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RE STATE-OF-THE-ART PAPERS

Echocardiographic Evaluation of Patent Foramen Ovale Prior to Device Closure

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High-quality imaging of the atrial septum has never been so relevant to the adult cardiologist. This article focuses on the role of echocardiography in the evaluation of patent foramen ovale for closure. It provides a systematic and comprehensive approach to transesophageal echocardiographic study in such a patient. The salient information required for planning the device and equipment needed for the closure procedure are discussed. (J Am Coll Cardiol Img 2010;3:749–60) © 2010 by the American College of Cardiology Foundation

Patent foramen ovale (PFO) has been linked to several clinical syndromes including cryptogenic stroke in the young (1), decompression sickness in divers (2), and migraine with aura (3). PFO is common, occurring in 20.2% to 34.4% of autopsies depending on age (4).

The management of PFO remains controversial (1,5-7), and although not yet approved by the U.S. Food and Drug Administration, transcatheter approach to PFO closure continues to develop. Potential complications include device embolization, thrombus formation, atrial arrhythmias, residual shunting, and device erosion or perforation (8-11). A careful assessment of the anatomy of the atrial septum is necessary to reduce such risks. This article focuses on the role of echocardiography in the evaluation of PFO for transcatheter closure. It provides an easy to understand account of the development and functional anatomy of the atrial septum and provides the reader with a systematic and comprehensive approach to transesophageal echocardiographic (TEE) study in such a patient (Fig. 1). The salient information required for planning the device and equipment needed for the closure procedure are discussed.

Embryology of the Atrial Septum

In order to understand the principles of the detailed imaging performed by TEE in the assessment of a PFO for device closure, we should be clear on our understanding of the anatomy. To appreciate the functional anatomy, we need first to revise our embryology (12).

In embryonic life, the primitive atrium is a single cavity. A solid crest of tissue grows down from the roof of the atrium. This is the primary septum (gray area, Fig. 2A). It grows downward toward the developing inferior and superior endocardial cushions (pink area), which themselves are dividing the atrioventricular canal. This area between the leading edge of the developing primary septum and endocardial

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cushions is known as the primary foramen (ostium primum). The primary septum carries a prominent cap of mesenchymal tissue at its leading edge that eventually fuses with the superior endocardial cushion. Along the right side, a second protrusion of mesenchymal tissue known as the vestibular spine grows toward, and eventually fuses with, the inferior endocardial cushion (13). The primary foramen becomes smaller in size as the septum grows closer toward the endocardial cushions. They eventually fuse so that the foramen disappears.

Prior to the sealing of the primary foramen, multiple small perforations begin to develop at the superior aspect of the primary septum, near its point of original growth from the atrial roof (Fig. 2B). These perforations coalesce to form the secondary communication between the developing atria known as the secondary foramen (ostium

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional 3D = 3-dimensional CS = coronary sinus FO = fossa ovalis IVC = inferior vena cava PFO = patent foramen ovale RLS = right-to-left shunt SVC = superior vena cava TEE = transesophageal echocardiogram TTE = transthoracic echocardiogram secundum). This communication allows right-to-left shunting of oxygenated blood (bypassing the dormant pulmonary circulation) during the remainder of embryonic life.

In the 12th week, the atrial roof begins to fold inward (Fig. 2C). This *infolding of tissue* grows down along the right side of the primary septum and is known as the secondary septum or "septum secundum" (yellow area). It comes to lie over the secondary foramen. This "deep groove" of infolded tissue covers the right atrial side of the septum except for an area inferiorly. Through this deficiency, the primary septum is visible (Fig. 2D). Hence a flaplike valve (PFO) is formed between the 2 atria,

where the infolded secondary atrial septum forms a support against which the primary septum can press against and fuse after birth. This region where the primary atrial septum is exposed on the right atrial side is the fossa ovalis (FO).

Clinical Relevance of Anatomical Considerations

Figure 3 is a 3-dimensional (3D) TEE enface view of the right atrial aspect of the atrial septum and represents the right anterior oblique view of the atrial septum on fluoroscopy. The relevant structures are labeled. The FO does not lie exactly in the middle of the atrial septum but instead is displaced a little inferoposteriorly. Inferior to the FO is the inferior vena cava (IVC) and inferoanteriorly, the coronary sinus (CS). The superior vena cava (SVC) enters from above along the posterior aspect of the atrial septum. The tricuspid valve lies anteriorly. The aortic valve and root lie centrally in the heart, wedged between the 2 atria and resting on the atrial septum. Thus the anterosuperior border of the FO is related to the aortic root.

Anatomically, approaching from the right atrium, there are 3 elements essential to understanding the issues with device placement and transseptal puncture (14):

- 1. A significant proportion of the atrial septum is composed of infolded tissue. Interatrial passage through this infolding, that is, through the secondary septum, will take you outside the heart. This may cause a pericardial effusion with resultant tamponade. A transseptal puncture can be safely performed through the FO. This region is referred to as the true atrial septum (i.e., primary septum) as a puncture through here will take you directly into the left atrium.
- 2. There is a complex anatomical relationship between the FO and the structures adjacent to it that needs to be understood. The atrial septal tissue between each structure and the FO is called a "rim," of which there are 5 on the right atrial side (SVC rim, aortic rim, IVC rim, CS rim, tricuspid valve rim) and 2 on the left atrial side (mitral valve rim, right upper pulmonary vein rim) (Figs. 3 to 5).
- 3. The aortic root abuts the atrial septum and as a result the pericardium is reflected here as infolding. This is called the transverse sinus. Perforation of the atrial septum at this level may, therefore, cause a pericardial effusion or even perforation of the aortic root. The atrial septum has natural crevices (small indentations) that are often found in this region. It is important to be aware of these crevices with a "difficult to cross" PFO, because guidewire advancement into these indentations risks atrial perforation and tamponade.

The left atrial side of the septum is made up predominately of the primary septum, other than superiorly, where the remnant of the secondary foramen lies. Here, this deficiency in the primary septum is covered by the infolded secondary septum. This is where the PFO tract appears on the left atrial side (Fig. 6). Thus it exits into the superior and anterior part of the left atrium. If a device is placed through a PFO, then it has a tendency to lie high on the atrial septum. The left atrial wall in this region is only a few millimeters



thick and, therefore, care needs to be taken in manipulating devices within the left atrium.

Detection of a Right to Left Shunt Through a PFO

Several echocardiographic techniques can be utilized in the detection of a PFO shunt, including transthoracic echocardiogram (TTE), TEE, and transcranial Doppler ultrasonography (15). Because of its superior image resolution and ability to differentiate the location of shunting, TEE is most commonly used for PFO diagnosis. However, TEE is usually preceded by TTE. In our practice, when a patient is referred for echocardiography following an ischemic stroke, there are 3 possible stages to the assessment: 1) standard TTE; 2) transthoracic contrast echocardiogram; and 3) TEE.

Hierarchy of assessment. STANDARD TTE. This is undertaken to look for cardiac sources of embolism (16), because approximately 20% of ischemic strokes are of cardiac origin (17,18). Positive echocardiographic findings would include intracardiac masses, mural thrombus, and valvular pathology such as mitral stenosis.

TRANSTHORACIC CONTRAST ECHOCARDIO-GRAM. If the standard study reveals a structurally normal heart, the next step is to assess for the presence of a PFO, which may raise the possibility of paradoxical embolus. This is particularly relevant to the younger patient in the absence of other stroke risk factors. A transthoracic contrast study can be used for diagnosing a right-to-left shunt (RLS) and sensitivity is greater with harmonic, sensitivity range 63% to 100%, rather than fundamental imaging, range 97% to 100% (19). TTE allows the ability to perform a full range of provocative maneuvers to disclose a transient RLS; such provocative maneuvers significantly increase the sensitivity of TTE (19) and TEE (19) in diagnosis of RLS. Transcranial Doppler has been shown to have similar sensitivity in the detection of RLS (transcranial Doppler vs. harmonic TTE, 68% to 100% vs. 63% to 100%, respectively) (20) but fails to differentiate between cardiac versus pulmonary shunting (specificity 65% to 100% vs. 97% to 100%, respectively) (20,21).

Performing a contrast study. The best echocardiographic window allows the right heart to lie to the left of the screen, usually the apical 4-chamber view. This minimizes acoustic shadowing that will be cast behind the contrast.

A PFO is a "flap valve" that may only open at times in the cardiac cycle when the usual pressure relationship between the atria is reversed. There-



Figure 2. Development of the Atrial Septum

The primitive atrium is a single cavity. A solid crest of tissue grows down from the roof of the atrium, the primary septum (gray) (A), toward the developing inferior and superior endocardial cushions (pink). The primary foramen, the area between the leading edge of the developing primary septum and endocardial cushions, becomes smaller in size as the septum grows closer toward the endocardial cushions. They eventually fuse so that the foramen disappears. Multiple small perforations begin to develop at the superior aspect of the primary septum to form the secondary communication between the developing atria known as the secondary foramen (ostium secundum) (B). The atrial roof begins to fold inward (C) and grows down along the right side of the primary septum and is known as the secondary septum or "septum secundum" (yellow). It comes to lie over the serondary driatial septum is exposed on the right atrial side is the forsa ovalis. Hence a flaplike valve (patent foramen ovale [PFO]) is formed between the 2 atria.

fore, maneuvers may be necessary such as the Valsalva, on release of which, right atrial pressure exceeds left atrial pressure. The patient is asked to stop breathing in mid respiratory cycle, close their mouth and nose, and "bear down" or "strain." The right heart should shrink in size, as venous return falls. Contrast is injected (approximately 10 to 20 ml of solution [20]). As contrast enters the right heart, the patient is asked to release the strain. It is ideal to see the atrial septum bow into the left atrium as the Valsalva is released (confirms momentary increase in right atrial pressure above left atrial pressure). The study may be repeated several times until satisfied that an adequate reversal of atrial pressures has been achieved.

If Valsalva maneuvers have been negative, or incompletely performed, repeat contrast injections can be made with different provocation. A sharp sniff or cough lifts the diaphragm suddenly upward, imparting a surge to venous return that may open the PFO.

Diagnosing the Presence of RLS

The timing of bubble appearance in the left heart is crucial in making the correct diagnosis and differentiating intracardiac and transpulmonary shunts. If shunting is occurring at the cardiac level, then contrast appears in the left heart usually within 3 cardiac cycles of the contrast entering the right heart (19,21). In the presence of a particularly large pulmonary shunt, contrast may appear in the left heart within 3 cardiac cycles, and further detailed imaging (i.e., TEE) to clarify shunt location may be necessary (22).

Shunt grading. There is no single widely accepted grading scheme for assessing the degree of left-to-right shunt from a PFO. Definitions in existence tend to focus on numbers of bubbles seen in a single still frame in the left atrium. The protocol we use for shunt grading incorporates 4 grades: grade 1: <5 bubbles; grade 2: 5 to 25 bubbles; grade 3: >25 bubbles; and grade 4: opacification of chamber.

TRANSESOPHAGEAL ECHOCARDIOGRAM. There are a number of reasons to progress to TEE. These include:

- If the contrast study is negative but the index of suspicion for possible cardiac embolism is high. Under these circumstances, a TEE will be useful to assess the presence of left atrial appendage thrombus, spontaneous echo contrast, aortic atheroma, cardiac masses, and vegetations that may have been missed by transthoracic imaging. Assessment of the atrial septum anatomy should be included in the study.
- If the transthoracic images are inadequate to declare the contrast test negative.
- If the contrast study is positive for a RLS, a TEE is required to define the anatomy of the atrial septum, assess its suitability for device closure, and ideally to confirm that the shunt is due to a PFO rather than a pulmonary shunt or other defects of the atrial septum.

Figure 1 shows a schema for the role of echocardiography in these patients. Once the diagnosis of a RLS is made by the TTE, the next step is to define the anatomy of the atrial septum and assess suitability for device closure. With the information obtained, the type and size of the device to be used and the type of imaging required during the proce-

dure can be planned, but not stipulated, before the procedure. Additional procedural information from balloon assessment of the PFO may alter these plans. If the PFO is a "simple" defect (without an aneurysmal atrial septum), with an apparent short tunnel, device closure under fluoroscopy with contrast media alone may be preferred as this will obviate the need for general anesthesia (23). If the defect is "complex," for example with a long apparent tunnel or an exuberant aneurysm, then intracardiac echocardiography or TEE periprocedure will be required to ensure a safe and successful procedure.

Transesophageal Echocardiography

Imaging the atrial septum. Detailed assessment of the atrial septum is performed with TEE. The objective is to mentally reconstruct the atrial septum in 3D so as to be able to describe the morphology of the PFO and the location, number, and size of concomitant defects, the integrity of the remaining atrial septum and the presence of anatomical structures that may interfere with device placement.

TEE protocol. The same principles apply to imaging the atrial septum whether it is assessment of a PFO or a secundum defect for device closure. The probe positioning and angle of degrees are given as a guide, because this may vary depending on the orientation of the heart within the chest. The study begins with a scout of the entire atrial septum in the transverse plane, 0°. Any defects seen are then confirmed and their position and morphology further elucidated in the longitudinal plane, 90°. Two further specialized views are used to understand the morphology of the PFO and define the rims if other defects are present.

TRANSVERSE PLANE, 0°. Imaging begins high in the esophagus at the level of the SVC. To avoid missing other defects, we advocate the use of dual imaging, 2-dimensional (2D) imaging and 2D with color. This way any unexpected flow across the septum can be picked up and continually compared with the underlying anatomy. A slow continuous sweep of the atrial septum from the SVC (high esophageal level) down through the FO, at mid-esophageal level, and further inferiorly to the IVC and CS is performed. The typical appearance of a PFO in this plane is shown in Figure 7. The opening of the PFO in the left atrium is seen in the high to mid-esophageal views. The superior aspect of the FO comes into view as the probe moves into the mid-esophageal level. The thin septum of the FO is

IVC Figure 3. 3D TEE Image, Enface View of Atrial Septum From the

Right Atrium

The fossa ovalis can be clearly seen and represents the primary septum. The remaining atrial septum outside this region is the secondary septum. AO = aortic root; CS = coronary sinus; FO = fossa ovalis; IVC = inferior vena cava; SVC = superior vena cava; 3D = three-dimensional; other abbreviations as in Figure 1.

clearly differentiated from the thicker secondary septum. As the probe moves to the lower esophagus, the IVC and CS can be visualized. This region may be difficult to image by TEE and may be better seen on intracardiac echocardiography.

Figure 4. 3D TEE Image, Atrial Septum Viewed From the Left Atrium

A guidewire lies through the patent foramen ovale tract and is stenting open the patent foramen ovale. Its point of opening (dotted red line) and direction (red arrow) are shown, opening into the superior and anterior aspect of the left atrium. The position of the fossa ovalis on the right atrial side is shown. MV = mitral valve; RUPV = right upper pulmonary vein; other abbreviations as in Figures 1 and 3.





Figure 5. Cartoon Illustrates the Opening of the PFO on the Atrial Septum

The atrial septum is viewed from the right atrium. The superior aspect of the fossa ovalis is the exit point of the PFO from the right atrium. The **dotted line** shows the extent of opening of the PFO flap into the left atrium. The **arrows** show the direction in which the PFO flap runs and opens into the left atrium. Abbreviations as in Figures 2 and 3.



Figure 6. 3D TEE Image Illustrating the Atrial Septum Components and the Opening of the PFO Into the Anterosuperior Aspect of the Left Atrium

Three-dimensional transesophageal echocardiographic image illustrating the atrial septum components (secondary septum [SS], primary septum [PS]) and the opening of the patent foramen ovale into the anterosuperior aspect of the left atrium (**red arrow**). One can appreciate how a guidewire easily slides across the roof of the left atrium and naturally toward the left atrial appendage (LAA). The ostium of the left upper pulmonary vein lies in the plane above the left atrial appendage. Abbreviations as in Figures 1 and 4.

LONGITUDINAL PLANE, 90°. Imaging again starts high in the esophagus at the level of the SVC. With dual imaging (2D and 2D color), the septum can be swept by rotating the probe gently right to left. The probe can then be advanced to the mid-esophageal level and then down toward the IVC. At each level, performing a sweep of the septum allows the entire septum to be mapped out. At the high esophageal level, the secondary septum is seen adjacent to the SVC. Here, the opening of the PFO is often well visualized on the left atrial side. Below this, where the septum becomes thin, is the region of the FO. The FO extends inferiorly toward the IVC. The inferior aspect of the FO is demarcated by secondary septum. The length of the secondary septum inferiorly at the origin of the IVC can vary significantly (Fig. 8).

SPECIALIZED VIEWS, SWEEP FROM 30° TO 120°. In the 50° view, at mid-esophagus, the aortic valve and root are visualized along with the FO, which lies adjacent to the aortic valve. Below this is the atrial septum, which may appear thicker if the secondary septum is visualized. The opening of the PFO may be seen over the aortic valve in the left atrium. A slow sweep from approximately 30° to 120° allows tracking of the PFO (sweeping along the superior aspect of the FO and helps establish the degree of patency, i.e., extent of flap opening on left atrial side), along with an appreciation of the possible length of the tract, and whether there is persistent color flow within the tunnel (Figs. 9 and 10).

SPECIFICS OF IMAGING A PFO. To ensure the PFO morphology is accurately defined, the concomitant use of 2D color mapping is very useful. Reducing the scale (pulse repetition frequency) on the color Doppler can be helpful to document flow across a PFO or within the tunnel. Once the morphology is clarified and the presence of any other defects established (e.g., small fenestrations in the FO or other larger defects, usually secundum atrial septal defects), intravenous contrast should be administered to confirm that contrast passage is through the defect. Sometimes there is no PFO but instead a small secundum atrial septal defect, or there may be both a PFO and a significant other defect. This contrast study therefore serves to confirm what we have identified with 2D imaging. To facilitate contrast passage, it is important to simulate the Valsalva maneuver. If the patient is sedated, we apply firm abdominal pressure over the liver, followed by release 20 s later. If the patient is awake, coughing, sniffing, and even Valsalva maneuver can



be performed during TEE. If the atrial septum is not bulging from right to left, you have not created such a gradient and you cannot exclude the presence of a PFO. Further injections of contrast are performed with visualization of all the pulmonary veins to rule out pulmonary shunts.

There are a number of important anatomical features of the atrial septum that should be docu-

mented that are helpful with respect to device implantation:

• A thick secondary septum (Fig. 11): in the presence of a thick secondary septum, an articulating device that conforms to the septum may give better closure than a nonarticulating device that will sit off the septum on its right atrial





The image shows the relationship of the aortic valve and aortic root to the atrial septum and demonstrates a large PFO. Spontaneous flow through the defect is seen. AV = aortic valve; RA = right atrium; other abbreviations as in Figures 1, 2, and 7.

aspect. Such devices include CardioSEAL, STARflex, and BioSTAR (NMT Medical, Boston, Massachusetts). These devices consist of a double umbrella with either Dacron (CardioSEAL and STARflex) or porcine collagen patches (BioSTAR) on an alloy framework. They are soft and flexible and able to maintain a low profile despite disproportionate thickening of regions of the septum.

• A long tunnel PFO (Fig. 12): long tunnels on echo do usually correspond with longer balloon tracts. The Premere PFO Closure System (St. Jude's Medical, St. Paul, Minnesota) is the only variable waist device currently widely available and is well suited to closure of a long tunnel PFO. It consists of 2 nitinol atrial anchors (left and right) that are attached by a polyester thread. Other strategies include balloon modification of the tunnel length and using a strong device that can effectively concertina the tunnel to close the PFO, such as the Amplatzer PFO Occluder device (AGA Medical Corporation, Plymouth, Minnesota). The operator may choose to close the PFO using a transseptal puncture at the base of the secondary septum, which will permit any PFO device to be used.

- A tunnel with a wide right or left atrial opening: a tunnel with a wide right or left atrial opening can be challenging to close. The device disc at the broad opening of the tunnel has the tendency to slip into the tunnel resulting in failure of closure or even device embolization. Larger, stronger devices tend to be chosen for such PFOs.
- An atrial septal aneurysm (Fig. 13): an atrial septal aneurysm is defined as redundant or excessive tissue of the atrial septum that may sway into either atrium of 10 mm (from an imaginary midline) or a total excursion of 15 mm (24,25). Atrial septal aneurysms are often



Figure 10. Illustration of the TEE 120° Specialist View Used to Understand the Morphology of the PFO and Define the Rims if Other Defects Are Present

Image shows the opening of the PFO in the left atrium and defines the margins of the primary and secondary septum. The coronary sinus and superior vena cava are seen in this view. Abbreviations as in Figures 1, 2, and 3.



associated with larger PFOs. Some operators plan to cover a large area of the septum in the presence of an aneurysm, effectively "stabilizing" the septum (e.g., Amplatzer PFO and Cribriform Occluder [AGA Medical] devices), whereas others prefer to use a soft and malleable device (such as the HELEX septal occluder [W. L. Gore & Associates Inc, Flagstaff, Arizona], or the BioSTAR device) that conforms to the existing anatomy. • Additional defects (Fig. 14): the nature and position of additional defects are important for planning. These defects, usually located in the region of the FO, are sometimes called "hybrid defects" (where small secundum defects or fenestrations on the FO coexist with a PFO). If 2 defects are close together, they may be effectively closed by a single device. Two distant defects usually require 2 separate devices but may be closed by a single device placed equidistant via a transseptal puncture.



Figure 12. 90° TEE View Illustrating a Tractlike PFO

Red arrows indicate the tractlike patent foramen ovale. Contrast was seen to transverse through the tract confirming its presence. Long tunnels on echocardiograms do usually correspond with longer balloon tracts. A device with a variable waist device, such as Premere PFO Closure System (St. Jude's Medical, St. Paul, Minnesota), is well suited to closure of a long tunnel PFO. Other strategies include balloon modification of the tunnel length and using a strong device that can effectively concertina the tunnel to close the PFO. Abbreviations as in Figures 1 and 2.





The **dotted line** represents an imaginary plane where the atrial septum would be if not aneurysmal. An atrial septal aneurysm is defined as redundant or excessive tissue of the atrial septum and is often associated with larger PFOs. Some operators plan to cover a large area of the septum in the presence of an aneurysm, effectively "stabilizing" the septum (e.g., Amplatzer PFO and Cribriform Occluder devices [AGA Medical Corporation, Plymouth, Minnesota]), whereas others prefer to use a soft and malleable device (such as the HELEX septal occluder [W. L. Gore & Associates Inc., Flagstaff, Arizona], or the BioSTAR device [NMT Medical, Boston, Massachusetts]) that conforms to the existing anatomy. ASA = atrial septal aneurysm; other abbreviations as in Figures 1, 2, and 3.

• Additional structures: the presence of a large Eustachian valve or a Chiari network in the right atrium may interfere with device placement and should be noted.

Role of 3D TEE

As real-time 3D TEE becomes increasingly available, it will compliment 2D imaging and allow a clearer understanding of PFO morphology. It is particularly helpful in delineating the relationship of the PFO defect with surrounding structures within the left and right atria and assistance during the closure procedure (26).

"3D zoom" mode is the preferred method to image the atrial septum. The entire atrial septum can be incorporated in the area of interest using 3D zoom mode. The "live" real-time 3D image can be rotated to view the right and left atrium as necessary. The best imaging in 3D is usually achieved where the atrial septum lies perpendicular to the ultrasound beam. This usually is at about 130°. The aim is to include the SVC and IVC (Fig. 3). We find that orientating the images as shown in Figures 3 and 4 are most useful for understanding the anatomy and for intraprocedural guidance.

Full volume 3D acquisition permits additional anatomical information as it allows a greater volume of the heart to be studied, although not in real time. To avoid stitching artifacts, suspending breathing (ventilator turned off) during the full volume acqui-





The nature and position of additional defects are important for planning. These defects, usually located in the region of the FO, are sometimes called "hybrid defects" (where small secundum defects or fenestrations on the FO coexist with a PFO). If 2 defects are close together they may be effectively closed by a single device. Two distant defects usually require 2 separate devices, but may be closed by a single device placed equidistant via a transseptal puncture. Abbreviations as in Figures 1, 2, and 3.

sition is usually necessary; although, this may not be avoidable in the setting of atrial fibrillation where the R-R interval may vary. It is particularly helpful in evaluating correct device position and orientation. Currently, 3D color can only be performed in full volume acquisition mode. This is helpful in complex defects.

Study limitations. Current limitations include inability to perform direct measurements in 3D imaging mode and lack of real-time 3D color Doppler. It therefore does not replace a systematic 2D assessment as described herein.

Conclusions

A structured and systematic approach allows for a rapid and comprehensive echocardiographic assess-

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ment of the atrial septum. Good echocardiographic assessment of the atrial septal anatomy before closure is of paramount importance to allow the procedure to remain safe and effective, with a zero tolerance of complications.

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