Contrast Transcranial Doppler Ultrasound in the Detection of Right-to-Left Shunts

Reproducibility, Comparison of 2 Agents, and Distribution of Microemboli

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Background and Purpose—Cardiac right-to-left shunts can be identified by transcranial Doppler ultrasound (TCD) with the use of different contrast agents and by transeophageal echocardiography (TEE). Systematic data are available on neither the reproducibility of contrast TCD, the comparison of different contrast agents, nor the comparison of simultaneous bilateral to unilateral recordings. Furthermore, we assessed the side distribution of thus provoked artificial cardiac emboli.

Methods—Fifty-four patients were investigated by TEE and by bilateral TCD of the middle cerebral artery. The following protocol was performed twice: injection of 9 mL of agitated saline without Valsalva maneuver, injection of 9 mL of agitated saline with Valsalva maneuver, injection of 5 mL of a commercial galactose-based contrast agent without Valsalva maneuver, and injection of 5 mL of the galactose-based contrast agent with Valsalva maneuver.

Results—In 18 patients, a right-to-left shunt was demonstrated by TEE and contrast TCD (shunt positive). Twenty-nine patients were negative in both investigations, 1 was positive on TEE and negative on TCD, and 6 patients were only positive on TCD. Both bilateral and repeated recordings increased the sensitivity of contrast TCD. There was a symmetrical distribution of microembolic signals in the right and left middle cerebral artery.

Conclusions—TCD performed twice and with the use of saline or a galactose-based contrast agent is a sensitive method in the identification of cardiac right-to-left shunts also identified by TEE. The cardiac microemboli in this study did not show any side preference for one of the middle cerebral arteries. 

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

The presence of a cardiac right-to-left shunt (RLS) is a well-recognized cause of thromboembolic stroke by paradoxical thrombotic embolism.1– 4 Transesophageal echocardiography (TEE) enhanced by echo contrast is superior to transthoracic echocardiography in the detection of RLS and is presently considered the “gold standard.”5–9 The performance of a Valsalva maneuver during the investigation increases right atrial pressure, thus facilitating or revealing intermittent RLS via an atrial septal defect or a patent foramen ovale.6,10,11 In a large group of 824 patients with stroke and other embolic events, TEE detected a patent foramen ovale in 13% of the patients and an atrial septal defect in 1%.12 These numbers reflect ≅50% of the shunts demonstrated during autopsy studies, in which very thin shunts, accessible only by a small probe, were also included (27%).13 In young patients with cryptogenic stroke, the prevalence of RLS of ≅50% is much higher than in controls, suggesting subclinical deep vein thrombosis and paradoxical embolism as the underlying etiology.14,15 The presence of an intracardiac shunt in symptomatic patients with no other detectable cause of stroke is usually treated by oral anticoagulation or cardio surgical or endovascular closure of the atrial septal defect.2,16–20 These therapeutic options require a reliable test to rule out RLS. TEE is a semi-invasive technique and is not feasible in uncooperative patients. Swallowing a thumb-thick tube for TEE is uncomfortable for the patient, sometimes necessitates sedation, and occasionally may cause mechanical irritation or injuries. Both the inserted TEE tube and the sedation hamper the proper performance of the Valsalva maneuver.

Contrast-enhanced transcranial Doppler sonography (TCD) is an attractive alternative to TEE and more comfortable for the patient. The technique is based on the intracranial detection of intravenously injected contrast agent, which is unable to pass the lung capillaries. In case of RLS, the contrast agent, similar to paradoxical emboli, enters the arterial circulation and produces microembolic signals (MES) in the TCD recording.21

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Circulating cerebral microemboli produce a visible and audible high-intensity signal of short duration within the transcranial Doppler frequency spectrum.\textsuperscript{22–24} Currently, there are 2 main contrast agents in use: agitated saline containing air bubbles and a galactose-based agent (Echovist, Schering AG) that, on dissolution and agitation in sterile water, generates air-filled microbubbles. These microbubbles are filtered in the pulmonary capillary circulation.\textsuperscript{25} In the present study, we (1) investigated the reproducibility of contrast TCD investigations and (2) systematically compared the 2 contrast agents concerning sensitivity and specificity for the detection of RLS in comparison to TEE.

Kaps et al\textsuperscript{26} had described a preferred migration of microemboli into the left or right middle cerebral artery (MCA), possibly predisposing for embolic stroke in this particular territory. Contrast agents passing through an RLS are an ideal model of cardiogenic embolism. A third purpose of our study was therefore to compare the distribution of cardiac microemboli in the left and right MCA territory during repetitive injections of contrast agents simulating embolizations.

Subjects and Methods

Patients
Fifty-four subjects (38 men, 16 women) with a mean age of 44 years (range, 23 to 79 years) were included in the study. Forty-six patients had suffered a stroke or a transient ischemic attack. In 1 patient, first thought to have suffered a stroke, a glioblastoma was diagnosed during subsequent investigations. One subject was a healthy co-worker of our department interested in his cardiac status. Eighteen subjects were smokers, 3 were diabetic, 19 had arterial hypertension, and 20 suffered from hyperlipidemia.\textsuperscript{27–29} No patient had a mechanical prosthetic cardiac valve.

In all 54 patients, transesophageal echocardiography was performed to rule out an intracardiac shunt. Apart from these 54 patients, 14 additional patients were not included in the study: in 10 patients, first a high-grade extracranial internal carotid artery stenosis. No additional high-grade stenoses or occlusions were observed.

For the TCD embolus detection, the MCA was bilaterally sononated through the temporal bone window. Two 2-MHz transducers were mounted on the temporal plane and secured in 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.\textsuperscript{30} Power was 22 mW/cm\textsuperscript{2}. 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 signal 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-88, 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.\textsuperscript{22–24,31} Single MES within clusters were discriminated by reducing the amplification during offline analysis.

The following procedures were performed twice in randomized order: injection of (1) galactose-based contrast agent without Val-salva strain, (2) saline without Val-salva strain, (3) galactose-based contrast agent with Val-salva strain, and (4) saline with Val-salva strain. Each of the 8 procedures required at least 2 minutes, with bolus injection of the contrast agent starting at 0 seconds, Val-salva 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 9 mL normal saline and 1 mL air between two 12-ML syringes connected by a 3-way stopcock. Once the contrast was prepared, it was injected as a bolus into a right cubital vein that had previously been cannulated with a 21-gauge indwelling intravenous catheter. Galactose-based contrast agent was prepared following the instructions of the manufacturer; 5 mL was injected. The Val-salva 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. In single cases, MES could still be detected after 80 to 120 seconds. 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. The presence of at least 1 MES in 1 MCA within 25 seconds after the beginning of contrast injection was the TCD criterion for RLS.

Statistical Analysis
For statistical analysis, the following comparisons of MES were made with the nonparametric Wilcoxon test: (1) galactose-based contrast agent versus saline, (2) with Val-salva maneuver versus without Val-salva maneuver, (3) left MCA versus right MCA, and (4) RLS concordantly identified on TCD and TEE versus RLS identified only on TCD and not on TEE. A Kruskal-Wallis 1-way ANOVA was used to detect possible individual side preferences for MES. Statistical significance was declared at the 0.05 level.

Results
Twenty-nine patients had no RLS on TEE and did not show any MES in any of the tests within 25 seconds after the beginning of the injection. The reason for choosing this time limit is given below. Eighteen patients had RLS on TEE and showed MES within 25 seconds after the beginning of the injection in both the galactose-based contrast agent investigation and the saline investigation with Val-salva maneuver. One patient had RLS under Val-salva strain on TEE but did not show any MES in any of the 8 TCD investigations within
25 seconds. Six patients had MES during TCD in both the galactose-based contrast agent investigation and the saline investigation with Valsalva maneuver but no RLS on TEE. When TEE was considered as a standard, sensitivity of contrast TCD was 95%, and specificity was 75%. This relationship is illustrated in Figure 1. None of the 4 patients with arterial stenosis or occlusion had RLS.

The subgroup of 18 patients with concordant identification of RLS by TEE and TCD were studied in more detail since the contrast pathway is most likely the interatrial RLS. In this group, the time of first MES appearance in cerebral arteries after the start of the injection varied from 3 to 34 seconds (Figure 2). In all but 2 tests, these first MES occurred within 25 seconds.

A limit of ≤25 seconds was chosen to qualify an MES to have directly passed the cardiac RLS, since late-occurring MES are considered to possibly not have directly passed the cardiac shunt (see Discussion). In these 18 patients with concordant RLS identification, the mean number of MES recorded in all the tests within 25 seconds was 15.8±43.5 without Valsalva maneuver, 27.6±39.4 with Valsalva maneuver (P=0.01, Wilcoxon test), 30.7±62.2 with galactose-based contrast agent, and 12.7±20.8 with agitated saline (P=0.21, Wilcoxon test).

Repetition of the TCD investigation increased the sensitivity of the method. Figure 3 shows the number of TCD investigations positive for RLS in both tests, only in the second test, only in the first test, and negative in both tests for the 18 patients with clear RLS on TCD and TEE. All of these 18 patients were identified as positive in at least 1 of the Valsalva maneuver tests (galactose-based contrast agent or saline).

Bilateral MCA recordings also increased the sensitivity compared with (fictive) unilateral recordings. This relationship is illustrated in Figure 4 for the group of 18 patients with RLS on TEE and TCD. The 2 gray parts of each column represent the number of investigations that were positive only on one side.

Within 25 seconds, 1572 MES were recorded in the left MCA and 1552 in the right MCA in the group of 18 patients with RLS on TCD and TEE (not significant, P=0.52). Figure 5 shows the absence of side differences for the 18 individual patients in the 8 recordings. The absence of a relationship is further demonstrated by a Kruskal-Wallis 1-way ANOVA (P=0.56).

There was a nonsignificant tendency for fewer MES in the 6 patients found to have RLS by TCD but not by TEE (mean, 5.3±7.1) compared with the 18 patients with concurrent RLS on TCD and TEE (mean, 21.7±37.1; P=0.39, Wilcoxon test).
Discussion

Our study demonstrates that contrast TCD detects TEE-proven RLS with a sensitivity of 95% and a specificity of 75%. These results are in accord with those reported in the literature.32–35

In only 1 of the 54 patients of our series, a tiny patent foramen ovale could not be demonstrated by contrast TCD. This patient was subsequently reinvestigated by both TEE and contrast TCD with identical results. Presumably, this phenomenon is due to the very small shunt volume.32,36 With positive TCD and negative TEE (11% or 6 cases in our study), it is usually the Valsalva strain that leads to positive TCD findings. The Valsalva maneuver is more easily performed with TCD than with TEE. Another possible explanation is the presence of small pulmonary shunts. Recent studies have shown that the differentiation between cardiac and pulmonary shunts by contrast TCD is hardly possible.37 Similar to intracardiac shunts, pulmonary shunts can produce early transit of contrast bubbles. Their clinical significance in stroke etiology is unclear. The search for pulmonary shunts on TEE is very time-consuming and is not routinely performed in our institution.

The time limit for the acceptance of MES to have directly passed the interatrial shunt is subject to discussion in the literature. Limits proposed are 6 heart beats,38 10 seconds,38 15 seconds,39 20 seconds,39 22 seconds,35 and 25 seconds.34 Many authors believe that MES occurring late may have passed pulmonary shunts.32,34,39 On the other hand, Horner et al37 reported that in pulmonary shunts, the transit time is in a range comparable to that of cardiac shunts and that this time does not allow reliable discrimination of the 2 conditions. Microbubbles detected in the circulation at any time must have passed a shunt. The explanation for these late bubbles remains unclear. They may have remained in the tip of injection needle or in a venous valve, or they may have remained in the auricle of the right heart or in the lung for many seconds before passing an interatrial or pulmonary shunt. Single late microbubbles cannot be part of a major bloodstream and are possibly due to small shunts not clinically relevant for paradoxical embolism. The time delays of first MES appearance given in Figure 2 suggest a limit for first-pass shunting of ≈25 seconds; therefore, this limit was chosen in the present study.

The Valsalva maneuver increased the total number of MES as well as the sensitivity of the method by increasing the right-to-left atrial pressure gradient with subsequent initiation or increase of RLS.6,10,11 The timing of the Valsalva maneuver is, however, still under debate. Zanette et al15 found the largest amount of MES when the injection was done before a Valsalva maneuver of 10 seconds. The timing of the Valsalva maneuver in the present study follows recent recommendations, taking into account that the contrast agent reaches the right atrium 5.1 ± 1.4 seconds after the injection.34,40,41

Even when 5 mL of galactose-based contrast agent and 9 mL of saline were used, there was a nonsignificant tendency for fewer MES with saline. However, this did not affect the sensitivity of both agents for the detection of RLS. The differences may be explained by increased number and stability of bubbles in galactose-based contrast agent compared with agitated saline. Therefore, the galactose-based contrast agent will possibly allow a better quantification of shunts compared with agitated saline.

In the study by Kaps et al26 on microemboli originating from prosthetic cardiac valves, a mild side preponderance was present in a minority of patients. This may be explained by natural fluctuations. Similar to our study, Horner et al37 could not demonstrate a side preponderance of induced microemboli. In our study MES were evenly distributed in both MCAs in individual patients as well as in the whole patient group. The results support the clinical assumption that small microemboli should have the same streaming behavior as the general bloodstream.

Contrast TCD is a valuable screening procedure with a high sensitivity in the detection of RLS, as confirmed by contrast TEE. Several aspects, such as the detection and clinical significance of pulmonary shunts, discrepant results of both techniques, and time limit for MES appearance on contrast TCD, require further investigations.

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![Figure 5. Absence of consistent side differences in the occurrence of MES. On the x-axis are the 18 patients with consistently identified RLS; on the y-axis are the side differences (left minus right) in MES in each of the 8 investigations per patient.](image)


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