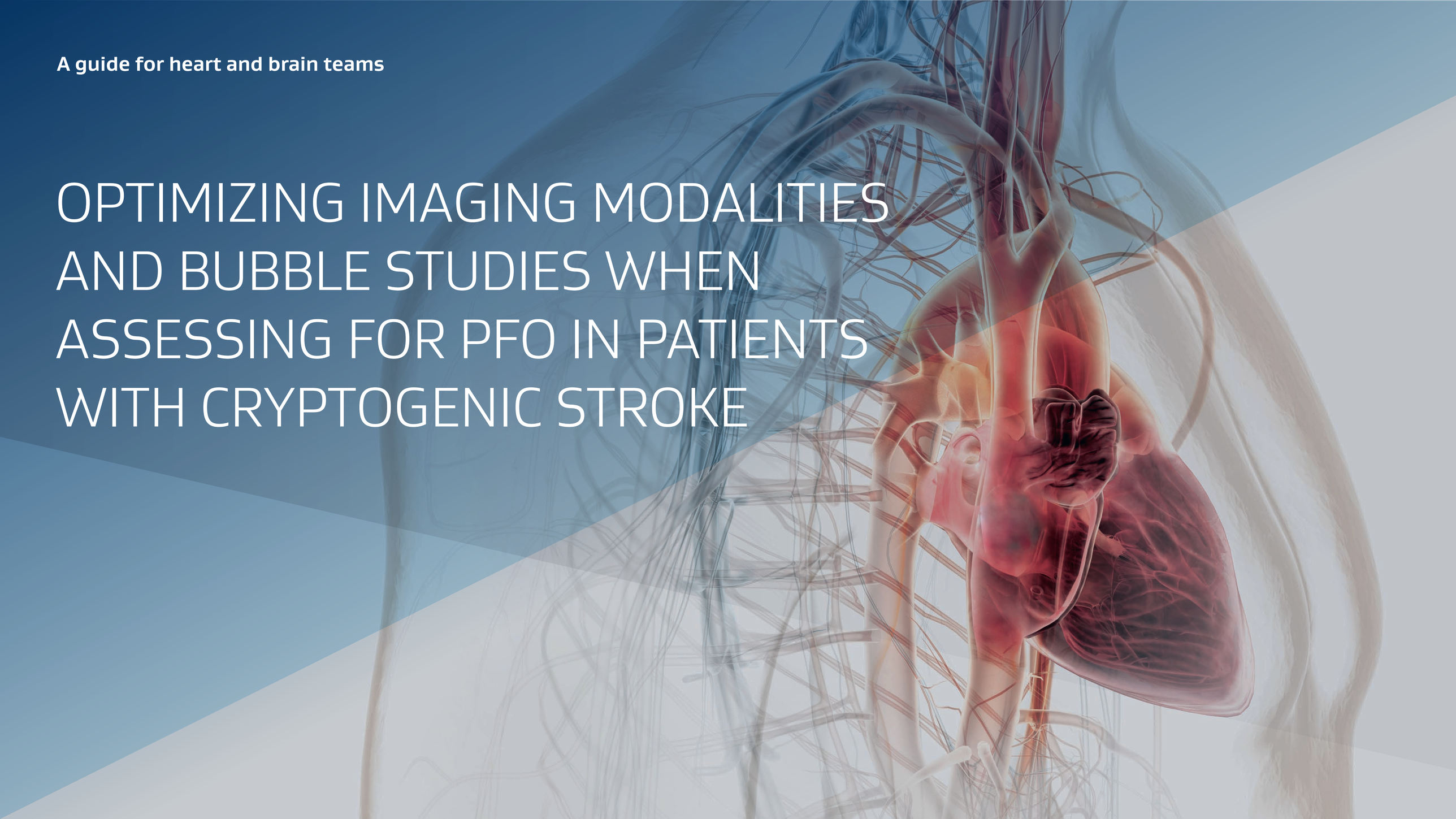
A guide for heart and brain teams

# OPTIMIZING IMAGING MODALITIES AND BUBBLE STUDIES WHEN ASSESSING FOR PFO IN PATIENTS WITH CRYPTOGENIC STROKE



# Guidelines on PFO detection

## American Academy of Neurology (AAN)[1]

TTE

**1**

**Transthoracic echocardiography**

TEE

**2**

*If high-risk stroke mechanism remains unidentified:*

**Transesophageal echocardiography**

## AAN guidelines

> *In patients being considered for PFO closure, clinicians should assess for cardioembolic sources using TTE followed by TEE assessment if the first study does not identify a high-risk stroke mechanism. Studies should use bubble contrast, with and without Valsalva maneuver, to assess for right-to-left shunt and determine degree of shunting.*

– Statement 1f[1]

> *. . .clinicians may use TCD agitated saline contrast as a screening evaluation for right-to-left shunt, but this does not obviate the need for TTE and TEE to rule out alternate mechanisms of cardio embolism and confirm that right-to-left shunting is intracardiac and transseptal.*

– Statement 1h[1]

**Glossary of terms:** Computed tomography (CT); Embolic stroke of undetermined source (ESUS); Magnetic resonance imaging (MRI); Patent foramen ovale (PFO); Transcranial Doppler (TCD); Transesophageal echocardiography (TEE); Transient ischemic attack (TIA); Transthoracic echocardiogram (TTE).

# American Heart Association/American Stroke Association (AHA/ASA)[2]

TTE → TEE → TCD

**1**

**TTE with or without contrast**

**2**

*In patients with ESUS:*

**TEE, cardiac CT or cardiac MRI**

**3**

*In patients with ischemic stroke or TIA considered for PFO closure:*

**TCD**

## AHA/ASA guidelines

> *In patients with cryptogenic stroke, echocardiography with or without contrast is reasonable to evaluate for possible cardiac sources of or transcardiac pathways for cerebral embolism.*
>
> – Guideline 3.6[2]

> *In patients with ESUS, transesophageal echocardiogram (TEE), cardiac CT or cardiac MRI might be reasonable to identify possible cardioaortic sources of or transcardiac pathways for cerebral embolism.*
>
> – Guideline 3.13[2]

> *In patients with ischemic stroke or TIA in whom patent foramen ovale (PFO) closure would be contemplated, TCD (transcranial Doppler) with embolus detection might be reasonable to screen for right-to-left shunt.*
>
> – Guideline 3.14[2]

**Glossary of terms:** Computed tomography (CT); Embolic stroke of undetermined source (ESUS); Magnetic resonance imaging (MRI); Patent foramen ovale (PFO); Transcranial Doppler (TCD); Transesophageal echocardiography (TEE); Transient ischemic attack (TIA); Transthoracic echocardiogram (TTE).

# Choosing a modality: **BASICS**

## Transthoracic echocardiography

- Transthoracic echocardiography (TTE) is a non-invasive, highly available preliminary testing modality for assessing left ventricular function and screening for valvular disease.[3]
- TTE is the primary front-line diagnostic for PFO and should be accompanied by a high-quality bubble study if possible.[4,5]
- TTE uses:
  - Color Doppler with appropriate Nyquist shift to show shunt: low for interatrial septal shunts and large ventricular septal defects (VSDs) and high for small VSDs[6]
  - Off-axis/nonstandard views[6]
  - Agitated saline contrast study (as appropriate)[6]

TTE's low sensitivity may result in a false negative.[7] Confirming a negative TTE result with a secondary, more sensitive testing modality is recommended.[1]

## Transesophageal echocardiography

- Transesophageal echocardiography (TEE) is a more sensitive and invasive test than TTE that allows a morphological characterization of interatrial septum and atrial structures, evaluation of the ascending aorta and a look at anatomical details of the PFO indicated for intervention.[8,9]
- TEE can be the initial or secondary study when assessing for PFO in patients with cryptogenic stroke and can be used to check for a false negative following a TTE result that is  negative or nondiagnostic for PFO.[6]
- TEE uses:
  - Color Doppler with appropriate Nyquist shift to show shunt: low for interatrial septal shunts and large VSDs and high for small VSDs[6]
  - Agitated saline contrast study (as appropriate)[6]

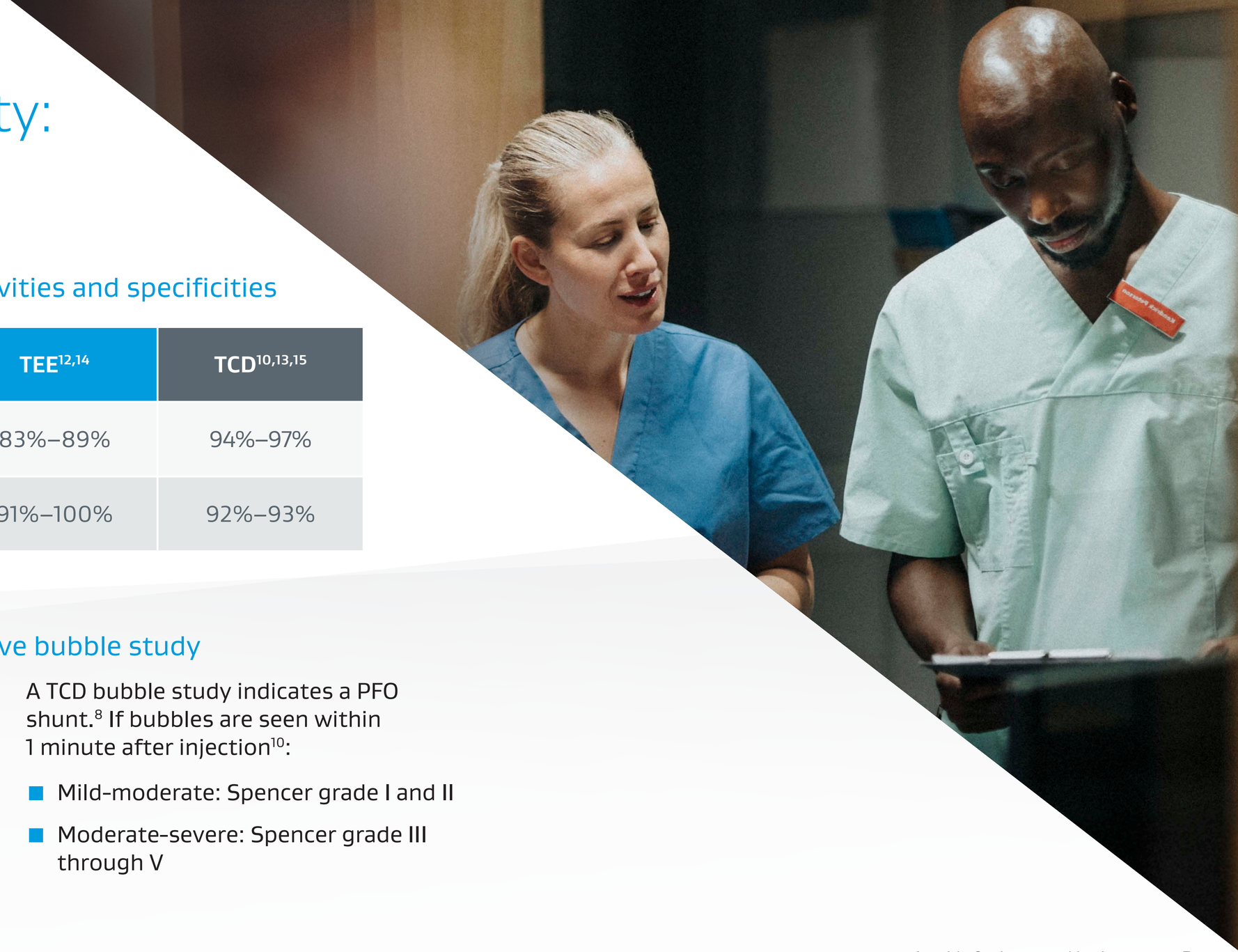
TEE is not possible in some patients, including those with previous esophageal surgery, dysphagia, musculoskeletal neck problems or esophageal varices.[8]

## Transcranial Doppler ultrasonography

- Transcranial Doppler (TCD) is a highly sensitive test for diagnosing right-to-left shunts at rest and after a Valsalva maneuver.[8]
- TCD visualizes contrast microbubbles in the acoustic windows (i.e., transtemporal, transorbital or suboccipital) using intravenously injected agitated saline.[10]

TCD should be paired with TTE or TEE for anatomical confirmation of the PFO.[1,10]

# Choosing a modality: SPECIFICS



## Comparing imaging modality sensitivities and specificities

| | TTE[5,10,11-13] | TEE[12,14] | TCD[10,13,15] |
|---|---|---|---|
| **Sensitivity** | 44%–88% | 83%–89% | 94%–97% |
| **Specificity** | 92%–99% | 91%–100% | 92%–93% |

## Identifying shunt severity in a positive bubble study

TTE and TEE bubble studies indicate a PFO shunt.[8] If bubbles are seen within the first 3 cardiac cycles of contrast entering the left atrium:

- Trace: ≤ 5 bubbles
- Moderate: 6–20 bubbles
- Severe: > 20 bubbles

A TCD bubble study indicates a PFO shunt.[8] If bubbles are seen within 1 minute after injection[10]:

- Mild-moderate: Spencer grade I and II
- Moderate-severe: Spencer grade III through V

# Choosing a modality:

## ADVANTAGES[8-10,16]

### TTE

- Non-invasive or minimally invasive
- More tolerable for severe stroke patients
- More readily available
- Quicker to perform
- Allows better and simpler Valsalva maneuver performance, in most cases with agitated saline contrast

### TEE

- Considered the gold standard for visualizing the foramen ovale and its associated anatomy
- Generally more sensitive than TTE
- Can be as sensitive as TCD for bubble detection with the proper Valsalva maneuver
- Better demonstrates the anatomic features of PFO than TTE

### TCD

- Minimally invasive
- High sensitivity for definitively identifying right-to-left shunting
- Best for quantifying bubbles
- Can determine shunt magnitude
- More accurately predicts shunt size

## DISADVANTAGES[8-10,16]

### TTE

- Can be limited by a patient's body habitus, other technical factors or noncompliance
- Limited anatomic assessment of the patient's intra-atrial septum
- Less sensitive for diagnosing PFOs
- Cannot resolve the nature of a septal defect
- Variable quality, consistency and competency

### TEE

- More invasive
- May require general anesthesia
- May be harder for sedated patients to perform the Valsalva maneuver
- Can result in local pharyngeal and esophageal trauma
- Requires a dedicated physician operator
- May not be appropriate for all patients

### TCD

- No anatomical visualization to confirm the type of shunt
- May not be readily available due to unique equipment needs and technician skillset requirements
- May be less clinically useful for some patient anatomies
- Highly operator dependent

# Performing bubble studies[17-21]

The American Society of Echocardiography (ASE) has a standardized protocol for performing bubble studies when assessing for PFOs.[17-19] Adhere to current guidelines and protocols specific to your institution or region for the most accurate and up-to-date procedures.

## 1 Prepare the patient

- Explain to the patient the purpose of the procedure and what to expect.
- Coach the patient through practice for performing the Valsalva maneuver with abdominal pressing if needed.
- Position the patient appropriately for the imaging modality being used to help concentrated bubbles rise and collect in the right atrium.
- Work bubble study timing into your diagnostic workflow as soon as possible.

## 2 Set up the equipment and agitate the saline solution

- Use a high-quality echocardiography machine that is capable of both 2D and Doppler imaging.
- Prepare an agitated saline solution (saline may be mixed with or without blood, and with a small amount of air or $CO_2$).

**Agitate the saline solution aggressively to maximize microbubbles (contrast bubbles)**

See the source

## 3 Take baseline imaging

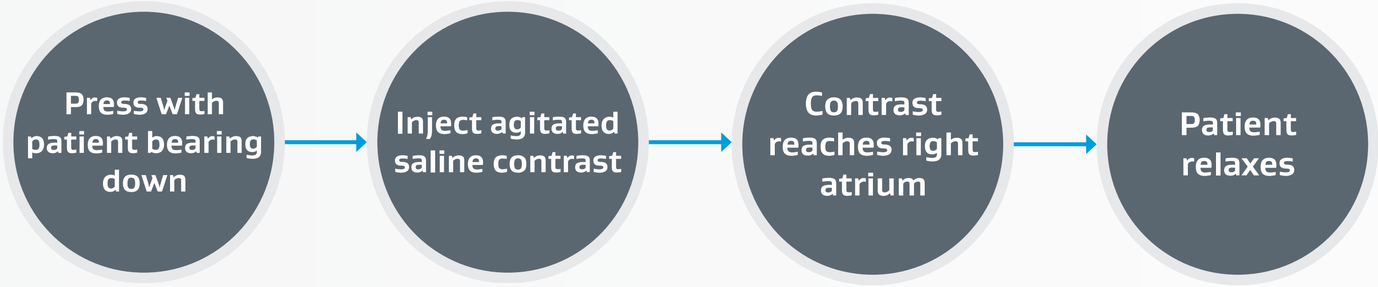
- Evaluate cardiac structure and function through a comprehensive echocardiographic examination and assess for any other abnormalities.

## 4 Inject agitated saline

- Intravenously administer the agitated saline with microbubbles and proceed directly to the next step.

  Note: Do the agitated bubble study toward the end of TEE, when the patient is less sedated. For the patient to perform the Valsalva maneuver during TEE, ask them to cough several times.

**When and how to inject agitated saline when imaging with the Valsalva maneuver**




Inject the saline solution while the patient bears down for 5–10 seconds. **Press on the patient's abdomen and ask them to use their abdominal muscles to push against your hand.** Once contrast enters the right atrium, the patient can relax. Acceptably performed Valsalva will cause the interatrial septum to shift to the left.

## 5 Acquire images

- Begin capturing imaging prior to injecting the agitated saline.
- Visualize the right atrium, right ventricle, interatrial septum and left atrium using both TTE and TEE, if necessary.
- If the first injection of agitated saline results in a positive shunt, no further imaging is necessary. If the first injection is negative, repeat with the patient performing Valsalva.

## 6 Detect bubbles

- Monitor for microbubbles crossing from the patient's right atrium to the left atrium through the interatrial septum.

**Avoid a false negative:** 4 steps to rule out a PFO[21]

**Step 1** **Confirm dense opacification:** The agitated saline must be prepared correctly and administered as to densely opacify the right heart.

**Step 2** **Confirm interatrial septum shift:** Correct use of the Valsalva maneuver will ensure the interatrial septum shifts visibly from right to left.

**Step 3** **Confirm the absence of bubbles in the left atrium:** No bubbles in the left atrium appearing within 1–3 cardiac cycles usually indicates there is no PFO.

**Step 4** **Observe late bubbles:** Bubbles appearing in the left atrium after 3 cardiac cycles usually rules out a PFO in favor of a pulmonary arteriovenous malformation. Bubbles appearing in the left atrium after 5 cycles suggests transpulmonary shunting.

Reminder: Per the guidelines, inconclusive studies should be considered for additional follow-up imaging.

## 7 Interpret

- Assess findings carefully. Determine if there is evidence of a right-to-left shunt, which suggests a PFO.
- When interpreting, consider commenting on:
  - Whether a shunt is detected
  - The timing of the bubbles' appearance in the left atrium
  - Any high-risk anatomy detected

Criteria for a positive bubble study typically include:

- The presence of microbubbles in the left atrium within 3–5 cardiac cycles after appearing in the right atrium
  - Other possible non-PFO anatomical shunts indicated by late bubbles after 5 cardiac cycles
- A large number of bubbles, usually over 20, appearing within a single cardiac cycle, which highly suggests a significant shunt

## 8 Document

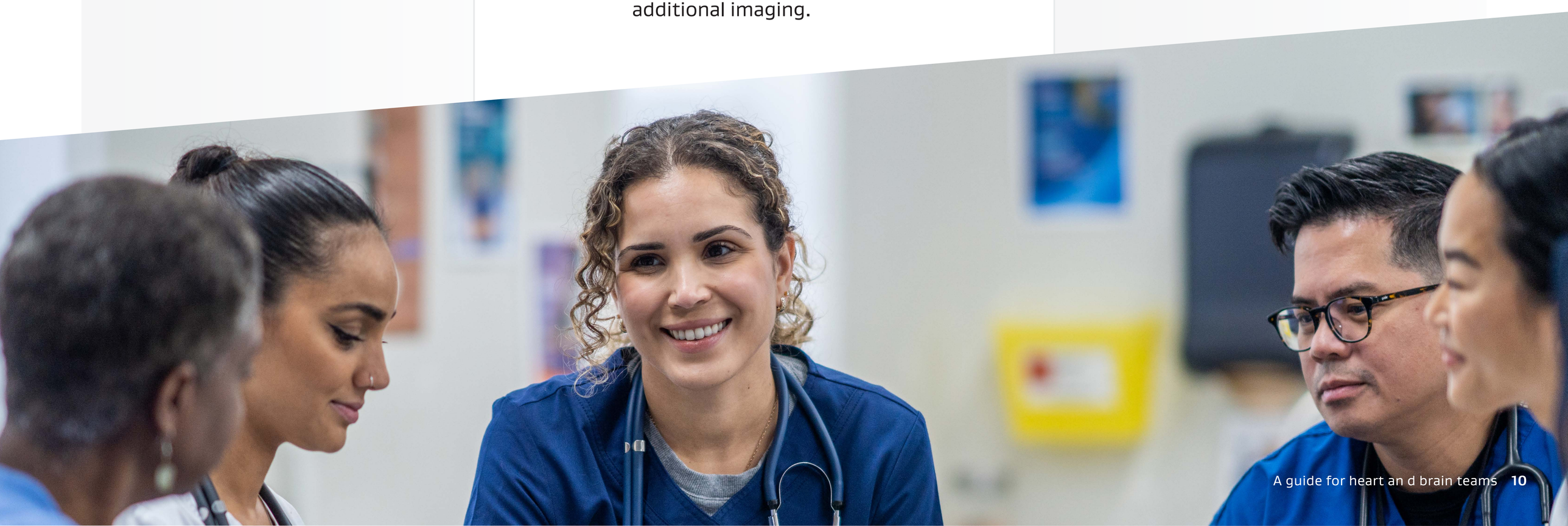
- Record and document findings clearly.

## 9 Follow up with the interpreting and patient physician

- Discuss the results with the interpreting physician, who will integrate these findings with clinical history and other diagnostic tests to determine their significance and next steps when consulting with the patient's physician.
- Inconclusive bubble studies may require additional imaging.

## 10 Continue ongoing patient care

- Monitor the patient for any adverse effects related to the procedure (though complications are rare).



# Additional resources for performing bubble studies

## TCD bubble study fundamentals

A short technical manual on bubble studies from David Goldemund, M.D., including quantifying bubbles or “HITS.”[22]

## A comparison of methods to detect and quantitate PFO: TCD, TTE, ICE, and TEE *(Patent Foramen Ovale)*

A comparison of imaging methods for PFO; also addresses intracardiac echocardiography.[23]

## Valsalva and how to optimize its use during bubble studies

Information on optimizing the Valsalva maneuver including mechanism of action, timing and exceptions.[21]

## Superiority of the combination of blood and agitated saline for routine contrast enhancement *(Journal of the American Society of Echocardiography)*

A comparison of opacification of the right atrium and ventricle in echocardiography using agitated saline with and without blood.[24]

## Ways to improve echo bubble studies

Ahmed Mohamed Fareed Ali, M.D., and Alexander Nossikoff, M.D., provide 6 bubble study optimization suggestions.[25]

## A critical review of patent foramen ovale detection using saline contrast echocardiography: when bubbles lie *(Journal of the American Society of Echocardiography)*

Timothy D. Woods, M.D., and Ashvin Patel, M.D., analyze false positive and negative saline contrast bubble studies.[26]

### Effect of body positioning during transcranial Doppler detection of right-to-left shunts *(European Journal of Neurology)*

An evaluation of the effects of varied patient body positions during agitated saline injection on shunt detection and grading.[27]

### Patent foramen ovale: anatomical complexity and long-tunnel morphology-related issues *(American Journal of Cardiovascular Disease)*

A look at anatomical issues that can lead to difficulty when performing PFO closure.[29]

### Femoral vein delivery of contrast medium enhances transthoracic echocardiographic detection of patent foramen ovale *(Journal of the American College of Cardiology)*

A study demonstrating how femoral vein contrast delivery enhances PFO diagnosis.[28]

### Techniques for identifying a patent foramen ovale: transthoracic echocardiography, transesophageal echocardiography, transcranial Doppler, right heart catheterization *(Cardiology Clinics)*

A look at the advantages and limitations of each diagnostic option.[10]

The information provided is intended to be general guidance based on current medical practices in the field. The steps described here may not be complete, and are not intended to be a replacement for the *Instructions for Use* (IFU) or the education, training and professional judgment of health care providers (HCP). Licensed HCP remain responsible for making decisions about patient care and the use of medical technologies.

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**W. L. Gore & Associates, Inc.**
goremedical.com

**Asia Pacific** +65 67332882 **Australia/New Zealand** 1800 680 424 **Europe** 00800 6334 4673
**United States** Flagstaff, AZ 86004 800 437 8181 928 779 2771