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

Reproducibility, Comparison of 2 Agents, and Distribution of Microemboli

Dirk W. Droste, MD; Martina Reisener; Vendel Kemény, MD; Ralf Dittrich; Gernot Schulte-Altedorneburg, MD; Jörg Stypmann, MD; Thomas Wichter, MD; E. Bernd Ringelstein, MD

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 transesophageal 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. (Stroke. 1999;30:1014-1018.)

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 tiny 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

Received December 4, 1998; final revision received January 7, 1999; accepted February 4, 1999.

From the Department of Neurology (D.W.D., M.R., V.K., R.D., G.S-A., E.B.R.) and Department of Cardiology and Angiology and Institute of Arteriosclerosis Research (J.S., T.W.), University of Münster (Germany).

Reprint requests to Dr Dirk W. Droste, Klinik und Poliklinik für Neurologie der WWU Münster, Albert-Schweitzer-Str 33, D-48129 Münster, Germany.

© 1999 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org
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, 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, 14 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, 14 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.

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 additional patients no TEE could be obtained, 3 additional patients did not have a bilateral temporal window suitable for TCD, and 1 additional patient had an intolerance to milk.

**Echocardiography**

All patients underwent TEE, which was performed by a trained echocardiographer. The investigations, which were performed in the Department of Cardiology of our hospital, 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 interatrial shunt, 10 mL of galactose-based contrast agent (Echovist) was injected as a bolus into a large antecubital vein 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 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. 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.

**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 MCA stenosis, another patient showed an extracranial internal carotid artery occlusion, and a third patient showed 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 sonicated 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, chrip, 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 Valsalva strain, (2) saline without Valsalva strain, (3) galactose-based contrast agent with Valsalva strain, and (4) saline with Valsalva strain. Each of the 8 procedures required 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 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 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. 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 Valsalva maneuver versus without Valsalva 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 Valsalva maneuver. One patient had RLS under Valsalva 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 TEE and TCD (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).

18 patients were identified as positive in at least 1 of the Valsalva maneuver tests (galactose-based contrast agent or saline).
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. 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. 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. 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, 10 seconds, 15 seconds, 20 seconds, 22 seconds, and 25 seconds. Many authors believe that MES occurring late may have passed pulmonary shunts. On the other hand, Horner et al 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 the 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. The timing of the Valsalva maneuver is, however, still under debate. 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.

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 al on microemboli originating from prostatic 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 al 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.

References

esophageal contrast echocardiography in the detection of interatrial right-

10. Lynch JJ, Schuchard GH, Gross CM, Wann LS. Prevalence of right-
to-left atrial shunting in a healthy population: detection by Valsalva

11. Nishimura RA, Tajik AJ. The Valsalva maneuver and response revisited.

12. Leung DY, Black IW, Cranney GB, Walsh WF, Grimm RA, Stewart WI,
Thomas JD. Selection of patients for transesophageal echocardiography
after stroke and systemic embolic events: role of transthoracic echocar-

13. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent
foramen ovale during the first 10 decades of life: an autopsy study of 965

Chedru F, Guerin F, Bousser MG, de Recondo J. Atrial septal aneurysm
and patent foramen ovale as risk factors for cryptogenic stroke in patients
less than 55 years of age: a study using transesophageal echocardiogra-

461–465.

Regli F, Aebischer N, Karpuz HM, Castillo V, Guffi M, Sadeghi H.
Prognosis after stroke followed by surgical closure of patent foramen
ovale: a prospective follow-up study with brain MRI and simultaneous
47:1162–1166.

Surgical prophylaxis of recurrent stroke in patients with patent foramen

Surgical closure of patent foramen ovale in cryptogenic stroke patients.

19. Nendaz M, Sarasin FP, Bogousslavsky J. How to prevent stroke recur-
rence in patients with patent foramen ovale: anticoagulants, antiag-

20. Rao PS, Ende DJ, Wilson AD, Smith PA, Chopra PS. Follow-up results
of transcatheter occlusion of atrial septal defects with buttoned device.

21. Teague SM, Sharma MK. Detection of paradoxical cerebral echo contrast
embolization by transcranial Doppler ultrasound. *Stroke*. 1991;22:
740–745.

22. Spencer MP, Thomas GI, Nicholls SC, Sauvage LR. Detection of middle
cerebral artery emboli during carotid endarterectomy using transcranial

216–230.

24. Ringelstein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps
M, Markus HS, Russell D, Siebler M. Consensus on microembolus


*Diabetes Care*. 1997;20(suppl 1):S1–S70.


8:205–271.

30. Drost DB, Markus HS, Brown MM. The effect of different settings of ultrasound pulse amplitude, gain and sample volume on the appearance of
emboli studied in a transcranial Doppler model. *Cerebrovasc Dis*. 1994;
4:152–156.

31. Consensus Committee of the 9th International Cerebral Hemodynamics
Symposium. Basic identification criteria of Doppler microembolic

32. Klötzsch C, Janssen G, Berlit P. Transesophageal echocardiography and
contrast-TCD in the detection of a patent foramen ovale: experiences with

33. Job FP, Ringelstein EB, Grafen Y, Flachskampf FA, Doherty C,
Stockmanns A, Hanrath P. Comparison of transcranial contrast Doppler
sonography and transesophageal contrast echocardiography for the
detection of patent foramen ovale in young stroke patients. *Am J Cardiol*.

of transesophageal echocardiography and transcranial Doppler sonogra-
yphy with contrast medium for detection of patent foramen ovale.

Patent foramen ovale and transcranial Doppler: comparison of different

patent foramen ovale by transcranial contrast Doppler ultrasound.

Simultaneous bilateral contrast transcranial Doppler monitoring in pa-
patients with intracardiac and intrapulmonary shunts. *J Neurol Sci*. 1997;
150:49–57.

38. Anzola GP, Reulandt E, Magoni M, Costa A, Cobelli M, Guindani M.
Validation of transcranial Doppler sonography in the assessment of patent

39. Yeung M, Khan KA, Shuaib A. Transcranial Doppler ultrasonography in
the detection of venous to arterial shunting in acute stroke and trans-


41. Schwarze JJ, Klengelöcher J, Sander D, Kukla C, Wittich I. Factors
influencing the sensitivity of the contrast-TCD method in the detection
of right-to-left shunts. In: Klengelöcher J, Bartels EM, Ringelstein EB, eds.
*New Trends in Cerebral Hemodynamics*. Amsterdam, Netherlands:
Contrast Transcranial Doppler Ultrasound in the Detection of Right-to-Left Shunts: Reproducibility, Comparison of 2 Agents, and Distribution of Microemboli

Dirk W. Droste, Martina Reisener, Vendel Kemény, Ralf Dittrich, Gernot Schulte-Altedorneburg, Jörg Stypmann, Thomas Wichter and E. Bernd Ringelstein

Stroke. 1999;30:1014-1018
doi: 10.1161/01.STR.30.5.1014
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/30/5/1014

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/