic stroke.

Subjects and Methods

Subjects

Transcranial sonography with adequate ultrasonic windows was performed in 13 healthy subjects (5 women, 8 men; median age, 28 years; age range, 21 to 44 years; median body mass index, 24.1 kg/m²; and body mass index range, 20.9 to 32.6 kg/m²). Exclusion criteria were pregnancy or lactation, a past medical history of cerebrovascular or cardiovascular disease, previous allergic reactions, and substance or alcohol abuse. A complete physical examination, 12-lead electrocardiogram, and routine blood tests were performed before and 24 hours after administration of the contrast agent. Written, informed consent was obtained from each volunteer before entry into the study. The study was approved by an ethics committee and was carried out in accordance with the guidelines of Good Clinical Practice and the Declaration of Helsinki (1964).
Ultrasound Contrast Agent

Optison is a perfluoropropane-containing ultrasound contrast agent based on a 1% albumin solution. This contrast agent is commercially available and was originally developed for echocardiography (generic FS069, Mallinckrodt Inc). The solution was prepared by following the manufacturer’s instructions. Two intravenous bolus injections of 0.5 and 1.5 mL (injection speed of 1 mL/s) were used. Each injection was followed immediately by a second bolus of 3 mL of 0.9% NaCl solution to ensure clearance of the residual ultrasound contrast agent in the venous system. The time between the 2 ultrasound contrast agent bolus injections was 5 to 10 minutes.

Transcranial Sonography

The investigation was performed as described earlier. Harmonic gray-scale imaging was performed with an HP SONOS 5500 ultrasound system (Agilent Technologies) connected to a 1.8-/3.6-MHz sector transducer (S4 probe, Agilent Technologies) at an investigation depth of 10 cm (focus at 8 cm). For gray-scale imaging, we used the integrated backscatter mode and the study type T-INT (mechanical index of 1.0 to 1.1).

After each contrast agent injection, 62 digitalized, gray-scale images of the brain triggered by the electrocardiogram were stored in continuous-loop-review memory and were then recorded on optical disc for offline analysis. We used the transient-response imaging mode with a frame rate of 1 image every 4 cardiac cycles. Gain and transmit power settings were optimized for each volunteer at the beginning of each investigation and were not changed throughout the procedure.

Postprocessing Image Data

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

Image data postprocessing consisted of 5 steps. (1) By evaluating the intensities of the 62 images within 1 loop, the onset and peak of contrast enhancement can be determined. (2) From images that were obtained before the onset of contrast enhancement, an averaged image (background image) was calculated. (3) Next, the background image was subtracted from the original images. (4) From various algorithms, the following 2 yielded the most promising results and were selected to calculate parameter images for analysis in this study: the averaged peak image (API) and pixelwise peak intensity (PPI). For API, an averaged image is calculated from the series of 5 consecutive images that show the highest contrast enhancement as defined by intensity. For PPI, the series of 5 consecutive images that show the highest contrast enhancement, as defined by intensity, is selected. Then, in a pixel-by-pixel evaluation, an image is calculated in which every pixel is set to the peak intensity found within this series. (5) Finally, the background, API, and PPI images are converted to a color scale. Gray-scale and color images are stored on hard disk and printed on paper from 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.

Image Analysis

Paper prints of background and parameter (API and PPI) images were analyzed by 2 investigators. We identified anatomic landmarks, noted the presence of artifacts, and evaluated the homogeneity of brain perfusion. We used an arbitrary scoring system to record whether an anatomic structure was “identified with certainty” (score of 2), “most probably identified” (score of 1), or “not identified” (score of 0). We sought to identify midline structures (ie, epiphyseal gland, third ventricle, and anterior interhemispheric fissure) and the M1 segment or main trunk of the middle cerebral artery in the lateral fissure.

Two types of artifact were encountered: (1) low-signal sections at the anterior or posterior border of the ultrasound section, which were due to limitations of the transtemporal bone window, and (2) thin, low-signal streaks oriented from the ultrasound probe toward the midline. We noted whether these artifacts caused significant decrease of signal (score of 2), a slight decrease of signal (score of 1), or were absent (score of 0).

As shown in the Figure, we used the epiphyseal gland, cerebral midline, and anterior interhemispheric fissure as anatomic landmarks to divide the ultrasound sections into the following areas: (1) anterior territory of the ipsilateral middle cerebral artery, (2) main territory of the ipsilateral middle cerebral artery, (3) ipsilateral thalamus, (4) cerebellum (this section also contains the posterior aspect of the temporal gyrus), (5) territory of the contralateral middle cerebral artery, and (6) contralateral thalamus. We noted whether brain perfusion led to a clearly visible increase in signal in 50% or less of the respective area (score of 0), in >50% of the respective area (score of 1), or whether homogenous perfusion was noted (score of 2).

Magnetic Resonance Imaging

In 1 subject, MR images were obtained parallel to the ultrasound section. During the ultrasound study, markers were attached to the subject’s head, which were visible on both ultrasound and MR images. MRI studies were performed on a 0.2-T MR scanner (Siemens Magnetom Open) using a 3D, T1-weighted fast low-angle shot sequence: repetition time/echo time=16.1/7 ms, flip angle=30°; effective thickness=4 mm; field of view=240 mm; matrix=240×256, and 2 acquisitions. MR images were reconstructed parallel to the anatomic markers.

Results

Anatomic Landmarks

A total of 24 hemispheres per dose, ie, 48 studies, were available for further analysis. The epiphyseal gland was identified with certainty (score of 2) in 45 studies, most probably identified (score of 1) in 2 studies, and not identified (score of 0) in 1 study. The third ventricle was identified with certainty in 31 studies, identified most probably in 12 studies, and not identified in 5 studies. The anterior interhemispheric fissure was identified with certainty in 37 studies, most probably identified in 7 studies, and not identified in 4 studies. In 1 study in which the epiphyseal gland could not be identified, the remaining midline structures, ie, third ventricle and anterior interhemispheric fissure, were identified. The lateral fissure was identified with certainty in 20 studies, most probably identified in 2 studies, and not identified in 26 studies.

Perfusion

Results are detailed in the Table. In all 48 studies, the effects of brain perfusion were seen. On the PPI parameter images, brain perfusion was visualized more homogeneously than on the API images (the Figure). The total score values for all regions were higher for those investigations that used the PPI method compared with the API method. The most homogeneous visualization of perfusion was found in the area of the ipsilateral thalamus, followed by the contralateral thalamus and the ipsilateral main territory of the middle cerebral artery. However, visualization of perfusion of the anterior territory of the ipsilateral middle cerebral artery was regarded as insufficient (score of 0) in 25% to 38% of hemispheres due to ultrasound field artifacts at the edge of the insonation plane.
No significant differences were found between injections of 0.5 and 1.5 mL of Optison.

Artifacts
Limitations of the transtemporal bone window were encountered in all 48 studies (the Figure, panel D). Low-signal areas at the anterior border of the ultrasound section caused a significant decrease in signal (score of 2) in 46 studies and a slight decrease in signal (score of 1) in 1 study and were absent (score of 0) in only 1 study. Low-signal areas at the posterior border of the ultrasound section caused a significant decrease in signal in 29 studies and a slight decrease in signal in 8 studies and were absent in 11 studies. Thin, low-signal streaks orientated from the ultrasound probe toward the midline were found in 44 of 48 studies (the Figure). Thirty-one studies contained 1 thin streak artifact, 12 studies contained 2, and 1 study contained 3 of these artifacts.

Discussion
It had been shown before that harmonic gray-scale imaging with Optison produces a strong echo-enhancement effect in the brain parenchyma. However, so far, all approaches for analyzing such harmonic-imaging perfusion data have been time-consuming and/or have required interactive region-of-
interest analyses.\textsuperscript{1–5} In this study, we have described a fast method to produce qualitative parameter images without the requirement for user interaction. Instead of displaying the area under the time-intensity curve, which is related to cerebral blood volume, we analyzed the peak intensity increase from baseline images after administration of the contrast agent. This parameter is related to the maximum amount of contrast agent in the tissue and, in a low-concentration range, showed a linear correlation to the contrast agent dose.\textsuperscript{8} As shown in the quantitative analysis of this study, we found no significant dose–peak intensity relation.\textsuperscript{4} Therefore, this parameter only indicates the presence of contrast agent in the microcirculation as a result of perfusion of this area.

To reduce the effects of motion and other artifacts, the algorithm that performed best in our study analyzed the complete loops of 62 ultrasound images, but in the end it used only a small subset of images to calculate the parameter image. If the frame rate of data acquisition is changed, it may be necessary to adjust the length of this subseries. In our study, an injection of 1.5 mL of Optison had no clear advantages over injection of 0.5 mL, as was shown in the earlier quantitative analysis of the data.\textsuperscript{4}

All evaluators stated that color coding of the parameter images greatly enhanced visualization of the perfusion effects in an easy-to-interpret way. Because of its speed (calculation of the images takes \textasciitilde 90 seconds), our method makes clinical examinations of stroke patients at the bedside more feasible. However, in stroke patients, diagnostic reliability may be improved by an additional parameter image that displays a time delay in perfusion (time-to-peak image). This approach needs further evaluation by using a higher frame rate to improve the time resolution for this kind of parameter image.

In summary, this study indicates that it is possible to visualize echo enhancement in perfused areas of the brain through the intact skull in an easy-to-interpret way. This observation is encouraging for further studies of evaluating brain perfusion in patients with acute brain infarctions.

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### Analysis of Brain Perfusion After Injection of 0.5 mL or 1.5 mL of Optison in 24 Hemispheres Each

| Contrast Agent Dose and Area | Parameter Image | |  |
|-----------------------------|-----------------|--|---|---|
|                            | API Score       | Total Score | PPI Score | Total Score |
| Optison, 0.5 mL             |                |            |            |            |
| Ipsilateral                |                |            |            |            |
| MCA 1                      | 0 1 16 7 18    | 6 20       | 0 2 16    | 0 2 16     |
| MCA 2                      | 5 18 1 0 52    | 6 53       | 6 17 1 0 53 |
| Thalamus                   | 15 8 1 0 62    | 22 69      | 22 1 1 0 69 |
| Cerebellum                 | 0 13 11 0 37   | 2 42       | 2 14 8 0 42 |
| Contralateral              |                |            |            |            |
| MCA                         | 0 20 3 1 43    | 2 49       | 2 21 1 0 49 |
| Thalamus                   | 7 16 1 0 54    | 17 64      | 17 6 1 0 64 |
| Optison, 1.5 mL             |                |            |            |            |
| Ipsilateral                |                |            |            |            |
| MCA 1                      | 0 1 14 9 16    | 0 20       | 0 3 14 7 20 |
| MCA 2                      | 2 1 21 0 49    | 5 53       | 5 19 0 0 53 |
| Thalamus                   | 15 9 0 0 63    | 19 67      | 19 5 0 0 67 |
| Cerebellum                 | 2 9 13 0 37    | 3 45       | 3 15 6 0 45 |
| Contralateral              |                |            |            |            |
| MCA                         | 0 20 4 0 44    | 0 48       | 0 24 0 0 48 |
| Thalamus                   | 5 18 1 0 52    | 14 62      | 14 10 0 0 62 |

MCA 1 indicates anterior territory of the ipsilateral middle cerebral artery; MCA 2, main territory of the ipsilateral middle cerebral artery; thalamus and cerebellum, section that also contains the posterior aspect of the temporal gyrus; contralateral MCA, territory of the contralateral middle cerebral artery; and contralateral thalamus. We noted whether brain perfusion led to a clearly visible increase in signal in 50% or less of the respective area (score of 0), in >50% of the respective area (score of 1), or whether homogenous perfusion was noted (score of 2). Total score was sum of scores reached for each area. Numerical values represent the number of brain hemispheres in each category. See text and the Figure for details.
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References
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