Background and Purpose—Cardiac right-to-left shunts can be identified by transesophageal echocardiography (TEE) and by transcranial Doppler ultrasound (TCD) with the use of different contrast agents and different provocation procedures. Currently, data on an appropriate time window for the appearance of contrast bubbles in the TCD recording after the injection of the contrast medium and the comparison of different provocation maneuvers to increase right-to-left shunting are insufficient.

Methods—Forty-six patients were investigated by both TEE and bilateral TCD of the middle cerebral artery. The following protocol with 6 injection modes was applied in a randomized way: (1) injection of 10 mL of agitated saline without Valsalva maneuver, (2) injection of 10 mL of agitated saline with Valsalva maneuver, (3) injection of 10 mL of a commercial galactose-based contrast agent (Echovist) without Valsalva maneuver, (4) injection of 10 mL of Echovist with Valsalva maneuver, (5) injection of 10 mL of Echovist with standardized Valsalva maneuver, and (6) injection of 10 mL of Echovist with coughing.

Results—In 20 patients, a right-to-left shunt was demonstrated by TEE and contrast TCD (shunt-positive). Sixteen patients were negative in both investigations, no patient was positive on TEE and negative on TCD, and 10 patients were only positive on at least 1 TCD investigation but negative during TEE. The amount of microbubbles detected in the various tests decreased in the following order: Echovist and Valsalva maneuver, Echovist with coughing, Echovist and standardized Valsalva maneuver, saline with Valsalva maneuver, Echovist, and saline. With a time window of 20 to 25 seconds for the bubbles to appear in the TCD recording and with a sequence of first Echovist and Valsalva maneuver and then Echovist with coughing, all shunts were reliably identified with a specificity of 65% compared with TEE as the traditional gold standard. The time of first microbubble appearance was not helpful to distinguish between shunts detected on TEE and other shunts.

Conclusions—TCD performed twice with 2 provocation maneuvers using Echovist is a sensitive method to identify cardiac right-to-left shunts also identified by TEE. (Stroke. 1999;30:1827-1832.)

Key Words: cerebrovascular disorders cerebral embolism foramen ovale, patent ultrasonography

Paradoxical thrombotic embolism via a cardiac right-to-left shunt (RLS) is a well-recognized cause of stroke, especially in younger patients. Transesophageal echocardiography (TEE) enhanced by echo-contrast agents is considered the “gold standard” for the detection of cardiac RLS. The Valsalva maneuver increases right atrial pressure, thus facilitating or demasking intermittent right-to-left shunting of contrast medium via an atrial septal defect or a patent foramen ovale.

Cardiac RLS can also be identified by the use of contrast-enhanced transcranial Doppler sonography (TCD). The technique is based on the detection of an intravenously injected contrast agent within intracranial arteries, eg, the middle cerebral arteries (MCAs). The echo-contrast agents used for this test are unable to pass the pulmonary capillary bed. In case of an RLS, the contrast agent enters the arterial circulation and produces microembolic signals (MES) during the TCD recording, thus mimicking the pathway of paradoxical cerebral emboli.

Two main contrast agents are in use: agitated saline containing tiny air bubbles and a galactose-based agent (Echovist-300, Schering AG), which is a suspension of galactose microparticles in an aqueous 20% galactose solution with adherent tiny microbubbles smaller than human
erythrocytes. Several procedural questions of contrast-enhanced TCD are unsolved. (1) Several authors hypothesized that MES passing pulmonary shunts appear later in the cerebral circulation than those passing cardiac shunts and that the choice of an appropriate diagnostic time window may increase the specificity of the test.\textsuperscript{11–13} Time windows proposed between the intravenous injection of the contrast medium and its appearance in the MCAs are 6 heart beats\textsuperscript{12} and 10,\textsuperscript{14} 15,\textsuperscript{15} 20,\textsuperscript{13} 22,\textsuperscript{16} and 25 seconds.\textsuperscript{11,17} (2) Different procedures to enhance right-to-left shunting have been proposed in the literature: a nonstandardized Valsalva maneuver, a standardized Valsalva maneuver, and coughing.\textsuperscript{16,18,19} (3) Only 1 direct comparison of saline and Echovist injections has been published thus far, but with different doses of these agents.\textsuperscript{11} In the present study, we (1) investigated the effect of different diagnostic time windows on the sensitivity and specificity of the test, (2) systematically compared different provocation maneuvers, and (3) compared identical doses of the 2 contrast agents with respect to sensitivity and specificity.

Subjects and Methods

Patients

Forty-six subjects (20 men, 26 women) aged 24 to 77 years (mean age, 47 years) were included in the study. All patients had suffered cerebral or retinal ischemic events. Eight patients had had recurrent events. There were 25 strokes, 16 transient ischemic attacks, 11 attacks of amaurosis fugax, and 1 central retinal artery occlusion. Eighteen subjects were cigarette smokers, 5 were diabetics, 20 had arterial hypertension, and 26 suffered from hyperlipidemia. No patient had a mechanical prosthetic cardiac valve.

In all 46 patients, TEE was performed to detect or rule out an intracardiac shunt. Apart from these 46 patients, 23 additional patients had been screened but had been excluded from the study for the following reasons: in 18 of them no TEE could be obtained, and in 5 patients there was no bilateral temporal window suitable for TCD.

Echocardiography

All patients underwent TEE, which was performed by trained echocardiographers from the Department of Cardiology of our hospital. The investigators used a Hewlett Packard Sonos 2500 or 5500 imaging system and a 4- to 7-MHz multiplane probe. After informed consent had been obtained, patients were examined in the fasting state and received local pharyngeal anesthesia with 10% topical lidocaine. Additional intravenous sedation (midazolam) was given if the probe was not well tolerated. For the diagnosis of an intracardial shunt, 10 mL of contrast agent (Echovist) was injected as a bolus into a large antecubital vein during 2-dimensional TEE. The Valsalva maneuver started 5 seconds after the beginning of the contrast injection with deep inspiration, followed by pressing against the closed glottis and expiration 10 seconds after the beginning of the injection. The standardized Valsalva maneuver was performed in like manner but with a manometer connected to a tube with a mouthpiece. The patients were instructed before the procedure to achieve and to maintain a pressure of 40 mm Hg lasting 5 seconds. The patients could see the manometer during the test for pressure control. For the coughing test, patients were instructed to cough 3 times in between seconds 5 and 10 after injection of the contrast agent.

In single cases, MES could still be detected 80 to 120 seconds after the injection. In these cases, the resting time preceding the next test was prolonged until an MES-free period of at least 40 seconds’ duration was documented. In each test, only the first 40 seconds after injection were used for MES analysis. Data from the right and left MCA were pooled.

Ultrasound Investigations

All subjects underwent a full color duplex investigation of their neck arteries (Sonos 2500, Hewlett Packard) and a continuous-wave Doppler investigation of the periorbital arteries. Subjects were also examined by TCD, including the intracranial segments of the internal carotid arteries, the MCAs, and the anterior and posterior cerebral arteries. One patient had a high-grade extracranial internal carotid artery occlusion, and 2 patients had a high-grade extracranial internal carotid artery stenosis.

For TCD embolus detection, the MCA was insonated bilaterally through the temporal bone windows. Two 2-MHz transducers were mounted on the temporal planes and secured with a head ribbon. A small sample volume of 8 mm in length and a low gain provided a setting optimal for embolus discrimination from the background spectrum. The bigate technique was used, with 2 sample volumes placed at a distance of 1 cm into each MCA main stem. Power was 22 mW/cm². The patients were lying comfortably on a stretcher. The investigations were well tolerated by the subjects without major side effects.

The same transcranial pulsed Doppler ultrasound device (TC4040, EME/Nicolet, software version 2.30) was used for all studies. The machine employed a 128-point fast Fourier transform analysis and used a graded color scale to display the intensity of the Doppler signals received. In addition to online recording onto the hard disk, the Doppler audio signal was recorded by an 8-channel digital audio tape deck recorder (TA-98, TEAC Corporation) with normal speed. An experienced observer’s analysis of MES comprised listening to each of the software-recorded signals, watching each signal on the screen, and evaluating the tapes. The following definition for MES was used: typical visible and audible (click, chirp, whistle) short-duration, high-intensity signal within the Doppler flow spectrum with a time delay in the 2 channels of each side.\textsuperscript{10} Single MES within clusters were discriminated by reducing the amplification during offline analysis.

The following 6 different procedures were performed in a randomized fashion: injection of (1) Echovist without Valsalva strain, (2) saline without Valsalva strain, (3) Echovist with nonstandardized Valsalva strain, (4) saline with nonstandardized Valsalva strain, (5) Echovist with standardized Valsalva maneuver, and (6) Echovist with coughing. Each of the these comprised at least 2 minutes, with bolus injection of the contrast agent starting at 0 seconds, Valsalva strain for 5 seconds starting at 5 seconds, bolus rinsing with nonagitated saline starting at 40 seconds, and resting phase until 120 seconds. Microcavitation saline contrast was generated by agitating a mixture of 10 mL of normal saline and 1 mL of air between two 12-mL syringes connected by a 3-way stopcock. Once the contrast was prepared, 10 mL was immediately injected as a bolus into a right cubital vein, which had previously been cannulated with a 21-gauge indwelling intravenous catheter. Echovist was prepared following the instructions of the manufacturer, and 10 mL was injected. The Valsalva maneuver started 5 seconds after the beginning of the injection with deep inspiration, followed by pressing against the closed glottis and expiration 10 seconds after the beginning of the injection. The standardized Valsalva maneuver was performed in like manner but with a manometer connected to a tube with a mouthpiece. The patients were instructed before the procedure to achieve and to maintain a pressure of 40 mm Hg lasting 5 seconds. The patients could see the manometer during the test for pressure control. For the coughing test, patients were instructed to cough 3 times in between seconds 5 and 10 after injection of the contrast agent.

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Statistical Analysis

With TEE used as the gold standard, the sensitivity and specificity of TCD were calculated as follows. Sensitivity was calculated as the percentage of true-positives (RLS confirmed by both methods) in comparison to true-positives plus false-negatives (TCD-negatives and TEE-positives). Specificity was determined as the percentage of true-positives (RLS confirmed by both methods) in comparison to true-positives plus false-positives (TCD-positives and TEE-negatives). For statistical analysis, the numbers of MES seen during the 6 procedures were compared with the nonparametric Friedman 2-way ANOVA. Furthermore, the numbers of MES and the times of the first appearance of MES were compared for the patients with an RLS on TEE and those with an
RLS only in the TCD investigation (nonparametric Mann-Whitney U tests). For these tests, the mean values of each patient were calculated and compared to avoid repeated measures. Statistical significance was determined at the 0.05 level.

Results
Sixteen patients had no RLS on TEE and did not show MES in any of the tests within 40 seconds after the beginning of the injection. Nineteen patients had an RLS on both tests: the TEE and within 40 seconds after the beginning of the injection in at least 1 TCD procedure. In 17 of these patients a patent foramen ovale was found, and in the remaining 2 patients an atrial septal defect was found. Eleven patients had MES in at least 1 TCD investigation but no RLS on TEE. Four of these patients underwent a second TEE, which demonstrated a patent foramen ovale in 1 patient. No patient had an RLS on TEE but failed to have one in the TCD investigation.

The subgroup of 20 patients with concordant identification of RLS by TEE and TCD and the 10 patients with a shunt only in the TCD investigation were studied in more detail to detect possible differences in the streaming characteristics of contrast material via the atrial RLS versus a presumed pulmonary shunt. As an example, the top sections of both panels in the Figure illustrate the appearance and amount of all MES seen in the TCD recordings of 2 of the tests, whereas the bottom sections depict the time of first MES appearance.

The distributions of MES occurrence in the other 4 tests were similar, with MES occurring up to 40 seconds after the injection and first appearances of MES up to 26 and even 30 seconds after the injection of the contrast agent. The 2 patient groups with concordant shunt identification in both investigations (n=20) and with shunt demonstration only in the TCD investigation (n=10) were compared concerning the time of first MES appearance in the TCD recording. For these comparisons, the mean times of first appearance of all 6 tests (only the positive tests) were calculated for each single patient. The mean time of first MES appearance in the first group was 12.0 seconds (range, 7.5 to 16.0 seconds) and in the second group was 14.6 (range, 6.5 to 30 seconds). There was no difference in the time of first MES appearance between the 2 patient groups (P=0.37, Mann-Whitney U test). These 2 groups were also compared concerning the mean numbers of MES in all 6 tests of each patient (positive and negative tests). There was a significant difference indicating more MES in the group of 20 patients with concordant shunt identification (P=0.006). The mean number was 20.09 (range, 0.33 to 103.83) in the group of 20 patients with concordant shunt identification and 2.77 (range, 0.17 to 3.84) in the 10 patients with a shunt only during TCD. Although in general there were fewer MES in the patient group with a shunt only in the TCD investigation compared with the group with concordant shunt identification, introducing a threshold in number of MES could not reliably discriminate the 2 groups. As an example, in the test with Echovist and the nonstandardized Valsalva maneuver, the total numbers of MES in the individual patients within 40 seconds after the injection were 0, 0, 0, 0, 0, 1, 1, 4, 12, and 25 (shunt only in the TCD recording) and 0, 0, 2, 2, 3, 9, 11, 12, 15, 15, 19, 23, 32, 38, 60, 69, 81, 88, 100, and 107 (concordant shunt identification).

In the 30 patients with a positive TCD test, the total number of MES recorded in all tests within 40 seconds was 729 for Echovist with nonstandardized Valsalva maneuver (mean rank in a Friedman 2-way ANOVA, 4.14), 664 for Echovist with coughing (mean rank, 4.00), 553 for Echovist with standardized Valsalva maneuver (mean rank, 3.99), 335 for saline with nonstandardized Valsalva maneuver (mean rank, 3.32), 223 for Echovist without Valsalva maneuver (mean rank, 3.00), and 73 for saline without Valsalva maneuver (mean rank, 2.55; P<0.0001). The number of MES in the single tests varied from 0 to 109 in patients with a TEE-proven shunt and from 0 to 25 in patients with a shunt only seen during contrast TCD.

With TEE used as the traditional gold standard, sensitivity and specificity of each injection mode were calculated on the basis of a variety of proposed time windows (Table 1).
Besides the individual tests, the classic combinations of Echovist without and with the nonstandardized Valsalva maneuver, of saline without and with the nonstandardized Valsalva maneuver, and the combination of the 2 most sensitive TCD tests (Echovist with nonstandardized Valsalva maneuver and Echovist with coughing) were also considered. This latter combination reliably identified all TEE-proven shunts.

**Discussion**

Our study demonstrates that contrast TCD detects TEE-proven RLS with a sensitivity of 100% and a specificity of 65% when Echovist with Valsalva maneuver is combined with Echovist with coughing and when a diagnostic window of 20 to 25 seconds is chosen for the microbubbles to appear within the MCAs. No single test had the desired sensitivity of 100%. The values for sensitivity and specificity of the present study are in agreement with those reported in the literature (Table 2).

It is a well-known phenomenon that more patients are identified as having an RLS when investigated by contrast TCD than with TEE (see the specificities in Table 2). In these cases, the lungs are the most likely location of venous-arterial shunts, allowing the contrast material to bypass the pulmonary capillaries and to slip into the cerebral arteries. As another option, these shunts may correspond to very small intracardiac shunts unnoted during TEE. In our study, smaller amounts of bubbles could pass these shunts compared with the shunts also demonstrated on TEE. Differences in the performance of the Valsalva maneuver may also account for these discrepancies. Despite training and control, the Valsalva maneuver may occasionally not have been as effective during TEE compared with the TCD investigation because of the TEE tube in the esophagus and sedation. Some authors believe that those MES that occur late after contrast injection may have passed these pulmonary shunts. However, Horner et al reported that in pulmonary shunts, the transit time is in a range comparable to that in cardiac shunts and that this parameter does not allow reliable discrimination between the 2 conditions. Microbubbles detected in the arterial circulation at any time must have passed a shunt. Our study proves

### Table 1. Sensitivity and Specificity of Different Contrast TCD Procedures Using Different Time Windows of First MES Appearance in the Detection of Interatrial RLS Demonstrated on TEE

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Values are percentages.
the overlapping time spans of the first appearance of MES in the cerebral circulation of patients with and without an RLS demonstrated by TEE and the inability to distinguish the 2 shunt entities by means of the TCD investigation. Similar to intracardiac shunts, pulmonary shunts can also allow an early transit of contrast bubbles. The clinical significance of pulmonary shunts in stroke etiology, however, is completely unknown thus far. TCD is more sensitive than TEE in the detection of RLS. The therapeutic consequences to be drawn in stroke patients with a shunt during TCD and not during TEE warrant further research.

In 2 cases without shunt on TEE, the first MES during TCD occurred beyond 25 seconds after the injection of the contrast medium. Therefore, a time window of 20 to 25 seconds is recommended to achieve a higher specificity of the TCD investigation. Time windows shorter than 20 seconds decreased sensitivity and should not be used.

Interestingly, the standardized Valsalva maneuver did not give better results than the “normal,” nonstandardized Valsalva maneuver, probably because of the fact that the patients were trained beforehand and proper performance was ensured. The nonstandardized Valsalva maneuver is sufficient for the TCD-based detection of RLS.

The tests using Echovist were better than the corresponding tests using agitated saline. A higher amount of bubbles and greater bubble durability may account for this finding. We recommend performance of TCD-based tests for RLS with Echovist instead of agitated normal saline.

The sensitivity of contrast TCD depends on the amount of bubbles injected, the number of occasions for bubbles to trespass a possible shunt, and the sensitivity of the TCD device to detect the microbubbles in the cerebral arteries. A previous study had shown that sensitivity is increased with the use of bilateral instead of unilateral TCD recordings and repeated instead of single testings. This study corroborates the necessity of repeated bilateral recordings, here once with Valsalva maneuver and once with coughing to achieve high sensitivity. Additionally, the present investigation demonstrated that the sensitivity is higher with the use of Echovist than with the same quantity of saline.

In addition to the sole identification of an existing RLS, the need for quantification of the RLS measured by the amount of MES recorded has been postulated to possibly better quantify stroke risk. Given the low reproducibility of these tests, such quantifications are difficult to perform and obviously warrant bilateral and repeated recordings, preferentially with the use of Echovist.

In our study 1 RLS identified in the contrast TCD investigation, but first unnoted on TEE, could be identified as persistent foramen ovale in a repeated TEE. Our study emphasizes the value of a second TEE opinion in these discordant cases. The combination of contrast TCD and TEE, although associated with redundancy, increases the treating physician’s confidence in the case of concordant findings and enables the physician to take appropriate therapeutic measures.

References


TABLE 2. Review of the Literature on Sensitivity and Specificity of Contrast TCD Compared With TEE

<table>
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</table>

Studies using only TEE were not included.


Contrast Transcranial Doppler Ultrasound in the Detection of Right-to-Left Shunts: Comparison of Different Procedures and Different Contrast Agents

Dirk W. Droste, Jens-Uwe Kriete, Jörg Stypmann, Marco Castrucci, Thomas Wichter, Ralf Tietje, Birgitta Weltermann, Peter Young and E. Bernd Ringelstein

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