Comparison Between Echo Contrast Agent–Specific Imaging Modes and Perfusion-Weighted Magnetic Resonance Imaging for the Assessment of Brain Perfusion

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Background and Purpose—Contrast burst imaging (CBI) and time variance imaging (TVI) are new ultrasonic imaging modes enabling the visualization of intravenously injected echo contrast agents in brain parenchyma. The aim of this study was to compare the quantitative ultrasonic data with corresponding perfusion-weighted MRI data (p-MRI) with respect to the assessment of brain perfusion.

Methods—Twelve individuals with no vascular abnormalities were examined by CBI and TVI after an intravenous bolus injection of 4 g galactose-based microbubble suspension (Levovist) in a concentration of 400 mg/mL. Complementary, a dynamic susceptibility contrast MRI, ie, p-MRI, of each individual was obtained. In both ultrasound (US) methods and p-MRI, time-intensity curves were calculated offline, and absolute time to peak intensities (TPI), peak intensities (PI), and peak width (PW) of US investigations and TPI, relative cerebral blood flow (CBF) and relative cerebral blood volume (CBV) of p-MRI examinations were determined in the following regions of interest (ROIs): lentiform nucleus (LN), white matter (WM), posterior (PT), and anterior thalamus (AT). In addition, the M1 segment of the middle cerebral artery (MCA) was evaluated in the US, and the precentral gyrus (PG) was examined in the p-MRI examinations. In relation to a reference parenchymal ROI (AT), relative TPIs were compared between the US and p-MRI methods and relative PI of US investigations with the ratio of CBF (rCBF) of p-MRI examinations in identical ROIs.

Results—Mean TPIs varied from 18.3 to 22.0 seconds; mean CBF ranged from 0.0093 to 0.0134 \( \times 10^{-6} \) \( \text{mL/sec/mm}^3 \) arbitrary units (MCA) in CBI mode and from 9.1 to 15.0 (WM) to 17.5 to 23.0 (LN) to 18.2 (MCA) seconds in TVI examinations. Mean TPI was significantly shorter and mean PI and mean PW were significantly higher in the MCA compared with all other ROIs \( (P<0.05) \). Mean TPI of the p-MRI examinations ranged from 22.0 to 34.0 (LN) to 27.0 to 26.7 (MCA) seconds in TVI examinations. Mean TPI was significantly shorter and mean PI and mean PW were significantly higher in the MCA compared with all other ROIs \( (P<0.05) \). Mean TPI of the p-MRI examinations ranged from 22.0 (LN) to 23.0 (WM) seconds; mean CBF ranged from 0.0093 to 0.0041 (LN) to 0.0043 to 0.0021 (WM). There was no significant difference in rTPI in any ROI between US and p-MRI measurements \( (P>0.2) \), whereas relative PIs were significantly higher in areas with lower insonation depth such as the LN compared with rCBF.

Conclusions—In contrast to PI, TPI and rTPI in US techniques are robust parameters for the evaluation of cerebral perfusion and may help to differentiate physiological and pathological perfusion in different parenchymal regions of the brain. (Stroke. 2002;33:2433-2437.)

Key Words: contrast media ■ magnetic resonance imaging, perfusion-weighted ■ perfusion ■ ultrasonography, Doppler, transcranial

In recent years, there have been advances in ultrasound (US) technology enabling the identification of perfusion in a variety of parenchymal organs.\(^1\)\(^2\) The discovery that contrast microbubbles resonate and create backscatter signals not only at the fundamental (transmitted) frequency but also at multiples (harmonics) of this frequency is used in harmonic imaging because tissue produces a smaller harmonic signal than contrast microspheres.\(^3\)\(^4\) Various studies have shown that transcranial harmonic imaging enables identification of parenchymal cerebral echo contrast enhancement under physiological and pathological conditions.\(^5\)\(^-\)\(^10\) More recently, it has been observed that diagnostic US transmitted at high...
energy levels may destroy or modify the morphology of microbubbles. These changes in microbubble shape and size are reflected in the amplitude and spectral energy distribution of the ultrasonic echoes so that short sequences of 6 to 10 pulses per line can reveal the presence of microbubbles. The changes are then detected as broadband noise in the Doppler spectrum (contrast-burst imaging [CBI]) or as characteristic features of microbubbles using dedicated algorithms (time variance imaging [TVI]). The result of the detection is preferably displayed in color-coded US images.\textsuperscript{11} In 2 pilot studies, it has been shown that echo contrast–specific imaging modes exploiting this phenomenon, like CBI and TVI, are sensitive techniques for the identification of parenchymal microbubble distribution in the brain.\textsuperscript{12,13} A major disadvantage that all US techniques have in common is the fact that physical properties like nonlinear relationship between microbubble concentration and optic intensities\textsuperscript{14} and the depth-dependent attenuation of the received harmonic signals make absolute quantification of peak intensities (PIs) impossible.

Furthermore, the diagnostic value of different US parameters is unknown because there has been no comparative study between US techniques and reference methods. Validated indicators of absolute quantification of cerebral blood flow (CBF) and cerebral blood volume (CBV) are PET\textsuperscript{15} and xenon CT.\textsuperscript{16} Perfusion-weighted MRI (p-MRI) provides semiquantitative information of brain perfusion that can be easily compared with recently developed US perfusion methods. The present study was designed to evaluate the reliability of quantitative parameters of US brain perfusion examinations compared with corresponding p-MRI data.

Material and Methods

Subjects
Twelve patients (8 women, 4 men; mean age, 38.3 years; range, 26 to 50 years) without history of cerebrovascular or cardiovascular disease with adequate acoustic temporal bone window were included in the present study after informed consent was obtained. Exclusion criteria were pregnancy, galactosaemia, abnormal extracranial and transtemporal color-coded real-time sonography, abnormalities in T1- and T2-weighted MRI examinations, and pathological blood pressure or pulse rates. The study was approved by the local ethics committee.

Ultrasound Examinations

Routine Color-Coded Duplex Examination of the Extracranial and Intracranial Brain-Supplying Vessels and CBV Measurements
We performed all examinations using a Siemens Sonoline Elegra US system (Siemens Medical Systems, Inc, Ultrasound Group) equipped with a 7.5-MHz linear-array transducer for the extracranial arteries and a 2.5-MHz phased-array transducer for the intracranial vessels. For diagnosis of an occlusion or a high-grade stenosis, criteria identical to those in previously published studies were used.\textsuperscript{17,18} In all patients, CBF volume was calculated according to Schöning and Scheel.\textsuperscript{19} CBF volume was determined as the sum of the flow volumes of the internal carotid and vertebral arteries of both sides.

Physical Principle of CBI and TVI
CBI and TVI have been introduced in a recently published article.\textsuperscript{13} Briefly, both US techniques exploit the fact that microbubbles undergo partial or complete destruction or splitting when exposed to a high-energy ultrasound field. CBI, which is derived from power Doppler, uses short sequences of typically 6 broadband pulses with an elevated output power level to minimize acquisition time, improve axial resolution, and optimize microbubble destruction. Processes associated with the destruction of microbubbles produce broadband noise in the Doppler spectrum that partially passes the wall filter and can be displayed color coded as in conventional power Doppler. These signals can be obtained even from nonmoving or very slowly moving microbubbles and are consequently associated with perfusion. TVI uses a different processing of the echo data. This technique extracts the amplitude and spectral slope from 10 echoes acquired per beam line. The spectral slope is a parameter describing the symmetry of the power spectrum with respect to the center frequency. Both parameters, amplitude and spectral slope, will vary over time if the multiple insonifications alter the structure of the microbubbles. TVI identifies characteristic variation using a stochastic model for bubble destruction and then quantifies these variations.

Protocol of the Examination With Echo Contrast–Specific Imaging Modes
US examinations were performed unilaterally with the transtemporal approach. An axial diencephalic plane was adjusted by slightly tilting the transducer toward the parietal lobe. The third ventricle, adjacent hypophyseal thalamus, and frontal horns of the lateral ventricles were orientation landmarks. Complementarily, visualization of the M\textsubscript{3} segment of the middle cerebral artery (MCA) after echo contrast agent injection ensured the correct position in the diencephalic plane. Mechanical indexes were <1.5 and <1.0 for CBI and TVI examinations, respectively. After application of the echo contrast agent, series of 50 to 70 images were acquired at a frame rate of 0.5 Hz. The field of view was set to an imaging depth of 10 cm; the sector angle was 90°. CBI and TVI examinations of the ipsilateral brain hemisphere were performed; the time interval between both investigations was at least 30 minutes to ensure that all microbubbles were removed from the circulation. All examinations were performed with the left-sided temporal approach and were digitally recorded and evaluated offline.

Physical Properties and Application Mode of the Echo Contrast Agent
In all examinations, 4 g of a galactose-based microbubble suspension (Leovist, Schering AG) in a concentration of 400 mg/mL was injected into a venous access with a standardized size (18 to 20 gauge) and localization (antecubital vein) by means of an US power injector (Medrad Inc) at a rate of 8 mL/s. Leovist consists of air bubbles surrounded by a galactose shell and stabilized by palmitic acid. Mean particle size is 2.0 to 4.5 μm; 97% of the microbubbles are <10 μm.

Evaluation of Quantitative Parameters
Regional cerebral echo contrast enhancement was quantified using time-intensity curves (TIC). Peak intensities (PIs), time to peak intensities (TPIs), and peak widths (PW, or the width of the TIC at a 90% value of the PI) were calculated from a model function that was fitted to the measured curve in at least mean square sense. The model function has been described earlier.\textsuperscript{13} Unlike filter approaches, it does not disregard any of the information in the measurements but incorporates knowledge on the expected signal. Quantitative data were calculated for the following manually placed regions of interest (ROIs): in the ipsilateral hemisphere, posterior parts of the thalamus (ROla), anterior parts of the thalamus (ROib), lentiform nucleus (ROlc), white matter (ROid), and MCA (M\textsubscript{3} segment; ROe) (see Figure 1). Finally, parameter images for TPI, PI, and PW were formed by dividing each image within a series into 1×1-mm regions. Extracted data from corresponding regions were displayed in a color-coded parameter image for each individual. Mean values and SD of TPI, PI, and PW were calculated.

MRI Examinations

Protocol
Dynamic susceptibility contrast MRI, ie, p-MRI, based on the acquisition of the signal time course after bolus administration of contrast medium was performed on a 1.5-T whole-body Magnetom
time curves to a $\gamma$-variate function and then integrating the fitted curve.

ROI analyses of TPI, CBF, and CBV were performed unilaterally according to the US examinations in the following manually placed regions: posterior parts of the thalamus (ROIa), anterior parts of the thalamus (ROIb), lentiform nucleus (ROIc), white matter adjacent to the lentiform nucleus (ROId), and precentral gyrus (ROIe). Mean values and SD of these parameters were calculated.

All data of the US and p-MRI examinations were obtained by the same investigator (S.M.) to achieve identical localized ROIs in the examinations.

### Comparison Between US and p-MRI Examinations

For comparison of the TPI in US and p-MRI examinations, the TPI of ROIb (thalamus anterior) was subtracted from the TPI in each other ROI to obtain relative TPI (rTPI). This procedure was chosen to reduce the variance of data induced by different US and p-MRI examinations settings; eg, noisy p-MRI examinations under clausrophobic conditions are more likely to produce tachycardia and elevated blood pressure, hence influencing blood circulation times. The anterior thalamus was selected as reference region because of its favorable insonation angle in mid parts of the ultrasonic beam and its clearly depicted neighboring anatomical structures such as the third ventricle in transcranial B-mode images.

A $t$ test for paired samples was used to compare rTPI of US with p-MRI measurements.

Pls of the US studies were compared with CBFs of the p-MRI studies. US-PI represents the maximal intensity increase in grayscale images caused by the echo contrast agent in a defined sample volume and is related to the maximum amount of contrast agent bubbles but also to, for example, insonation depth. CBF is a measure of the volume of blood delivered to the tissue in a given amount of time, and regional CBF, known as tissue perfusion, is proportional to the height of the tissue concentration-versus-time curve after a bolus; therefore, regional CBF is related to PI. The ratios of the relative PI (rPI) and CBF (rCBF) of each ROI and the reference region ROIb, respectively, were calculated, and a $t$ test for paired samples was applied to compare the US methods with the p-MRI examinations.

### Table 1. Mean Values and SD of Quantitative Parameters in 12 CBI Examinations

<table>
<thead>
<tr>
<th>ROI</th>
<th>TPI, s</th>
<th>PI, AU</th>
<th>PW, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROIa</td>
<td>18.5±4.7</td>
<td>862.8±661.3</td>
<td>7.8±4.6</td>
</tr>
<tr>
<td>ROIb</td>
<td>18.3±5.0</td>
<td>810.5±618.8</td>
<td>7.3±4.5</td>
</tr>
<tr>
<td>ROIc</td>
<td>19.2±5.1</td>
<td>1522.9±574.2</td>
<td>9.1±4.0</td>
</tr>
<tr>
<td>ROId</td>
<td>20.1±5.8</td>
<td>581.9±342.4</td>
<td>8.3±4.4</td>
</tr>
<tr>
<td>ROIe</td>
<td>17.2±4.9*</td>
<td>3400.9±621.7*</td>
<td>24.3±12.8*</td>
</tr>
</tbody>
</table>

AU indicates arbitrary units.

*Values of ROIe differ significantly from all other ROIs ($P<0.05$).

### Table 2. Mean Values and SD of Quantitative Parameters in 12 TVI Examinations

<table>
<thead>
<tr>
<th>ROI</th>
<th>TPI, s</th>
<th>PI, AU</th>
<th>PW, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROIa</td>
<td>19.2±4.3</td>
<td>11.9±6.0</td>
<td>8.7±5.2</td>
</tr>
<tr>
<td>ROIb</td>
<td>19.4±5.3</td>
<td>12.2±5.3</td>
<td>7.1±3.9</td>
</tr>
<tr>
<td>ROIc</td>
<td>19.8±5.1</td>
<td>17.5±4.9</td>
<td>8.7±3.5</td>
</tr>
<tr>
<td>ROId</td>
<td>20.4±4.3</td>
<td>7.5±4.6</td>
<td>7.4±4.6</td>
</tr>
<tr>
<td>ROIe</td>
<td>17.3±4.0*</td>
<td>46.3±7.1*</td>
<td>26.7±18.2*</td>
</tr>
</tbody>
</table>

AU indicates arbitrary units.

*Values of ROIe differ significantly from all other ROIs ($P<0.05$).
The rPI and rCBF of ROIa demonstrated no significant difference between the US and p-MRI modes. However, rPIs of ROIc and ROId were significantly higher in US compared with rCBF in p-MRI-examinations (Table 5).

**Discussion**

In various studies, p-MRI has been shown to visualize ischemic brain parenchyma in acute stroke patients. However, MRI is intolerable in critical ill patients because it is time consuming and is not generally available in the community and its running costs are high. In contrast, US is an easily available bedside method. Various US studies exploiting harmonic signals or signals resulting from destruction of microbubbles were able to demonstrate physiological and pathological brain tissue perfusion. Standard parameters, however, for the analysis of TICs of US perfusion studies such as PI and area under the curve could be evaluated only qualitatively because of specific physical properties such as depth-dependent attenuation of the ultrasound signals, inhomogeneous temporal bone window, and nonlinear relation between echo contrast concentration and video intensity. From an in vitro study, it is known that TPI in US perfusion examinations may provide a more robust parameter. In only 1 previously published study, TPI was examined in different brain regions and revealed intraindividual homogeneous values in different brain regions consistent with our present findings. In accordance with all previously published US studies, we observed a marked depth-dependent decrease in PI in TVI and CBI examinations, whereas TPI was not influenced by the insonation depth, which supports an in vivo study by Bos et al. Hereby, a quantitative comparison of ROIs is possible. The characteristic time delay between a branch of a major artery and parenchyma found in our study is a further criterion that helps to characterize physiological brain perfusion.

Even though TPI is influenced by various factors such as heart rate, heart ejection fraction, and position of the venous canula, its potential to demonstrate hemodynamic impairment of cerebral perfusion in conditions of acute stroke has been shown in p-MRI. This is the first study to compare p-MRI with US perfusion studies. We found no significant differences between rTPI in US and MRI examinations in any ROI, thus supporting the robustness and reliability of this parameter.

In contrast, rPIs were highly depth dependent and had a high interindividual variability in all ROIs compared with corresponding rCBF in p-MRI examinations. This finding is in accordance with all previously published studies on the ultrasonic assessment of brain perfusion and confirms that this parameter is not suitable for quantification of perfusion.

In return, PW as another diagnostic parameter has not been regarded in previous ultrasonic studies. The PW was signifi-
stantly higher in the M1 segment than in the parenchymal ROIs because destroyed microbubbles in large vessels are rapidly replaced. These characteristic features of TICs allow the differentiation of vessels and brain parenchyma. In future US perfusion studies on acute stroke patients, shortened PW might be a hint for the diagnosis of impaired perfusion.

In conclusion, our study demonstrates that TPI provides a reliable parameter in US perfusion examinations because it is not as depth dependent as other parameters like PI. Previously published p-MRI studies in acute stroke patients demonstrated the diagnostic value of TPI maps for differentiation between unaffected parenchyma, penuabra, and ischemic core area. From the results of this study, future US studies should include TPI maps in stroke patients to investigate the potential for a semiquantitative differentiation between affected and unaffected tissue. Additionally, these studies should be compared with other quantitative techniques that assess brain perfusion like p-MRI.

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References
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