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Diagnostic Accuracy of Transesophageal Echocardiogram for the Detection of Patent Foramen Ovale: A Meta-Analysis

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Background: Patent foramen ovale (PFO) is a remnant of the fetal circulation present in 20% of the population. Right-to-left shunting (RLS) through a PFO has been linked to the pathophysiology of stroke, migraine with aura, and hypoxemia. While different imaging modalities including transcranial Doppler, intra-cardiac echo, and transthoracic echo (TTE) have often been used to detect RLS, trans- esophageal echo (TEE) bubble study remains the gold standard for diagnosing PFO. The aim of this study was to determine the relative accuracy of TEE in the detection of PFO. Methods and Results: A sys- tematic review of Medline, using a standard approach for meta-analysis, was performed for all prospec- tive studies assessing accuracy of TEE in the detection of PFO using confirmation by autopsy, cardiac surgery, and/or catheterization as the reference. Search results revealed 3105 studies; 4 met inclusion criteria. A total of 164 patients were included. TEE had a weighted sensitivity of 89.2% (95% CI: 81.1–94.7%) and specificity of 91.4% (95% CI: 82.3–96.8%) to detect PFO. The overall positive likelihood ratio (LR+) was 5.93 (95% CI: 1.30–27.09) and the overall negative likelihood ratio (LR) was 0.22 (95% CI: 0.08–0.56). Conclusion: While TEE bubble study is considered to be the gold standard modality for diagnosing PFO, some PFOs may still be missed or misdiagnosed. It is important to understand the limitations of TEE and perhaps use other highly sensitive screening tests, such as trans- cranial doppler (TCD), in conjunction with TEE before scheduling a patient for transcatheter PFO closure. (Echocardiography 2014;31:752–758)

Key words: patent foramen ovale, TEE, echocardiography

Background:

Patent foramen ovale (PFO) is a remnant of the fetal circulation present in 15–35% of the general population based on autopsy and imaging studies.[1-4] While most people with a PFO remain asymptomatic, some develop medical syndromes that can be chronic and debilitating. Transient right-to-left shunting (RLS), usually through a PFO, has currently been linked to cryptogenic stroke, migraine with aura, acephalgic migraine, sleep apnea, platypnea-orthodeoxia, and decom- pression illness.[5–8] A meta-analysis of observational studies and the combined data from the CLOSURE 1, RESPECT, and PC Trials suggest that PFO occluding devices reduce the recurrence of

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stroke and transient ischemic attack at higher rates than conventional medicaltreatmentalone (pooled HR 0.59, 95% CI 0.36–0.97; P=0.04).[9–11]This data along with the anticipated results of the PREMIUM trial—a double-blinded sham-controlled study to evaluate the effect of PFOclosureinpatientswithmigraineheadaches(Gov.Trials #NCT00355056)—have made it essentialtoaccuratelydiagnosePFOforpatients beingconsideredfortranscatheterclosure.

Transesophageal echo (TEE) with agitatedsal-ine bubble study is considered by some authors as the best technique available for the diagnosis of PFO.[12,13]Other commonly used imaging modalities include transthoracic echo (TTE)withor without harmonic imaging,[14]transcranial doppler (TCD),[15]and intra-cardiac echo.[16]TEE is often used as the reference test whencomparingthe sensitivities and specificities of these modali- ties. It is thus important to understand the diag- nostic accuracy of TEE for the detection ofP F O .

The purpose of this meta-analysis wastodetermine the accuracy of TEE for the diagnosis of PFO. TEE was compared with PFO detection by autopsy, cardiac surgery and/or septalprob-ing during catheterization as the gold standard reference.

Methods:

Search Strategy:

RelevantcitationsweresearchedforonPubMedusingtheterms"'PFO'OR'patentforamenovale'OR'right to left shunt'AND'transesophageal echo'OR'echo'OR'echocardiography'OR'transesophageal echocardiogram'."

The references of all of the retrieved primary studies as well as those of other knownpriorreviews were manually searched tofindcitedarticles that were not found by the database search. No restrictions were used regarding publication language. Other methodological searchfilters were not applied.[17]Abstracts lacking peer-reviewed manuscripts wereomit-ted as they would not have enoughdatarequired for the meta-analysis (i.e. true positive [TP], true negative [TN], false positive[FP],false negative [FN]). The search was completed in February 2013, covering published literature since1956.

Selection Criteria:

Articles that were identified were analyzedbytwo independent reviewers (N. B. and J. D.C.).Disagreements between the two reviewersweresettled by consensus with a third reviewer (M.K.M.). Each article was screened for preset inclusion criteria:

1) Original prospective studies (retrospective studies, reviews, abstracts, isolatedcases,commentaries, editorials, and letters)wereexcluded.
2) Studies were selected for the review iftheyincluded at least 20 patients withsuspectedPFO who were screened by contrastTEEbubble study and confirmed by cardiac catheterization, autopsy and/or intra-surgi- cal confirmation as the referencetests.
3) Provided the TP, TN, FP, and FN results of the contrast TEE bubble study, thusallow-ingthecalculationofsensitivity,specificity, positivelikelihoodratios,andnegativelike-lihoodratios(LR+andLR−).

Statistical Analyses:

Analyses were conducted using the Meta-DiSc software (Version 1.4).[18]Potential variations due to threshold effect were assessed graphically by

visual inspection of accuracy estimates pairs in forest plots and summary receiver operating characteristic (sROC) curves as well as statistically by computing the spearman correlationcoeffi-cient between the logit of sensitivity and the logit of 1-specificity.[18,19]To assess between-study het-erogeneity (other than threshold effect)andbetween-study inconsistency, the CochranQstatistic, and the inconsistency index (I^2) were calculated, respectively, and the level ofsignifi- cance for the corresponding P-value was setatP=0.10. Due to anticipated inter-study hetero- geneity, a random effects analysis model (DerSi- monian–Laird)[20]was used for this meta-analysis because it provides more conservative estimates of the pooled data. sROC were constructed using the DerSimonian–Laird random effectsmodel.The area under the curve (AUC) and indexQ*were used to assess and summarize the discrimi- nating ability of the sROC curve.[21]To assess the stability of the diagnostic accuracy results, one-way sensitivity analysis was performedbyomitting every study (one at a time) fromthemeta-analysis. Values of 95% confidenceintervals(CI) were used for all pooled data; all P valuesaretwo tailed and a P-value of<0.05 was considered statistically significant unless where otherwise specified.

Quality Assessment:

The quality of each study was evaluated bydeter-mining 14 items considered relevant tothereview topic, based on the Quality AssessmentofDiagnostic Accuracy Studies (QUADAS) instru- ment.[22]

Results:

Characteristics of Studies:

Of the 11 potential studies identified,[16,23–32]4 prospective studies comprising 164 patientsmetthe inclusion criteria and formed the dataset.[29–32]Figure 1 describes the study selection method used for thisanalysis.

QualityAssessment:

Using the recommended 14-item checklistforevaluating imaging studies using QUADAS,items2, 5, 8, 9, and 11 either were scored poorlyorwereconsidereduncle ar:item2(“selectioncrite- ria described?”), item 5 (“partial verification avoided?”), item 8 (“index test described in detailtopermitreplication?”),item9(“reference standard described in detail to permit replica- tion?”), and item 11 (“reference standardresults blinded?”). When assessing for selection criteria (i.e. item 2), one study failed to clearly define their inclusion criteria when selectingpartici-pants.Regardingitem5whichisused toavoid

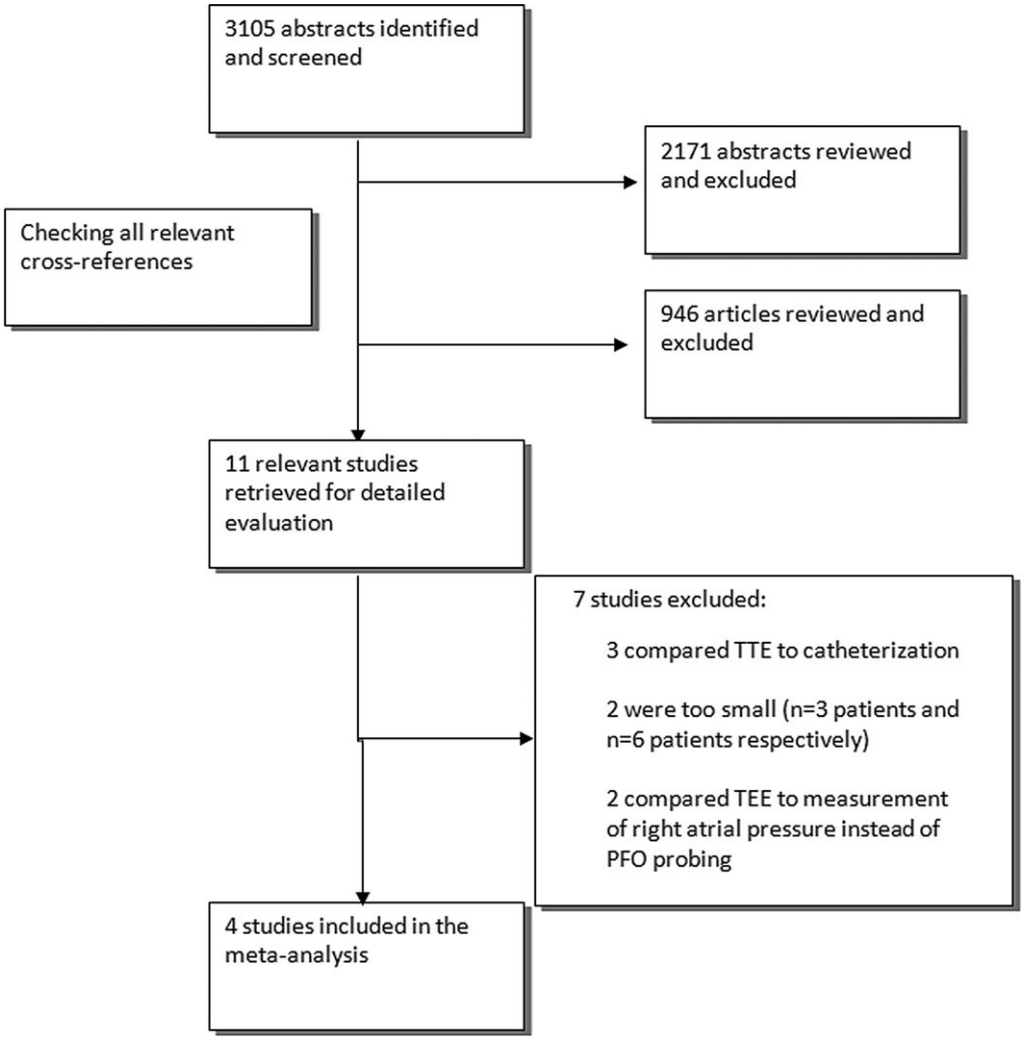

Figure 1.Selection of studies.

selection bias, in 2 studies not all participants underwent the reference standard test. Inbothof these studies, this was not influenced bytheindex test nor did they include these patientsinthefinal analysis. With regard to items 8 and 9, one study did not provide a detailed description of the diagnostic procedures which can increase the variability in the test's performance. Item11refers to blinding and may affect diagnosticaccu-racy leading to potential review bias; inonestudy, it was not clear if the reference test results were blinded. Otherwise, all studiesdemon-strated high-quality scoring on the remaining9items (Fig.2).

TEE Diagnostic Value:

Table I describes the characteristics oftheincluded studies and Table II summarizestheaccuracies of the studies. When all eligiblestudies

were pooled into the diagnostic accuracy meta-analysis, the overall sensitivity of TEEforPFO detection was 89.2% (95% CI: 81.1–94.7%; I^2=65.9%; Fig. 3A), the overall specificity was 91.4% (95% CI: 82.3–96.8%; I^2=7 2 . 2 % ; Fig. 3B), the overall LR+was 5.93 (95% CI: 1.30–27.09; I^2=80.3%; Fig. 3C), and the overall LR was 0.22 (95% CI: 0.08–0.56; I^2=37.3%; Fig.3D).

The included studies were significantly heter-ogenous in their estimates of sensitivity,specific-ity, LR+(Q statistic P values<0.1) with the exception of LR (Q statistic P=0.19). Thresh- old effect was not significant (spearman r=0.6;P=0.4). The sROC curve is shown in Figure4.The pooled AUC and index Q*were 0.93(95%CI:0.83–1.0)and0.86(95%CI:0.75–0.98), respectively (Fig. 4). The stability of ourmodelwas confirmed by the leave-one-outsensitivity

	Representative spectrum?	Described criteria?	Acceptable reference standard?	Time between tests acceptable?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Index test described in detail to permit replication?	Reference test described in detail to permit	Index test results blinded?	Reference standard results blinded?	Relevant clinical information?	Uninterpretable data reported?	Withdrawals reported?
Spencer, M et al. 2004	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(-)	(-)	(+)	(-)	(+)	(+)	(+)
Augoustides, J et al. 2004	(+)	(+)	(-)	(+)	(-)	(+)	(+)	(+)	(+)	(+)	(?)	(+)	(+)	(+)
Schneider, B et al. 1996	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
Chen, WJ et al. 1992	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(+)

Figure 2.Methodological Quality Table.

TABLE I

Characteristics of the Included Studies

First Author (Year) N	Male (%)	Contrast Used?	Site of Injection	Bubble Studies PerTEE	Provocation Maneuver (Valsalva/Other)	CalculationsDone duringProvocation?	Micro-Embolic Threshold for Positive TEE
Cheneta l. (1992)[30] 32	53%	Yes	NS	3	Valsalvamaneuver	Yes	≥5Mb
Schneider et al. (1996)[31] 35	57%	Yes	Anticubital or central line	3–6	Valsalvamaneuver	Yes	≥1Mb
Spencer et al. (2004)[32] 56	56%	Yes	Anticubital	≥2	Valsalva maneuver	Yes	≥1 Mb
Augoustides et al. (2004)[29] 417	7%	Yes lineinto	Central superior vena cava	NS	Mechanically ventilated, at end-expiration and at releaseof 25 cm H_2O RPAP	Yes (most pts)	≥1 Mb

Mb=microbubbles; TEE=transesophageal echocardiogram; RPAP=Release of positive airway pressure; NS=not specified.

TABLE II

Accuracies of the Included Studies

First Author (Year)	Sensitivity (95% CI)	Specificity (95% CI)	P-LR (95% CI)	N-LR (95% CI)
Chen et al. (1992)[30]	1.00 (0.82–1.00)	0.92 (0.64–1.00)	9.10 (2.00–41.35)	0.03 (0.00–0.43)
Schneider et al. (1996)[31]	0.89 (0.52–1.00)	1.00 (0.86–1.00)	44.20 (2.80–696.51)	0.15 (0.03–0.67)
Spencer et al. (2004)[32]	0.91 (0.79–0.97)	0.33 (0.01–0.91)	1.36 (0.61–3.04)	0.28 (0.05–

				1.72)
Augoustides et al. (2004)[29]	0.67 (0.35–0.90)	0.90 (0.73–0.98)	6.44 (2.05–20.23)	0.37 (0.17–0.84)

P-LR=positive likelihood ratio; N-LR=negative likelihood ratio; CI=confidence interval.

analysis which generated pooled estimates close to those obtained with all eligible studies (mean sensitivity 89.0%, range 86.5–92.6%; mean specificity 91.2%, range 86.7–94.0%; mean LR+ 6.2, range 3.96–8.73; mean LR− 0.21, range 0.14–0.30).

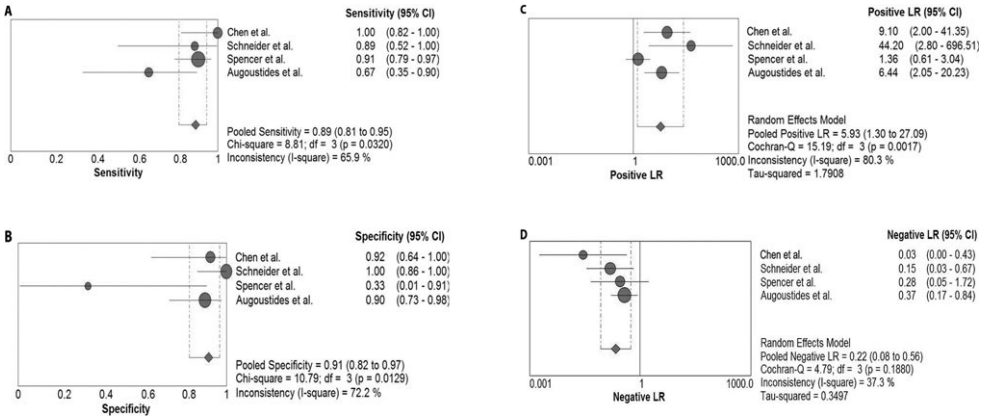

Figure 3.Diagnostic accuracy forest plots. Forest plots of the overall sensitivityA. specificityB. positive likelihood ratioC. and negative likelihood ratioD. of PFO detection by TEE are presented. The size of each square is proportional to sample size. The hori- zontal lines in each square show the corresponding 95% confidence intervals (CI). The center of the diamond indicates the overall sensitivity, specificity, positive likelihood, and negative likelihood ratios, respectively, and the ends correspond to the 95% CI. PFO=patent foramen ovale; TEE=transesophagealechocardiogram.

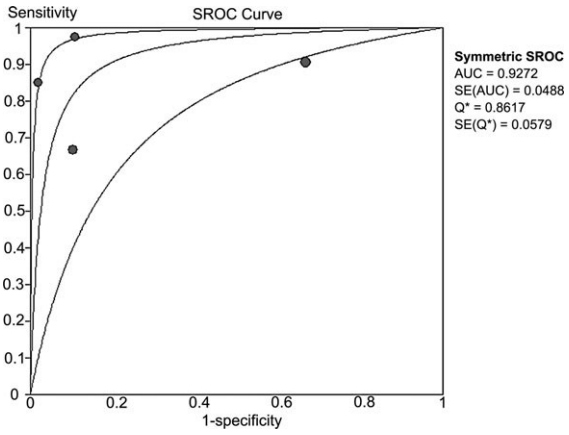

Figure 4.Summary receiver operating characteristic (SROC) curves. Individual study estimates of sensitivity and 1–speci-ficity are represented by the circles. Circle sizes are proportional to study weights. The lateral lines represent 95% confidence intervals.

Discussion:

When evaluating patients for a PFO, several imaging modalities are available to determine whether a right-to-left shunt is present.Theseinclude TTE with or without harmonic imaging, TCD, intra-cardiac echo, and TEE. Whileeachmethod has its benefits and limitations,TEEremains the best performing test availablefordiagnosing a PFO due to its minimal invasiveness, safety profile and ability to accurately visualize the atrial septal anatomy.[12,13]In addition, TEE is superior to other modalities for the detectionandmeasurement of atrial septalaneurysms.[33]

Some studies have shown similar sensitivities for PFO detection when comparing TTE with

second harmonic imaging to TEE.[34–36]However, the high sensitivity of TTE with harmonicimag-ing is often accompanied by a lower relative specificity, whereas TEE can more accuratelydif-ferentiate between a PFO and pulmonaryarte-riovenous malformation.[37]Standard TTE is often limited in its ability to detect smaller shunts.TTEonly detects 50–60% of PFOs whencomparedwith TEE.[38–40]The benefits of TTE include its low cost, noninvasiveness, and easy availability. TCD is commonly used as a screening testfordetection of PFO. Compared with TEE, the sensi- tivity of TCD ranges between 68and100%.[15,38,41–47]Although the sensitivity of TCD is higher than that of standard TTE, TCDdoesnot directly visualize the atrial septum and thus cannot differentiate between a PFO andanASD or intra-pulmonary shunt which limitsitsspecificity.

This study is thefirst meta-analysis to investi-gate the accuracy of TEE in PFO detectioncom-pared with confirmatoryfindingsbycath eterization, autopsy and/or cardiac surgery. While these modalities may be the ultimategoldstandard for PFO detection, it would be impracti- cal to subject every patient with a suspected PFO to catheterization or surgery, let aloneanautopsy. Therefore, each method ofconfirmingthe presence of a PFO has inherent biases astoappropriate subjects who would be included.TEEis a much less invasive test that is widely consid- ered to be the most reasonable benchmarkforPFO diagnosis. The imperfect accuracy ofTEEdemonstrated in this article may be explainedbytechnical limitations including patient intolerance for the TEE probe, difficulty performing an ade-quate Valsalva maneuver with a probe inthe

esophagus, variations in patients'anatomy, and operator experience.[36]

Our observation is also limited by the small number of studies available that comparetheaccuracy of TEE for the detection of PFO tocath-eterization, autopsy and/or surgicalfindings.The164 patients that encompassed the studypopu-lation were either severely ill, referred for PFOclo- sure for PFO-related conditions, or hadothercardiac diseases which required surgery.Thiscohort may have been different from the majority of other studies that often include patientswhounderwent TEE after being referred foreitherrecurrent stroke ormigraines.

In conclusion, our data demonstrates TEEtohave a sensitivity of 0.89 and specificity of0.91for the diagnosis of PFO. The low negative likeli- hood ratio of TEE suggests that it is a proficient test of exclusion forPFO.

Conflict of Interest:

Dr. Tobis is a consultant for AGA Medical, Inc.;
W.L. Gore, Inc.; and Coherex, Inc.

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