Comparison of Diagnostic Techniques for the Detection of a Patent Foramen Ovale in Stroke Patients

Marco Di Tullio, MD; Ralph L. Sacco, MD; N. Venketasubramanian, MD; David Sherman, MD; J.P. Mohr, MD; Shunichi Homma, MD

Background and Purpose: The prevalence of a patent foramen ovale has been shown to be increased in patients with ischemic stroke. Transesophageal echocardiography, transthoracic echocardiography, and transcranial Doppler examination with contrast injection can all be used to search for a patent foramen ovale. We compared the accuracy of these techniques for identifying a patent foramen ovale in 49 patients with acute ischemic stroke or transient ischemic attack.

Methods: Transcranial Doppler examination of the right middle cerebral artery was performed during simultaneous transthoracic echocardiography with aerated saline injection, and again during transesophageal echocardiography; the latter was adopted as the “gold standard” for assessing the sensitivity of the other two tests.

Results: Contrast transesophageal echocardiography detected a patent foramen ovale in 19 of 49 patients (39%), during normal respiration in 15 of them and during Valsalva maneuver in 4. Transcranial Doppler correctly identified 13 patients with a patent foramen ovale and all 30 patients without it. Therefore, the sensitivity of transcranial Doppler was 68% (13/19), and its specificity 100% (30/30). The 6 patients misclassified by transcranial Doppler (false negatives) had a very small right-to-left shunt detected by transthoracic echocardiography. Contrast transthoracic echocardiography was found to be the least sensitive test, detecting a patent foramen ovale in only 9 of 19 patients (47%). The specificity of transthoracic echocardiography was 100% (30/30 patients). The low sensitivity of transthoracic echocardiography was principally due to the suboptimal image quality obtained in false-negative patients. Both transcranial Doppler and transthoracic echocardiography were more sensitive in patients with cryptogenic stroke than in patients with stroke of determined origin. This may indicate the presence of larger, more easily detectable shunts in patients with cryptogenic stroke.

Conclusions: Transesophageal echocardiography is more sensitive than transcranial Doppler examination in detecting a patent foramen ovale, but only in cases of minimal right-to-left shunts, the clinical relevance of which remains to be established. The sensitivity of transthoracic echocardiography is heavily hampered by the frequency of inadequate heart visualization. (Stroke 1993;24:1020-1024)

Key Words • cerebrovascular disorders • Doppler • echocardiography • foramen ovale, patent

Paradoxical embolization through a patent foramen ovale is a well-recognized mechanism for embolic stroke, although its relative importance has not been established. The prevalence of patent foramen ovale has been shown to be higher in stroke patients than in control subjects, especially in cases of unexplained or cryptogenic infarctions. Contrast transthoracic echocardiography has been used to detect the presence of a patent foramen ovale. Recently, transesophageal echocardiography with contrast injection has been shown to be more sensitive than transthoracic echocardiography, and it is currently considered the “gold standard” to establish the presence of a patent foramen ovale. Transesophageal echocardiography, however, is a semi-invasive technique and may be difficult to perform in stroke patients with swallowing dysfunction. Transcranial Doppler examination of the middle cerebral artery during Valsalva maneuver has been recently proposed as an alternative method for the detection of right-to-left shunts. The aim of the present study was to compare the accuracy of echocardiographic and transcranial Doppler techniques in detecting a patent foramen ovale in patients with stroke.

Subjects and Methods

Forty-six patients with completed acute ischemic stroke and 5 patients with transient ischemic attack consecutively undergoing transesophageal echocardiography were entered in the study. Reasons for performing transesophageal echocardiography included the lack of a plausible cause for the cerebrovascular ischemic episode (cryptogenic stroke) or the suspicion of a possible embolic mechanism with no cardiac source identified on transthoracic echocardiography. Esoph-
geal intubation was not successful in 2 patients (4%). Therefore, the study population consisted of 49 patients (27 men, 22 women; mean age, 63.6±13.3 years). According to Stroke Data Bank criteria, 25 patients were classified as having a stroke of determined cause (8 large-vessel atherosclerotic, 6 cardioembolic, 10 small-vessel lacunar, 1 vertebral artery dissection) and 19 as having a cryptogenic stroke or infarct of undetermined cause. The remaining 5 patients were considered as having a transient ischemic attack. In 14 of the 19 cryptogenic stroke patients, duplex Doppler examination of the carotid arteries showed no or less than 40% stenosis. Three patients had more than 40% narrowing of one carotid artery, which was felt to be secondary to embolism with no identifiable cardiac source in 2 patients (intracarotid thrombus documented by arteriography, and simultaneous arm embolus) and an asymptomatic carotid stenosis in 1 patient. The remaining 2 patients did not have Doppler examination of the carotid arteries because their stroke was located in the posterior circulation territory. Risk factors for stroke were present in 15 of 19 (79%) cryptogenic stroke patients: arterial hypertension in 8 (42%), cigarette smoking in 5 (26%), diabetes mellitus in 2 (11%), and mitral valve prolapse in 1 (5%).

All patients underwent transcranial Doppler examination during simultaneous transesophageal and transthoracic echocardiography with aerated saline injection. Echocardiography was performed using Hewlett-Packard Sonos 1000 equipment with a 2.5-MHz transducer for transthoracic imaging and a 5.0-MHz biplane transducer for transesophageal imaging. Transcranial Doppler examination was performed using EME TC 2-64B pulsed Doppler equipment with a 2-MHz transducer.

The right middle cerebral artery was insonated and the apical four-chamber view was imaged during contrast injection (transthoracic study). The basilar artery was insonated in two patients because of the inability to insonate the middle cerebral artery. The middle cerebral artery was insonated through the temporal window at a depth of 50 to 55 mm; the basilar artery was insonated from the suboccipital window at a depth of 80 to 85 mm. The same protocol was followed during four-chamber view imaging in the transverse plane for the transesophageal study. Contrast material was prepared by mixing 10 mL of saline with 0.5 to 1.0 mL of air by means of two syringes mounted on a three-way stopcock. The suspension contained air microbubbles ranging from 30 to 110 μm in diameter (direct microscopy measurement).

During the test, the suspension was rapidly injected into an antecubital vein. A patent foramen ovale was considered to be present when at least one microbubble was seen in the left atrium within three cardiac cycles from their appearance in the left atrium (transcranial and transesophageal echocardiography; Fig 1) or when typical spikes were insonated on the baseline cerebral artery tracing (transcranial Doppler; Fig 2), along with a characteristic acoustic signal. The tests were repeated during Valsalva maneuver to increase their sensitivity. The studies were then independently interpreted by two experienced readers, each one blinded to the results of the other studies.

Sensitivity and specificity for the detection of a patent foramen ovale by transcranial Doppler and transthoracic echocardiography were calculated using transesophageal echocardiography as the gold standard. Sensitivity was then recalculated stratified by infarct subtype. Differences between proportions were tested using χ² or Fisher's Exact Test (two-tailed).

**Results**

Contrast transesophageal echocardiography detected a patent foramen ovale in 19 of the 49 patients (39%). Actual determination of the foramen size (defined as the separation between septum primum and septum secundum in longitudinal view) was possible in 11 of them (58%) and ranged from 1 to 4 mm. Two patients also had an atrial septal aneurysm (defined as a localized outpouching of the fossa ovalis region with base width of 1.5 cm or more and excursion into either the left or the right atrium or both of 1.1 cm or more). In 4 patients the study was positive only during Valsalva maneuver. Two patients had evidence of intrapulmonary shunt, suggested by the late appearance of microbubbles into the left atrium and confirmed by their direct visualization in the pulmonary veins (Fig 3). One of these 2 patients also had evidence of a patent
Sensitivity and Specificity of Transcranial Doppler and Transthoracic Echocardiography for Patent Foramen Ovale Detection, With Transesophageal Echocardiography as the ‘Gold Standard’

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tbody>
<tr>
<td>In entire study group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCD</td>
<td>13/19 (68)</td>
<td>30/30 (100)</td>
</tr>
<tr>
<td>TTE</td>
<td>9/19 (47)</td>
<td>30/30 (100)</td>
</tr>
<tr>
<td>In cryptogenic stroke patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCD</td>
<td>7/9 (78)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>TTE</td>
<td>6/9 (67)</td>
<td>3/3 (100)</td>
</tr>
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TCD, transcranial Doppler; TTE, transthoracic echocardiography.

in 3, an ulcerated plaque or thrombus in the aortic arch in 2, mitral valve strands in 1, and severe mitral annular calcification in 1. Three of these 7 patients also had a patent foramen ovale (1 patient with left atrial appendage thrombus, 1 with mitral valve strands, and 1 with severe annular calcification). Aortic arch atherosclerotic plaques 0.5 cm or greater were seen in 6 of 49 patients (12%).

Transcranial Doppler identified a patent foramen ovale in 13 of the 19 patients (68%) detected by transesophageal echocardiography. All patients without a patent foramen were also correctly identified. Sensitivity of transcranial Doppler was therefore 68% (13/19), and its specificity was 100% (30/30; Table). In the 6 discordant cases, transesophageal echocardiography showed the size of the foramen to be small (2 mm in 1 patient, 1 mm in 3 patients, no direct visualization in the remaining 2 patients); the contrast study was weakly positive (less than 5 microbubbles seen) and was positive only during Valsalva maneuver in 2 patients. Transcranial Doppler detected the passage of microbubbles in the patient who had a patent foramen ovale and intrapulmonary shunt, but not in the patient with intrapulmonary shunt alone.

Contrast transthoracic echocardiography correctly identified 9 of the 19 patients with a patent foramen ovale, and all the 30 patients without it. Its sensitivity

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**Fig 2.** Microbubble detection in right middle cerebral artery by transcranial Doppler examination during aerated saline injection. Baseline tracing is shown in the top panel; spikes originating from the passage of microbubbles (arrowheads) are shown in the bottom panel.

foramen ovale. Transesophageal echocardiography also detected another potential cardiac source of emboli in 7 patients (14%): a thrombus in the left atrial appendage

**Fig 3.** Microbubble visualization (arrowheads) in left upper pulmonary vein (LUPV) secondary to intrapulmonary shunt. LA, left atrium.
was therefore 47%, and its specificity 100% (Table). Inadequate image quality accounted for 6 of the 10 false-negative cases; had these 6 patients been excluded from the analysis, the sensitivity of transthoracic echocardiography would have risen to 69% (9/13 patients). The sensitivity of transthoracic echocardiography was slightly greater in patients aged younger than 55 years (3/5; 60%) than in older patients (6/14; 43%), probably due to the better image quality achievable in younger individuals. Transthoracic echocardiography failed to identify any of the patients with intrapulmonary shunt and only identified 1 patient (2%) with another potential cardiac embolic source (mitral annular calcification).

Although statistical significance was not reached, the prevalence of patent foramen ovale by transeosophageal echocardiography was greater in patients with cryptogenic stroke (9/19; 47%) than in patients with stroke of determined origin (8/25; 32%). Two of the 5 patients with transient ischemic attack (40%) also had a patent foramen ovale. The size of the foramen was slightly greater in cryptogenic stroke patients than in patients with stroke of determined origin (2.0±3.8 mm versus 0.9±1.1 mm). The sensitivity for patent foramen ovale detection of transthoracic echocardiography was slightly greater in patients with cryptogenic stroke (6/9 patients; 67%) than in patients with stroke of determined origin (2/8 patients; 25%; Table), but the small sample size limited the statistical significance. A similar trend was observed for transcranial Doppler (7/9 patients, or 78%, in cryptogenic stroke patients versus 4/8 patients, or 50%, in patients with stroke of determined origin; Table).

Discussion

The association between patent foramen ovale and stroke has recently been demonstrated by several studies. Lechat et al. found a 40% prevalence of patent foramen ovale in young patients (aged younger than 55 years) with stroke compared with 10% in control subjects. The prevalence was even greater (54%) in patients with cryptogenic stroke. Webster et al. also found a higher prevalence of patent foramen ovale in a younger group (aged younger than 40 years) of patients with stroke (prevalence, 50%) compared with control subjects (15%). More recently, we demonstrated that a patent foramen ovale was more frequent in patients with cryptogenic stroke (42%) than in patients with stroke of determined origin (7%), even after controlling for the presence of other known stroke risk factors such as hypertension, diabetes mellitus, cigarette smoking, and history of prior stroke. Furthermore, an increased prevalence of patent foramen ovale in patients with cryptogenic stroke was observed both in patients younger than 55 years (48% compared with 4% in patients with stroke of determined cause) or older (38% versus 8%). This observation suggested that a patent foramen ovale may be a risk factor for cryptogenic stroke regardless of patient age.

The search for a patent foramen ovale in patients with ischemic stroke requires diagnostic tests that are sensitive, specific, widely available, and easy to perform even in acutely ill patients. Transeosophageal echocardiography is considered the most sensitive noninvasive technique for detecting a patent foramen ovale. In our series transeosophageal echocardiography led to the detection of the greatest number of patients with a patent foramen ovale and was considered to be the gold standard for this diagnosis. Transeosophageal echocardiography also detected other cardiac abnormalities in 14% of our patients. Therefore, the overall yield of transeosophageal echo for a potential cardiac source of emboli approached 50% in our study, confirming its diagnostic usefulness. Esophageal intubation was not successful in only two patients, and no complications were observed during or after the test. Transeosophageal echocardiography, therefore, can be safely performed in the majority of patients with acute stroke.

Transcranial Doppler examination detected a patent foramen ovale in 68% of patients identified by transeosophageal echocardiography. In a recent study, Nemec et al. observed that transcranial Doppler had 100% sensitivity for patent foramen ovale, but only 50% for intrapulmonary shunt. The latter was defined by the late appearance of microbubbles in the left atrium during transeosophageal echocardiography; no attempt was reported to directly visualize the microbubbles in the pulmonary veins. If one combines the figures for patent foramen ovale and intrapulmonary shunt, the overall sensitivity of transcranial Doppler for right-to-left shunt drops to 84% in that study and to 68% in ours. In another recent study, Karnik et al. reported an 87% sensitivity of transcranial Doppler for patent foramen ovale detection, without addressing the issue of intrapulmonary shunts. Overall, transcranial Doppler examination appears to be very sensitive in detecting large or moderate shunts, but less sensitive for smaller ones. These “microshunts” are characterized by a lower number, and possibly smaller size, of shunting microbubbles. Their clinical relevance, in terms of target organ involvement after paradoxical embolization, remains to be established.

Transsthoracic echocardiography was the least sensitive technique for detecting a patent foramen ovale among those compared in our study. This was partially accounted for by the difficulty in obtaining an optimal transthoracic image in some patients who had adequate transeosophageal and transcranial studies. The exclusion of these patients from the study would have resulted in an improved sensitivity of transthoracic echocardiography (69%) but would also overestimate the value of the test in real-life, everyday use. Transthoracic echocardiography has been documented to be less sensitive than transeosophageal echocardiography and even transcranial Doppler for the detection of a patent foramen ovale. The increased prevalence of patent foramen ovale documented by transthoracic echocardiography in recent case-control studies on patients with stroke may in fact represent an underestimation because of the frequent occurrence of false-negative or nondiagnostic studies. However, transthoracic echocardiography is a sensitive technique for detecting other cardiac abnormalities, such as valvular diseases and left ventricular dysfunction or thrombi, which may be related to embolic stroke.

In our study, the sensitivity for patent foramen ovale detection of both transcranial Doppler and transsthoracic echocardiography was slightly greater in patients with cryptogenic stroke than in patients with stroke of determined origin. This could indicate that larger, more easily detectable shunts occurred through the patent...
foremen ovale of patients with cryptogenic stroke. The size of the foramen in our study tended to be larger in cryptogenic stroke patients than in patients with stroke of determined origin (2 versus 0.9 mm). The quantitation of the shunt might identify those patent foramina that are more likely to result in a paradoxical embolization. The finding of larger shunts in patients with cryptogenic stroke might help to explain the established association between patent foramen ovale and cryptogenic stroke.6

How aggressively a patent foramen ovale should be sought in patients with stroke depends on the therapeutic changes that would be introduced on the basis of its detection. Prospective data on the recurrence rate of stroke in patients with a patent foramen ovale are needed to ascertain the risk of such patients and the potential benefits from therapeutic interventions. Until then, oral anticoagulation appears to be warranted in patients with documented venous thrombosis,4 while its indication should be evaluated individually in other patients.22 Percutaneous closure of the foramen may be indicated in selected cases, especially for large shunts.23,24

Our study showed that transesophageal echocardiography with contrast injection is the most sensitive test for detecting a patent foramen ovale, particularly when associated with a small right-to-left shunt. This, along with its superiority in detecting other cardiac sources of emboli, indicates that transesophageal echocardiography should be performed in patients with stroke of undetermined origin. In patients in whom the test is not feasible, the combined use of transthoracic echocardiography and transcranial Doppler examination provides good sensitivity for the detection of significant intracardiac shunts and a baseline assessment of cardiac morphology and function. The efficient use of more sensitive diagnostic procedures among patients with acute ischemic stroke will decrease the number of cases labeled as cryptogenic13 and lead to more informed choices among our current long-term therapeutic options.

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