

Accuracy of Transcranial Doppler for the Diagnosis of Intracardiac Right-to-Left Shunt

A Bivariate Meta-Analysis of Prospective Studies

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OBJECTIVES The aim of this meta-analysis was to determine the accuracy of transcranial Doppler (TCD) compared with transesophageal echocardiography (TEE) as the reference.

BACKGROUND Right-to-left shunting (RLS), usually through a patent foramen ovale (PFO), has been associated with migraine, cryptogenic stroke, and hypoxemia. With emerging observational studies and clinical trials on the subject of PFO, there is a need for accurate diagnosis of PFO in patients with these conditions, and those being considered for transcatheter closure. Although a TEE bubble study is the current standard reference for diagnosing PFO, the TCD bubble study may be a preferable alternative test for RLS because of its high sensitivity and specificity, noninvasive nature, and low cost.

METHODS A systematic review of Medline, the Cochrane Library, and Embase was done to look for all the prospective studies assessing intracardiac RLS using TCD compared with TEE as the reference; both tests were performed with a contrast agent and a maneuver to provoke RLS in all studies.

RESULTS A total of 27 studies (29 comparisons) with 1,968 patients (mean age 47.8 ± 5.7 years; 51% male) fulfilled the inclusion criteria. The weighted mean sensitivity and specificity for TCD were 97% and 93%, respectively. Likewise, the positive and negative likelihood ratios were 13.51 and 0.04, respectively. When 10 microbubbles was used as the embolic cutoff for a positive TCD study, TCD produced a higher specificity compared with when 1 microbubble was used as the cutoff ($p = 0.04$); there was, however, no significant change in sensitivity ($p = 0.29$).

CONCLUSIONS TCD is a reliable, noninvasive test with excellent diagnostic accuracies, making it a proficient test for detecting RLS. TCD can be used as a part of the stroke workup and for patients being considered for PFO closure. If knowledge of the precise anatomy is required, then TEE can be obtained before scheduling a patient for transcatheter PFO closure. (*J Am Coll Cardiol Img* 2014;7:236–50)
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Patent foramen ovale (PFO) is a remnant of the fetal circulation that is present in 20% to 25% of the population (1–3). Transient right-to-left shunting (RLS), usually through a PFO, has been implicated in the pathophysiology of stroke, migraine, and hypoxemia (3–6). A meta-analysis of observational studies and a recent meta-analysis of the CLOSURE 1 (Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale), RESPECT (Closure of Patent Foramen Ovale Versus Medical Therapy After Cryptogenic Stroke), and PC (Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism) trials suggest that PFO occluding devices reduce the recurrence of stroke and transient ischemic attack at higher rates than conventional medical treatment alone (pooled hazard ratio: 0.59, 95% confidence interval [CI]: 0.36 to 0.97; $p = 0.04$) (7,8). These data, along with the evaluation of patients with severe migraines or other PFO-associated conditions, make it essential to accurately diagnose RLS in patients being considered for PFO closure.

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Whereas contrast transesophageal echocardiography (TEE) is considered the gold standard for diagnosing PFO (9,10), contrast transcranial Doppler (TCD) is increasingly being used for safe, noninvasive, and cost-effective screening of intracardiac RLS (11–37). The aim of this study was to expand on prior reviews of TCD to provide the first meta-analysis that methodically assesses the diagnostic accuracy of TCD in evaluating for an intracardiac RLS.

METHODS

Literature review. Relevant citations were searched for on Medline, the Cochrane Library, and Embase. The search was completed in August 2013, yielding literature since 1913. The terms used in the search were “PFO” OR “patent foramen ovale” OR “right to left shunt” OR “atrial septal defect” AND “TCD” OR “transcranial Doppler” OR “TEE” OR “echo” OR “transesophageal echo” OR “transesophageal echocardiogram” OR “transesophageal echocardiography.”

The references of all primary studies as well as those from known reviews were analyzed to find cited studies that were not found by initial searches. No restrictions were used regarding publication language. Abstracts lacking peer-reviewed manuscripts

were omitted because they would not have enough data required for the meta-analysis.

Selection of studies. Studies that were identified were analyzed by 3 independent reviewers (M.K.M., S.C.R., and J.S.W.). Each study was screened for pre-set inclusion criteria:

1. Original prospective studies (reviews, abstracts, isolated cases, commentaries, editorials, and letters were excluded)
2. Subject age ≥ 18 years
3. Studies were selected if they included at least 20 patients with suspected intracardiac RLS who were screened by TCD and confirmed by TEE as a reference. If a study conducted both TCD and TEE, but did not consider TEE as the gold standard, we calculated the appropriate parameters assuming TEE as the reference comparison.
4. TCD and TEE accuracies calculated utilizing a provocation maneuver.
5. Able to interpret diagnostic accuracies by adequate demonstration of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN).
6. If a study compared different TCD protocols (such as comparing accuracy of different contrast injection sites or different types of contrast) and also provided the variables to calculate the different accuracies (i.e., the TP, FP, FN, and TN), then each methodology was considered a separate comparison in the final analysis. A sensitivity analysis was then conducted to demonstrate the effect of varying methodologies on accuracy of TCD.

ABBREVIATIONS AND ACRONYMS

CI	= confidence interval
FN	= false negative
FP	= false positive
LR	= likelihood ratio
MCA	= middle cerebral artery
PFO	= patent foramen ovale
QUADAS	= Quality Assessment of Diagnostic Accuracy Studies
RLS	= right-to-left shunt
ROC	= receiver-operating characteristic
TCD	= transcranial Doppler
TEE	= transesophageal echocardiography
TN	= true negative
TP	= true positive

Data extraction. The data were extracted onto a spreadsheet with information regarding study design, cohort size, age, sex, TCD/TEE indication, contrast type, method of provocation (Valsalva maneuver or cough), microbubble cutoff used for a positive TCD/TEE study, and test accuracy results (TP, FP, FN, and TN).

Quality assessment. The quality of each study was assessed by evaluating items considered relevant to the review topic, on the basis of the Quality Assessment of Diagnostic Accuracy Studies (version 2) instrument (QUADAS-2) (38). Three reviewers (M.K.M., S.C.R., and J.R.) independently assessed the quality items, and discrepancies were resolved by consensus.

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