A Comparison of Transesophageal Echocardiography and Transcranial Doppler Sonography With Contrast Medium for Detection of Patent Foramen Ovale

M. Jauss, MD; M. Kaps, MD; M. Keberle; W. Haberbosch, MD; W. Dornendorf, MD

**Background** Patent foramen ovale as a possible stroke risk factor can be diagnosed with transcranial Doppler sonography (TCD) by detecting intravenous contrast medium crossing from the right to the left atrium. The present study evaluates the reliability of this method.

**Summary of Report** We performed TCD and transesophageal echocardiography simultaneously in 50 patients using galactose microbubbles. We observed bubble signals passing the middle cerebral artery in 7 patients less than 20 seconds after injection; we found positive TCD tests in 14 patients.

Previous studies suggest that at least 16% of all cerebral ischemic events have a cardiac origin. In particular vascular territories this percentage is assumed to be even higher (anterior cerebral artery, 53%; middle cerebral artery [MCA], 25%; cerebellum, 29%). Young people with cerebral ischemia often display mitral valve prolapse or patent foramen ovale (PFO) as a probable cause. This is not only due to lack of other vascular risk factors but also because young people have a higher incidence of PFO (age 20 to 29 years, 33%; age 70 to 79 years, 24%).

Detection of PFO using transesophageal echocardiography (TEE) with contrast medium is the method of choice as a noninvasive technique, with high reliability proven by autopsy and cardiac catheterization. In the case of PFO, bubbles passing from the right to the left atrium can be observed. Conventional transthoracic color Doppler sonography usually fails because the Valsalva maneuver, which is necessary to create the right-to-left shunt, leads to a decrease in image quality. TEE requires considerable technical and personal prerequisites and cannot be applied immediately after stroke onset in the majority of stroke victims. Therefore, a simpler method for detection of PFO with transcranial Doppler sonography (TCD), which may serve as a screening test, was introduced by Teague and Sharma.

Although the described method is simple to use, there are some unsolved problems: (1) How reliable is TCD with contrast medium in detection of PFO, and how do the sensitivity and specificity compare with those of TEE? (2) What is the best timing for Valsalva strain? (3) When is pulmonary passage responsible for the appearance of bubbles in the MCA?

**Subjects and Methods**

In a prospective study we examined 40 consecutively admitted stroke patients (mean age, 54.3 ± 14.6 years; 26% female) simultaneously with TCD and TEE (transient ischemic attack [TIA] or prolonged reversible ischemic neurological deficit [PRIND], 15 patients; completed stroke, 25 patients). Ten additional patients received TEE because of cardiac disease. None had a history of pulmonary disease; three stroke patients had a history of deep venous thrombosis. The TEE/TCD examination in patients with TIA, PRIND, or stroke was performed during neurological workup fewer than 10 days after the ischemic event.

The patients gave informed consent. Before injection of contrast medium, TEE examination was routinely performed to exclude other reasons for cardiac embolism.

TEE was performed using a color-coded Doppler system (Sonos 1000, type 77030A, Hewlett-Packard) with a uniplanar, two-dimensional, 5-MHz TEE probe (type 21362C). Basal short-axis views and four-chamber views were obtained. For transcranial examination we used a 2-MHz pulsed-Doppler device (TCD2-64B, EME) and output power of 100 mW/cm². Patients were supine with the left side down. The head was slightly elevated to protect the patient from aspiration during insertion of the TEE probe.

We used a commercially available galactose particle suspension as contrast medium (Echovist 300, SH U 454, Schering). This agent contains 5-μm galactose microparticles with adherent air bubbles on their surfaces. The contrast medium was delivered in two bottles, one containing the galactose particles and the other the galactose solution. They were mixed together and were injected into the right cubital vein when the Doppler sample volume was adjusted to the M1 segment of the MCA and the heart was imaged in a four-chamber view to determine bubbles crossing through the PFO. We injected 5 mL of the galactose particle suspension during 5 seconds.
The injection was repeated after 3 minutes, and the Valsalva maneuver was performed when bubbles appeared in the right atrium and was continued for 5 seconds. TEE and TCD examinations were performed simultaneously, and both displays were recorded on video for off-line evaluation.

We considered TEE positive when direct crossing of bubbles through the PFO could be observed and lung passage could be excluded by observation of pulmonary veins. Echo contrast signals were identified by the typical overloading spike artifact in the frequency spectrum of fast Fourier-transformed video display. The bubble artifact was usually accompanied by a chirp that indicated a power amplitude of short duration in a high-frequency spectrum. When at least one spike appeared less than 25 seconds after injection, we considered TCD positive and assumed direct passage through the PFO. When the onset of bubble shower was later than 25 seconds, pulmonary passage was assumed.

For statistical purposes, TEE served as the “gold standard.” Statistical significance for distribution in cross tables was calculated using Fisher’s exact test because of low sample size (n=50).

**Results**

We detected PFO with TEE in 6 of the 25 stroke patients (24%), 4 of the 15 TIA/PRIND patients (27%), and 5 of 10 patients with cardiac disease (50%) confirmed by transmigration of bubbles from the right to the left atrium. Entrance of bubbles to the left atrium through pulmonary veins was not observed. In addition, we found a severe morphological defect with B-scan that indicated an atrial septal defect in 2 of the stroke patients. The average time when bubbles appeared in the right atrium was 5.1±1.4 seconds without the Valsalva maneuver and 5.2±1.2 seconds with the Valsalva maneuver. There was no significant difference (P>.05).

The delay until the first bubbles were observed in the right MCA in the case of PFO (both with and without the Valsalva maneuver) is shown in the Figure. When bubbles passed the sample volume later than 25 seconds after injection, TCD was considered negative and pulmonary passage was assumed. Using this criterion, TCD and TEE revealed concordant findings in 13 patients. One patient with chronic cardiac failure who exhibited a galactose particle suspension to differentiate between PFO and transpulmonary passage. The time limit was chosen from our data to ensure high sensitivity and specificity and was later than in other studies (mean of 11.5±3.5 seconds compared with 2.6±0.4 seconds during the Valsalva maneuver 6). There was no significant difference (P>.05).

In one patient (aged 23 years) with clear evidence of PFO on TEE as well as on TCD, phlebography was performed immediately. There was no evidence of deep venous thrombosis. Later evaluation of this patient revealed a protein C deficiency.

**Discussion**

TEE with contrast medium is a reliable method for detection of PFO and can detect shunting even in the absence of pulmonary hypertension. The higher sensitivity of TEE compared with transthoracic echocardiography for detection of PFO may be responsible for the high concordance between TCD and TEE findings.

**TABLE 1. Cross Table for Transesophageal Echocardiography Compared With Transcranial Doppler Sonography Without Valsalva Maneuver**

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<tr>
<th>TCD</th>
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<tr>
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</tbody>
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TCD indicates transcranial Doppler sonography; TEE, transesophageal echocardiography; +, detection of patent foramen ovale; -, no detection of patent foramen ovale. Sensitivity=0.47, specificity=1; P<.01, Fisher’s exact test.
TABLE 2. Cross Table for Transesophageal Echocardiography Compared With Transcranial Doppler Sonography With Valsalva Maneuver

<table>
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<th></th>
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TCD indicates transcranial Doppler sonography; TEE, transesophageal echocardiography; +, detection of patent foramen ovale; -, no detection of patent foramen ovale. Sensitivity = 0.93, specificity = 1; P < .01, Fisher's exact test.

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maneuver). This may be due to the prolonged circulation time of galactose microparticles compared with air bubbles or gelatine. We suggest a long time limit to prevent false-negative results. We prefer a fixed time limit to distinguish between PFO and transpulmonary passage instead of counting heart cycles. Heart cycles and ejected blood volume may vary during different conditions of circulation, particularly during the Valsalva maneuver, because cardiac preload is reduced and venous stasis occurs. False-negative results in TCD may occur if the chosen time limit is too short. We did not ask patients to sustain breathing during injection to keep the test simple and reliable.

Animal studies revealed that the lung serves as a filter for microbubbles with a cutoff diameter of 20 μm.12 Because galactose particle suspension bubbles are smaller (5 μm), they may pass the lung, although they were not detected in the MCA main stem. This may be due to decreased echogenicity under conditions of elevated pressure during lung passage in the capillary vessels caused by decay of galactose microparticles, as demonstrated in laboratory studies.13,14 We did not observe bubbles entering the left atrium from pulmonary veins. However, this cannot be ruled out by TEE because TEE does not display all four pulmonary veins at one time. However, we can exclude that a considerable number of bubbles pass through the lung with this method.

The galactose particle suspension we used (Echovist 300) is stable for approximately 60 seconds after injection in the venous system. This stability may lead to higher sensitivity in detection of PFO compared with other studies with air bubbles9 and with gelatine,10,11 but it necessitates determining a time limit to prevent false-positive results due to lung passage. Nonstabilized albumin solutions showed a faster decay in laboratory experiments and were more vulnerable to elevated ambient pressure than the galactose particle suspension.13 They may also serve as a suitable contrast agent for detection of PFO, but to our knowledge there is no TEE/TCD study using nonstabilized albumin as a contrast agent. Our study emphasizes the necessity of individual evaluation for different kinds of contrast media.

Compared with agitated saline solution9 and gelatine,10,11 all contrast agents offer high sensitivity and specificity. The advantages of galactose particle suspension are comfortable use and independence of different modes of preparation as well as standardized bubble size and standardized ultrasound properties. This agent has been thoroughly pharmacologically tested in this particular application form for side effects and toxicity; it may offer more safety to the patient, but it is much more expensive than other contrast agents.13

We suggest that an examination should be performed immediately after stroke onset to hasten further diagnostic evaluation. Other diagnostic procedures, such as phlebography, may follow in the early stages to detect possible sources of venous clots to confirm the mechanism of crossed embolism.

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References

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