

Original article

Diagnosis and Quantification of Patent Foramen Ovale. Which Is the Reference Technique? Simultaneous Study With Transcranial Doppler, Transthoracic and Transesophageal Echocardiography

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ABSTRACT

Introduction and objectives: Patent foramen ovale (PFO) is the most common cause of cryptogenic stroke in patients younger than 55. Transesophageal echocardiography (TEE) has been accepted as the reference diagnostic technique. The purpose of this study was to compare the accuracy of transthoracic echocardiography (TTE), TEE and transcranial Doppler (TCD) in the diagnosis and quantification of patent foramen ovale.

Methods: We studied 134 patients prospectively. Simultaneous TTE with TCD and TEE with TCD were performed, using agitated saline solution to detect right to left shunt.

Results: In 93 patients diagnosed with PFO, the shunt was visualized at baseline by TCD in 69% of cases, by TTE in 74% and by TEE in 58%. The Valsalva maneuver produced a similar improvement in shunt diagnosis with all 3 techniques (26%–28%). TTE and TCD showed higher sensitivity (100% vs 97%; non significant difference) than TEE in the diagnosis of PFO (86%; $P < .001$). TCD performed during TEE did not diagnose 12 (13%) shunts previously diagnosed during TTE. Similarly, TEE underestimated shunt severity.

Conclusions: TTE enables adequate diagnosis and quantification of PFO. TEE is less sensitive and tends to underestimate the severity of the shunt.

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Diagnóstico y cuantificación del foramen oval permeable. ¿Cuál es la técnica de referencia? Estudio simultáneo con Doppler transcraneal, ecocardiografía transtorácica y transesofágica

RESUMEN

Introducción y objetivos: El foramen oval permeable (FOP) es la causa más frecuente de ictus criptogénico en menores de 55 años. La ecocardiografía transesofágica (ETE) ha sido aceptada como la técnica diagnóstica de referencia. El propósito del estudio es comparar la exactitud de la ecocardiografía transtorácica (ETT), la ETE y el Doppler transcraneal (DTC) en el diagnóstico y la cuantificación del FOP.

Métodos: Se estudió de forma prospectiva a 134 pacientes. Se practicaron simultáneamente DTC y ETT, y DTC y ETE con moderada sedación, utilizando la inyección de suero salino agitado para detectar cortocircuito derecha-izquierda.

Resultados: Se diagnosticó FOP a 93 pacientes. El cortocircuito se visualizó basalmente por DTC en el 69% de los FOP, por ETT en el 74% y por ETE en el 58%. La maniobra de Valsalva aumentó el diagnóstico del cortocircuito de forma similar en las tres técnicas (26–28%). La ETT y el DTC mostraron mayor sensibilidad (el 100 y el 97%; diferencias no significativas) que la ETE en el diagnóstico de FOP (86%; $p < 0,001$). El DTC practicado durante la ETE no diagnosticó 12 (13%) cortocircuitos previamente diagnosticados en el estudio durante la ETT. La severidad del cortocircuito también se subestimó mediante la ETE.

Conclusiones: La ETT permite un adecuado diagnóstico y cuantificar la severidad del FOP. La ETE tiene menor sensibilidad y tiende a subestimar la severidad del cortocircuito.

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Palabras clave:

Ecocardiografía

Doppler transcraneal

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Abbreviations

ASA: atrial septal aneurysm
PFO: patent foramen ovale
TCD: transcranial Doppler
TEE: transesophageal echocardiography
TTE: transthoracic echocardiography

INTRODUCTION

Patent foramen ovale (PFO) has been associated with several disease processes such as paradoxical embolism in cryptogenic stroke,¹ arterial gas embolism due to decompression,² or platypnea-orthodeoxia syndrome.³ In recent years, the role of PFO in cryptogenic stroke and migraine and its therapeutic management has generated debate^{4–10} and the clinical method of choice for the diagnosis and quantification of right-to-left shunt remains undecided.^{11–13} Agitated saline serum has been used in transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and transcranial Doppler ultrasound (TCD) in the detection of intracardiac shunts. Although TEE has been considered the reference technique in PFO diagnosis, recent studies have suggested that it leads to false negatives due to the problems involved in performing the Valsalva maneuver.^{14–17} On the other hand, its association with atrial septal aneurysm (ASA) and its assessment of the severity of the shunt have been associated with an increased risk of recurrence.^{18,19} The use of TTE with harmonic imaging has led to the improved assessment of interatrial shunt.^{14–17,20} Few studies have analyzed the most suitable strategy for the diagnosis and quantification of PFO. The aim of the present study was to compare the results obtained by the simultaneous performance of TEE with TCD and of TTE with TCD in the diagnosis and quantification of shunt due to PFO and to define the most suitable diagnostic strategy for its assessment in clinical practice.

METHODS

We conducted a prospective study which included 134 patients (75 men and 59 women, mean age 46.4 ± 14.2 [17–75] years) referred to the echocardiography laboratory by the neurology department to rule out PFO after presenting transient stroke (28; 21%), stroke (91; 68%), or migraine episodes (15; 11%). The study was approved by the Vall d'Hebron Hospital Ethics Committee and all the patients had previously given signed informed consent. Previous intracranial or extracranial arterial disease, abnormalities on TCD, or lacunar infarction were ruled out using computed tomography or magnetic resonance imaging. Table 1 shows the characteristics of the study population.

Table 1
Demographic Characteristics of the Population.

Patients	134
Age (years)	46.4 ± 14.2 (17–75)
Men	75 (56)
Women	59 (44)
Smoking	57 (43)
Hypertension	31 (23)
Diabetes mellitus	12 (9)
Dyslipidemia	35 (26)

Data are expressed as n (%) or mean $\pm$ standard deviation (range).

Protocol

TCD with TTE were performed simultaneously and then, 5 minutes later, TCD with TEE, using agitated saline solution to detect right-to-left shunt. The patient was in left lateral decubitus position during both studies. The Valsalva maneuver, which all patients had been taught to perform, was considered effective when there was a peak Doppler flow velocity reduction $> 25\%$ in the middle cerebral artery²¹ (Fig. 1).

Transcranial Doppler Ultrasound

The TCD study was performed using a TCD 100 ML system (Spencer Technology, Seattle, Washington, USA) and MultiDop X4 (DWL Electronic Systems, Sipplingen, Germany). Middle cerebral artery flow was monitored through the temporal bone window using a 2 MHz transducer. The TCD transducer was kept in place with an elastic headband fitted with the probe at a depth of 65 mm with stable insonation. The study was performed by a neurologist specialized in this technique and blinded to the results of the echocardiographic study.

The middle cerebral artery blood flow velocity value obtained by TCD, simultaneously performed with TTE and with TEE, served as a reference to confirm the effectiveness of the Valsalva maneuver.

Transthoracic Echocardiography

All the studies were performed using the Vivid 7 system (General Electric, Milwaukee, Wisconsin, USA) fitted with a 4.3 MHz multi-frequency probe with harmonic imaging. The apical 4-chamber view was used to optimize visualization of the atria, ventricles and interatrial septum (Fig. 2). In total, 3 patients had a suboptimal acoustic window, but were not excluded from the study. ASA was diagnosed when there was a ≥ 10 -mm midline shift in anatomical M-mode or when total bidirectional shift was > 15 mm.

Transesophageal Echocardiography

TEE with color Doppler was performed using the same system fitted with a 2.9–8 MHz multi-frequency probe. To improve tolerance to the test, patients were sedated with intravenously administered midazolam at a starting dose of 2 mg followed by 2-mg increments until tolerance was reached and the patient felt comfortable. Blood pressure, heart rate and oxygen saturation were monitored. Baseline values were recorded during TTE and once every minute during TEE. An N-550 pulse oximeter (Nellcor, Boulder, Colorado, USA) and an automatic M4-I Intellisense blood pressure gauge (Omron, Schaumburg, Illinois, USA) were used.

In line with the study aims, the area of the atrial septum in which the foramen ovale was located was visualized in the sagittal plane between 90° and 110° in the caval view (Fig. 3). Maximum PFO diameter was measured during the Valsalva maneuver at the distal extreme of the tract formed by the ostium primum and ostium secundum. ASA was diagnosed using the same criteria described for the TTE study.

Agitated Saline Contrast Test

A mixture of 9 mL physiological saline and 1 mL air was agitated 10 times in 2 10-mL syringes connected to a 3-way stopcock to exchange the air-saline mix and achieve good dilution. The bolus of saline solution was injected via an antecubital vein. The study was

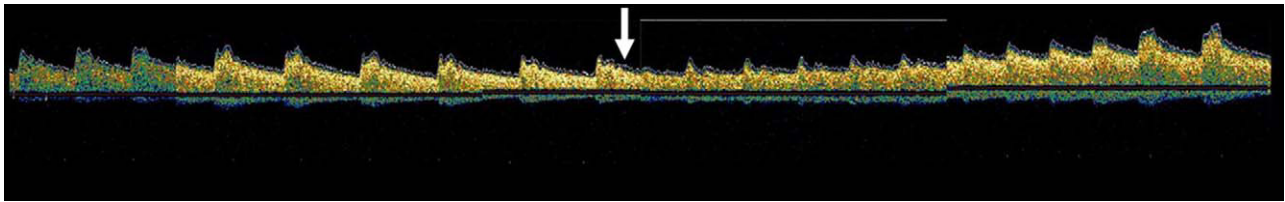


Figure 1. Transcranial Doppler ultrasound recording during Valsalva maneuver. The arrow indicates the beginning of the Valsalva maneuver.

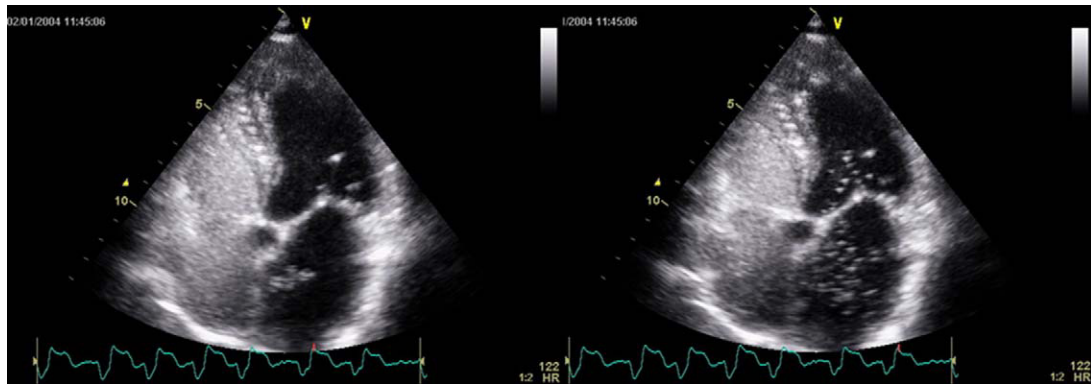


Figure 2. Transthoracic echocardiography showing contrast medium passing through the patent foramen ovale.

not begun until adequate filling of the right atrium was achieved. At least 2 injections were administered at baseline and up to 2 injections with the Valsalva maneuver in both the TTE and TEE studies. The Valsalva maneuver was begun when the contrast filled the right atrium and was maintained for >5 s; the shunt was assessed during the first 3 heartbeats following the Valsalva maneuver. During TEE, the passage of contrast medium through the PFO was assessed; if its passage was not visualized, additional injections were administered and the openings of the pulmonary veins assessed to rule out intrapulmonary shunt.

Diagnosis and Quantification

The TTE or TEE contrast studies were considered positive for PFO when bubbles were observed in the left atrium within the first 3 heartbeats after opacification of the right atrium, whether at baseline or after the Valsalva maneuver. The severity of the shunt was quantified as mild (<10 microbubbles), moderate (10–20

microbubbles), or severe (>20).¹⁶ Right-to-left shunt was diagnosed when TCD detected microsignals in the middle cerebral artery, and the degree of severity was quantified according to established criteria²² (Fig. 4). A definitive diagnosis of PFO was established when there was concordance between the 2 techniques in their diagnosis.

Statistical Analysis

Sensitivity, specificity and predictive values were determined by the percentage of patients with true positive and true negative results (95% confidence interval). The criteria applied for diagnosing true positives and true negatives was concordance between 2 of the 3 techniques (TTE, TEE and TCD) in the diagnosis of PFO. The diagnostic accuracy of TCD was established during simultaneous TTE study, since in clinical practice TCD is performed without sedation. Continuous values were expressed as mean $\pm$ standard deviation. The kappa test was used to assess concordance in quantifying the severity of the shunts using different methods. The SPSS 13.0 software package was used for statistical analysis. A P value of <0.05 was used as a cutoff for statistical significance.

RESULTS

In total, 93 (69%) of the 134 patients studied were diagnosed with PFO.

Diagnosis of Right-to-Left Shunt

The right-to-left shunt was visualized at baseline by TTE in 69 patients (74%), TCD in 64 (69%), and TEE in just 54 (58%). The Valsalva maneuver was effective in all TTE studies. In 10 patients, the Valsalva maneuver was considered ineffective during TEE, thus external abdominal compression was performed until a reduction $>25\%$ in peak blood flow velocity was obtained in the middle

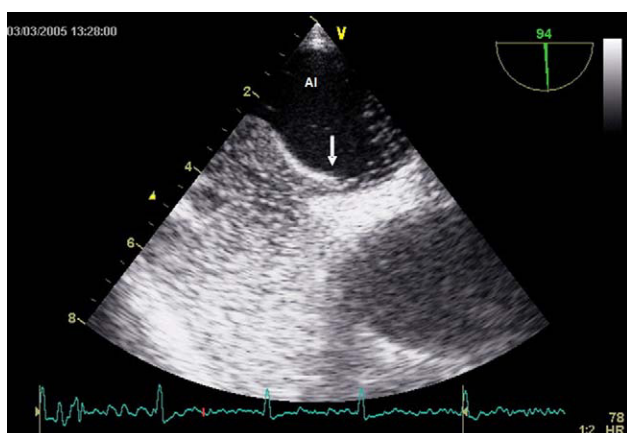


Figure 3. Transesophageal echocardiography showing contrast medium passing through the patent foramen ovale.

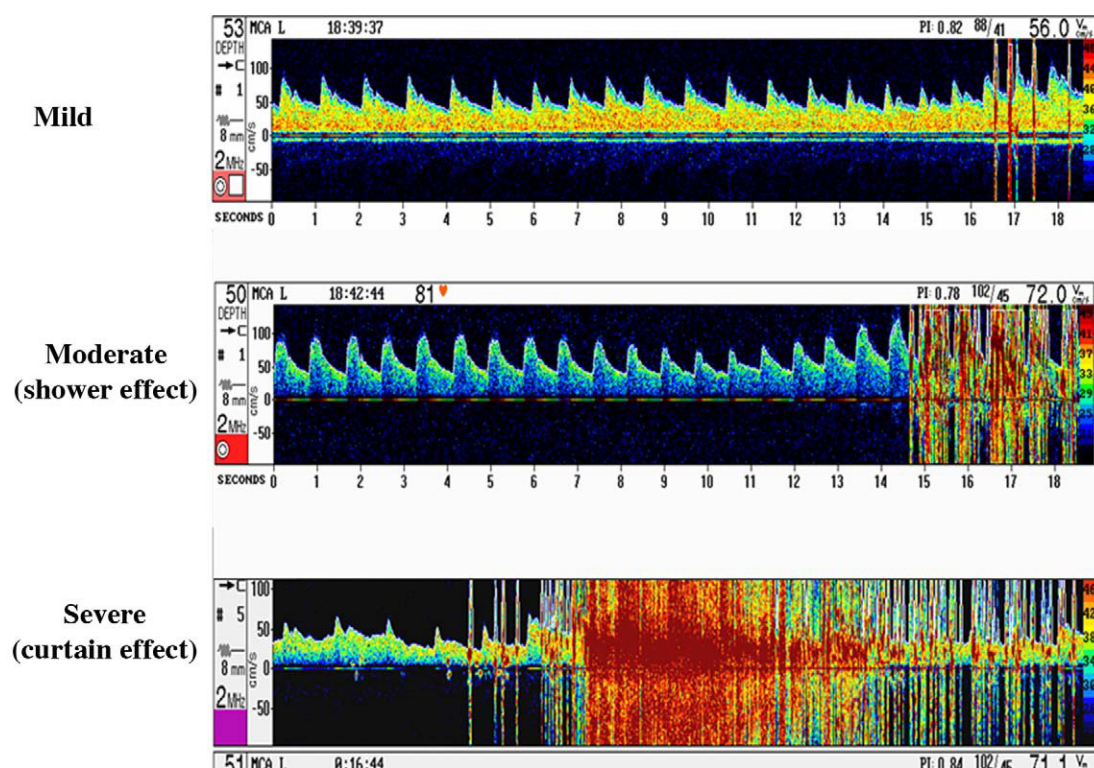


Figure 4. Quantification of the shunt by transcranial Doppler ultrasound.

Table 2
Diagnosis of Patent Foramen Ovale Using Different Imaging Techniques.

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Transcranial Doppler ultrasound	97	98	99	93
Transthoracic echocardiography	100	100	100	100
Transesophageal echocardiography	86	100	100	76

NPV, negative predictive value; PPV, positive predictive value.

cerebral artery. The Valsalva maneuver produced a similar improvement in the diagnosis of right-to-left shunt not visualized at baseline in each of the 3 techniques: TTE 24/93 (26%), TCD 26/93 (28%), and TEE 26/93 (28%). The sensitivity, specificity, and predictive values of the 3 techniques are shown in Table 2.

Differences in the Diagnosis of Patent Foramen Ovale

During the TTE study, TCD failed to diagnose 3 mild shunts and gave a false positive in 1 patient with a pulmonary arteriovenous fistula, showing the contrast medium reaching the left atrium from a pulmonary vein (Fig. 5). TCD performed during the TEE study failed to diagnose 2 mild shunts shown by TEE and gave the same false positive in the patient with pulmonary arteriovenous fistula. In 13 patients, TEE did not diagnose a shunt shown by TTE, which was mild in 11 cases, moderate in 1 and severe in 1 (Table 3). TCD performed simultaneously with TTE diagnosed 12 (13%) shunts more than when TCD was performed simultaneously with TEE; of these, 10 were mild, 1 moderate and 1 severe.

The dose of midazolam was similar in the group of patients in whom the results of TTE and TEE were in concordance and the group in whom results differed (8.1 ± 3.2 mg vs 8.2 ± 1.3 mg, respectively). During the TEE study, heart rate increased (74 ± 18 bpm vs 94 ± 18 bpm; $P < .001$), whereas there was a decrease

in systolic blood pressure (121 ± 11 mmHg vs 101 ± 32 mmHg; $P < .05$) and oxygen saturation ($98\% \pm 2\%$ vs $93\% \pm 4\%$; $P < .001$). There were no significant differences in diastolic blood pressure (72 ± 8 mmHg vs 72 ± 10 mmHg).

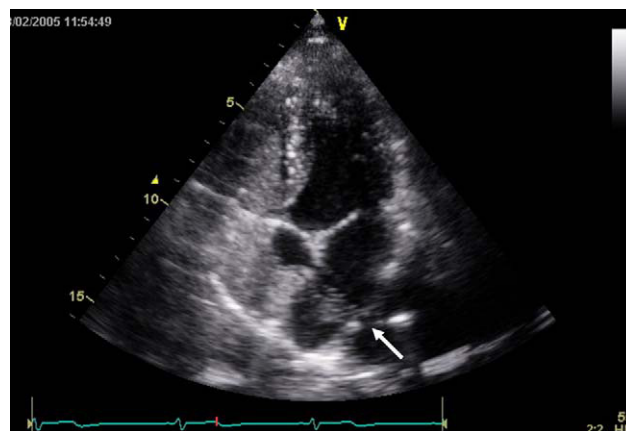


Figure 5. Transthoracic echocardiography in apical 4-chamber view showing contrast-filled right cavities and bubbles arriving from the right inferior pulmonary vein (arrow) in the left atrium.

Table 3

Echocardiographic Characteristics and Sedation Dose in Cases of False Negatives by Transesophageal Echocardiography.

Patient	Shunt on TCD	Shunt on TTE	ASA	Midazolam (mg) during TEE
1	No	Mild	No	8
2	No	Mild	Yes	10
3	No	Mild	No	8
4	Mild	Mild	No	8
5	Mild	Mild	No	6
6	Mild	Mild	Yes	5
7	Mild	Mild	No	12
8	Mild	Mild	Yes	8
9	Mild	Mild	No	10
10	Mild	Mild	Yes	8
11	Moderate	Mild	No	6
12	Moderate	Moderate	Yes	8
13	Severe	Severe	No	9

Abbreviations: ASA, atrial septal aneurysm; TCD, transcranial Doppler ultrasound; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Quantification of the Shunt

Shunt was quantified as severe by TTE in 69% of the patients (64/93), by TCD in 76% (68/90) and by TEE in 59% (47/80) (Fig. 6). In the quantification of shunt, concordance between TTE and TCD was 93% (84/90) ($\kappa = 0.83$; $P < .0001$); between TEE and TCD, 74% (59/80) ($\kappa = 0.41$; $P < .0001$); and between TTE and TEE, 81% (65/80) ($\kappa = 0.59$; $P < .0001$). As visualized by TEE, PFO size during the Valsalva maneuver was 3.81 ± 2.62 mm in the patients with shunt and only 0.3 ± 0.8 mm in the patients without shunt ($P < .001$). PFO diameter was greater in the patients with a more severe shunt as determined by TTE; thus, in patients with a mild shunt the diameter was 2.3 ± 1.3 mm; with moderate shunt, 3.6 ± 1.6 mm; and with severe shunt, 5.6 ± 3.5 mm ($P < .001$).

Atrial Septal Aneurysm

In 57 patients with right-to-left shunt, TEE study diagnosed ASA (61%), whereas in the patients without PFO ASA was only found in 5/41 patients (12%). TTE study diagnosed ASA in all patients except for one. The patients with PFO and ASA more often presented moderate or severe shunt than the patients with PFO without ASA (71% vs 13%; $P < .001$).

DISCUSSION

This study assessed a large series of patients to rule out the presence of right-to-left shunt, and demonstrated that TTE is superior to TEE in the diagnosis of PFO. TEE gave a false negative in more than 10% of the patients and tended to underestimate the severity of right-to-left shunt. TCD performed simultaneously with TTE and with TEE showed that these false negatives were not due to the imaging technique used itself, since TCD performed during TEE also gave a similar number of false negatives. TEE is less sensitive than TTE in the diagnosis of right-to-left shunt at baseline, with a similar number of cases diagnosed with Valsalva maneuver. The results are of clinical importance, since they suggest that TEE does not provide greater accuracy in the diagnosis and quantification of PFO than TTE or TCD. TEE would be indicated only in the presence of poor echocardiographic windows or when assessing the morphological characteristics of PFO before percutaneous closure.

Diagnosis of Patent Foramen Ovale by Different Imaging Techniques

Several studies have assessed the usefulness of TCD^{6,13,23}, TTE^{14–17,20} and TEE^{24,25} in the diagnosis of PFO, but differences in the results obtained have led to great controversy. Neurologists have widely used TCD to diagnose PFO. Comparative studies with TEE suggest that its sensitivity is higher than 90%, but that its

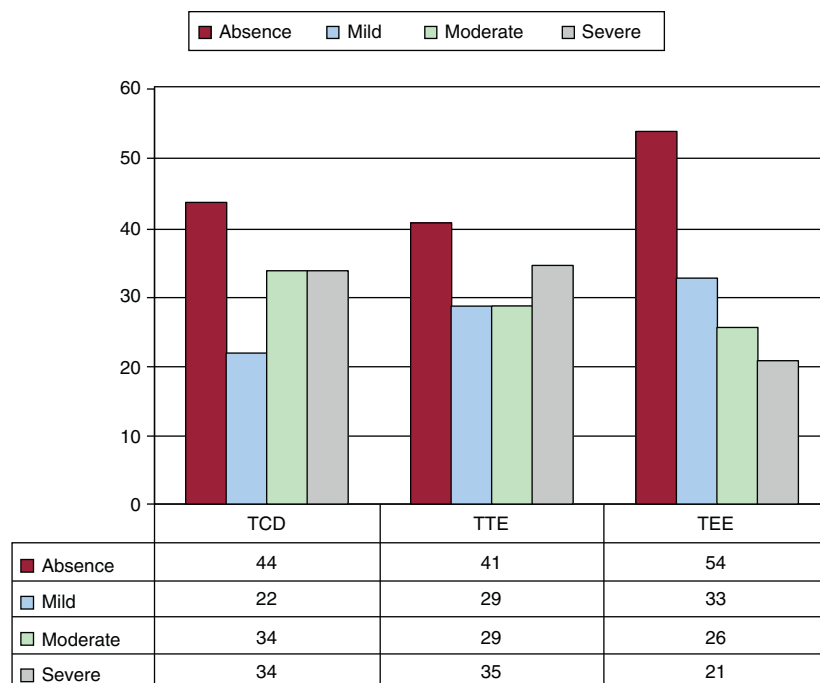


Figure 6. Quantification of the shunt using the 3 techniques. TCD, transcranial Doppler ultrasound; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

specificity is 65%-90%.^{15,26,27} Several studies have suggested that the low specificity of TCD may be due to extracardiac shunts.²⁶ In the present study, there was good concordance between the TCD performed simultaneously with the 2 echocardiographic techniques, with only 1 false positive due to a right-to-left shunt arising from a pulmonary fistula. TCD did not detect 3 mild shunts diagnosed by TTE and 2 mild shunts diagnosed by TEE. These results show that a limitation of TCD is that it cannot be used to visualize the contrast medium entering the right atrium, and thus the Valsalva maneuver may not be performed when the right atrium is completely filled with contrast, and consequently mild shunts may be overlooked.

Several previous studies highlighted the low sensitivity of TTE compared to TEE, because interatrial shunt was detected in only 31%-47% of cases.^{27,28} The suboptimal quality of the images is considered the most limiting factor.²⁹ Nevertheless, with the introduction of harmonic imaging, image quality and the detection of microbubbles in agitated serum have markedly improved. Recent studies have noted that TTE with harmonic imaging and TEE have similar accuracy in the detection of right-to-left atrial shunt^{14,20,30} and it is accepted that, when image quality is good, TTE can be effective in the detection of PFO.³¹

In young patients without clinical evidence of heart disease or atrial fibrillation, TTE appears to be effective in the diagnosis and quantification of PFO. Recently, preliminary studies have suggested the possible use of 3-dimensional TTE for this diagnosis.^{32,33}

False Negatives on Transesophageal Echocardiography

In total, 13 of the 93 patients with PFO (14%) were not diagnosed on TEE; 2 had moderate-severe shunt. In some studies, TEE obtained false negatives in the diagnosis of PFO, which were attributed to a poorly performed Valsalva maneuver.²⁶ In the study conducted by Külhet al,¹⁴ interatrial shunt was not diagnosed on TEE in 6 of 57 patients with PFO diagnosed by TTE.

Both sedation and esophageal intubation are considered limiting factors when performing an adequate Valsalva maneuver. Nevertheless, in our series, the Valsalva maneuver contributed to a similar number of positive diagnoses on TTE (26%) and on TEE using moderate sedation (33%). Strikingly, without the Valsalva maneuver, TTE diagnosed shunt in 74% of patients and TEE in only 58%. Souteyrand et al¹⁵ showed that at baseline TTE diagnosed shunt in 50% of patients, whereas TEE with moderate sedation (midazolam 5 mg) only diagnosed shunt in 33%. There is no definitive explanation for these results, but it is possible that the delicate balance between intra-atrial pressures³⁴ can be modified by small hemodynamic changes due to sedation or esophageal intubation itself.

The present study is the first to use TCD simultaneously with TTE and with TEE, showing that, under moderate sedation and with esophageal intubation, TCD has reduced sensitivity to detect right-to-left shunt. On the other hand, continuous monitoring during the procedure demonstrated significant reductions in systemic systolic blood pressure and an increase in heart rate. This hemodynamic response can be explained by the fact that midazolam moderately reduces systolic blood pressure and also the mean pulmonary blood pressure.^{35,36} On the other hand, low-dose atropine and the difficulties involved in the test itself can explain tachycardia during TEE. It may be that these hemodynamic changes or intubation hinder the reversal of the interatrial right-to-left pressure gradient³⁴ and thus the passage of microbubbles between the atria.

Severity of Right-to-Left Shunt and Assessment of Atrial Septal Aneurysm

This study demonstrated that TEE can underestimate the severity of shunt, probably due to the difficulty involved in performing an adequate Valsalva maneuver in sedated patients. PFO size (maximum separation) during the Valsalva maneuver was significantly greater depending on the degree of shunt, and it was observed that all the patients who had a PFO diameter >4 mm presented moderate or severe shunt.

ASA is frequently associated with PFO and increases the risk of stroke recurrence.^{4,37} Although TCD cannot be used to diagnose ASA, both TTE and TEE are of use in its detection. Harmonic imaging facilitates diagnosis by TTE, with accuracy similar to TEE. In the present study, 57 of the patients with PFO presented ASA (61%), whereas among the patients without PFO only 5/41 patients (12%) presented ASA.

Limitations

The results of the present study are only applicable to the selected population group. The patients received moderate sedation that was slightly higher than that administered in other series. TEE is a semi-invasive test that is poorly tolerated without sedation, especially in the young population. In this regard, we followed the same sedation protocol as for other indications of the technique, since the assumption that the degree of intolerance would be greater for this indication appeared questionable. Although the patients were instructed in the correct performance of the Valsalva maneuver and its effectiveness was verified by a 25% reduction in middle cerebral artery peak flow velocity on TCD, this does not mean that the intensity of the Valsalva maneuver was identical to that performed without sedation and without esophageal intubation. The study did not analyze observer or interobserver variability, given that the greatest variability is generated by administration of the contrast medium and the effectiveness of the Valsalva maneuver, rather than by reviewing the acquired images, and that it was considered unethical to repeat the tests, given the study design.

CONCLUSIONS

TTE with harmonic imaging and the administration of agitated physiological saline solution enables adequate assessment and quantification of right-to-left shunt due to PFO. TEE with moderate sedation tends to give false negatives and underestimates the severity of the shunt. However, the TEE technique would be especially indicated in cases of poor image quality or to accurately assess the morphology of the interatrial partition when PFO closure is planned.

CONFLICTS OF INTEREST

None declared.

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