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Journal

Interventional Cardiology Clinics, 6(4)

ISSN

2211-7458

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Publication Date

2017-10-01

DOI

10.1016/j.iccl.2017.05.002

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Identification and Quantification of Patent Foramen Ovale–Mediated Shunts

Echocardiography and Transcranial Doppler

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KEYWORDS

• Patent foramen ovale • Right-to-left shunt • Bubble study • Echocardiography • Transcranial Doppler

KEY POINTS

- Patent foramen ovale (PFO) is diagnosed using either direct imaging of the interatrial septal defect with echocardiography (transesophageal, transthoracic, or intracardiac echocardiography), or by physiologic quantification of a right-to-left shunt through the PFO using transcranial Doppler.
- Contrast transesophageal echocardiography is considered the standard technique for identifying a PFO and visualizing the atrial septal anatomy, allowing assessment of PFO size and shunt severity, and differentiation between PFO and other right-to-left shunts.
- Transthoracic echocardiography bubble study is the most commonly used method for diagnosing a PFO, being cost-effective and readily available, but with a lower sensitivity.
- Transcranial Doppler is a highly sensitive test that indirectly assesses for the presence of a right-to-left shunt; it is unable to differentiate between cardiac and pulmonary shunts. However, it is the best method to quantitate the severity of right-to-left shunts and is more sensitive than transthoracic and transesophageal echocardiography so is our preferred method of screening for PFO.

INTRODUCTION

The identification and quantification of patent foramen ovale (PFO)–mediated right-to-left shunting is crucial for the management and interventional planning of PFO-associated clinical syndromes. Ultrasonographic assessment of right-to-left shunting, either directly with echocardiography (transthoracic, transesophageal, or intracardiac) or indirectly using transcranial Doppler (TCD), remains the diagnostic approach of choice.[1] Transthoracic echocardiography (TTE) with bubble study is the most commonly used initial imaging modality for the diagnosis

Disclosure: Dr J.M. Tobis was a consultant for St. Jude Medical Inc and W.L. Gore Inc. No funding was provided by these companies to write this article. All other authors have no disclosures.
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Intervent Cardiol Clin 6 (2017) 495–504
http://dx.doi.org/10.1016/j.iccl.2017.05.002
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of PFO.[2–4] Contrast transesophageal echocardiography (TEE) is considered the standard technique for visualizing the atrial septal anatomy, assessment of PFO size and shunt severity, and differentiation between PFO and other right-to-left shunts.[5] TCD is a highly sensitive alternative screening modality to TTE for the diagnosis of PFO-mediated shunting.[6]

This article compares the different available diagnostic modalities and describes the benefits and limitations of the various imaging techniques.

GENERAL PRINCIPLES FOR DETECTION OF RIGHT-TO-LEFT SHUNTING BY ULTRASONOGRAPHY

Ultrasonographic detection of shunting from the right to left atria can be accomplished by TTE, TEE, TCD, or intracardiac echocardiography (ICE). An echocardiographic contrast is injected into the venous circulation while an ultrasonography probe is placed on the patient's chest wall (TTE), in the esophagus (TEE), on the cranium (TCD), or in the right atrium (ICE) to detect Doppler signals generated by the contrast flow. Because normal left atrial pressure is higher than right atrial pressure, a provocation maneuver is necessary to reverse the interatrial pressure gradient and induce a transient right-to-left shunt across a PFO.

Contrast Agents

Agitated saline is the most common contrast agent used for the detection of PFO-mediated right-to-left shunting given its low cost and high efficacy.[7] Agitated saline is prepared by connecting two 10-mL syringes to a 3-way stopcock with one end connected to the patient's intravenous access site. An 18-gauge needle or large bore is preferred to allow a large bolus of contrast to reach the right atrium. One of the 2 syringes is filled with 9 mL of saline and 0.5 to 1 mL of air. The saline and air are then rapidly agitated, by alternating injections between the two syringes at least 5 times, followed by rapid injection of the full bolus into the patient's venous circulation.[7] Addition of a small amount of the patient's blood to the saline before agitation improves the sensitivity of the bubble study; the protein within the plasma permits more microbubbles to remain within a given volume, allowing the contrast to last longer in the patient's circulation. In addition, the air does not coalesce as readily and thus mixing blood reduces the risk of an air embolus and stroke.[8,9] Other contrast agents that have been described in the literature for the detection of right-to-left shunts include gelatin-based solutions, Echovist, hydroxyethylamidon, D-galactose, and Gelifundol.[10–14]

Site of Contrast Injection (Antecubital vs Femoral)

The injection of contrast agent may be performed either through the antecubital vein to the superior vena cava and right atrium or via the femoral vein to the inferior vena cava and right atrium. Each access site has advantages and disadvantages. The femoral route follows the embryologic pathway of oxygenated blood from the placenta directly through the inferior vena cava to the interatrial septum (IAS) and PFO. This direct route may be facilitated by the presence of a residual eustachian valve, and gives femoral access a higher accuracy compared with antecubital access. However, most clinicians do not use femoral injections because of the impracticality of obtaining femoral venous access for a bubble study, except in the cardiac catheterization laboratory. In addition, the use of femoral venous access is discouraged by the Centers for Disease Control and Prevention (CDC), given the higher risk of embolization and infections compared with upper extremity access.[15] Thus, femoral access is usually reserved for either catheter-guided or intraoperative evaluation of right-to-left shunts.[16] Although antecubital access is easier to obtain, it may be associated with lower diagnostic accuracy than femoral access, because the contrast agent could flow from the superior vena cava to the right atrium and directly through the tricuspid valve without reaching the IAS, especially with the presence of a persistent eustachian valve.[7]

Provocation Maneuvers

Unlike atrial septal defects (ASDs), right-to-left PFO shunts are usually transient and occur when right-sided cardiac pressure increases, resulting in a reversal in interatrial pressure gradient (eg, during coughing or after release of the Valsalva maneuver). Thus, provocation maneuvers are necessary during ultrasonographic evaluation of a PFO to reveal this transient shunt that would otherwise remain undetected. A commonly used provocation maneuver is asking the patient to perform a Valsalva maneuver either during or immediately after injection of the contrast agent. However, patients are often unable to perform a Valsalva maneuver during a TEE in the setting of conscious sedation and with a probe in the esophagus. In these situations, other provocation maneuvers can be performed, such as maintaining gentle abdominal pressure for 10 to 20 seconds and then releasing it during or immediately after contrast injection. The release of the Valsalva maneuver permits the sudden return of venous blood to the right atrium with right atrial pressure transiently exceeding left atrial pressure.[17]

Criteria for Diagnosis of Intracardiac Right-to-Left Shunts

The diagnosis of intracardiac right-to-left shunting is confirmed when microbubbles are seen in either the left atrium or ventricle (TTE and TEE) or the middle cerebral arteries (TCD) after injection of contrast and a provocation maneuver. The exact number of microbubbles that correspond with a positive test is not well defined and varies from one institution to another; a positive TTE or TEE is considered if at least 1 to 5 microbubbles are visualized after 3 to 5 cardiac cycles after complete opacification of the right atrium following contrast injection and provocation.[18–21] Despite some interinstitutional variability, most clinicians accept that a positive intracardiac right-to-left shunt comprises the passage of 1 or more microbubbles into the left atrium within 3 cardiac cycles. Microbubbles passing to the left cardiac chambers after 3 cardiac cycles may indicate the presence of an intrapulmonary rather than an intracardiac shunt. The TCD criteria for diagnosis of intracardiac shunt are better defined, more sensitive, and are discussed in detail later.

DIAGNOSIS OF RIGHT-TO-LEFT SHUNT BY TRANSTHORACIC ECHOCARDIOGRAPHY

TTE is the most common initial screening modality for the detection of right-to-left shunts primarily because it is most readily available, but it has the poorest sensitivity.[2,3,22] Given the posterior position of both atria, direct visualization of interatrial shunts by color Doppler provides a lower yield; agitated saline bubble study is thus the technique of choice.[23–25]

Transthoracic Echocardiography Protocol for Detecting Right-to-Left Shunt

1. The TTE probe is placed either at the apical 4-chamber or subxiphoid 4-chamber views.
2. The agitated saline contrast agent is then injected into the patient's antecubital vein, while acquiring a prolonged image by TTE.
3. After the first study is performed at rest, a second study is obtained during a Valsalva maneuver. The test is considered positive if microbubbles are visualized in the left atrium or ventricle within 3 to 5 cardiac cycles after complete opacification of the right atrium (Fig. 1).

Diagnostic Accuracy of Transthoracic Echocardiography for Detection of Intracardiac Right-to-Left Shunt

Multiple factors affect the sensitivity and specificity of TTE bubble studies. In general, TTE bubble study is characterized by a high specificity (except if a pulmonary arteriovenous malformation is present), making it an acceptable rule-in test.[4,26] Although the sensitivity of fundamental TTE is much lower than that of TEE for the detection of right-to-left shunt, modern echocardiography uses second harmonic imaging, which has improved the sensitivity of the TTE bubble study.[26]

In a meta-analysis of 13 prospective studies including 1436 patients, the overall weighted sensitivity of fundamental TTE for the detection of intracardiac right-to-left shunts was 46.4% (95% confidence interval [CI], 41.1%–51.8%) and specificity was 99.2% (95% CI, 98.4%–99.7%) compared with TEE as the reference. The sensitivity and specificity were not affected by different contrast agents, different cutoffs for the minimum number of bubbles that determine a positive test, or different cutoffs for the number of cardiac cycles that determine a positive test.[4] In contrast, a meta-analysis including 15 prospective studies determined that TTE with harmonic imaging has a sensitivity of 90.5% (95% CI, 88.1%–92.6%) and specificity of 92.6% (95% CI, 91.0%–94.0%), compared

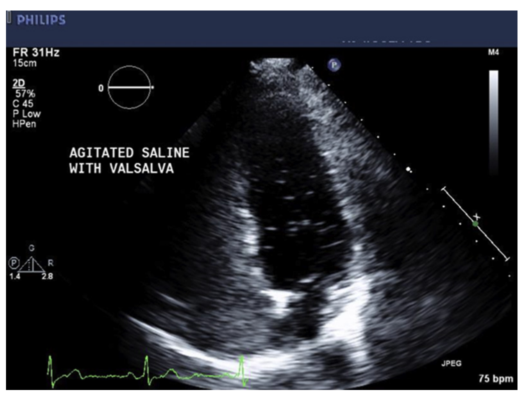

Fig. 1. Positive transthoracic echocardiogram (apical 4-chamber view) bubble study in a 33-year old patient with severe migraine with visual aura. (*From* Mojadidi MK, Gevorgyan R, Tobis JM. A comparison of methods to detect and quantitate PFO: TCD, TTE, ICE and TEE. In: Amin Z, Tobis JM, Sievert H, et al, editors. Patent foramen ovale. London: Springer; 2015. p. 55–65; with permission.)

with TEE as the reference. A cutoff of 1 or more microbubbles (instead of ≥5), within 3 cardiac cycles (instead of 5), resulted in a higher specificity of TTE harmonic imaging without compromising sensitivity. In addition, the mixture of a patient's blood to agitated saline increases the sensitivity of TTE harmonic imaging without compromising specificity.[26] Table 1 summarizes the diagnostic accuracy of TTE (with and without harmonic imaging) for the detection of intracardiac right-to-left shunt compared with TEE as the reference. However, all of these studies are flawed because the true comparison for the diagnosis of a PFO should be a right heart catheterization with documentation of passage of a guidewire across the atrial septum. However, few studies have been performed with right heart catheterization as the gold standard.

Advantages and Disadvantages of Transthoracic Echocardiography for Detection of Intracardiac Right-to-Left Shunt

Advantages of TTE bubble study include its noninvasive nature, easy availability, lower cost (compared with TEE), and high specificity. However, TTE is limited by a lower sensitivity, low resolution, and poor visualization of the IAS. Table 2 shows the advantages and disadvantages of TTE for detection of intracardiac right-to-left shunt.

Although TTE bubble study is the most common screening modality for the detection of PFO-mediated right-to-left shunting, its lower sensitivity, often poor acoustic windows, and poorly visualized IAS make it a less than ideal screening test. PFOs are often missed if clinicians rely on TTE alone; alternative screening such as TCD or use of TTE with TEE is often necessary to make a definitive diagnosis.

Table 1
Diagnostic accuracies of transthoracic echocardiography, transcranial Doppler, and transesophageal echocardiography bubble studies for the detection of intracardiac right-to-left shunt

	Sensitivity (%)	Specificity (%)	LR+	LR−
TTE-F[4]	46	99	20.85	0.57
TTE-HI[26]	91	93	13.52	0.13
TCD[6]	97	93	13.51	0.04
TEE[5]	89	91	5.93	0.22

TTE-F, TTE-HI, and TCD compared with TEE as the reference standard. TEE compared with PFO confirmation by cardiac catheterization, surgery, and/or autopsy as the reference standard.

Abbreviations: TTE-F, fundamental TTE; TTE-HI, TTE with harmonic imaging; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

PATENT FORAMEN OVALE IMAGING BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TEE is considered by many clinicians to be the standard for diagnosing a PFO.[1,27] TEE provides anatomic details of the IAS and can differentiate a PFO from an ASD but may still incorrectly diagnose pulmonary shunts.[1] Moreover, TEE can more accurately detect the presence of an atrial septal aneurysm compared with TTE. The presence of a PFO with an atrial septal aneurysm has been linked to a higher risk of cryptogenic stroke.[28,29] In patients with stroke, TEE can detect other sources of embolism (left ventricular thrombus, aortic plaque burden, and left atrial appendage clot) that may otherwise be missed by TTE.

Transesophageal Echocardiography Protocol for Detecting a Patent Foramen Ovale

1. The IAS is first visualized in multiple views (ie, bicaval, 4 chamber, short and long axis) using multiplane angles for accurate determination of the IAS anatomy and ruling out other causes of stroke or hypoxemia.
2. Both the 4 chamber and bicaval views can be used for direct visualization of the PFO.
3. Agitated saline contrast is injected in a similar fashion as described with TTE. Because it is often difficult for the patient to perform an adequate Valsalva maneuver with sedation and a probe in the esophagus, transient external abdominal pressure can be applied over the liver for 10 to 20 seconds, which is then released during or immediately after injecting contrast to increase intrathoracic and right atrial pressure.
4. The test is considered positive if at least 1 microbubble is seen in the left atrium with evidence of transient opening of the PFO canal during the first 3 cardiac cycles, after injection of agitated saline and complete opacification of the right atrium (Fig. 2). The international consensus for TEE grading is often used to quantify the size of shunts[17] (Table 3).

Diagnostic Accuracy of Transesophageal Echocardiography for Detection of Patent Foramen Ovale

Although TEE bubble study is considered the gold standard noninvasive modality for detecting a PFO, one study comparing TEE with PFO

Table 2
Advantages and disadvantages of transthoracic echocardiography, transcranial Doppler, and transesophageal echocardiography for the diagnosis of patent foramen ovale

	Advantages	Disadvantages
TTE	• Readily available • Cost-effective • Excellent safety • Easy to perform	• Low resolution • Less sensitive than TCD • Images may be limited by patient's body habitus and poor echocardiographic windows • Often difficult to differentiate between PFO, ASD, and pulmonary shunts
TCD	• Highly sensitive • Cost-effective • Excellent safety • Easy to perform	• Positive test based on an arbitrary cutoff • Inability to differentiate between PFO, ASD, and pulmonary shunts (ie, lower specificity) • Inability to visualize atrial septum
TEE	• Highly accurate imaging modality • Can visualize atrial septal anatomy • Accurate assessment of PFO size • Accurate assessment of shunt severity • Differentiates PFO from ASD and pulmonary shunts • Useful for closure planning • In addition to diagnosing PFO, can detect other sources of embolism	• Semi-invasive procedure • Need for sedation • Difficulty performing Valsalva with a probe in the esophagus • Carries a risk of complications • May not be used in patients with esophageal stricture, cancer, or varices • Difficulty in uncooperative patients with swallowing dysfunction

confirmation by autopsy found TEE to have a sensitivity of 89%.[30] Studies comparing TEE with PFO confirmation during cardiac catheterization or intraoperative detection similarly found that 10% of PFOs are missed by TEE.[31–34] In a meta-analysis of 4 prospective studies comparing TEE with PFO confirmation by surgery, right heart catheterization, and/or autopsy, 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%), indicating that approximately 10% of PFOs are either missed or misdiagnosed if the clinician relies on TEE alone.[5] This finding may be explained by the difficulty of performing a Valsalva maneuver with a TEE probe in the patient's esophagus, at times poor patient compliance, different patient anatomies, and operator experience.

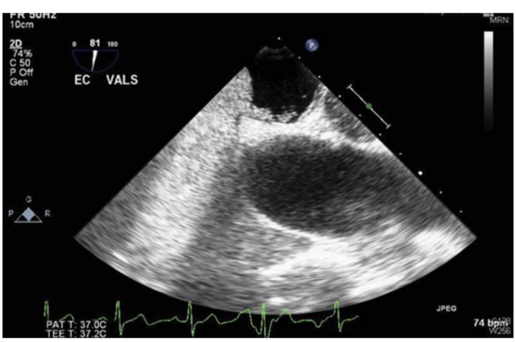

Fig. 2. Transesophageal echocardiogram with positive bubble study through a PFO. (*From* Mojadidi MK, Gevorgyan R, Tobis JM. A comparison of methods to detect and quantitate PFO: TCD, TTE, ICE and TEE. In: Amin Z, Tobis JM, Sievert H, et al, editors. Patent foramen ovale. London: Springer; 2015. p. 55–65; with permission.)

Advantages and Disadvantages of Transesophageal Echocardiography

Advantages of TEE include accurate description of the IAS anatomy, ability to detect an aneurysmal atrial septum, differentiating a PFO from an ASD, PFO sizing, and functional assessment of shunt severity by color flow Doppler or agitated saline bubble study. However, TEE is an uncomfortable procedure requiring conscious sedation. TEE also carries a risk of bleeding and perforation, particularly in patients with known esophageal disorders such as varices, strictures, and achalasia.[34] Table 2 summarizes the advantages and disadvantages of TEE for PFO imaging.

Table 3
International consensus for transthoracic echocardiography grading

Grade	mB
Grade 0	None
Grade 1	1–10
Grade 2	10–20
Grade 3	>20; curtain appearance of mB

Abbreviation: Mb, microbubbles.

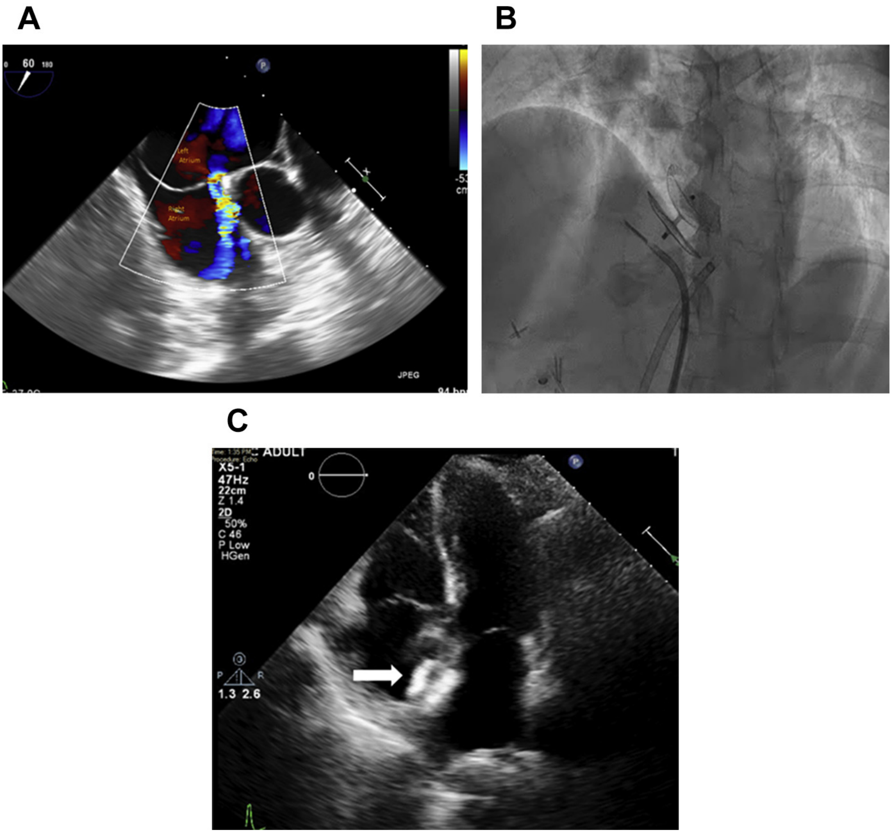

Fig. 3. A 38-year-old woman presenting with cryptogenic stroke. Color Doppler transesophageal echocardiography images revealed a significant left-to-right shunt through a PFO (*A*). Bubble study was positive for transient right-to-left shunting. The patient underwent successful percutaneous PFO closure with an Amplatzer Multifenestrated (Cribiform) Septal Occluder (St Jude Medical, St. Paul, MN) seen on fluoroscopy (*B*) and transthoracic echocardiography (*arrow in C*).

In summary, TEE offers an acceptable diagnostic accuracy compared with autopsy, cardiac catheterization, and/or surgical detection of PFO. The main advantage of TEE is the anatomic determination of PFO structure and ruling out other causes of right-to-left shunting. Thus, TEE is an excellent confirmatory tool for identification and evaluation of PFO-mediated shunting, after an initial noninvasive screening modality (Figs. 3 and 4). However, clinicians should be aware that the diagnosis of a PFO by TEE alone may be misleading. If the clinical scenario justifies a higher level of certainty, a right heart catheterization may be necessary to determine an accurate diagnosis.

DIAGNOSIS OF INTRACARDIAC RIGHT-TO-LEFT SHUNT BY TRANSCRANIAL DOPPLER

TCD bubble study is an alternative imaging modality for indirectly detecting a PFO by assessing for the presence of right-to-left shunting. It

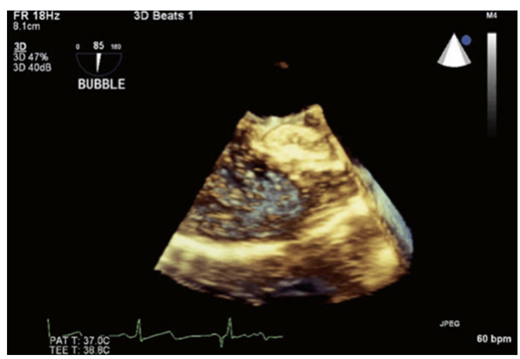

Fig. 4. Three-dimensional transesophageal echocardiographic image after placement of a 25-mm Gore Helex Septal Occluder (Gore & Associates, Flagstaff, AZ). During agitated saline bubble study, bubbles are visualized in the right atrium, but not on the left atrial side. (*From* Mojadidi MK, Gevorgyan R, Tobis JM. A comparison of methods to detect and quantitate PFO: TCD, TTE, ICE and TEE. In: Amin Z, Tobis JM, Sievert H, et al, editors. Patent foramen ovale. London: Springer; 2015. p. 55–65; with permission.)

Table 4 Spencer Logarithmic Scale for transcranial Doppler grading	
Grade	**mB**
Grade 0	0
Grade 1	1–10
Grade 2	11–30
Grade 3	31–100
Grade 4	101–300
Grade 5	>300

allows functional assessment of the shunt through insonation of the middle cerebral arteries after venous injection of agitated saline and release of the Valsalva maneuver. The degree of shunting with TCD can be quantified by using the Spencer logarithmic scale. The Spencer scale scores the severity of shunts using 5 grades (0–5) with 0 being absence of a shunt and 5 being consistent with a large shunt (Table 4). Based on a comparative study with right heart catheterization, a TCD is considered positive if the score is grade 3 or higher on the Spencer scale.[31] Lower grades usually correlate to small, clinically insignificant pulmonary shunts or pinhole septal defects. Modern TCDs are fitted with power M-mode software, which allows better microbubble signal detection, and therefore a more accurate quantification of right-to-left shunting. Studies comparing power M-mode TCD with older TCD models show that power M-mode TCD has a higher sensitivity and accuracy.[31]

Transcranial Doppler Protocol for Detecting Intracardiac Right-to-Left Shunt

1. The TCD ultrasonography probe is placed in an acoustic window (eg, transtemporal, transorbital, or suboccipital window) (Fig. 5).
2. Agitated saline is injected into the antecubital vein and the patient is asked to perform a Valsalva maneuver.
3. The circulation of microbubbles in the insonated vessel is visualized by M-mode Doppler and the grade of right-to-left shunt is quantified over 1 minute using the Spencer logarithmic scale (Fig. 6).

Diagnostic Accuracy of Transcranial Doppler for Detecting Intracardiac Right-to-Left Shunts

TCD is a highly sensitive imaging modality for detection of intracardiac right-to-left shunts. In a study comparing TCD and TEE bubble studies versus PFO probing during right heart catheterization, TCD was more sensitive than TEE.[31] In a large meta-analysis of 27 prospective studies including 1968 patients, TCD bubble study had a sensitivity of 97% (95% CI, 94%–98%) and specificity of 93% (95% CI, 86%–97%) for the detection of intracardiac right-to-left shunts compared with TEE as the reference.[6]

Advantages and Disadvantages of Transcranial Doppler for Detection of Intracardiac Right-to-Left Shunt

Besides its high sensitivity, TCD provides useful information on the size of the shunt using the Spencer scale. In addition, TCD is easily tolerated, cost-effective, and safe. The indirect functional assessment for a shunt without anatomic imaging of the atrial septum limits TCD in differentiating between a PFO, ASD, and pulmonary shunts; this largely explains the lower specificity of TCD. Table 2 summarizes the advantages and disadvantages of TCD for the detection of intracardiac right-to-left shunts.

In summary, TCD is a highly sensitive diagnostic modality that is cost-effective and easy to perform. These qualities make TCD an

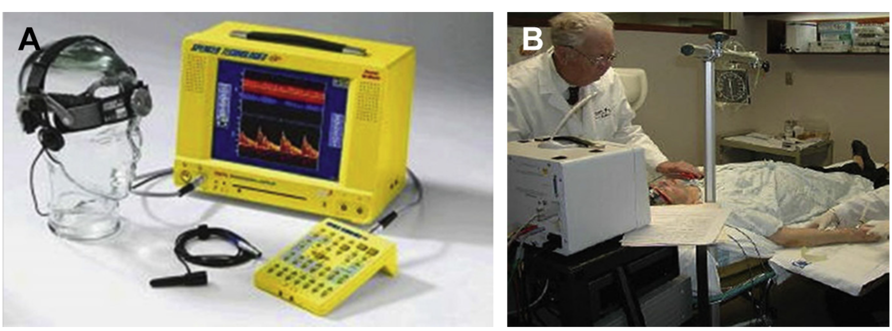

Fig. 5. (*A*) TCD machine and setup. (*B*) Dr Spencer demonstrates the technique for TCD that he developed. The patient is supine with a headband on and an intravenous line in the right antecubital fossa. The power M-mode equipment shows the headband, ultrasonography transducers, and the arterial waveform on Doppler. (*Courtesy of* Spencer Technologies, Redmond, WA; with permission.)

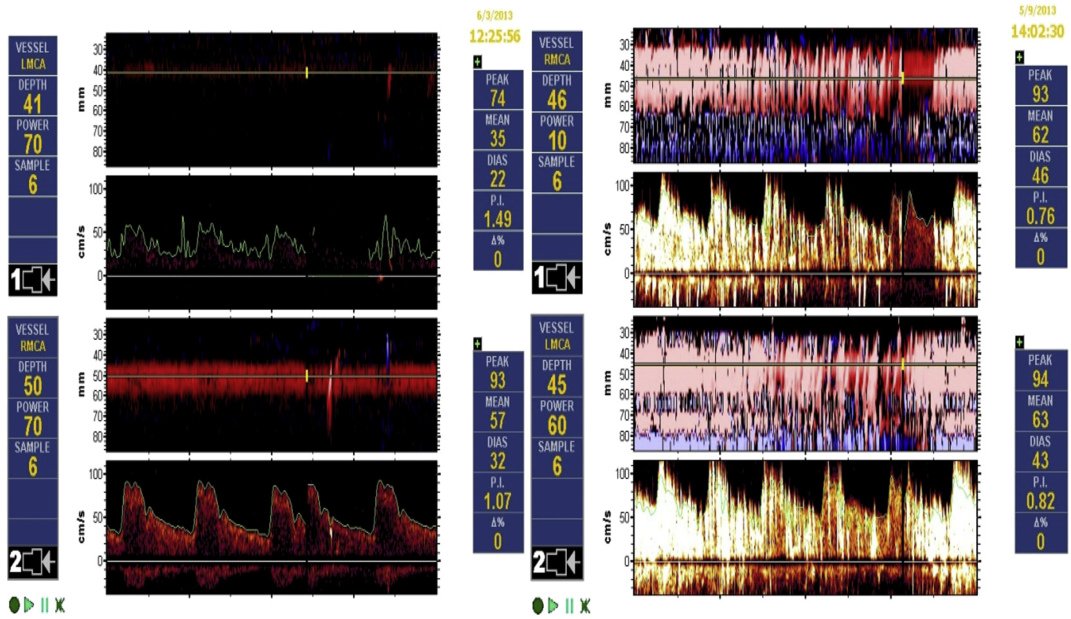

Fig. 6. TCD grading with microembolic signals that measure degree of right-to-left shunting ranging from grade 1 (*left*) to grade 5 (*right*).

excellent initial screening modality for the detection of PFO. A positive test with TCD, although accurate in detecting a right-to-left shunt, carries the possibility of being a false-positive for the presence of a PFO either from an ASD or intrapulmonary shunt. TCD is an indirect functional test that does not visualize the IAS and thus a confirmatory test either with TEE or ICE (during percutaneous PFO closure) should be performed following a positive TCD.

OTHER DIAGNOSTIC MODALITIES FOR IDENTIFICATION AND QUANTIFICATION OF A PATENT FORAMEN OVALE

ICE and cardiac MRI are other imaging options that are used for both anatomic visualization of the IAS and evaluation of right-to-left shunting. ICE has emerged as an invasive imaging modality that is primarily used during transcatheter PFO closure.[35] A PFO is visualized with ICE in a horizontal view of the septum posterior to the aortic bulge (Fig. 7).[36] Advantages of ICE include highly detailed visualization of the IAS, low procedure cost, no need for general anesthesia, and the ability of the interventionist to control the ICE probe without the requirement of another specialist during the procedure.[1] ICE is also useful for the immediate detection of residual shunting after percutaneous PFO closure (Fig. 8). Disadvantages include the need for a second venous access, increasing the risk of vascular access–related complications. In a study comparing ICE with TEE, ICE had a similar preclosure right-to-left shunt detection rate. However, the detection rate was much lower following device closure, which could be attributed to the monoplane nature of ICE or the presence of a device between the ICE probe and contrast microbubbles, resulting in a lower image yield.[37]

Cardiac MRI is less frequently used as an imaging modality for the detection of PFO, given the low sensitivity of MRI compared with TEE.

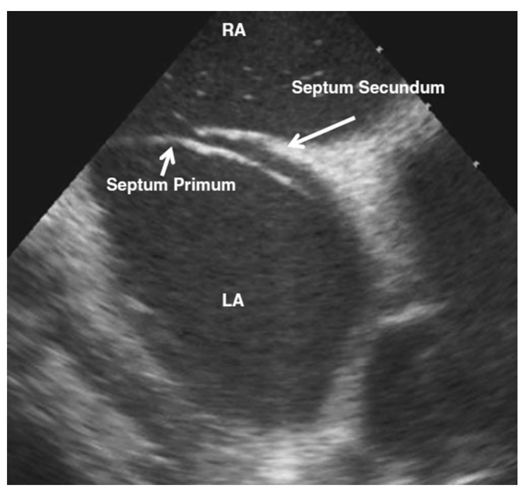

Fig. 7. Patent foramen ovale shown on ICE. LA, left atrium; RA, right atrium.

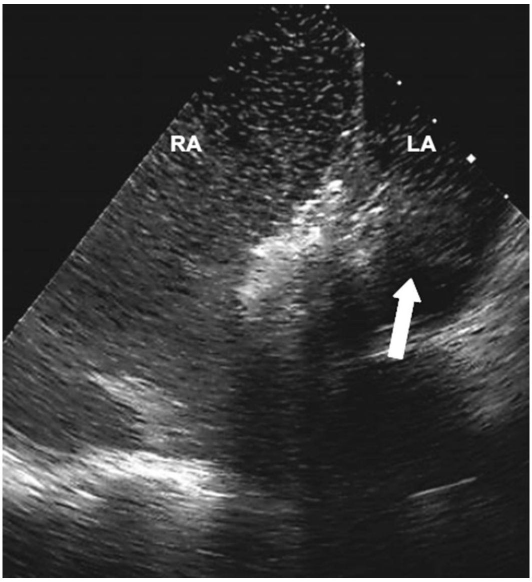

Fig. 8. Gore Helex Septal Occluder with moderate residual shunting (*arrow*) through the device on ICE.

The low sensitivity of MRI may be explained by a lack of continuous and prolonged images that are required given the transient nature of right-to-left shunting across a PFO.[38,39]

SUMMARY AND RECOMMENDATIONS

TCD bubble study has the highest sensitivity for the detection of PFO-mediated right-to-left shunt, making it the initial screening modality of choice. In centers where TCD is unavailable, TTE with harmonic imaging can be used for initial screening, keeping in mind that a significant fraction of PFOs are missed with TTE. A subsequent TEE bubble study will provide additional information on IAS anatomy before transcutaneous or surgical closure. If TEE is not feasible because of contraindications or patient intolerance, ICE can be used during percutaneous PFO closure. Cardiac MRI should not be routinely used for the detection of PFO given its low sensitivity and high cost compared with other available imaging modalities.

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