A Transpulmonary Contrast Medium Enhances the Transcranial Doppler Signal in Humans

Fernand Ries, MD; Claudia Honisch, MD; Markus Lambertz; Reinhard Schlief, MD, PhD

**Background and Purpose:** Transtemporal insonation in transcranial Doppler sonography is often impaired by an insufficient signal-to-noise ratio, especially in elderly patients. A transpulmonary stable air microbubble suspension was injected intravenously in humans as an intracranial ultrasonic contrast agent.

**Methods:** In a clinical phase II study, 20 patients (15 women, 5 men; mean age, 65.5±11.5 years) presenting with clinical indications for transcranial Doppler investigation were examined. A total of 97 intravenous injections with different concentrations (200, 300, and 400 mg/mL of suspension) of air microbubbles bound to galactose microparticles as a carrier were performed. The signal enhancement of color-coded pulse curves of basal cerebral arteries was evaluated off-line in comparison to an integrated color-coded decibel scale, considering quality, quantity, and time course of enhancement requiring a 3-dB level above the native signal. The overall diagnostic information was assessed according to a reliability score.

**Results:** The first acoustic signal increase was registered after an average of 21 seconds. Time intervals for a dose-dependent peak intensity and maximal duration were 41.3±17.1 seconds and 118.0±69.8 seconds (200 mg/mL); 55.5±27.7 seconds and 237.0±112.3 seconds (300 mg/mL); and 66.1±31.8 seconds and 293.0±122.0 seconds (400 mg/mL), respectively. Duration of signal enhancement increased significantly (P<.05) with higher concentrations. The extent of signal enhancement during the whole pulse curve reached an average of 9.1±5.0 dB for 200 mg/mL, 12.0±5.4 dB for 300 mg/mL (significant on P<.05 level), and 13.1±5.6 dB for 400 mg/mL concentration (P=NS). Respective maximal intensity spots reached 17.5±6.0, 20.7±5.5, and 22.7±5.9 dB for increasing concentrations, respectively. Overall visual assessment of enhanced pulse curves for diagnostic reliability showed a sufficient result in 38.1% of all injections with 200 mg/mL, in 88.6% with 300 mg/mL, and in 84.2% with 400 mg/mL concentration. Minimal side effects occurring in 12.4% of all injections were all reversible.

**Conclusions:** Transtemporal stable air microbubbles bound to a galactose carrier represent a useful and safe contrast agent in case of an insufficient native signal in transcranial Doppler investigation. (Stroke. 1993;24:1903-1909.)

**KEY WORDS** • contrast media • diagnostic imaging • ultrasonics

An insufficient signal-to-noise ratio is the most frequent technical cause for an unsuccessful investigation by transcranial Doppler sonography (TCD), especially using the transtemporal approach.\(^1\) The underlying hyperostosis is mostly found in elderly female patients.\(^2\) Despite electronic improvements in signal processing in TCD devices, this anatomic hindrance can only be overcome by means of an improved backscattering of the emitted ultrasound, which is normally reflected only weakly by streaming blood cells. The principle of ultrasound enhancement is based on the difference in acoustic impedance of two reflecting media, which is highest at the border zone of air to soft or solid tissue.\(^3\) Different handmade as well as industrially manufactured contrast media have been described, mostly representing the disadvantage of a nonstandardized, nonreproducible, or even risky application.\(^4\) First results concerning underlying mechanisms and problems in application modalities of industrially manufactured air microbubbles as a contrast medium in TCD have been studied in an animal model.\(^5\) The contrast medium used in that pilot study was based on galactose microparticles (MP; SH U 454, Echovist, Schering AG, Berlin, FRG); it was shown to enhance the TCD signal after intra-arterial injection. However, because of an insufficient stability of these air microbubbles during the transpulmonary passage, the intravenous application could not be used for transcranial insonation until now. Changes in the pharmaceutical design of the drug led to an improved stability in the presence of similar contrast properties.

Results of a clinical phase II trial in humans\(^7\) considering quality and quantity of signal enhancement in transcranial insonation are reported. This represents a first quantitative evaluation of Doppler signal enhancement after use of contrast agents in humans.

**Subjects and Methods**

A watery suspension of galactose MP (99.9% of total content) and a small amount of palmitic acid stabilizing air microbubbles was used as a contrast medium (SH U 508A, Schering AG).
The clinical phase II study was an open-labeled study. The protocol included patients with an indication for TCD examination according to the established criteria, ie, intracranial stenosis or occlusion, cerebrovascular spasms after subarachnoid hemorrhage, cerebrovascular malformations, cerebral microangiopathy as reflected indirectly by the increase of peripheral flow resistance, assessment of the hemodynamic effect of an extracranial stenosis, or occlusion of cerebral arteries.

The examination was performed in 20 patients (15 women, 5 men) with a mean age of 65.5±11.5 years (range, 29 to 86 years; mean age of female patients, 66.4±13.0 years; mean age of male patients, 62.8±5.5 years) (Table 1). Patients were selected on the basis of an insufficient (n=5) or absent (n=15) native transcra-nial Doppler signal in the transtemporal insonation, corresponding to an abnormally thick temporal bone in computerized tomography in 19 of 20 patients. Exclusion criteria were defined as galactosemia; myocardial infarction within 12 weeks before the investigation; any acute illness, especially of the cardiopulmonary system; application of x-ray or other contrast media within 48 hours before the investigation; preexamination with SH U 508 A within this study; or pregnancy. Informed consent was obtained by all the patients. No patient admissible to the study refused to participate. Electrocardiogram and blood pressure measurement were carried out on all patients immediately before the first injection (time point A), during the whole investigation time, half an hour after the last injection (B), and 24 hours later (C). Blood samples for extensive laboratory tests were taken at time points A, B, and C. An x-ray of the chest and extracranial continuous-wave-Doppler sonography were performed in all patients. The preexisting individual drug schedule was not changed for the purpose of this study.

A series of intravenous contrast media injections (10 mL) with a minimal time interval of 5 minutes between two injections followed in various concentrations according to the protocol. In fact, the interval between the end of the signal-enhancing effect and the following injection was more than 5 minutes as a rule because of preparation of the next injection.

The TCD examination started by insonating the left middle cerebral artery (MCA) after injecting SH U 508 A with 200, 300, or 400 mg MP per milliliter of solution. The concentration showing the best signal-enhancing effect was used for the following injections in evaluating the right MCA. Thus, of a total of 97 injections, 22 were done with a 200-mg MP concentration, 35 with a 300-mg MP concentration, and 40 with a 400-mg MP concentration. An approximative total of 1300 pulse curves for all injections in 20 patients were stored and evaluated off-line. Three injections could not be used for technical reasons, ie, loss of stored data. Thus, the following data are based on the remaining total of 94 injections.

Of this patient group, a subgroup of 60 injections fulfilling optimal criteria of a continuously documented, technically artifact-free signal enhancement after injection of various concentrations was used for further evaluation of pharmacodynamic effects, as represented
in the graphics of Figs 1 and 2. In this subgroup, a native Doppler signal was absent in 51 (85%) of 60 investigations, compared with 9 (15%) of 60 injections with only an insufficient native signal.

The TCD examination was done with a pulsed 2-MHz ultrasound probe fixed in a system of rods and joints allowing control of a permanently fixed insonation point ("trans-scan" TCD, EME Eden Medizin Elektronik, Uberlingen, FRG). The device offers a color-coded display for blood flow velocity and flow direction as well as for the reflected signal amplitude (Fig 3). The investigation was performed with a fixed ultrasound emission power of 32% of the spatial peak time-averaged energy corresponding to 240 mW/cm². The pulse repetition frequency defining the burst width of the ultrasound pulse was not changed during the investigation and ranged between 4.16 and 5.24 kHz. Relevant data could be stored in short intervals of a few seconds on hard disk to be evaluated off-line.

The evaluation of signal increase was based on the color-coded decibel scale as visualized and documented in 3-dB steps, in correlation with the time needed for increase or decrease in signal intensity. The signal was considered enhanced until it dropped to an amplitude less than 3 dB above the nonenhanced native signal, ie, less than 3-dB signal-to-noise ratio in case of a completely absent native signal. Because the enhancement can be inhomogenous for the frequency spectrum of a single pulse curve, maximal increase spots (dBmax) in certain phases of a pulse curve cycle were to be distinguished from a basal increase (dBbas) present over the whole heart cycle and defining the contours of the pulse curve, thus allowing further assessment (Table 3).

Evaluation criteria defined according to this enlarged investigation protocol included the following for the different concentrations: (1) interval to the first signal increase (acoustic/documented); (2) time to peak intensity of dBmax and dBbas values; (3) duration of the signal increase for dBmax and dBbas values; (4) pharmacodynamic effects in increase and wash-out phases; (5) peak intensity of dBmax and dBbas values; (6) evaluation of possible flow pattern changes due to the contrast agent; (7) clinically manifest side effects; and (8) diagnostic reliability.

Diagnostic assessment responding to the clinical indication for TCD investigation was based on an overall visual evaluation of the enhanced pulse curves, requiring interobserver agreement of two experienced investigators. The following score was used: 0, no diagnostic information; 1, slight increase of diagnostic information; 2, fair to sufficient diagnostic evaluation; and 3, overenhanced Doppler signal impairing diagnostic evaluation.

Eventual side effects were documented during TCD examination as well as for the subsequent 24 hours after contrast medium injections; they were classified as not probable, possible, or probable side effect related to the contrast medium.

Results

Transcranial Doppler insonation was successful in documenting an enhanced Doppler signal in at least one transtemporal insonation in 20 of 20 investigated patients. However, considering single vessels, none of the different concentrations yielded a diagnostically sufficient signal increase in terms of duration and quality in 5 of 37 vessels. The individually optimal concentrations with corresponding duration of enhancement and extent of signal increase are shown in Table 2.

The first evaluable pulse curves could be seen on screen after approximately 25 to 30 seconds (average, 28 seconds) after injection, the interval increasing slightly with higher concentrations. The first acoustic signal increase appeared after approximately 21 seconds (average value) after the contrast medium injection. The wide time range is explained by the fact that in case of a nonexisting native signal, the insonated vessel first has to be detected, which may lead to a longer silent time period (Table 3). The injection time has to be taken into account for this calculation.

The time from starting the injection to reaching the peak of signal increase for both dBmax and dBbas values reflects a dose-dependent maximal increase time (Table 3). Similarly, the average duration of signal increase shows a significant correlation with increasing concentrations, even considering a wide variation for all concentrations (Table 3). However, these figures do not reflect that in individual patients a longer lasting signal
below the required 3-dB level could be documented for several minutes. In 13 of 94 injections, the end of signal increase was possibly overlapped by a faint native signal not detected before the injection of contrast media.

As shown in Fig 3, increase and decrease of signal enhancement are linear, and there is no plateau or reincrease during the wash-out phase of the contrast medium.

The averaged basal and maximal dB increase for the different concentrations is also dose dependent (Table 4). Standard deviation for all peak values illustrates a good reproducibility of evaluation criteria. The upper range in decibel increase for both basal and maximal values is also concentration dependent, with a higher absolute increase from the 200-mg to the 300-mg MP concentration than from the 300-mg to the 400-mg MP concentration for the dB_max value.

A minimal signal increase of 3 dB above the original signal intensity is required. The last Doppler signal fulfilling this criterion for evaluation was determined for the different concentrations. The last dB_max increase was, on average, approximately 5 dB for all concentrations, corresponding to an average 9-dB increase for the dB_max value. These still-high decibel values indicate that in individual patients, this last documented increase was followed by a permanent native signal found only after injecting contrast medium.

Statistical analysis using the two-tailed Wilcoxon test and the Friedman test could be done for the left MCA because according to the study protocol, the number of injections and the use of different concentrations had to be limited on the right side to optimal settings. Peak decibel values were significantly higher for the 300-mg/mL concentration compared with the 200-mg/mL concentration (P<.05) but were not significant compared with the 400-mg/mL concentration. Duration of signal enhancement for higher concentrations significantly increased in time both from the 200-mg/mL to the 300-mg/mL concentration and from the 300-mg/mL to the 400-mg/mL concentration (P<.05).

This quantitative evaluation of signal enhancement may be different from the diagnostic reliability, as evaluated by a score from 0 to 2. There was a dose-dependent increase in first getting a reliable diagnostic evaluation, i.e., n=3 (15%) for the 200-mg, n=12 (60%) for the 300-mg, and n=5 (25%) for the 400-mg MP per milliliter concentrations. Results for different concentrations are shown in Table 5. In summary, the 300-mg MP per milliliter concentration was most recommended in case of a missing native signal. Pathological Doppler findings led to the diagnosis of intracranial stenoses in 2 patients (10%) and microangiopathy in 11 patients (55%), whereas 7 investigations (35%) were normal.

Evaluation of flow pattern changes after contrast medium injection is restricted by the fact that, as an inclusion criterion, an insufficient or absent native signal was required. Comparing flow patterns of optimally
enhanced pulse curves in the MCA to pulse curves as normally found in TCD insonation, it is evident that the contrast medium often is leading to a display of blood flow in both directions, without reducing the physiologically predominant flow direction (see also Fig 3).

After injection of a 400-mg MP concentration in one patient (No. 10), there was an evidently pathological short interval to the first signal increase, most probably indicating an intracardiac or intrapulmonary shunt. The problem of finding a first acoustic Doppler signal in a

### Table 3. Time Course of Signal Increase

<table>
<thead>
<tr>
<th>Concentration, mg MP/mL</th>
<th>1st Signal, s</th>
<th>$t_{peak}$, s</th>
<th>$t_{max}$, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>25.3±5.9</td>
<td>41.3±17.1</td>
<td>118±69.8</td>
</tr>
<tr>
<td>Median</td>
<td>25</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>Range</td>
<td>15-39</td>
<td>17-76</td>
<td>30-247</td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>27.6±7.8</td>
<td>55.5±27.7</td>
<td>237±112.3</td>
</tr>
<tr>
<td>Median</td>
<td>27</td>
<td>46</td>
<td>196</td>
</tr>
<tr>
<td>Range</td>
<td>12-45</td>
<td>19-143</td>
<td>60-477</td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>30.6±12.3</td>
<td>66.1±31.8</td>
<td>293±122</td>
</tr>
<tr>
<td>Median</td>
<td>30</td>
<td>62</td>
<td>265</td>
</tr>
<tr>
<td>Range</td>
<td>7-68</td>
<td>25-154</td>
<td>73-600</td>
</tr>
</tbody>
</table>

MP indicates microparticles; $t_{max}$, time to peak increase; and $t_{max}$, time of maximal duration of signal enhancement.

### Table 4. Extent of Signal Increase

<table>
<thead>
<tr>
<th>Concentration, mg MP/mL</th>
<th>Peak SI, dB</th>
<th>Last SI, dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>9.1±5.0</td>
<td>17.5±6.0</td>
</tr>
<tr>
<td>Median</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Range</td>
<td>2-20</td>
<td>8-32</td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>12±5.4</td>
<td>20.7±5.5</td>
</tr>
<tr>
<td>Median</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Range</td>
<td>5-28</td>
<td>13-37</td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>13.1±5.6</td>
<td>22.7±5.9</td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Range</td>
<td>5-30</td>
<td>10-42</td>
</tr>
</tbody>
</table>

MP indicates microparticles; SI, signal increase.
TABLE 5. Diagnostic Reliability for Different Concentrations in 94 Injections

<table>
<thead>
<tr>
<th>Concentration, mg MP/mL</th>
<th>DR Score 0</th>
<th>DR Score 1</th>
<th>DR Score 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>200</td>
<td>6</td>
<td>28.6</td>
<td>7</td>
<td>33.3</td>
</tr>
<tr>
<td>300</td>
<td>1</td>
<td>2.8</td>
<td>3</td>
<td>8.6</td>
</tr>
<tr>
<td>400</td>
<td>4</td>
<td>10.5</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>11.7</td>
<td>12</td>
<td>12.8</td>
</tr>
</tbody>
</table>

MP indicates microparticles; DR, diagnostic reliability. Score for diagnostic information: 0, none; 1, slight increase, but insufficient; and 2, fair to sufficient.

Discussion

The principle of ultrasound signal enhancement relies on the fact that acoustic properties of physiological media, ie, blood or soft tissue, differ greatly from those inherent to contrast media, ie, mainly air bubbles. Different acoustic impedance values lead to a high degree of reflection. Different substances such as hand-shaken solutions, hydrogen peroxide, angiographic contrast media, albumin, and different saccharides are used as contrast agents. They differ by their stability characteristics and possible risks. Sonicated albumin microspheres were shown to be sufficiently stable in in vitro studies. They were mainly used in enhancing B-mode signals in echocardiography; new studies report a short-lasting signal-enhancing effect in TCD. This may be due to instability of sonicated albumin to left ventricular pressure peaks during cardiopulmonary passage. The substance used in this study is thus far the only one to have demonstrated a long-lasting stability during cardiopulmonary passage.

Contrast-enhancing techniques were used first in echocardiography but increasingly have been used in different vascular ultrasound applications; today they are even used in tissue perfusion measurement or in tumor characterization. Because of higher sensitivity in detecting reflected ultrasound signals, the Doppler mode based on a frequency shift of the reflected signal profits more from these enhancing media compared with imaging by B-mode ultrasound technique.

Feasibility and application modalities of signal enhancement in TCD by air microbubbles similar to those used in this study were established in an animal model. However, the development of a transpulmonary stable suspension was a requirement for the intracranial use of contrast media in humans. Transcranial color-coded duplex imaging may use contrast media to improve the spatial resolution of this newly developed neuroimaging device. However, the diagnostic reliability of signal-enhancing techniques has to be assessed further, including the quantification of signal increase and pharmacokinetic properties that may possibly influence ultrasound imaging.

Methodological problems in this study are mainly related to the visual evaluation of signal increase on a color-coded decibel scale, with the development of computerized Doppler intensitometry. In favor of preferably underestimating the signal increase, evaluation criteria included a minimal signal-to-noise ratio of 3 dB above the original noise level. Moreover, patient inclusion criteria required a highly insufficient or completely missing native signal, corresponding to temporal hyperostosis on computed tomographic scan in nearly all patients. Thus, the starting decibel level may well have been far below the noise level, thereby corresponding to an even higher effective signal increase. The differentiation between a maximal increase during only part of the pulse curve cycle and a basal increase allowing a complete hemodynamic assessment will have to be analyzed further, looking for potential changes in the physiological frequency spectrum or representation of flow patterns that otherwise would not be documented. The problem of reliably evaluating pharmacodynamic aspects was reduced by the documentation of one and the same insolation point with the “trans-scan” coordinate system, thus allowing a quantification of signal increase over time. This represents the first attempt to replace the normally restricted visual assessment by videodensitometry with assessment by Doppler intensitometry.

Contraindications for use of the contrast medium in neurosonology are limited and rather infrequent. Adverse events observed in this study were only related to injection problems or immediately reversible sensations, mostly a feeling of warmth. Because the highest concen-
tration (400 mg MP per milliliter) seems to be responsible for most side effects without a reproducible gain in diagnostic value, the 300-mg MP per milliliter concentration would be recommended in case of a highly insufficient native signal. No relevant complications were reported in a review of different contrast media applications.21

The onset of signal increase depends on the time elapsing between the intravenous injection and the first appearance of air microbubbles in the cerebrovascular bed after cardiac and transpulmonary passage. Thus, decreased cardiac ejection and insufficiency may prolong this silent period, whereas an intracardiac shunt, such as a patent foramen ovale, should shorten it below the minimal time requested for the heart-lung passage. The pharmacodynamic evaluation should consider recirculation of microbubbles, clustering, interdependent bubble stabilization, and increased destabilization in terminal low concentrations of the injected suspension.

The necessity of a signal enhancement in TCD occurs mostly in elderly patients. Because of the still increasing indications for TCD, the possibility of achieving a sufficient evaluation of intracranial hemodynamic parameters should be helpful. Normal reference values22 commonly used should be checked, using findings of contrast-enhanced pulse curves, especially with regard to systolic peak values.

However, as the intravenous application of ultrasound contrast media turns TCD into an invasive (although mildly invasive) investigation, the indication for signal-enhancing procedures has to be strictly defined. On the other hand, addition of an invasive component to a formerly noninvasive investigation can only be discussed and weighed in regard to its value considering possible diagnostic and therapeutic implications, which has recently been done, in favor of contrast media, in regard to computed tomography and nuclear magnetic resonance imaging.

References
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