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C H A P T E R

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Echocardiography, Transcranial Doppler, and Oximetry for Imaging and Quantification of PFO-Mediated Shunts

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O U T L I N E

PFO Closure for Stroke, Myocardial Infarction, Peripheral Embolism, Migraine, and Hypoxemia
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INTRODUCTION

Patent foramen ovale (PFO) is characterized by a transient intracardiac right-to-left shunt that is found in one-quarter of the general population [1]. Although most people with a PFO will remain asymptomatic, a wide range of pathologies and clinical syndromes may arise mediated by the PFO including stroke (Chapters 4–7), myocardial infarction (Chapter 8), peripheral embolism (Chapter 9), migraine headache (Chapters 10 and 11), hypoxemia (Chapter 12), and decompression sickness in divers (Chapter 13) [2–7].

A number of diagnostic imaging modalities can be utilized to directly or indirectly detect and quantify a PFO, all with different advantages and limitations [8–11]. Direct visualization of the interatrial septum, most commonly by ultrasonography, and less frequently by cardiac computed tomography (CT) or magnetic resonance imaging (MRI), can help identify the defect and its anatomic characteristics. Transthoracic echocardiography (TTE) with agitated saline bubble study remains the most commonly used modality to screen for a PFO. Transesophageal echocardiography (TEE) with bubble study allows the clinician to diagnose a PFO with direct visualization of the atrial septal anatomy [11]. Transcranial Doppler (TCD) bubble study has emerged as an acceptable alternative to TTE for PFO screening; it carries a higher sensitivity than TTE and TEE, with a negative test virtually excluding a PFO [12]. Catheter probing and angiography are used to document and categorize a PFO ad hoc or complement prior imaging. Imaging assessment of a PFO, for diagnostic and interventional purposes, is crucial to aid clinicians in making management decisions and planning potential percutaneous closure of an offending right-to-left shunt. PFO imaging for interventional purposes is discussed in Chapter 3. Percutaneous PFO device closure has recently re-emerged into the spotlight, after the results were published of several randomized trials of PFO closure for stroke and migraine [13,14]. This chapter will discuss the different imaging modalities used to detect and quantitate a PFO, and describe the advantages and limitations of each method.

ULTRASOUND DETECTION OF A PFO

In most cases, imaging of a PFO involves direct visualization of the anatomical defect or functional detection of a right-to-left shunt. Ultrasound assessment of right-to-left shunts, either directly utilizing echocardiography (TTE, TEE, or intracardiac echocardiography [ICE]), or indirectly using TCD, remains the most common diagnostic approach. Ultrasonography allows the clinician to use color flow Doppler to detect blood flow between the 2 atria as a colored signal [3]. The advent of three-dimensional (3D) echocardiography has also enabled clinicians to visualize the atrial septum anatomy in real time and view surrounding structures [15,16]. For larger PFOs, color flow Doppler may be all that is needed to detect the defect. However, injection of a contrast agent (such as agitated saline) with a provocation maneuver (Valsalva or cough) is usually needed to reverse the interatrial pressure gradient, induce the right-to-left shunt, and detect crossing of bubbles with ultrasonography [11] (Video 2.1).

CONTRAST AGENT DURING A BUBBLE STUDY

During echocardiography with a bubble study, the sonographer first gets the optimal view of the interatrial septum, and then injects contrast into the venous circulation to detect the right-to-left shunt. Agitated saline remains the most commonly used contrast agent; it is formed by mixing about 9 mL of saline and 0.5–1 mL of air in 2 syringes. The mixture is rapidly agitated by 5–6 alternating injections from the 2 syringes using a 3-way stopcock; this bolus is then infused into the patient's venous circulation while watching for the appearance of microbubbles in the left atrium (TTE, TEE, or ICE) or the middle cerebral arteries (TCD) [17,18]. Studies have demonstrated that addition of a small amount (1–2 mL) of the patient's blood to the agitated saline mixture can increase the sensitivity of a bubble study without compromising specificity. The addition of plasma protein coats the air bubbles and stabilizes their surface tension, allowing more microbubbles to be contained within the same volume, thus increasing the test's sensitivity and lowering the small risk of air embolism from large bubbles of air coalescing during the injection [12,18–20]. Although other contrast agents have been developed for use during bubble studies, agitated saline remains the most commonly used mixture in many countries due to its low cost, ease of use, and high efficacy [18].

INJECTION SITE FOR A BUBBLE STUDY (ANTECUBITAL VS. FEMORAL)

Studies have compared the performance of bubble studies with different venous injection sites (i.e., antecubital vs. femoral access). In the embryonic period, oxygenated placental blood flows through the inferior vena cava to the right atrium where the Eustachian valve directs the blood superiorly and medially across the foramen ovale and into the left atrium. The nonaerated fetal lungs create a high pulmonary artery resistance, which increases the right atrial pressure to keep the foramen open. The oxygenated placental blood thus passes directly to the left atrium (Chapter 1). This direct pathway to the PFO, along with reduced bubble transit time, explains the increased diagnostic accuracy observed with a femoral vein bubble study injection compared with an arm vein injection. However, obtaining femoral venous access solely for an agitated saline study is usually impractical. Additionally, femoral access increases the risk of line-associated infections compared with antecubital venous access. Thus, femoral vein bubble studies should be utilized when a femoral venous catheter already exists for another indication [21] or a Eustachian valve keeps the bubbles away from the PFO.

PROVOCATION MANEUVERS DURING A BUBBLE STUDY

Since the baseline left atrial pressure is slightly higher than right atrial pressure, the use of a provocation maneuver (Valsalva or cough) is essential to reverse the interatrial pressure gradient and allow for the detection of PFO-mediated right-to-left shunting [22]. Maneuvers that increase thoracic pressure such as the Valsalva maneuver, obstruct venous return to the right atrium. Upon release of Valsalva, there is a fall in intrathoracic pressure, and venous return to the right atrium is increased. This large volume of blood in the right atrium causes a transient reversal of the interatrial pressure gradient, which moves the septum primum to the left and opens the PFO. Alternatively, a cough or a vigorous nasal sniff during the bubble study may open the PFO and demonstrate the right-to-left passageway. Such maneuvers increase the diagnostic yield of bubble studies, allowing the detection of otherwise silent shunts such as a PFO with a closed septal flap or small atrial septal defects (ASDs). A provocation maneuver is performed during or immediately before contrast medium injection. However, an adequate Valsalva can be difficult to perform during a TEE due to a probe in the esophagus or deep sedation; in such circumstances, moderate external abdominal pressure can be applied for 15–20 seconds with immediate release of pressure during the agitated saline injection [23,24] (Videos 2.2a and b).

DIAGNOSTIC CRITERIA FOR INTRACARDIAC RIGHT-TO-LEFT SHUNT

The diagnosis of a PFO starts with detection of microbubbles that cross the interatrial septum, from the venous to the systemic circulation (Fig. 2.1). These microbubbles can be detected in the left atrium with echocardiography (TTE, TEE, and ICE) or at the level of the middle cerebral arteries with TCD. An extracranial artery or digital artery could more easily be used but traditionally are not. The number of microbubbles that correlate to a positive bubble test is not well defined and can vary depending on the institution; a TTE or TEE is considered positive when at least 1–5 microbubbles are visualized within 3–5 cardiac cycles after contrast medium injection, provocation, and complete right atrial opacification [22–28]. Despite some interinstitutional inconsistency in the exact cutoff, it is widely accepted that a positive bubble study comprises the detection of at least 1 microbubble within 3 cardiac cycles. The passage of microbubbles after 3 cardiac cycles is attributed to intrapulmonary shunting rather than an intracardiac shunt [29]; however, other investigators have demonstrated that this echocardiographic criterion is often invalid because a PFO may open sporadically or late during the bubble injection. The severity of the shunt can be graded using the international consensus for TTE grading (Table 2.1). The diagnostic criteria used for a positive TCD are better defined, and discussed later in detail. Most early reports about accuracy of echocardiography and bubble studies did not use a diagnostic right heart catheterization, with documentation of crossing the atrial septum with a guidewire, to prove that the chosen bubble criteria actually correspond to the anatomic presence of a PFO. Using the current criteria, we often see patients who have false-positive or false-negative bubble studies.

TRANSTHORACIC ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF PFO

TTE is the most commonly utilized screening modality for a PFO as it is readily available, but TTE has the lowest sensitivity. The anatomically posterior position of the atria makes direct visualization by color Doppler difficult with a low yield; thus, agitated saline bubble study is the preferred technique (Fig. 2.1) [8,26,30].

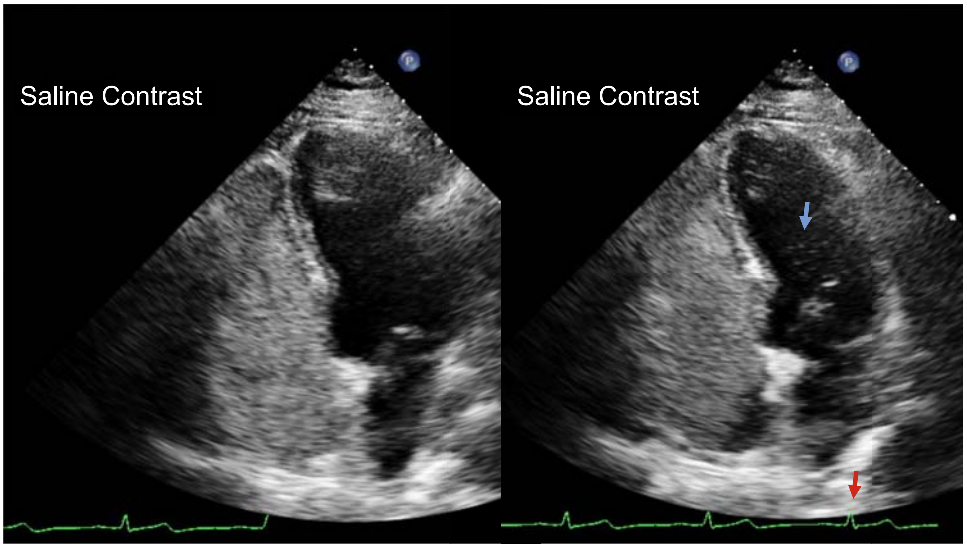


FIGURE 2.1 Apical 4-chamber view by transthoracic echocardiography showing a positive bubble study. In the image on the left, the agitated saline bubbles are seen in the right atrium and right ventricle. In the image on the right, saline contrast (*blue arrow*) is visualized in the left ventricle before the third cardiac cycle (*red arrow*), indicative of an intracardiac right-to-left shunt (PFO or atrial septal defect).

TABLE 2.1 The International Consensus for Grading of Right-To-Left Shunt Severity With Echocardiography.

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

Protocol for a Transthoracic Echocardiography Bubble Study

1. The echocardiography probe is placed at the apical 4-chamber or subcostal view.
2. Using an antecubital venous access (or femoral venous access if already available), agitated saline or a contrast medium is injected and a prolonged image is acquired by TTE.
3. The study is then repeated, this time with a provocation maneuver such as Valsalva. A positive test is considered when microbubbles are documented passing through the atrial septum or seen in the left atrium or ventricle within 3–5 cardiac cycles, following complete right atrial opacification (Video 2.1).

Diagnostic Accuracy of Transthoracic Echocardiography Bubble Study

The sensitivity and specificity of a TTE bubble study are affected by several factors related to the imaging modality itself and the protocol used. TTE carries a high specificity (unless a pulmonary shunt is present), which makes it an adequate rule-in test [10,29]. While the sensitivity of TTE with fundamental imaging is considerably lower than that of TEE for detecting a right-to-left shunt [10], modern day echocardiography is equipped with second harmonic imaging; this has enhanced the sensitivity of TTE [29].

One meta-analysis including 13 prospective studies (1436 patients) reported that TTE with fundamental imaging carries an overall weighted sensitivity of 46.4% (95% confidence interval [CI], 41.1%–51.8%) and specificity of 99.2% (95% CI, 98.4%–99.7%) for the detection of intracardiac right-to-left shunt, when compared with TEE as the reference. The sensitivity and specificity of the test did not change by the use of different contrast agents, different cutoffs for the minimum microbubbles that define a positive study, or different cutoffs for the number of cardiac cycles that define a positive study [10]. In comparison, a meta-analysis of 15 prospective studies (1995 patients) reported that

TTE with harmonic imaging carries a sensitivity of 90.5% (95% CI, 88.1%–92.6%) and specificity of 92.6% (95% CI, 91.0%–94.0%), when compared with TEE as the reference. Adding a small amount of the patient's blood to the agitated saline mixture increased the sensitivity of TTE harmonic imaging without lowering specificity. Moreover, a cutoff of ≥1 microbubbles (as opposed to ≥5), within 3 cardiac cycles (as opposed to 5), increased the specificity of TTE harmonic imaging without lowering sensitivity [29]. The diagnostic accuracy of TTE (with and without harmonic imaging) for the detection of intracardiac right-to-left shunt is summarized in Table 2.2. All studies using TEE bubble study as the reference are flawed since the true comparator for the diagnosis of PFO should be a right heart catheterization with angiographic iodinated contrast passage through the PFO gap (Fig. 2.2), or fluoroscopic visualization of a guidewire passing across the atrial septum. However, only a paucity of echocardiographic studies utilized right heart catheterization as the gold standard. In addition, TTE may provide a low-resolution image and is often unable to provide the clinician with important information regarding the anatomy of the interatrial septum (i.e., aneurysmal or hypermobile septum [seen in Video 2.1] or the size of the defect) [11].

Advantages and Limitations of Transthoracic Echocardiography for Detecting a PFO

The advantages of TTE bubble study include its high specificity, noninvasive nature, easy availability, and low cost (compared to TEE). However, TTE's low resolution, often poor acoustic windows, inability to clearly visualize the interatrial septum, and low sensitivity make it a suboptimal screening test. The advantages and disadvantages of TTE for the detection of intracardiac right-to-left shunt are summarized in Table 2.3. When clinicians depend on a TTE alone, a PFO will often be missed. To make a definitive diagnosis, alternative screening, using TCD or TTE plus TEE, is preferable. [31,32].

TABLE 2.2 Diagnostic Accuracies of Transthoracic Echocardiography (With and Without Harmonic Imaging), Transcranial Doppler (TCD), and Transesophageal Echocardiography (TEE) Bubble Studies for the Detection of Intracardiac Right-To-Left Shunt.

Imaging Modality	Sensitivity (%)	Specificity (%)	LR+	LR−
TTE-F [10]	46	99	20.85	0.57
TTE-HI [29]	91	93	13.52	0.13
TCD [12]	97	93	13.51	0.04
TEE [41]	89	91	5.93	0.22

*TTE-F, transthoracic echocardiography with fundamental imaging; TTE-HI, transthoracic echocardiography with harmonic imaging; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

***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.*

Adapted with permission from Ref. [11].

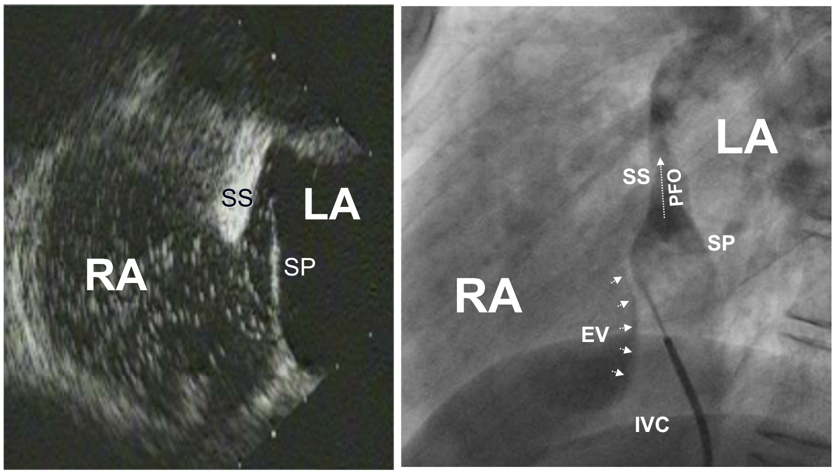


FIGURE 2.2 Definite documentation of a PFO by transesophageal echocardiography obtained during an agitated saline bubble study (left, placed in the projection corresponding to angiography) and angiography (right) with iodinated contrast medium. *EV*, Eustachian valve; *IVC*, inferior vena cava; *LA*, left atrium; *RA*, right atrium; *SP*, septum primum; *SS*, septum secundum.

TABLE 2.3 Advantages and Limitations of Transthoracic Echocardiography (TTE), Transcranial Doppler (TCD), Transesophageal Echocardiography (TEE), Intracardiac Echocardiography (ICE), and Angiography for the Diagnosis of PFO.

Imaging Modality	Advantages	Limitations
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 (i.e., 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 while typically being sedated • Carries a risk of complications • May not be used in patients with esophageal stricture, diverticula, cancer, or varices • Difficulty in uncooperative patients with swallowing dysfunction
ICE	• Detailed visualization of atrial septal anatomy • Allows guidance during device deployment • Residual shunt assessment post-PFO closure • Performance without general anesthesia • Second operator not needed	• Need for second venous access • Increased risk of vascular access-related complications • Possible limitations by operator inexperience • Procedural cost
Angiography	• Accurate • Less uncomfortable than TEE • Combinable with device closure	• Needs catheterization laboratory • X-ray exposure

ASD, atrial septal defect.
Adapted with permission from Ref. [11].

TRANSESOPHAGEAL ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF PFO

Many clinicians consider TEE as the reference standard for the diagnosis and quantification of PFO-mediated right-to-left shunting. TEE allows direct visualization of the atrial septal anatomy, with the ability to identify an atrial septal aneurysm, the presence of a Eustachian valve or a Chiari network (Fig. 2.3), and grade shunt severity [33,34]. PFO associated with an atrial septal aneurysm or large shunt has been found to increase the risk of stroke [4,34–36]. Additionally, TEE can differentiate a PFO from an ASD but may still misdiagnose pulmonary shunts. TEE has the added advantage of detecting other sources of potential embolism, such as left atrial appendage thrombus, left ventricular thrombus, or atherosclerotic aortic plaque, which is often missed by TTE [5,33,34].

Protocol for a Transesophageal Echocardiography Bubble Study

1. After esophageal intubation, the interatrial septum is visualized in multiple projections using multiplane angles; these include the bicaval, 4-chamber, short and long axis views. This allows accurate assessment of the interatrial septum anatomy.
2. The short axis and bicaval views can be used for direct visualization of the PFO (Fig. 2.4).
3. Similar to TTE, agitated saline or a contrast medium is injected. Given that an adequate Valsalva is difficult to perform with sedation and a probe in the esophagus, moderate external abdominal pressure can be applied for 10–20 seconds, followed by release of pressure during or immediately after contrast medium injection, to increase venous return and right atrial pressure (Videos 2.2a and b).

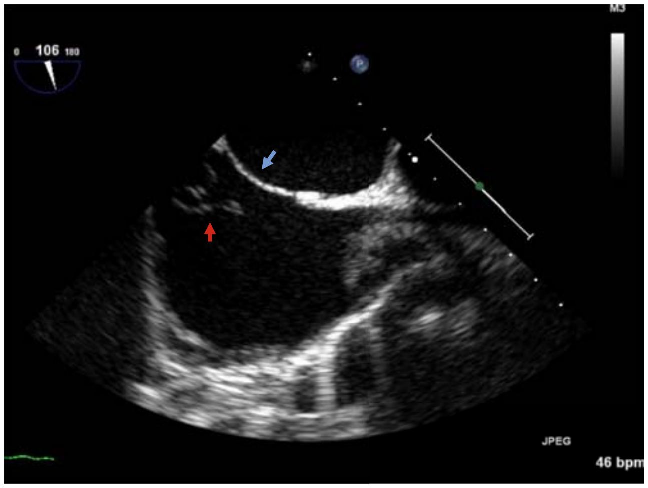


FIGURE 2.3 Bicaval view by transesophageal echocardiography showing anatrial septum that proved aneurysmal during motion (*blue arrow*) with the presence of a Chiari network (*red arrow*).

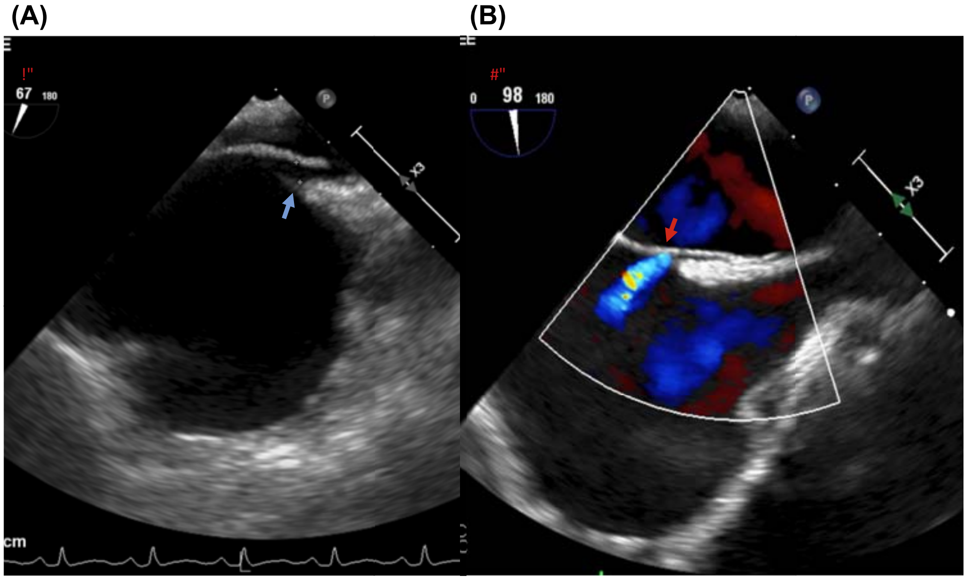


FIGURE 2.4 Bicaval view by transesophageal echocardiography showing the presence of PFO (*blue arrow*) that is partially open (A) resulting in baseline left-to-right shunting, indicated by the Doppler color flow across the PFO (*red arrow*) (B).

4. A positive test is defined by the appearance of at least 1 microbubble in the left atrium with transient opening of the PFO flap during the first 3 cardiac cycles, following contrast medium injection and complete right atrial opacification. Documentation of bubbles (Fig. 2.2) or a Doppler flow (Fig. 2.4) passing through the PFO gap is pathognomonic. Similar to TTE, the international consensus for echocardiographic grading is used to quantify the size of shunts (Table 2.1).

Diagnostic Accuracy of Transesophageal Echocardiography Bubble Study

Although TEE is considered the reference standard for detecting a PFO, one observational study that compared TEE with the confirmation of PFO by autopsy reported TEE to have a sensitivity of 89% [37]. A meta-analysis comparing TEE to PFO confirmed by surgery, right heart catheterization, and/or autopsy found that TEE had a weighted sensitivity of 89% and specificity of 91% [38]; these results suggested that ~10% of PFOs are either missed or misdiagnosed if one relies on a TEE alone. Likely explanations of this observation include poor patient compliance, individuals with different anatomies, operator experience, and patients' challenge of performing a Valsalva maneuver with a probe in the esophagus [38,39]. The diagnostic accuracy of TEE for the detection of PFO is summarized in Table 2.2.

Advantages and Limitations of Transesophageal Echocardiography for Detecting a PFO

The use of TEE for diagnosing a PFO carries a number of advantages including accurate documentation of the atrial septal anatomy, identifying an atrial septal aneurysm (Video 2.3), recognizing a Eustachian valve or Chiari network (Fig. 2.3, Videos 2.2a and b), distinguishing an ASD from a PFO, size measurement, and assessment of shunt severity by bubble study or color flow Doppler. However, the need for sedation may increase procedural risk, especially in patients with depressed ventricular function. Moreover, TEE is associated with a small risk of esophagus-related injury such as perforation and bleeding, particularly in patients with known esophageal pathology (varices, strictures, diverticula, cancer, and achalasia) [39]. The advantages and limitations of TEE for the detection of PFO are summarized in Table 2.3.

The diagnostic accuracy of TEE is acceptable when directly compared with autopsy, right heart catheterization, and/or PFO detection during surgery. TEE's superiority over other modalities is predominantly due to its ability to determine the anatomical structure of the PFO and rule out non-PFO-mediated right-to-left shunting. Following an initial noninvasive imaging modality for right-to-left shunt screening, TEE is an excellent confirmatory test for the detection and quantification of PFO-mediated shunting. Yet, it is important to note that the diagnosis of PFO by TEE alone may be misleading if there are only a few bubbles seen in the left atrium. If clinically indicated, a right heart catheterization may be required for a correct diagnosis [35–41].

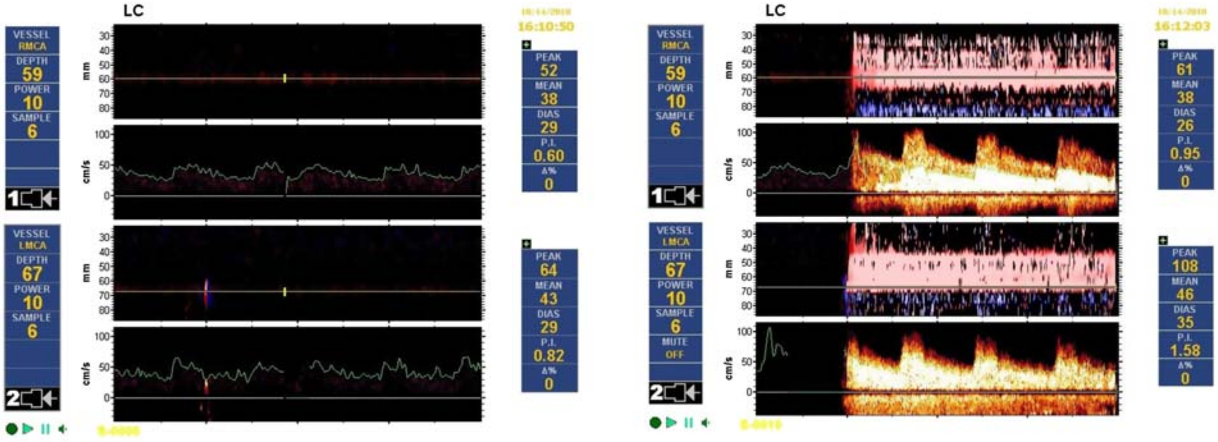
TRANSCRANIAL DOPPLER FOR THE DIAGNOSIS OF PFO

Unlike TEE and occasionally TTE that provide direct visualization of the atrial septum, a TCD bubble study is an alternative imaging modality for indirect PFO detection by assessing for the presence of a right-to-left shunt. Similar to TTE, agitated saline is intravenously injected and a right-to-left shunt is detected following release of the Valsalva maneuver. However, with TCD, insonation of the middle cerebral arteries following injection and a Valsalva measured with a manometer allows functional assessment of the right-to-left shunt (Fig. 2.5). The Spencer logarithmic scale can be used to quantify the degree of shunting, with shunt severity scored on a grading scale of 0–5 (0 being no shunt

FIGURE 2.5 Left: A patient is seen wearing a transcranial Doppler headset that has bilateral ultrasound probes mounted at the level of the temples, for insonation of the middle cerebral arteries. The patient is seen performing a Valsalva maneuver using visual feedback with the aid of a manometer. Right: A 3-way stopcock is used to prepare the agitated saline-blood mixture, which is intravenously injected immediately before release of the Valsalva maneuver.

TABLE 2.4 The Spencer Logarithmic Scale for Transcranial Doppler Grading.

Grade	Microbubbles	Interpretation
0	0	No shunt
1	1–10	Insignificant shunt
2	11–30	Insignificant shunt
3	31–100	Positive for shunt
4	101–300	Positive for shunt, moderate to large
5	>300	Positive for large shunt



Grade 1 Rest

Grade 5 Valsalva

FIGURE 2.6 Transcranial Doppler grading with microembolic signals that measure the degree of right-to-left shunting ranging from grade 1 (left) to grade 5 (right).

and 5 being large shunt) (Table 2.4). The TCD study is considered positive for a PFO if the score grade is 3 or more on the Spencer scale because this result corresponds to the presence of a PFO during heart catheterization. Smaller grades (grade 1 and 2) usually indicate clinically insignificant pulmonary shunts or pinhole septal defects (Fig. 2.6) [22,42].

Protocol for a Transcranial Doppler Bubble Study

1. An acoustic window (i.e., transtemporal, transorbital, or suboccipital) is identified and the TCD ultrasound probe is placed.
2. The agitated saline mixture is intravenously injected as the patient performs a Valsalva maneuver with the subject forcefully exhaling into a tube connected to a manometer to maintain the pressure at 40 mmHg for 10 seconds. The addition of 1 mL of blood increases the sensitivity of the study. A dedicated echocardiographic contrast medium is an alternative.
3. If a right-to-left shunt is present, the circulating microbubbles in the insonated artery can be visualized with M-mode Doppler; the shunt is quantified over a 1-minute period using the Spencer scale.
4. If the cerebral vessels cannot be identified, a carotid artery can be used but that is not validated.

Diagnostic Accuracy of Transcranial Doppler Bubble Study

A TCD bubble study is very sensitive for the detection of right-to-left shunting. Some studies reported a higher sensitivity of TCD than that of TEE, when PFO confirmation with a right heart catheterization (PFO probing with a guidewire under fluoroscopy) was used as the reference [22,42]. One large meta-analysis of 27 prospective studies (1968 patients) reported the TCD bubble study to have a sensitivity of 97% and specificity of 93% for the detection of intracardiac right-to-left shunt, when compared with TEE as the reference [12]. Modern TCD machines are equipped with power M-mode software, which increases microbubble signal detection and thereby enhances the accuracy of right-to-left shunt quantification. Spencer et al. compared TCD with and without power M-mode to TEE; they reported that power M-mode provides a higher sensitivity and accuracy for the detection of intracardiac right-to-left shunt when compared with older TCD models [42]. The diagnostic accuracy of TCD for the detection of intracardiac right-to-left shunt is summarized in Table 2.2.

Advantages and Limitations of Transcranial Doppler for Detecting a PFO

TCD carries a number of advantages, which make it a superior screening test for PFO; these include its high sensitivity, low cost, good safety profile, and tolerability. Given that TCD indirectly assesses for a shunt without anatomic imaging of the atrial septum, it is unable to distinguish between a PFO, ASD, or pulmonary shunt. This explains the lower specificity of TCD compared with TTE or TEE. The advantages and disadvantages of TCD for intracardiac right-to-left shunt detection are summarized in Table 2.3.

TCD is highly sensitive, affordable, and easily performed. These merits make TCD an excellent initial screening test to detect a PFO. A positive TCD carries the possibility of being a false-positive test for a PFO (albeit still a true positive for a right-to-left shunt), due to either the presence of an ASD or pulmonary shunt. A pulmonary arteriovenous malformation is only present in 1% of positive TCD studies (unless subjects with suspected hereditary hemorrhagic telangiectasia are studied). Therefore, 99% of positive TCD studies (grade 3 or higher) are due to the presence of an intracardiac right-to-left shunt (usually a PFO and sometimes an ASD). Since TCD employs indirect functional testing that does not visualize the atrial septum, a positive test usually requires a subsequent confirmatory test with TEE or intracardiac echocardiography (during percutaneous PFO device closure). However, given its very high sensitivity and negative predictable value, a negative TCD usually does not require further testing for an intracardiac shunt. When a patient has a compelling history compatible with a PFO but the TCD is negative, a TEE is unlikely to be diagnostic, but a right heart catheterization may reveal that a guidewire may pass across the atrial septum into the left atrium.

INTRACARDIAC ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF PFO

ICE is another imaging modality that is used for both direct anatomical visualization of the atrial septum and evaluation of right-to-left shunt severity [43]. Predominantly used during percutaneous PFO closure, ICE has emerged as a helpful invasive imaging modality for guidance of occluder devices during deployment and assessment of residual shunting post-PFO closure. With ICE, a PFO is seen in a horizontal view of the septum posterior to the aortic bulge. ICE is useful for visualizing the inferior vena cava rim and the inferior aspect of the interatrial septum, which may be more difficult to assess with TEE [44]. A number of advantages make ICE a useful imaging tool during PFO closure procedures; these include detailed visualization of the atrial septal anatomy, guidance during device deployment, residual shunt assessment post-PFO closure, performance without general anesthesia, and the interventionalist's ability to control the ICE probe during the procedure without the need for another specialist (Fig. 2.7). Disadvantages of ICE include need for a second venous access, procedural cost, increased risk of vascular access-related complications, and possible limitations by operator inexperience [45].

In one study, Van et al. found that compared with TCD, ICE had a similar detection rate for preclosure right-to-left shunting. However, after closure, ICE failed to detect 34% of residual shunts detected by TCD [46]. This can be explained by the monoplane nature of ICE or the lower resultant image yield due to the presence of an occluder device between the probe and contrast microbubbles.

ANGIOGRAPHIC ASSESSMENT OF PFO AND ITS CHARACTERISTICS

The advantage of angiographic PFO screening and characterization (Fig. 2.2) is that it allows simultaneous closure and is less uncomfortable for the patient than TEE but equally sensitive and more specific, although it has never been validated in these respects. The details are discussed in Chapter 16.

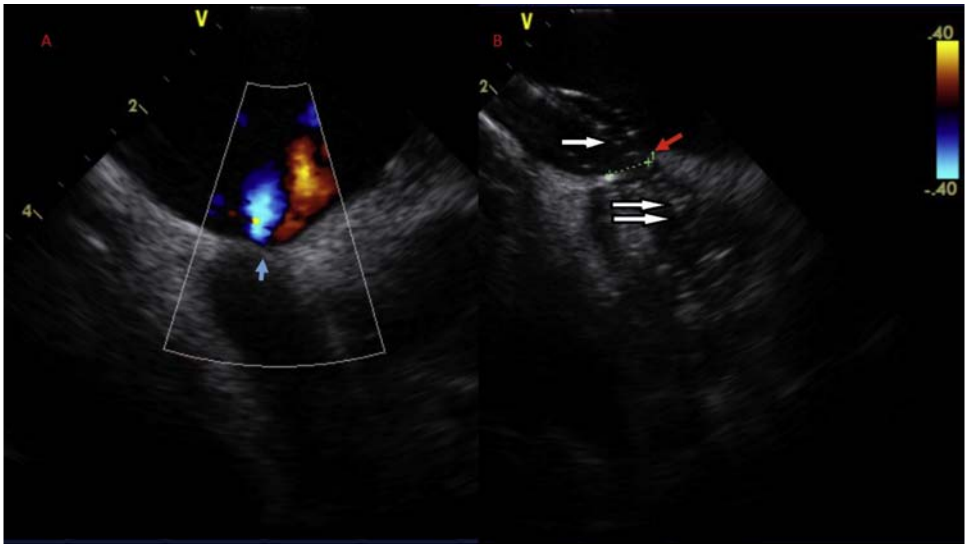


FIGURE 2.7 (A) Intracardiac echocardiography showing the presence of Doppler color flow across the PFO (*blue arrow*) and (B) the use of intracardiac echocardiography intraprocedurally for adequate balloon sizing of a PFO (*red arrow*) to determine the optimal septal occluder device size that should be used. The white arrow indicates the inflated balloon in the right atrium (*single arrow*) and left atrium (*double arrow*).

EAR OXIMETRY FOR THE DIAGNOSIS OF PFO

Indirect assessment for a right-to-left shunt with the ear oximetry method was first reported over 50 years ago but still lacks clinical validation. In 1959, Lüthy et al. described temporary arterial oxygen desaturation obtained from the earlobe in individuals with various congenital heart defects, including those who had a right-to-left shunt [47]. Since then, several other studies have reported transient arterial desaturation measured by ear oximetry after release of the Valsalva maneuver, among patients with a PFO. Karttunen et al. evaluated the accuracy of ear oximetry for detecting a PFO compared with TEE as the reference; among 83 included patients, they reported a sensitivity of 85% and specificity of 100% [48]. It should be noted that this study was performed in a small cohort of cryptogenic stroke patients with a high pretest probability for a PFO. Although the ear oximetry method is safe, easily performed, and cost-effective, other larger observational studies have not been able to reproduce a high diagnostic accuracy for PFO detection using ear oximetry alone [49].

CARDIAC COMPUTED TOMOGRAPHY FOR THE DIAGNOSIS OF PFO

The use of CT for cardiac imaging has increased in recent years, with a number of studies investigating the potential use of cardiac CT for the detection of PFO. Although echocardiographic imaging relies on documenting right-to-left shunting with a provocation maneuver, cardiac CT has been used to diagnose a PFO by documenting the appearance of contrast in the left atrium during the resting state [50,51]. Kim et al. found that compared with TEE as the reference, cardiac CT had a low sensitivity of 73% and a specificity of 98%, making the test an inferior screening modality for PFO, hindering its routine use in clinical practice [50]. Another observational study compared cardiac CT to TTE for the detection of PFO; the authors reported cardiac CT to have a sensitivity and specificity of 53% and 75%, respectively. When PFO was detected, CT provided enhanced imaging of the interatrial septum and better detection of other septal variations such as an atrial septal aneurysm [51]. The use of cardiac CT is not currently considered an adequate imaging modality for the identification or quantification of PFO-mediated right-to-left shunting.

MAGNETIC RESONANCE IMAGING FOR THE DIAGNOSIS OF PFO

Recent radiological advancements have made MRI a crucial diagnostic tool for various cardiac pathologies, with many applications currently under review. However, cardiac MRI is less frequently used to detect a PFO, given its low sensitivity compared with TEE. The low diagnostic yield of MRI for a PFO may be due to lack of continuous and prolonged images that are needed to make the diagnosis (which renders provocation maneuvers impossible), considering that PFO-mediated right-to-left shunting generally occurs only transiently [52]. Moreover, imaging artifacts from occluder devices make cardiac MRI an inadequate test for residual shunt assessment post-PFO closure [53,54].

CONCLUSIONS AND RECOMMENDATIONS

Compared with other imaging modalities, a TCD bubble study has the highest sensitivity for the detection of PFO-mediated right-to-left shunting, making it an excellent initial screening test. In institutions where TCD is unavailable, an initial TTE bubble study with harmonic imaging mode should be utilized for PFO screening. Before percutaneous PFO closure, a TEE bubble study can provide additional information on the atrial septal anatomy. For patients who do not tolerate a TEE or those with contraindications, angiographic contrast medium injections or ICE can be used instead during percutaneous PFO closure. During cardiac catheterization, a right heart catheterization, with angiography or visualization of a guidewire crossing the atrial septum under fluoroscopy, remains an accurate invasive method to document a PFO; it features the option of ad hoc device closure without prior imaging. Cardiac CT and MRI should not be utilized for routine detection of PFO given their low sensitivity and high cost when compared with other available imaging alternatives [55].

SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online at https://doi.org/10.1016/B978-0-12-816966-7.00002-6.

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