

# 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 systematic review of Medline, using a standard approach for meta-analysis, was performed for all prospective 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 transcranial 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.<sup>1–4</sup> 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 decompression illness.<sup>5–8</sup> 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 medical treatment alone (pooled HR 0.59, 95% CI 0.36–0.97; P=0.04).<sup>9–</sup>

<sup>11</sup>This data along with the anticipated results of the PREMIUM trial—a double-blinded sham-controlled study to evaluate the effect of PFO closure in patients with migraine headaches (Gov. Trials #NCT00355056)—have made it essential to accurately diagnose PFO for patients being considered for transcatheter closure.

Transesophageal echo (TEE) with agitated saline bubble study is considered by some authors as the best technique available for the diagnosis of PFO.<sup>12,13</sup> Other commonly used imaging modalities include transthoracic echo (TTE) with or without harmonic imaging,<sup>14</sup> transcranial doppler (TCD),<sup>15</sup> and intracardiac echo.<sup>16</sup> TEE is often used as the reference test when comparing the sensitivities and specificities of these modalities. It is thus important to understand the diagnostic accuracy of TEE for the detection of PFO.

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

#### Methods:

##### Search Strategy:

Relevant citations were searched for on PubMed using the terms "PFO'OR'patent foramen ovale'OR'right to left shunt'AND'transeosophageal echo'OR'echo'OR'echocardiography'OR'transeosophageal echocardiogram'."

The references of all of the retrieved primary studies as well as those of other known prior reviews were manually searched to find cited articles that were not found by the database search. No restrictions were used regarding publication language. Other methodological search filters were not applied.<sup>17</sup> Abstracts lacking peer-reviewed manuscripts were omitted as they would not have enough data required 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 since 1956.

##### Selection Criteria:

Articles that were identified were analyzed by two independent reviewers (N. B. and J. D.C.). Disagreements between the two reviewers were settled 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, isolated cases, commentaries, editorials, and letters) were excluded.
- 2) Studies were selected for the review if they included at least 20 patients with suspected PFO who were screened by contrast TEE bubble study and confirmed by cardiac catheterization, autopsy and/or intra-surgical confirmation as the reference tests.
- 3) Provided the TP, TN, FP, and FN results of the contrast TEE bubble study, thus allowing the calculation of sensitivity, specificity,

positive likelihood ratios, and negative likelihood ratios (LR+ and LR-).

##### Statistical Analyses:

Analyses were conducted using the Meta-DiSc software (Version 1.4).<sup>18</sup> 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 correlation coefficient between the logit of sensitivity and the logit of 1-specificity.<sup>18,19</sup> To assess between-study heterogeneity (other than threshold effect) and between-study inconsistency, the Cochran Q statistic, and the inconsistency index ( $I^2$ ) were calculated, respectively, and the level of significance for the corresponding P-value was set at  $P=0.10$ . Due to anticipated inter-study heterogeneity, a random effects analysis model (DerSimonian-Laird)<sup>20</sup> was used for this meta-analysis because it provides more conservative estimates of the pooled data. sROC were constructed using the DerSimonian-Laird random effects model. The area under the curve (AUC) and index Q\* were used to assess and summarize the discriminating ability of the sROC curve.<sup>21</sup> To assess the stability of the diagnostic accuracy results, one-way sensitivity analysis was performed by omitting every study (one at a time) from the meta-analysis. Values of 95% confidence intervals (CI) were used for all pooled data; all P values are two-tailed and a P-value of  $<0.05$  was considered statistically significant unless otherwise specified.

#### Quality Assessment:

The quality of each study was evaluated by determining 14 items considered relevant to the review topic, based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument.<sup>22</sup>

#### Results:

##### Characteristics of Studies:

Of the 11 potential studies identified,<sup>16,23-32</sup> 4 prospective studies comprising 164 patients met the inclusion criteria and formed the dataset.<sup>29-32</sup> Figure 1 describes the study selection method used for this analysis.

##### Quality Assessment:

Using the recommended 14-item checklist for evaluating imaging studies using QUADAS, items 2, 5, 8, 9, and 11 either were scored poorly or were considered unclear: item 2 ("selection criteria described?"), item 5 ("partial verification avoided?"), item 8 ("index test described in detail to permit replication?"), item 9 ("reference standard described in detail to permit replication?"), and item 11 ("reference standard results blinded?"). When assessing for selection criteria (i.e. item 2), one study failed to clearly define their inclusion criteria when selecting participants. Regarding item 5 which is used to avoid

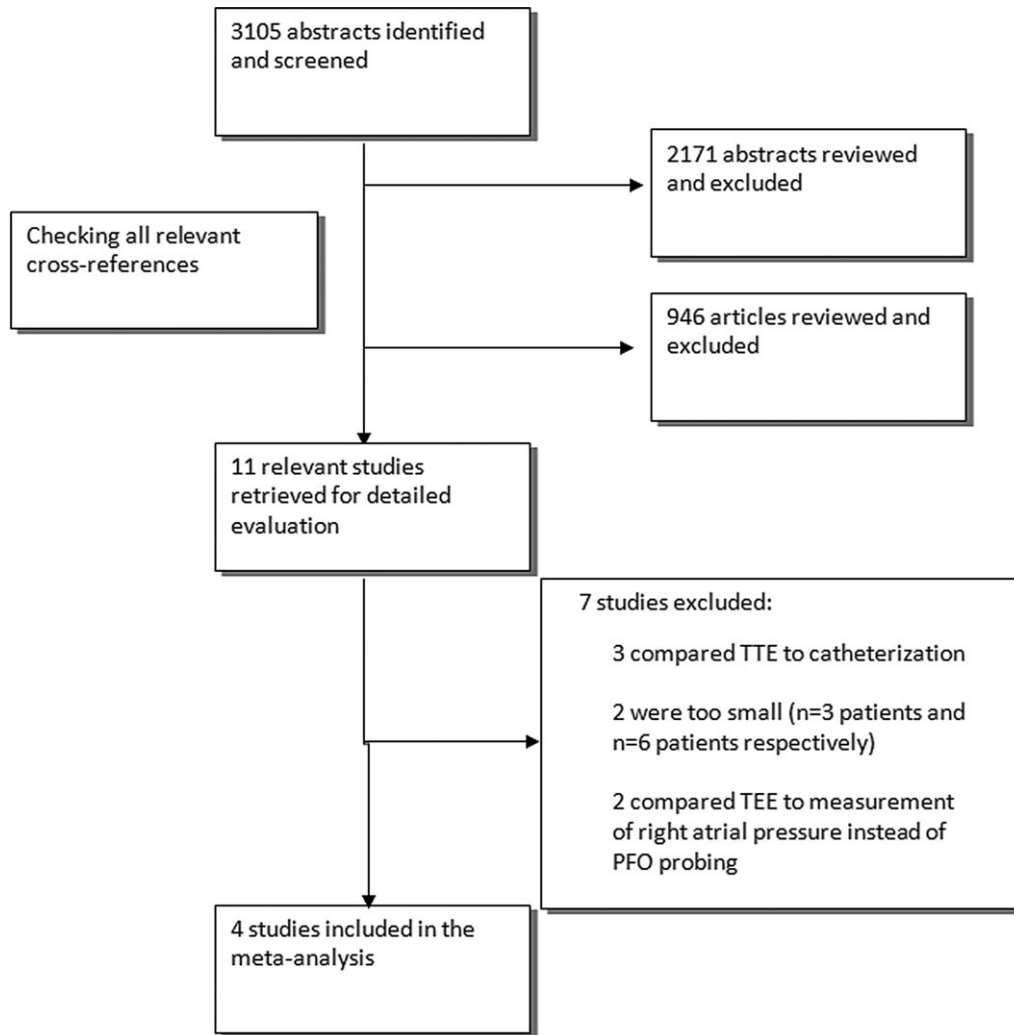


Figure 1. Selection of studies.

selection bias, in 2 studies not all participants underwent the reference standard test. In both of these studies, this was not influenced by the index test nor did they include these patients in the final 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. Item 11 refers to blinding and may affect diagnostic accuracy leading to potential review bias; in one study, it was not clear if the reference test results were blinded. Otherwise, all studies demonstrated high-quality scoring on the remaining 9 items (Fig. 2).

TEE Diagnostic Value:

Table I describes the characteristics of the included studies and Table II summarizes the accuracies of the studies. When all eligible studies

were pooled into the diagnostic accuracy meta-analysis, the overall sensitivity of TEE for PFO 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%;  $I^2=72.2\%$ ;

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 heterogeneous in their estimates of sensitivity, specificity, LR+ (Q statistic P values < 0.1) with the exception of LR (Q statistic P = 0.19). Threshold effect was not significant (Spearman  $r=0.6$ ; P = 0.4). The sROC curve is shown in Figure 4. The pooled AUC and index Q\* were 0.93 (95% CI: 0.83-1.0) and 0.86 (95% CI: 0.75-0.98),

respectively (Fig. 4). The stability of our model was confirmed by the leave-one-out sensitivity

	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 replication?	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.

First Author (Year)	N	Male (%)	Contracept Used?	Site of Injection	Bubble Studies PerTEE	Provocation Maneuver (Valsalva/Other)	Calculations Done during Provocation?	Micro-Embollic Threshold for Positive TEE
Chen et al. (1992) <sup>30</sup>	32	53%	Yes	NS	3	Valsalva maneuver	Yes	≥5Mb
Schneider et al. (1996) <sup>31</sup>	35	57%	Yes	Anticubital or central line	3-6	Valsalva maneuver	Yes	≥1Mb
Spencer et al. (2004) <sup>32</sup>	56	56%	Yes	Anticubital	≥2	Valsalva maneuver	Yes	≥1 Mb
Augoustides et al. (2004) <sup>29</sup>	417	77%	Yes	Central superior vena cava	NS	Mechanically ventilated, at end-expiration and at release of 25 cm H <sub>2</sub> O RPAP	Yes (most pts)	≥1 Mb

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

First Author (Year)	Sensitivity (95% CI)	Specificity (95% CI)	P-LR (95% CI)	N-LR (95% CI)
Chen et al. (1992) <sup>30</sup>	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) <sup>31</sup>	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) <sup>32</sup>	0.91 (0.79-0.97)	0.33 (0.01-0.91)	1.36 (0.61-3.04)	0.28 (0.05-

Augoustides et al. (2004) <sup>29</sup>	0.67 (0.35-0.90)	0.90 (0.73-0.98)	6.44 (2.05- 20.23)	1.72) 0.37 (0.17- 0.84)
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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%; meanLR+ 6.2, range 3.96-8.73; meanLR 0.21, range 0.14-0.30).



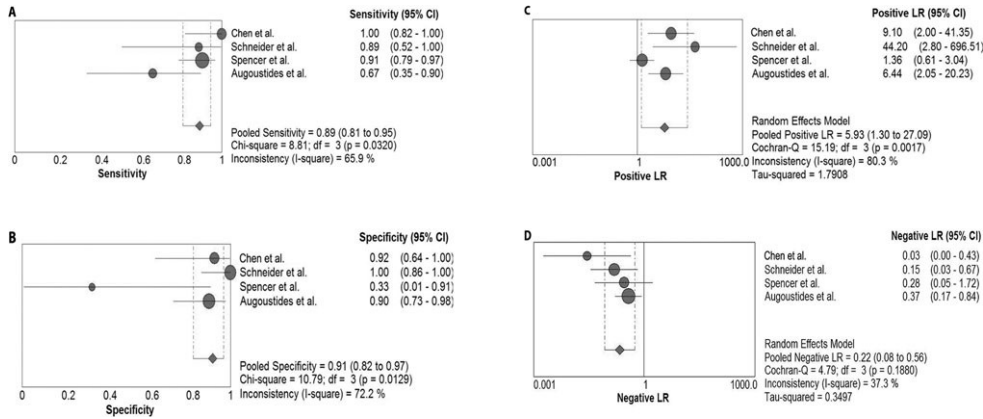


Figure 3. Diagnostic accuracy forest plots. Forest plots of the overall sensitivity A, specificity B, positive likelihood ratio C, and negative likelihood ratio D, of PFO detection by TEE are presented. The size of each square is proportional to sample size. The horizontal lines in each square show the corresponding 95% confidence intervals (CI). The center of the diamond indicates the overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratios, respectively, and the ends correspond to the 95% CI. PFO=patent foramen ovale; TEE=transesophageal echocardiogram.

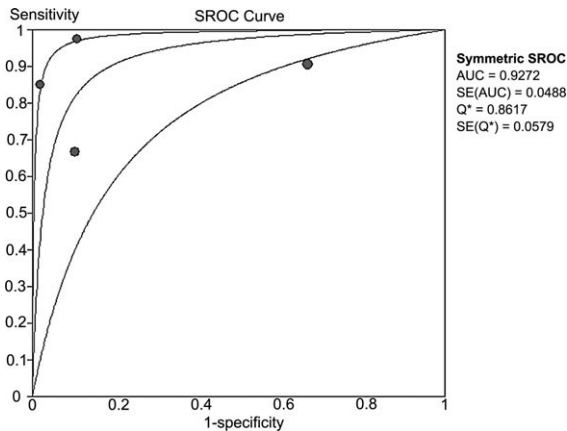


Figure 4. Summary receiver operating characteristic (SROC) curves. Individual study estimates of sensitivity and 1-specificity are represented by the circles. Circle sizes are proportional to study weights. The lateral lines represent 95% confidence intervals.

Discussion:

When evaluating patients for a PFO, several imaging modalities are available to determine whether a right-to-left shunt is present. These include TTE with or without harmonic imaging, TCD, intra-cardiac echo, and TEE. While each method has its benefits and limitations, TEE remains the best performing test available for diagnosing a PFO due to its minimal invasiveness, safety profile and ability to accurately visualize the atrial septal anatomy.<sup>12,13</sup> In addition, TEE is superior to other modalities for the

detection and measurement of atrial septal aneurysms.<sup>33</sup> Some studies have shown similar sensitivities for PFO detection when comparing TTE with

second harmonic imaging to TEE.<sup>34-36</sup> However, the high sensitivity of TTE with harmonic imaging is often accompanied by a lower relative specificity, whereas TEE can more accurately differentiate between a PFO and pulmonary arteriovenous malformation.<sup>37</sup> Standard TTE is often limited in its ability to detect smaller shunts. TTE only detects 50-60% of PFOs when compared with TEE.<sup>38-40</sup> The benefits of TTE include its low cost, noninvasiveness, and easy availability. TCD is commonly used as a screening test for detection of PFO. Compared with TEE, the sensitivity of TCD ranges between 68 and 100%.<sup>15,38,41-47</sup> Although the sensitivity of TCD is higher than that of standard TTE, TCD does not directly visualize the atrial septum and thus cannot differentiate between a PFO and an ASD or intrapulmonary shunt which limits its specificity. This study is the first meta-analysis to investigate the accuracy of TEE in PFO detection compared with confirmatory findings by catheterization, autopsy and/or cardiac surgery. While these modalities may be the ultimate gold standard for PFO detection, it would be impractical to subject every patient with a suspected PFO to catheterization or surgery, let alone an autopsy. Therefore, each method of confirming the presence of a PFO has inherent biases as to appropriate subjects who would be included. TEE is a much less invasive test that is widely considered to be the most reasonable benchmark for PFO diagnosis. The imperfect accuracy of TEE demonstrated in this article may be

explained by technical limitations including patient intolerance for the TEE probe, difficulty performing an adequate Valsalva maneuver with a probe in the

esophagus, variations in patients' anatomy, and operator experience.<sup>36</sup>

Our observation is also limited by the small number of studies available that compare the accuracy of TEE for the detection of PFO to catheterization, autopsy and/or surgical findings. The 164 patients that encompassed the study population were either severely ill, referred for PFO closure for PFO-related conditions, or had other cardiac diseases which required surgery. This cohort may have been different from the majority of other studies that often include patients who underwent TEE after being referred for either recurrent stroke or migraines.

In conclusion, our data demonstrates TEE to have a sensitivity of 0.89 and specificity of 0.91 for the diagnosis of PFO. The low negative likelihood ratio of TEE suggests that it is a proficient test of exclusion for PFO.

#### Conflict of Interest:

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

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