Contrast transcranial Doppler compared to transesophageal echocardiography in detection of right-to-left shunt

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ABSTRACT

Objective: To assess contrast transcranial Doppler (TCD) for detection of right-to-left shunt (RLSh).

Methods: We studied 30 patients aged between 25-45 years admitted to Al-Zahra Hospital, affiliated to Isfahan University of Medical Sciences, between May 2003 and May 2005. All patients underwent transesophageal echocardiography (TEE) with contrast and contrast TCD.

Results: Eleven (36.6%) patients had RLSh detected by TEE with contrast, and 19 (63.3%) patients had no shunt by TEE. Eighteen patients (60%) patients had no RLSh by contrast TCD, and 12 (40%) patients had RLSh by contrast TCD. Ten (33.3%) patients had RLSh by contrast TCD and TEE with contrast procedures. One patient had RLSh by TEE, and it was negative on TCD test, and 2 patients were positive on TCD test and negative in TEE. With contrast TEE as the gold standard, the sensitivity of contrast TCD was 90.9% and specificity was 89.4%, with an accuracy of 90%. Meanwhile, the positive predictive value of contrast TCD was 83.3% and the negative predictive value was 94.4%.

Conclusion: In our study, the negative predictive value of contrast TCD was excellent. Therefore, this examination is able to exclude RLSh with a high level of confidence.

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Right-to-left shunt (RLSh) is a well-established risk factor for ischemic stroke and transient ischemic attack (TIA),[1] especially in young subjects and in patients with stroke of unknown origin (cryptogenic).[2] Transesophageal echocardiography (TEE) with contrast injection is considered the gold standard to detect an RLSh, presumed due to patent foramen ovale (PFO) in the majority of cases. A number of studies,[3-7] have recently shown that contrast transcranial Doppler (TCD) examination of the middle cerebral arteries (MCAs) is highly sensitive and specific compared with contrast TEE to detect RLSh. Contrast TCD has a sensitivity of >90%, and a specificity of 75% for identifying PFO when compared with TEE.[6] Contrast TCD is a noninvasive and safe technique that does not cause the patient discomfort.[3] The injection of contrast before Valsalva maneuver (VM) appeared to be the most effective TCD procedure in determining the transit of microbubbles through an RLSh, and subsequently in the middle cerebral artery.[4] The TCD is a new technique for evaluation of patients at stroke units in Iran. Although, the capability of TCD to detect an RLSh has been established, this technique in Iran is under study. Indeed, TCD has not been evaluated for detection of RLSh compared to the gold standard method of TEE in Iran. This study was undertaken to assess the sensitivity and specificity of contrast TCD compared to TEE with contrast in detection of RLSh.

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Methods. We studied 23 anterior circulation, and 7 posterior circulation stroke patients admitted in Al-Zahra Hospital, affiliated to Isfahan University of Medical Sciences, with the clinical diagnosis of ischemic stroke, between May 2003 and May 2005. The ethics committee at Isfahan University of Medical Sciences approved the study. All patients signed a consent document approved by the institutional review board at the study site. A TEE with contrast and contrast TCD was performed on all patients. Inclusion criteria were as follows: age between 15-45 years; ischemic stroke confirmed by neuroimaging; consent to undergo contrast TCD; temporal window suitable for TCD; negative laboratory data for vasculitis and coagulopathy, and any other etiology for stroke in young adults. Doppler sonography of cervical vessels and transthoracic echocardiography (TTE) was performed on all patients at the beginning of the study. Patients, according to inclusion criteria, were divided into 2 groups based on the mechanism of emboli stroke. Group 1 patient had an established high-risk carotid or cardiac source of cerebral embolism, and group 2 patients had no known embolic risk factor. Patients with prosthetic heart valves, high-grade ipsilateral (70%) carotid stenosis, acute myocardial infarction, atrial thrombus, significant congestive heart failure, atrial fibrillation (AF), PFO, atrial septal aneurysm, mitral valve strands, chronic (>6 months) left ventricular thrombus, and carotid occlusion were included in group 1. Patients with stroke and no embolic risk factors were included in group 2. We excluded group 1 and studied group 2 patients. Transcranial Doppler examination was carried out using a TCD monitoring device (TCD-8.11 b/c, DWL 2.55e). Both middle cerebral arteries (MCAs) were simultaneously monitored through the temporal window by the use of 2-MHz probes. An elastic headband fit the TCD probes. The contrast of the study was obtained by a mixture of saline solution (9 ml) and air (1 ml), agitated between two 10-ml syringes connected by a 3-way stopcock. The solution was immediately injected with a 20-gauge/32 mm catheter placed in the antecubital vein to obtain a bolus of air microbubbles. This procedure was performed 2 times during normal breathing and VM. We asked them to maintain the VM for a period of at least 5-7 seconds. The bolus of air microbubbles was injected 1-2 seconds before the beginning of the VM.[4] The subjects had been previously instructed in the performance of the VM, and the efficacy of which was shown by a reduction in the mean velocity of the MCA of at least 25%. To reduce the risk of misclassifying intrapulmonary shunt as intracardiac shunt, only the appearance of air-embolism signal in the MCA within 7 seconds of the injection was considered positive for intracardiac shunt.[8] Microembolic signals (MES) were defined by; 1) brief-duration (<0.1 second); 2) intensity greater than 3dB above the background; and 3) variable location in the TCD waveform.[9] We quantified the importance of RLSh by counting the number of MES in one MCA. Patients were divided in to 3 different groups on the basis of the maximum number of MES in the MCA in any single frame after intravenous injection of agitated saline solution: normal TCD study (if 0 MES were detected), small RLSh (<10 MES), and large degree of shunt (>10 MES). In this last group, shower (>25 MES) and curtain (uncountable MES) were identified. Patients with cryptogenic stroke underwent contrast TEE. The TTE study was performed before TEE. These examinations were performed by an experienced cardiologist, who was blinded to the contrast TCD results. The TEE study was performed on each patient after topical anesthesia of the oropharynx and mild sedation with intravenous midazolam (0.5-1.5 mg). Contrast material was prepared and injected into the antecubital vein, as previously described. The contrast examination was performed studying the patient, 3 times breathing normally, and 3 times during a VM. An RLSh was diagnosed when microbubbles were detected in the left atrium within 3 cardiac cycles of their appearance in the right atrium. 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 positive (RLSh confirmed by both methods) in comparison too true positive plus false negative (TCD negative and TEE-positive). Specificity was determined as the percentage of true negative compared with true negative plus false positive (TCD-positive and TEE-negative).

Results. Thirty patients were included in this study. Of these subjects, 18 were male and 12 were female, 23 patients had anterior circulation stroke, and 7 patients had posterior circulation stroke. The mean age of patients was 38.8 (SD = 5.2). Eleven (36.6%) patients had RLSh detected by TEE with contrast, and 19 (63.3%) patients had no shunt by TEE. Eighteen (60%) patients had no RLSh by contrast TCD, and 12 (40%) patients had RLSh by contrast TCD. Ten (33.3%) patients had RLSh by 2 contrast TCD and TEE with contrast procedures. One patient had RLSh by TEE that was negative on TCD test, and 2 patients had positive TCD test and negative TEE. With contrast TEE as the gold standard, the sensitivity of contrast-TCD was 90.9% and specificity was 89.4%, and the overall accuracy was 90%. Meanwhile, positive predictive value of contrast TCD was 83.3%

and negative predictive value was 94.4%. Twelve (40%) patients had RLSh by contrast TCD, of these, 4 patients had small shunt and 8 patients had large shunt. Of all these patients, 3 patients had 10-25 MES and 4 patients had >25 MES; one patient had uncountable MES.

Discussion. Paradoxical embolism through RLSh, such as the PFO is widely accepted as a potential cause of cerebral ischemia.[5,10] The French Study Group[11] observed an annual rate of recurrence for stroke or TIA of 3.4% in patients with intracardiac RLSh. De Castro et al,[12] found a cumulative risk for recurrence of stroke at 3 years of 19.5%. The prevalence of RLSh was greater among those with cryptogenic stroke (39.2%) than among these in whom a potential pathogenesis of stroke could be identified (29.9%; $p<0.02$).[13] The prevalence of RLSh was 40% in our study. This agrees with a previous study, which finds a prevalence of 41% for RLSh in patients below 55 years with cryptogenic stroke.[10] The prevalence of RLSh in 54 patients with cryptogenic stroke was also reported as 41%.[14] The study by Serena et al,[8] on 117 patients, found 50% of cryptogenic stroke patients had RLSh.

The TEE with contrast is currently viewed as the gold standard in the detection of RLSh.[15] More recently, contrast TCD has been proposed as an alternative method in the detection of RLSh.[14] Our data confirms the capability of contrast TCD to detect a right-to-left shunt. Our study demonstrates that contrast TCD detects TEE-proven RLSh with a sensitivity of 90.9% and specificity of 89.4%. Zanette et al[4] studied 38 cerebrovascular patients (21 men, 17 women) with positive contrast study for PFO on TTE, and reported a sensitivity of contrast TCD of 78.9%. Droste et al,[16] demonstrated that contrast TCD detects TEE-proven RLSh with a sensitivity of >90% and a specificity of 76%. In a study by Job et al,[17] sensitivity and specificity of TCD compared to TEE were 89% and 92%. In other study, sensitivity and specificity of TCD on detection of RLSh in 50 patients were 93% and 100%.[18] Using TEE as the gold standard, the sensitivity of contrast TCD was 91.3%, specificity 93.8% and accuracy 92.8% in Klotzsch's study.[19] By evaluation of 54 patients, Droste et al[6] reported a sensitivity of 95% and specificity of 75% with contrast TCD on detection of RLSh in stroke patients.

With positive TCD and negative TEE (6.8% or 2 cases in our study), usually the VM leads to positive TCD findings. The VM is more easily performed with TCD than with TEE. Another possible explanation is the presence of small pulmonary shunts.[20]

We conclude that, contrast TCD is a highly sensitive method for detecting a right-to-left shunt. In our study, the negative predictive value of contrast TCD was excellent. Therefore, this examination is able to exclude RLSh with a high level of confidence. It advantages are low cost, it ability to detect single contrast medium embolism, and control of VM by observing the decrease of cerebral blood flow. For these reasons, contrast TCD is a preferred screening procedure over TEE.[19] Several aspects, such as detection and significance of pulmonary shunt and time limit for MES appearance on contrast TCD require further investigation.

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References

1. Ward R, Jones D, Haponik EF. Paradoxical embolism: an under recognized problem. ***Chest*** 1995; 108: 549-558.
2. Angeli S, Del Sette M, Beelke M, Anzola GP, Zanette E. Transcranial Doppler in the diagnosis of cardiac patent foramen ovale. ***Neurol Sci*** 2001; 22: 353-356.
3. Anzola G, Renaldini E, Magoni M, Costa A, Cobelli M, Guindani M. Validation of transcranial Doppler sonography in the assessment of patent foramen ovale. ***Cerebrovasc Dis*** 1995; 5: 194-198.
4. Zanette E, Mancini G, De Castro S, Solaro M, Cartoni D, Chiarotti F. Patent foramen ovale and transcranial Doppler: comparison of different procedures. ***Stroke*** 1996; 27: 2251-2255.
5. Schwarze J, Sander D, Kukla C, Wittich I, Babikian VL, Klingelhöfer J. Methodological parameters influence the detection of right-to-left shunts by contrast transcranial Doppler ultrasonography. ***Stroke*** 1999; 30: 1234-1239.
6. Droste DW, Reisener M, Kemeny V, Dittrich R, Schulte-Altedorneburg G, Stypmann J, et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: reproducibility, comparison of 2 agents, and distribution of microemboli. ***Stroke*** 1999; 30: 1014-1018.
7. Droste DW, Kriete J, Stypmann J, Castrucci M, Wichter T, Tietje R, et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: comparison of different procedures and different contrast agents. ***Stroke*** 1999; 30: 1827-1832.
8. Serena J, Segura T, Perez-Ayuso MJ, Bassaganyyas J, Molins A, Davalos A. The need to quantify right-to left shunt in acute ischemic stroke: a case-control study. ***Stroke*** 1998; 29: 1322-1328.
9. Tong DC, Alpers GW. Transcranial Doppler-detected microemboli in patients with acute stroke. ***Stroke*** 1995; 26: 1588-1592.
10. Overell JI, Bone I, Lees KR. Interatrial septal abnormalities and stroke. A meta-analysis of case–control studies, ***Neurology*** 2000; 55: 1172–1179.
11. Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack: French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. ***Am Heart J*** 1995; 130: 1083-1088.

12. De Castro S, Cartoni D, Fiorelli M, Rasura M, Anzini A, Zanette EM, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. ***Stroke*** 2000; 31: 2407-2413.
13. Halperin JL, Fuster V. Patent foramen ovale and recurrent stroke. ***Circulation*** 2002; 105: 2580-2587.
14. Teague SM, Sharma MK. Detection of paradoxical cerebral echo contrast embolization by transcranial Doppler ultrasound. ***Stroke*** 1991; 22: 740-745.
15. Chmowitz MI, Nemec JJ, Marwick TH, Lorig RJ, Furlan AJ, Salcedo EE. Transcranial Doppler ultrasound identifies patients with right-to-left cardiac or pulmonary shunts. ***Neurology*** 1991; 41: 1902-1904.
16. Droste DW, Silling K, Stypmann J, Grude M, Kemeny V, Wichter T, et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: time window and threshold in microbubble numbers. ***Stroke*** 2000; 31: 1640-1645.
17. Job FP, Ringelstein EB, Grafen Y, Flachskampf FA, Doherty C, Stockmanns A, et al. Comparison of transcranial contrast Doppler sonography and transesophageal contrast echocardiography for the detection of patent foramen ovale in young stroke patients. ***Am J Cardiol*** 1994; 74: 381-384.
18. Jauss M, Kaps M, Keberle M, Haberbosch W, Dorndorf W. A comparison of transesophageal echocardiography and transcranial Doppler sonography with contrast medium for detection of patent foramen ovale. ***Stroke*** 1994; 25: 1265-1267.
19. Klotzsch C, Janssen G, Berlit P. Transesophageal echocardiography and contrast-TCD in the detection of a patent foramen ovale: experiences with 111 patients. ***Neurology*** 1994; 44: 1603-1609.
20. Dittrich R, Ritter MA, Droste DW. Microembolus detection by transcranial Doppler sonography. ***Eur J Ultrasound*** 2002; 16: 21-30.
21. Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Smith C, Mohr JP. Surgical closure of patent foramen ovale in cryptogenic stroke patients. ***Stroke*** 1997; 28: 2376-2381.