Contrast Burst Depletion Imaging (CODIM): A New Imaging Procedure and Analysis Method for Semiquantitative Ultrasonic Perfusion Imaging

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Background and Purpose—Established methods of ultrasonic perfusion imaging using a bolus application of echo contrast agent provide only qualitative data because of various physical phenomena. This study was intended to investigate whether a new ultrasound perfusion imaging method termed contrast burst depletion imaging (CODIM) may provide semiquantitative measures of parenchymal perfusion independent of examination depth and acoustic energy distribution.

Methods—In a system with a constant concentration of contrast agent, analyzing the decrease in image intensity that occurs with microbubble-destructive imaging modes yields parameters that are considered to correlate with tissue perfusion. This method was first evaluated with a perfusion model that showed that the main resulting parameter “perfusion coefficient” (PC) is a monotonic nonlinear function of flow velocity. Seventeen human volunteers were then scanned according to this method with the use of 2 different contrast agents. Results were correlated with those from perfusion-weighted MRI examinations.

Results—The PC did not show significant differences in gray matter areas (ranging from $1.466 \times 10^{-2}$ to $1.641 \times 10^{-2}$ s$^{-1}$) of the brain despite different insonation depths (eg, ipsilateral and contralateral thalamus). In contrast, white matter exhibited significantly lower perfusion values in both imaging modes (PC: $0.604 \times 10^{-2}$ s$^{-1}$ to $0.745 \times 10^{-2}$ s$^{-1}$; $P<0.05$).

Conclusions—CODIM is a promising new tool of imaging parenchymal (brain) perfusion in healthy persons. The method provides semiquantitative and depth-independent perfusion parameters and in this way overcomes the limitations of the perfusion methods using a bolus kinetic. Further investigations must be done to evaluate the potential of the method in patients with perfusion deficits. (Stroke. 2003;34:77-83.)

Key Words: cerebrovascular circulation ■ magnetic resonance imaging ■ perfusion ■ ultrasonography

In recent years, new ultrasound methods have achieved many advances in imaging parenchymal perfusion. Ultrasound contrast agents and contrast agent–specific imaging modes are the key to functional imaging in parenchyma. The first contrast agent–specific imaging technique was second harmonic imaging, visualizing the harmonic frequencies generated by insonated contrast agents in perfused capillaries. Later, time variance imaging and contrast burst imaging (CBI) were introduced, both based on the detection of ultrasound-induced destruction or splitting of microbubbles. Destructive imaging techniques are the most sensitive for determining contrast agent–specific imaging modes and therefore are best suited for the assessment of parenchymal perfusion. After a bolus injection of a contrast agent, characteristic wash-in/wash-out curves can be observed in a given region of interest (ROI). These curves can provide only qualitative information because image intensity depends nonlinearly on the acoustic power within the ROI. Furthermore, microbubble concentration is governed not only by physiological conditions but also by the ultrasound-induced destruction of microbubbles. Although the time to peak intensity in a wash-in/wash-out examination can be considered a semiquantitative parameter, it is important to note that the time to peak intensity is related not only to the perfusion rate but also to the vessel topology. Another drawback for the practical application of the “bolus approach” is that the examination is limited to 1 image plane per injection. Between 2 injections, the concentration of microbubbles has to decrease to a negligibly low value, which may take 20 minutes. Consequently, comparisons such as those between the right and left brain hemispheres are time consuming. Alternative imaging approaches that might overcome the aforementioned drawbacks assume a constant microbubble concentration in the blood pool during data acquisition. The “replenishment approach” intends to destroy all microbubbles in the imaging plane with a high-intensity, low-frequency, and low...
bandwidth insonation and then to image the refilling at a low-power level, ie, without destroying more bubbles. If the destruction of bubbles during imaging is not negligible, the destruction must be estimated. In addition, low-power imaging may not provide sufficient signal-to-noise ratio in the brain.

The purpose of this study was to investigate the potential of a new semiquantitative ultrasonic method of imaging parenchymal perfusion in healthy volunteers, referred to as contrast burst depletion imaging (CODIM), with the use of Levovist and Optison as contrast agents. This method makes use of the decrease in contrast agent concentration during destructive imaging to combine the advantages of high-contrast, high-signal-to-noise ratio imaging techniques with the semiquantitative information and easy-to-access information that the replenishment method may also provide. To analyze and validate the proposed method, 3 steps were undertaken: in vitro evaluation with the use of a perfusion phantom, in vivo evaluation with examination of healthy volunteers, and comparison of the method with perfusion-weighted MRI (PWI), ie, the present "gold standard" of brain perfusion measurement in clinical settings. The focus of this study was chosen with respect to the diagnosis of perfusion deficits in patients with acute ischemic stroke.

Subjects and Methods

Ultrasound Examinations

Principle of CODIM

The number of microbubbles in a sample volume depends on the percentage of blood in the sample volume and on the microbubble concentration in the blood. Insonation of the sample volume by an ultrasound pulse will cause microbubble destruction so that the microbubble concentration decreases instantaneously. Perfusion of the sample volume washes out blood with destroyed microbubbles, and washes in new microbubbles, thus repeatedly increasing the concentration between subsequent insonations. Once the insonation of the sample volume at a constant pulsing interval, eg, the frame rate, has started, the observable microbubble concentration, ie, the concentration at the time of insonation, in the sample volume drops until it reaches equilibrium. Since both effects, destruction and perfusion, influence the time-concentration curve in different ways, the effects can be quantified by analyzing the curve.

Technical Background of CODIM

CODIM is an algorithm that, in combination with microbubble-destructive imaging techniques, estimates perfusion, with some constraints, independent of imaging depth, ie, independent of tissue attenuation. The major constraint is that the contrast imaging method must provide a measure of microbubble concentration. To account for the poor imaging conditions in the brain, a very sensitive contrast agent imaging technique, ie, CBV, was chosen. Nevertheless, the penetration depth is less than that for the morphological B-mode image, and the near field up to 20 to 30 mm is not accessible. A prerequisite for this method is a stable concentration of microbubbles within the circulation during data acquisition achieved by either infusion or bolus application, with a time delay between injection and insonation. In case of contrast agent infusion, the infusion rate must be adjusted carefully to first establish a sufficient microbubble concentration in the blood pool and then to compensate for the slow decay in concentration. According to our experience, a fairly constant microbubble concentration can be assumed after a bolus injection of contrast agent some time after the maximum concentration has been reached because the life span of microbubbles in the blood pool is far longer than the time of data acquisition. For the aforementioned reasons, bolus injection is even more reliable than infusion unless the microbubble concentration is being monitored and the infusion rate is adjusted accordingly. Therefore, we chose the bolus injection for all examinations. After 40 seconds without insonation, imaging using a destructive image mode (eg, CBV) with a high pulse repetition frequency is started. The image intensity in perfused tissue will decrease and approach an equilibrium, which is defined by the destruction by ultrasound and reperfusion of microbubbles (Figure 1). At least 10 images should be acquired, covering a decrease in intensity of 6 to 30 dB in the perfused tissue within the first 5 images, depending on the local perfusion rate. Under these conditions, the number of measurements is greater than the number of parameters that are estimated, and the changes in the measured intensities are also greater than those that might arise from noise and other artifacts. The transmit power and the frame rate must be chosen accordingly. The evaluation of the quantitative data corresponding to the sample volume is based on fitting the measured time-intensity curve to a theoretical model. The concentration of microbubbles c(t) in a sample volume at the time of the first insonation is given by the concentration of microbubbles in the blood pool weighted by the blood-to-tissue ratio in the sample volume (V_sample), as follows

\[ c(1) = c_{0}\cdot \frac{V_{blood\ pool}}{V_{sample}} \]

For any given sample volume it is assumed that the blood supply does not originate primarily from regions within the same imaging plane. Destruction of microbubbles occurs during or immediately after the insonation and will be observable at high pulse repetition rates. However, compared with the time between 2 frames, the destruction can be considered instantaneous. Between 2 frames, the blood with the destroyed microbubbles is exchanged so that the concentration of microbubbles will approach the concentration in the blood pool c_0 again following an exponential curve

\[ c(n+1) = c(n) \cdot e^{p\cdot d\cdot t\cdot \Delta t} + c_{0} \cdot (1 - e^{-p\cdot d\cdot t\cdot \Delta t}) \]

where n=number of insonations, \( \Delta t = 1/\text{frame rate} \), d=destruction coefficient, and p=perfusion coefficient. Concentration can only be observed at discrete positions in time denoted by the number of insonations n. For concentration as a function of insonations, a closed form solution exists

\[ c(n) = c_{0}\left(x^{n-1} + y^{n-1}\right) \]

where

\[ x = e^{-d\cdot t\cdot \Delta t}, \]
\[ y = (1 - e^{-p\cdot d\cdot t\cdot \Delta t}) \]

Given a sufficient number of measurements with reasonable signal-to-noise ratio, a least squares fit of the model to the measurements yields all parameters of the model. The residual error of the least squares fit is also determined to quantify the reliability of the parameters. The most critical precondition of this
type of evaluation is to find a function that converts image intensity to a parameter that is proportional to the concentration of microbubbles. Image intensities had to be normalized to an unit that may be (nonlinearly) rescaled to be proportional to microbubble concentration. The factor of proportionality may still vary within the imaging plane. Maps of $c_w$ will therefore still reflect depth-dependent variations that are typical for ultrasonic imaging. $e^{-d}$ specifies the normalized amount of microbubbles after an isonon. $p$ characterizes an exchange rate, so that its unit is $s^{-1}$. In the following, the perfusion coefficient $p$ will be termed PC and the destruction coefficient $d$ will be termed DC.

**In Vitro Experiments**
CODIM was initially investigated in vitro with the use of a perfusion phantom. The phantom consisted of a cylindrical sponge with open pores in the submillimeter range. The sponge had a diameter of 24 mm and a length of approximately 80 mm and was embedded in agar at a mean depth of 50 mm. A rotary pump controlled the flow of contrast agent in the direction of the cylinder axis. According to the size of the phantom, a 7.5-MHz linear array was used for scanning at a frame rate of 2 Hz. The experiments covered a flow velocity range of 0 to 10 mm/s. Transmit power, frame rate, and flow velocity were varied to model different flow and isonon conditions. The experiments confirmed a correlation between flow velocity and the perfusion coefficient as defined in Equation 2. Figure 2 shows an example for Levovist, 100% transmit power, 2 frames per second.

**In Vivo Examinations**
The present study included 17 volunteers with sufficient temporal bone window (9 women and 8 men; mean age, 36.06 years; range, 21 to 51 years). Five volunteers were examined with Levovist alone, 10 with both Levovist and Optison, and 2 with Optison alone (resulting in 15 Levovist and 10 Optison examinations). Exclusion criteria were history or physical signs of cerebrovascular diseases, diseases that might influence brain perfusion, galactosemia, heart insufficiency, known allergy, and pregnancy. Usual extracranial and transcranial ultrasonic examinations had to be normal according to previously published criteria. MRI and ultrasonic examinations were performed within 7 days. Informed consent was obtained before subjects entered the study. A positive vote of the local ethics committee was obtained. The procedures followed in this study were in accordance with institutional guidelines. Statistical analysis was performed with the use of ANOVA for repetitive measurements when similarity of values was expected and with the Wilcoxon test for dependent samples when difference of values was expected. The level of significance was defined as 0.05 (2-sided).

**Protocol of In Vivo Examinations**
A Siemens Sonoline Elegra ultrasound system equipped with a 2.5-MHz phased array transducer (Siemens Medical Systems, Inc, Ultrasound Group) was used for all in vivo examinations, which were performed unilaterally with the trans temporal approach. The field of view was set to an imaging depth of 100 mm and a sector angle of 90 degrees. Ultrasound examinations were performed in CBI mode (a destructive imaging technique that visualizes the ultrasound-induced effects on microbubbles; see above and Reference 4) after intravenous bolus injection of either a galactose- and palmitic acid–based microbubble suspension (Leovist, Schering AG [400 mg/mL], 8 mL; injection speed 2 mL/s) or a perfluoropropane-filled agent (Optison, Mallinckrodt GmbH [0.5 mL], injection speed 0.5 mL/s) through an 18-gauge venous access into an antecubital vein. Injection started once the diencephalic plane was correctly adjusted with the third ventricle used as a landmark of orientation. The adjacent thalamus was visualized as a semicircular hypoechogenic structure. Other parenchymal structures were depicted according to previously suggested criteria. The ultrasound system was frozen to stop any isonon of the field of view. Data acquisition was started after 40 seconds at a frame rate of 1 Hz and acoustic power set to 63% (mechanical index 1.8). Morphological images were acquired in parallel in the tissue harmonic imaging mode for orientation. Intervals between different examinations in 1 volunteer were 10 minutes. With this protocol, 15 examinations in which Levovist was used and 10 examinations in which Optison was used were undertaken.

**Evaluation of Quantitative Parameters With CODIM**
Ultrasound data were transferred to a personal computer, where offline evaluation of raw B-mode and CBI data (beam-formed B-mode or power-mode data) was performed with the use of dedicated software developed by our group. Manually placed rectangular ROIs were as follows: ipsilateral anterior thalamus, ipsilateral posterior thalamus, ipsilateral head of caudate nucleus, ipsilateral lentiform nucleus, ipsilateral white matter, contralateral anterior thalamus, contralateral posterior thalamus, and contralateral head of caudate nucleus. Defining a ROI for “white matter” is somewhat controversial because white matter and gray matter exhibit identical echogenicity in B-mode (tissue harmonic imaging mode) images. For this reason it is necessary that experienced transcranial B-mode examiners place this specific ROI using the lentiform nucleus and the isonon depth as landmarks of orientation. Size of ROIs varied as previously described, ie, for head of the caudate nucleus, anterior thalamus, and posterior thalamus between 20 and 40 mm² and for lentiform nucleus and white matter between 70 and 100 mm². For each ROI, perfusion coefficients (PC) and destruction coefficients (DC) were determined as described above.

**MRI Examinations**
**Protocol of MRI Examinations**
MR measurements were performed on a 1.5-T clinical whole-body MR scanner (Magnetom Symphony Quantum, Siemens AG) equipped with a gradient overdrive, with the use of the standard head coil. In addition to the ordinary examination protocol (T1, T2), an axial echo-planar PWI sequence was performed. The parameters of the perfusion study with gradient echo were as follows: 7 to 9 slices, slice thickness 5 to 6 mm, interslice gap 20% of slice thickness, echo time 45 ms, field of view 250 mm, and matrix 128×128. Fifty T2*-weighted measurements per slice at intervals of 1.5 seconds were taken. The contrast agent (0.2 mmol/kg Gd-DTPA) was injected at a rate of 5 ml/s.

**Evaluation and Postprocessing Image Analysis**
PWI data were transferred to a separate personal computer and computed pixel by pixel to create mean transit time, regional cerebral blood volume (rCBV), and regional cerebral blood flow (rCBF) maps with the use of MEDx 3.3.6 software (Sensor Systems Inc). ROIs were placed into anterior and posterior thalamus, lentiform nucleus, head of the caudate nucleus, white matter, and precnental gyrus of both sides to obtain semiquantiative data (rCBV and rCBF in arbitrary units; regional mean transit time in seconds). ROI sizes were defined in a manner similar to that used for the ultrasound examination, which was guaranteed because the examination was
undertaken by the same investigator. The size of precentral gyrus ROIs varied between 20 and 40 mm$^2$.

### Results

#### Ultrasound Examinations

**In Vitro Experiments**

In the in vitro experiments, PC values corresponding to 0, <1 (below measurement precision), 4, and 8.5 mm/s were $1\times10^{-1}$ s$^{-1}$, $1.54\times10^{-1}$ s$^{-1}$, $6.3\times10^{-1}$ s$^{-1}$, and $7.2\times10^{-1}$ s$^{-1}$. The experiment showed that the PC is a monotonic, nonlinear function of flow velocity. These results, however, cannot be used to derive an absolute scale for the in vivo measurement because the transducer and the phantom do not match the in vivo setting closely enough.

**In Vivo Examinations**

All in vivo examinations were well tolerated; no side effects were observed for either contrast agent except for local side effects in 4 volunteers using Optison. For practical reasons, 16 of 17 volunteers were examined from the left side; 1 volunteer had a sufficient bone window only on the right side. For this reason data were not referred to as “right side” or “left side” but as “ipsilateral” (ie, in 16/17 cases “left”) and “contralateral,” which means at the same time “close to” and “distant from” the transducer. All individuals had an adequate bone window that allowed visualization of the third ventricle and the thalamus. Of the 17 volunteers, 5 were examined with Levovist alone, 10 with both Levovist and Optison, and 2 with Optison alone (resulting in 15 Levovist and 10 Optison examinations).

With the use of Levovist, in 2 examinations no depletion curve was obtained in contralateral anterior thalamus and contralateral posterior thalamus, and in 1 examination no contrast enhancement could be achieved in contralateral head of caudate nucleus, ipsilateral head of caudate nucleus, ipsilateral anterior thalamus, ipsilateral posterior thalamus, and ipsilateral white matter. With the use of Optison, the acquisition of usable data failed in 1 examination in contralateral head of caudate nucleus, contralateral anterior thalamus, and contralateral posterior thalamus. In all other ROIs, sufficient data, as shown in Figure 3, could be obtained (a total of 178 of 200 ROIs in 25 examinations).

#### CODIM

Quantitative results of CBI and PWI are summarized in Tables 1 to 4, with relevant data combined for comparison of PC and rCBF values in Tables 1 and 2. Clearly, similar PC values in the following regions of gray matter independent of depth of examination were found: ipsilateral anterior thalamus, ipsilateral posterior thalamus, ipsilateral head of caudate nucleus, ipsilateral lentiform nucleus, contralateral anterior thalamus, contralateral posterior thalamus, and contralateral head of caudate nucleus. The range of mean values of PC in these ROIs was $1.466$ to $1.633\times10^{-2}$ s$^{-1}$ with Levovist and

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**Figure 3.** a through d, Typical images of a CODIM examination. The first (a) and last (b) tissue harmonic B-mode images provide anatomic orientation with ROIs in the ipsilateral lentiform nucleus (iLN), ipsilateral posterior thalamus (iPT), and contralateral posterior thalamus (cPT). The decrease in microbubble concentration between a and b is visible, although tissue harmonic imaging is not as sensitive to contrast agents as CBI. All parameters are therefore derived from CBI. The CBI images corresponding to a and b are given in c and d. Note that morphological information is suppressed in c and d. In e and f, time-intensity curves derived from CBI images of the ROIs are shown: iPT and cPT (e) and iLN (f). Colored lines represent actual measurements; black lines represent the fitted model function of CODIM. PC implies the relative depth independence of the analyzing method.
1.505 to $1.641 \times 10^{-2} \text{ s}^{-1}$ with Optison. When we compared PCs in these ROIs statistically (with similarity expected), no significant differences could be found in either group. On the other hand, the PC of ipsilateral white matter was significantly lower (with difference expected) than the PC of all other ROIs with both Levovist and Optison (mean, 0.6042 and $0.7446 \times 10^{-2} \text{ s}^{-1}$, respectively).

For better comparison of these data with PWI data, we calculated (in accordance with established MR criteria10) relative indices by dividing values of identical ROIs from both sides (“mirror regions”). Since contralateral lentiform nucleus values were not obtained by the described ultrasonic method because of shallow insonation depth, we divided ipsilateral lentiform nucleus values by contralateral anterior thalamus values to obtain a relative value for ipsilateral lentiform nucleus. This was only possible because PWI data showed no significantly differing rCBF values between contralateral anterior thalamus and contralateral lentiform nucleus (see below). Data shown in Table 4 indicate that there were no significant differences between different mirror regions.

To evaluate whether the PC depended on the contrast agents used, values of those subjects who were examined with both Levovist and Optison were analyzed. No significant differences between any of the examined ROIs could be found (with the use of both ANOVA and the Wilcoxon test).

DC values, representing acoustic energy in the field of view, showed a great range with a large SD (Table 3). It was not possible to outline similarities or differences between the different ROIs in either direction statistically.

### MRI Examinations (PWI)

MRI examinations were also well tolerated without side effects; in all examinations sufficient data for postprocessing analysis were obtained, with a total of 204 of 204 ROIs in 17 examinations. Figure 4 shows typical parameter images for rCBF and rCBV of the adequate plane as well as a time-intensity curve with the ROI placed into the “ipsilateral” posterior thalamus. In accordance with the individual ultrasound data (see above), “right” and “left” were changed to “ipsilateral” and “contralateral.”

Tables 1 and 2 summarize rCBF values of the PWI examination. Mean values of rCBF in regions of gray matter (ipsilateral anterior thalamus, ipsilateral posterior thalamus, ipsilateral head of caudate nucleus, ipsilateral lentiform nucleus, contralateral anterior thalamus, contralateral posterior thalamus, contralateral head of caudate nucleus, contralateral lentiform nucleus) ranged from 6.797 to $7.869 \times 10^{-3}$ and from 8.657 to $9.772 \times 10^{-3}$ in the 2 groups (ie, volunteers who had been examined with either Levovist

### TABLE 1. Mean Values of PC of CODIM and rCBF of PWI of All Available ROIs, Levovist Group

<table>
<thead>
<tr>
<th>ROI</th>
<th>PC [s⁻¹] (CODIM) Mean±SD (× 10⁻⁵)</th>
<th>n</th>
<th>rCBF [AU] (PWI) Mean±SD (× 10⁻⁵)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAT</td>
<td>1.603±0.149</td>
<td>14</td>
<td>7.415±0.579</td>
<td>15</td>
</tr>
<tr>
<td>IPT</td>
<td>1.529±0.147</td>
<td>14</td>
<td>7.869±0.520</td>
<td>15</td>
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<tr>
<td>ICN</td>
<td>1.477±0.223</td>
<td>14</td>
<td>6.797±0.427</td>
<td>15</td>
</tr>
<tr>
<td>ILN</td>
<td>1.633±0.347</td>
<td>15</td>
<td>7.142±0.436</td>
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<tr>
<td>IWM</td>
<td>0.064±0.241</td>
<td>14</td>
<td>3.024±0.269</td>
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</tr>
<tr>
<td>IPG</td>
<td>*</td>
<td></td>
<td>10.36±6.393</td>
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</tr>
<tr>
<td>cAT</td>
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<td>7.771±0.086</td>
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<td>cPT</td>
<td>1.528±0.136</td>
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<td>7.864±0.496</td>
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<td>1.466±0.189</td>
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<td>7.127±0.532</td>
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<tr>
<td>cLN</td>
<td>*</td>
<td></td>
<td>6.898±4.226</td>
<td>15</td>
</tr>
<tr>
<td>cWM</td>
<td>*</td>
<td></td>
<td>3.161±3.046</td>
<td>15</td>
</tr>
<tr>
<td>cPG</td>
<td>*</td>
<td></td>
<td>10.33±6.429</td>
<td>15</td>
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### TABLE 2. Mean Values of PC of CODIM and rCBF of PWI of All Available ROIs, Optison Group

<table>
<thead>
<tr>
<th>ROI</th>
<th>PC [s⁻¹] (CODIM) Mean±SD (× 10⁻⁵)</th>
<th>n</th>
<th>rCBF [AU] (PWI) Mean±SD (× 10⁻⁵)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>IAT</td>
<td>1.631±0.231</td>
<td>10</td>
<td>9.156±6.387</td>
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</tr>
<tr>
<td>IPT</td>
<td>1.505±0.180</td>
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<td>9.559±6.252</td>
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<tr>
<td>ICN</td>
<td>1.590±0.142</td>
<td>10</td>
<td>8.657±6.384</td>
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<tr>
<td>ILN</td>
<td>1.544±0.162</td>
<td>10</td>
<td>8.958±6.496</td>
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<tr>
<td>IWM</td>
<td>0.745±0.473</td>
<td>10</td>
<td>3.987±3.595</td>
<td>10</td>
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<tr>
<td>IPG</td>
<td>*</td>
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<td>13.18±9.125</td>
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<tr>
<td>cAT</td>
<td>1.641±0.166</td>
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<td>9.452±6.162</td>
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<td>cPT</td>
<td>1.510±0.192</td>
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<td>9.772±6.219</td>
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<tr>
<td>cCN</td>
<td>1.576±0.156</td>
<td>9</td>
<td>8.851±6.046</td>
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<tr>
<td>cLN</td>
<td>*</td>
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<td>8.941±6.540</td>
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<tr>
<td>cWM</td>
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<td>4.159±3.700</td>
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<tr>
<td>cPG</td>
<td>*</td>
<td></td>
<td>12.88±6.999</td>
<td>10</td>
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### TABLE 3. Destruction Coefficient (DC) of All Available ROIs, Levovist and Optison Groups

<table>
<thead>
<tr>
<th>ROI</th>
<th>DC (CODIM) Mean±SD (× 10⁻³)</th>
<th>n</th>
<th>DC (PWI) Mean±SD (× 10⁻³)</th>
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<tbody>
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<td>IAT</td>
<td>24.64±29.29</td>
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<td>7.123±36.47</td>
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<tr>
<td>IPT</td>
<td>9.2±11.68</td>
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<td>15.74±27.98</td>
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<tr>
<td>ICN</td>
<td>15.63±13.92</td>
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<td>9.16±7.305</td>
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</tr>
<tr>
<td>ILN</td>
<td>20.93±23.81</td>
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<td>26.87±21.13</td>
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<tr>
<td>IWM</td>
<td>11.08±15.81</td>
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<td>40.09±10.59</td>
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</tr>
<tr>
<td>cAT</td>
<td>13.48±10.98</td>
<td>13</td>
<td>6.832±4.842</td>
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</tr>
<tr>
<td>cPT</td>
<td>21.91±21.01</td>
<td>13</td>
<td>9.523±9.625</td>
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</tr>
<tr>
<td>cCN</td>
<td>20.17±20.9</td>
<td>13</td>
<td>8.883±3.948</td>
<td>9</td>
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</tbody>
</table>

Abbreviations as in Table 1.
or Optison, respectively); significant differences between these ROIs (with similarity expected) could not be found.

Comparison of the calculated mirror region values did not show significant differences (Table 4). Mean values of rCBF for ipsilateral and contralateral white matter in both groups (3.024 versus 3.987×10^-3 and 3.161 versus 4.159×10^-3, respectively) were significantly lower than for the aforementioned ROIs (with difference expected), and mean values of ipsilateral and contralateral precentral gyrus were significantly higher in both groups (10.36 versus 13.18 and 10.33 versus 12.88×10^-3, respectively).

**Comparison of CODIM and PWI**

Finally, we compared CODIM PC values with PWI rCBF data. Between the calculated relative indices (mirror regions) for the regions, we did not find significant differences in the 2 groups (with both similarity and difference expected; Table 4).

**Discussion**

Established contrast agent–specific ultrasound methods using a bolus application of the agent to assess parenchymal cerebral perfusion result in qualitative rather than quantitative data. Parameters such as peak intensity and area under the curve showed high intradividual and interindividual variations even in parenchymal regions of similar perfusion because not only the maximum contrast enhancement but also the shape of the complete time-intensity curve depends on the local acoustic intensity. Consequently, the curve reflects not only the (physiological) wash-in/wash-out process but also the interaction between perfusion, dilution, and destruction.

The first attempt to overcome these limitations was the “refill kinetics” model, ie, the replenishment method, introduced by Wei and coworkers7 for echocardiography in 1998. More recently, it was shown that the resulting parameters also semiquantitatively describe perfusion in the brain of the dog11 and can be used to calculate CBF values in dogs with craniotomies by means of radiolabeled microspheres.12 The first results of a study with volunteers indicate that the method can be performed effectively in humans as well.13 In 12 probands, within the ipsilateral thalamus it was possible to display a homogeneous visualization of perfusion according to the parameters describing blood flow and refill velocity. However, the examination takes approximately 100 seconds, which is a disadvantage of the method because patients with acute stroke often are uncooperative during the examination. Another problem is that imaging techniques that do not destroy microbubbles still cannot provide a good signal-to-noise ratio in the brain.

In the new CODIM method, the “depletion” technique is based on the assumption that insonation decreases the concentration of a specific contrast agent depending on the potential of refilling the insonated area with the agent. With the use of specific algorithms that consider the ultrasound-induced destruction and reperfusion, the semiquantitative parameter PC can be mathematically calculated from the resulting time-intensity curves of the CBI examination. Given that the theoretical model applies, this parameter is, within a certain range, independent of sound intensity within the ROI and therefore independent of depth, which would be a major advantage compared with all other established methods using the bolus method. Furthermore, examination can be shortened to 60 seconds, ie, 40 seconds to establish a constant microbubble concentration in the blood pool and the imaging plane and another 20 seconds for the actual acquisition of 20 frames at 1 Hz.

The aim of the present study was to evaluate the diagnostic potential of this method. As a first step we examined a gel perfusion phantom. Using the flow rate of the model as a

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**Table 4. Mean Values of Relative Values (RV) of Corresponding ROIs of CODIM and PWI Examinations, Levovist and Optison Groups**

<table>
<thead>
<tr>
<th>ROIs</th>
<th>CODIM (PC) Mean±SD</th>
<th>PWI (rCBF) Mean±SD</th>
<th>P</th>
<th>CODIM (PC) Mean±SD</th>
<th>PWI (rCBF) Mean±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>iAT/cAT</td>
<td>1.0146±0.0915</td>
<td>0.9870±0.1411</td>
<td>&gt;0.05</td>
<td>1.0182±0.0537</td>
<td>0.9930±0.1737</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>IPT/cPT</td>
<td>0.9951±0.0788</td>
<td>1.0103±0.0951</td>
<td></td>
<td>1.0031±0.0373</td>
<td>0.9776±0.1022</td>
<td></td>
</tr>
<tr>
<td>iLN/cCN</td>
<td>1.0266±0.1552</td>
<td>0.9735±0.1616</td>
<td></td>
<td>0.9855±0.0765</td>
<td>0.9831±0.1471</td>
<td></td>
</tr>
<tr>
<td>iPT/cPT</td>
<td>1.0000±0.1151</td>
<td>0.9506±0.1264</td>
<td></td>
<td>0.9881±0.0431</td>
<td>0.9471±0.1601</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. cROI indicates corresponding ROI (“mirror regions”).

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**Figure 4.** Typical PWI parameter images: rCBV map for anatomic orientation (a), rCBF map (b), and time-intensity curve with ROI in “ipsilateral” posterior thalamus (c).
referential factor, we demonstrated that different flow rates correlated well with resulting PC values in a nonlinear relation. The fact that PC was non-zero for the no-flow condition is most likely due to 2 factors: the signal-to-noise ratio is poor for very low concentrations of contrast agent, and the agent can still circulate within the sponge. This circulation will occur because, for thermodynamic reasons, the systems will approach equilibrium with respect to temperature and microbubble concentration.

Next we compared the method with PWI in healthy volunteers. Resulting PC values did not differ significantly in any area of similar perfusion (ie, gray matter). The small size of both groups, however, limits statistical strength. PC in white matter was significantly lower by a factor of approximately 0.4 in both the Levovist and Optison groups. Relative values, ie, ratios of values in mirror regions, were approximately 1, indicating again that PC was independent of depth of examination. At the same time, PC was stable when different contrast agents were used, although the stability of the bubbles with respect to ultrasound exposure was quite different. As a probable marker for these differences, the second parameter, DC, showed high variations intraindividually and interindividually.

Finally, comparison with the established clinical “gold standard” PWI revealed that relative values of mirror regions of both methods showed no significant differences, which strongly suggests that both methods are equally independent of depth of examination. Still, it remains striking that PC values had a distinctly smaller range of parameter values interindividually.

Thus, CODIM seems to be a potent new method for semiquantitative assessment of parenchymal cerebral perfusion in healthy volunteers. As expected from former research, acoustic energy was inhomogeneous in the insonation field, as indicated by the DC. Nevertheless, the proposed data acquisition and model-based mathematical analysis could eliminate the depth dependency of former ultrasonic bolus methods (for which wash-in/wash-out method would be a better description), which is a major disadvantage of these methods, and facilitate the diagnostic procedure. The resulting data, although of a small group, may help to create “normal values” of brain perfusion. Furthermore, PC values of white matter were significantly lower than those of gray matter, suggesting the possible ability of CODIM to detect different perfusion rates. Therefore, the method should be tested not only in more healthy volunteers but also in patients with hypoperfused areas (eg, acute stroke), where the relative values could possibly detect regions of ischemia in agreement with PWI criteria. Furthermore, it would be of significant interest to compare the replenishment approach with CODIM in healthy volunteers as well as in acute stroke patients to obtain knowledge about the robustness of both methods under clinical conditions.

Some basic limitations of ultrasonic methods also apply for CODIM. Patients must cooperate, since the transducer must be held firmly without loss of the bone window (however, the correct positioning can be monitored during the examination with help of B-mode images on the screen). Second, to date no criteria for independently determining size and location of the chosen ROIs have been described, and therefore experienced examiners are needed to define comparable ROIs. Third, patients must have an adequate temporal bone window.

In conclusion, the present study introduces a new ultrasonic tool of semiquantitative perfusion imaging that was shown to be fairly independent of depth parameters and of physical properties of contrast agents. Moreover, CODIM reduces the time of examination considerably compared with other established methods.

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References

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