● *Review*

PATENT FORAMEN OVALE: PIVOTAL ROLE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN THE INDICATIONS FOR CLOSURE, ASSESSMENT OF VARYING ANATOMIES AND POST-PROCEDURE FOLLOW-UP

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Abstract—**Patent foramen ovale (PFO) is present in 15%−30% of the general population and has been associated with various pathologic states, including cryptogenic stroke, platypnea−orthodeoxia syndrome, decompression sickness and migraine with auras. Transesophageal echocardiography (TEE) has a major role in the diagnostic evaluation of PFO, as well as in the post-procedural assessment after transcatheter closure. The goals of this article were to synthesize the echocardiographic transesophageal techniques required for accurate PFO diagnosis and careful anatomic assessment of its anatomic variants, to focus TEE indications for device closure as complementary to clinical indications and to assess the role of TEE in the post-procedure follow-up. (E-mail: vitar@tiscali.it)   © 2019 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/).**

Key Words: **Transesophageal echocardiography, Patent foramen ovale, Device closure.**

INTRODUCTION

Patent foramen ovale (PFO), a remnant of the fetal circulatory system, is present in about one-fourth of the general population. It has been implicated in a number of pathologies, such as cryptogenic stroke, platypnea−orthodeoxia syndrome, decompression sickness, and migraine with auras (Mojadidi et al. 2018). Developments in bioengineering have made percutaneous transcatheter closure of PFO a safe treatment option (Ahmad et al. 2018; Wictor and Carroll 2018), and intraprocedural guidance of transesophageal echocardiography (TEE) is common (Bechis et al. 2017; Silvestry et al. 2015). The superiority of device closure over medical therapy for the prevention of recurrent strokes in patients with cryptogenic stroke and a PFO was reported in four recent randomized controlled trials (Lee et al. 2018; Mas et al. 2017, Saver at al. 2017; Søndergaard et al. 2017). However, the role of TEE in diagnosis and indications for closure as well as post-procedure assessment are not currently well defined. This article aims to summarize the echocardiographic transesophageal techniques required for accurate PFO diagnosis and careful evaluation of its anatomic variants, to focus TEE indications for device closure as complementary to clinical indications and to assess the role of TEE in the post-procedure follow-up.

DIAGNOSTIC METHODS

From a pathophysiologic point of view, whereas in atrial septal defect (ASD) the extent and direction of the shunt depend on the size of the defect and relative compliance and diastolic filling properties of the left and right ventricles (Vitarelli et al. 2012), in PFO, despite recent diagnostic methods, the cause of right-to-left atrial shunt in the presence of normal intracardiac pressures and pulmonary function has not been completely clarified (Rigatelli 2014). Some explanations have been proposed. First, a physiologic transient spontaneous reversal of left and right atrial pressures occurs at each cardiac cycle during right ventricular early diastole and isovolumetric contraction, and this reversal gradient may exhibit a substantial rise in physiologic conditions increasing the right atrial pressure (cough, inspiration, Valsalva maneuver) or morbidities producing high pulmonary vascular resistances (right ventricular infarction, acute pulmonary embolism, chronic obstructive pulmonary disease, obstructive sleep apnea [OSA] syndrome). Second, a physiologic change, probably exacerbated by

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the age, has been suggested in the relationship of right- and left-sided chamber compliance. Third, the right-to-left shunting with both normal atrial and pulmonary vascular pressures may be explained by a preferential blood flow directed from the inferior vena cava (IVC) toward the atrial septum re-evoking the prenatal pattern.

Transthoracic echocardiography (TTE) is the most common diagnostic method used for suspected PFO. Because a color Doppler study detects only 5%−10% of interatrial shunts, intravenous injection of agitated saline solution, performed with the patient at rest and with a Valsalva maneuver, increases diagnostic sensitivity (Ren et al. 2013). The main TTE limitations are its lower sensitivity compared with TEE and its incapability to supply detailed information on atrial septal morphology.

Transesophageal echocardiography (TEE) has a major role in the assessment of PFO compared with TTE because of easier identification of PFO with the use of intravenous agitated saline contrast and improved imaging of atrial structures (Fig. 1). In PFO patients, TEE identifies the shunt, spontaneous or under Valsalva maneuver as small, moderate and severe on the basis of an old but still valid
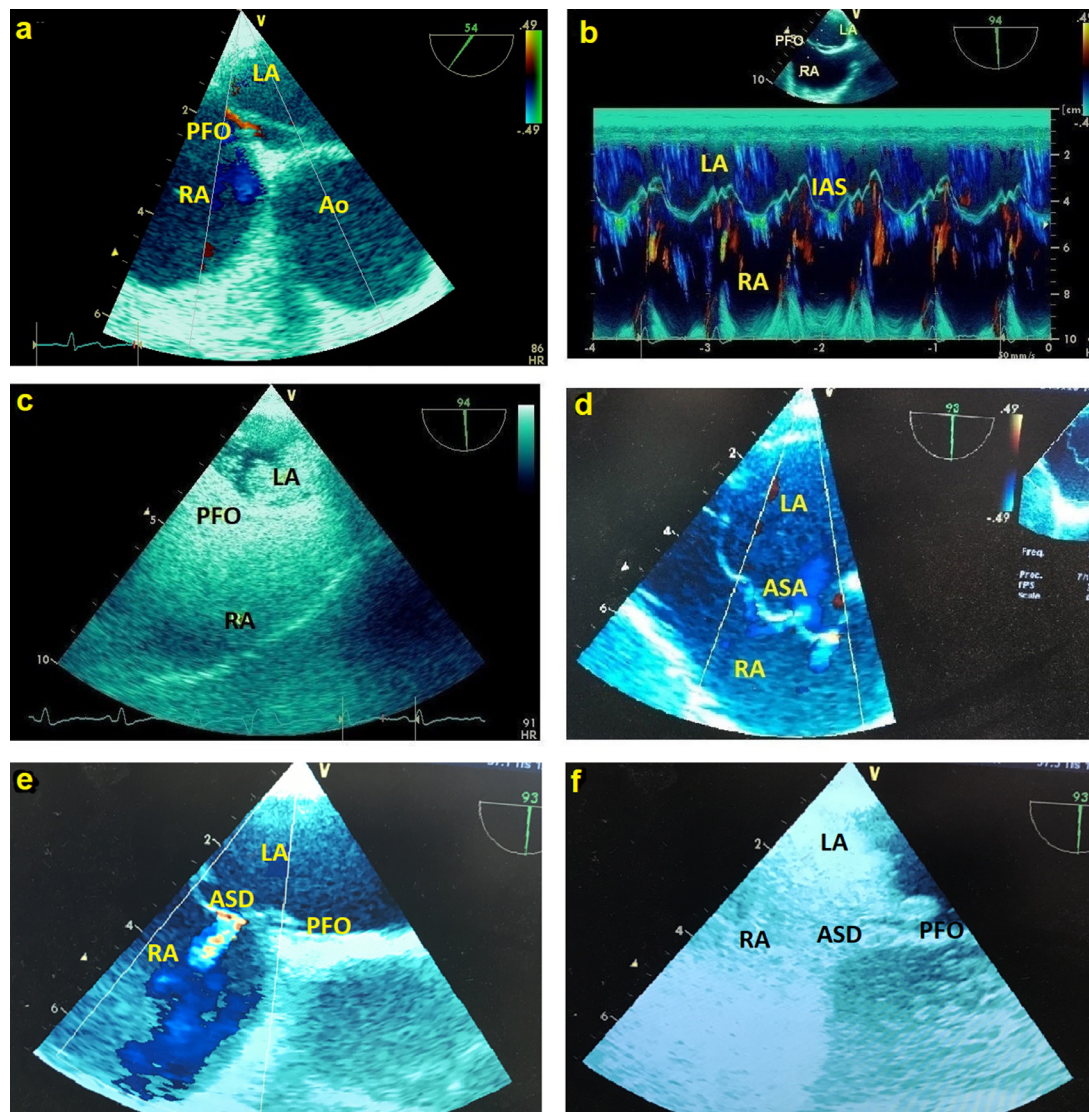

Fig. 1. Representative images of PFO 2-D-TEE views. (a) PFO with left-to-right shunt on TEE color Doppler, long tunnel and "double" atrial septum. (b) Hypermotility of interatrial septum (septum primum) and left-to-right shunt on TEE color M-mode. (c) PFO with large right-to-left shunt after Valsalva (2-D-TEE). (d) PFO with multi-fenestrated ASA and multiple jets by left-to-right shunt on TEE color Doppler. (e) PFO associated with a small ostium secundum ASD. Color Doppler reveals left-to-right shunt through ASD. (f) PFO associated with small ASD. Agitated saline contrast injection reveals right-to-left shunt through ASD and PFO. Ao = aorta; ASA = atrial septal aneurysm; ASD = atrial septal defect; IAS = interatrial septum; LA = left atrium; PFO = patent foramen ovale; RA = right atrium; TEE = transesophageal echocardiography.

classification (Mojadidi et al. 2014a; Saver et al. 2017; Silvestry et al. 2015; Thiagaraj et al. 2019; Vitarelli et al. 2014). The effectiveness of the maneuver can be assessed echocardiographically by the presence of a leftward shift of the primary atrial septum with the release phase, denoting the attainment of RA pressure greater than LA pressure. Although contrast TEE may result in false-negative injections both before and after PFO closure, whenever too small a pressure gradient is provided between the left and right atria (Silvestry et al. 2015), the use of multiple injections (Johansson et al. 2008) increases the sensitivity for detection of PFO. Microbubbles appearing in the left atrium >5 beats after they appear in the right atrium suggest the possibility of extracardiac shunting such as anomalous venous connection to the left atrium or pulmonary arteriovenous malformations. Intrapulmonary shunting is confirmed when the bubbles appear to enter the LA from one or more pulmonary veins and are not visualized traversing the atrial septum (Abushora et al. 2013). However, care should be taken to distinguish bubbles shunting from the right upper pulmonary vein simulating a PFO from those actually crossing a PFO, as well as to differentiate bubbles that are observed to retrogradely flow into the pulmonary veins after entering the left atrium *via* a PFO mimicking an intrapulmonary shunt. Other false-positive studies for PFO may be caused by undetected ASD, sinus venosus defect or transient stagnation of blood in the pulmonary veins (pseudocontrast) during the strain phase of Valsalva. False-negative studies for PFO may result from inadequate RA opacification, increased LA pressure, presence of a redundant Eustachian valve or inadequate Valsalva maneuver. Contrast-free blood flow from the IVC directed by the Eustachian valve may wash away contrast injected through an upper extremity vein and produce a false-negative result. In these cases, contrast injection *via* the femoral vein could enhance detection by TEE, with the streaming effect of IVC flow directed to the region of the fossa ovalis and PFO (Schuchlenz et al. 2006). Sedation status and/or the presence of the TEE probe inside the esophagus and laryngopharynx may also decrease patient effort during the Valsalva maneuver (Rodrigues et al. 2013). IVC compression, which involves manual compression of the abdomen to produce partial IVC collapse and increased IVC flow upon release, has been proposed as a feasible and reproducible provocation test to detect PFO (Yamashita et al. 2017).

Transcranial Doppler ultrasound (TCD) is a noninvasive ultrasound method used to examine the blood circulation within the brain and an alternative method to detect the presence of right-to-left shunt (RLS) in patients with suspected PFO (Mojadidi et al. 2014b). The study protocol includes monitoring of both middle cerebral arteries (MCAs) through the temporal window using 2-MHz probes. A venous injection bubble study

and Valsalva maneuver are performed, and insonation of at least one MCA is obtained. The Valsalva release phase allows right atrial pressure to briefly exceed left atrial pressure and results in transient reversal of left-to-right flow across the PFO. During this transient RLS, bubbles enter the systemic circulation and produce microembolic signals in the cerebral arteries that are detected by TCD. A pulsed Doppler transducer is commonly used to assess the velocity and intensity of cerebral arterial blood flow. Color duplex TCD can also be employed in addition to spectral TCD to confirm the test positivity.

In patients who had clinical events and present with RLS on TTE or TCD, TEE is subsequently performed (Vitarelli et al. 2014), especially when results would affect the management (possible transcatheter closure). TEE (Figs. 1 and 2, Table 1) should document PFO and its anatomic variations (atrial septal aneurysm, long PFO tunnel, double septum, large Eustachian valve, Chiari strands), assess other potential sources of emboli (endocarditis, cardiac tumor, left atrial appendage thrombus, aortic plaque),
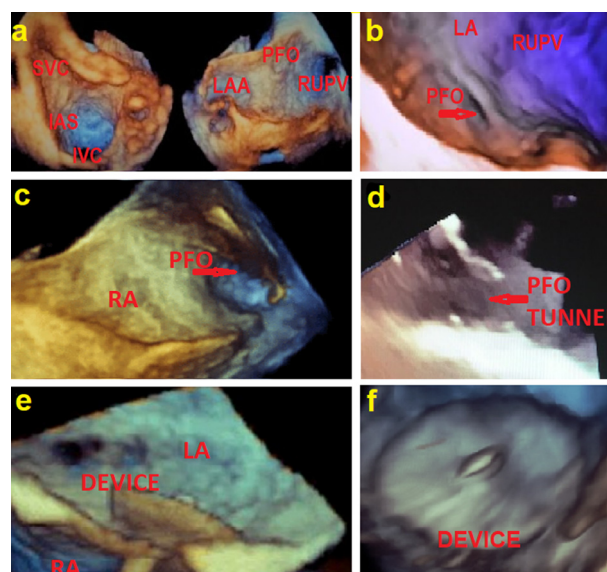

Fig. 2. Representative images of PFO 3-D-TEE views. (a) Three-dimensional TEE *en face* RA and LA views: different orientations of interatrial septum with SVC at the 11-o'clock position in RA and RUPV at the 1-o'clock position in LA, as recommended by the American Society of Echocardiography. (b) Left atrial exit of the PFO tunnel. (c) Right atrial perspective revealing PFO entrance and a spiral defect with wide separation between the left atrial and right atrial margins. (d) Long PFO tunnel. (e) Adequate positioning of the PFO device on the interatrial septum. (f) Three-dimensional TEE *en face* view of the left-sided disc of the PFO Amplatzer device after full deployment. IAS = interatrial septum (with fossa ovalis); IVC = inferior vena cava; LA = left atrium; LAA = left atrial auricle; RA = right atrium; RUPV = right upper pulmonary vein; PFO = patent foramen ovale; SVC = superior vena cava; TEE = transesophageal echocardiography.

Table 1. Potential clinical and TEE indications to PFO trans-
catheter closure

Clinical indications	Anatomo-functional TEE indications
Age ≤ 60 y	Moderate/large RLS at rest or Valsalva
Cryptogenic stroke or TIA (confirmed by cerebral imaging)	Presence of:
Presence of:	
RoPE score ≥6 (may be closed), RoPE score ≥8 (should be closed)	Normal-length atrial rims Simple PFO
Deep vein thrombosis	Complex PFO
Prior venous thromboembolism	ASA
Platypnea−orthodeoxia	Long tunnel
Decompression illness	Prominent Eustachian valve or ridge
Migraine with auras	Prominent Chiari network
Obstructive sleep apnea	Thick septum secundum (IASH, IASL)
High risk (clinical) of	"Double" or "spiral" atrial septum
High RoPE score, recurrent cryptogenic stroke, recurrent DVT, prior venous thromboembolism	"Double orifice" PFO "Multi-fenestrated" ASA
Absence of:	"Hybrid" PFO
Large artery or small vessel disease (lacunar stroke)	High risk (anatomic):
Carotid atheroma or dissection	Large size, RLS at rest, ASA, complex PFO
Hypercoagulable disorder requiring anticoagulation	Absence of:
Uncontrolled systemic hypertension	Endocarditis
Uncontrolled diabetes mellitus	Severe valve disease
Atrial fibrillation or flutter	Cardiac thrombus
Autoimmune or inflammatory vasculitides	Cardiac tumor
Recent history of alcohol or drug abuse	Aortic arch plaque

ASA = atrial septal aneurysm; IASH = interatrial septum hypertrophy; IASL = interatrial septum lipomatosis; PFO = patent foramen ovale; RLS = right-to-left shunting; RoPE = Risk of Paradoxical Embolism (see text); TEE = transesophageal echocardiography; TIA = transient ischemic attack.

assess other causes of RLS (small additional atrial septal defects, fenestrated septum, pulmonary arteriovenous fistula) and rule out congenital heart lesions not susceptible to percutaneous treatment (ostium primum defect, sinus venosus defect, partial anomalous pulmonary venous drainage).

INDICATIONS FOR TRANSCATHETER CLOSURE

In patients with cryptogenic stroke or transient ischemic attack and PFO diagnosis (Table 1), the ideal secondary prevention has been controversial and extensively debated (Baumgartner et al. 2010; Collado et al. 2018; Kent et al. 2011; Kernan et al. 2014; Van Dijk et al. 2017; Wein et al. 2018). Cryptogenic stroke is defined as a stroke of unknown cause, despite extensive investigations to exclude other etiologies, such

as large-vessel atherosclerosis, small-artery disease, carotid dissection, space-occupying lesions, intracerebral hemorrhage and atrial fibrillation. The syndrome of venous thrombus embolization to the right atrium and subsequently into the systemic circulation through the PFO, causing cerebrovascular embolic infarct, is supported by the high prevalence of PFO (≤50%) in patients with cryptogenic strokes as well as numerous case reports on *in vivo* and postmortem "thrombus-in-transit," that is, a thrombus visualized across the foramen (Barros-Gomes et al. 2018). However, care should be taken when assessing the need for PFO closure in patients who have had a cryptogenic stroke. Closure of an incidental PFO (not associated with the stroke event) would expose the patient to the risks of the procedure without any clinical benefit. PFO closure should be done with shared decisions after careful multidisciplinary evaluation. An echocardiologist (ideally with experience in adult congenital heart disease), interventional cardiologist, neurologist (ideally stroke neurologist), neuroradiologist, hematologist and vascular specialist should assess patients within a PFO-mediated stroke team.

The early randomized trials failed to determine the superiority of percutaneous PFO closure over pharmacotherapy for the secondary prevention of cryptogenic stroke (Collado et al. 2018). Various recommendations for percutaneous closure have been reported. Device closure for small ASDs is recommended in the European Guidelines (class IIa, C) for patients with a suspected paradoxical embolism after exclusion of other causes (Baumgartner et al. 2010). The 2015 American Society of Echocardiography guidelines report as potential indications for PFO closure PFO-cryptogenic stroke and evidence of right-to-left shunt (Silvestry et al. 2015). The 2014 American Heart Association/ASA (American Stroke Association) guidelines recommend anti-platelet therapy, otherwise anti-coagulation if there is a venous source of embolism. If anti-coagulation is contraindicated, an IVC filter is advised, whereas transcatheter PFO closure might be evaluated in the presence of a deep vein thrombosis (Kernan et al. 2014). The 2017 Dutch guidelines suggested (Van Dijk et al. 2017) that in patients with transient ischemic attack or cryptogenic stroke and at least one clinical risk factor, PFO closure "may" be considered in the presence of a Risk of Paradoxical Embolism (RoPE) score ≥6 and "should" be considered with a RoPE score ≥8. The RoPE is a score index used to indicate whether a PFO in cryptogenic stroke is stroke related or incidental (Kent et al. 2011). It is based on age, risk factors for atherosclerosis (systemic hypertension, diabetes, history of stroke, smoking) and presence of cortical infarct on imaging. Bayes' theorem was used to calculate how much of a patient's future

stroke risk was attributable to having a PFO. The score ranges from 0−10, with higher scores indicating higher likelihood. The optimal cutoff value to identify a stroke-related PFO was a RoPE score of at least 6; however, the presence of a large shunt or atrial septal aneurysm was not included in these initial reports (Kent et al. 2011; Van Dijk et al. 2017). In recently published trials, the RoPE score was still taken into account in the enrollment of patients suitable for PFO closure (Mas et al. 2017), but the additional importance of PFO characteristics to patient selection and treatment benefit was made clear (Wiktor and Carroll 2018).

Four randomized controlled trials (Lee et al. 2018; Mas et al. 2017; Saver at al. 2017; Søndergaard et al. 2017) reported that transcatheter PFO closure plus anti-platelet treatment is superior to anti-platelet therapy alone for secondary stroke prevention. These studies found that the frequency of recurrent embolic stroke can be reduced from 1.1 to 0.53 per 100 patient-year with the percutaneous PFO closure, corresponding to a 50% relative risk reduction and 2.11% absolute risk reduction. On the basis of these recent trials, updated societal guidelines on stroke prevention (Wein et al. 2018) are now recommending PFO closure for PFO-mediated stroke in patients aged ≤60 y (level of evidence: A). The CLOSE Trial (Mas et al. 2017) included patients aged 16-60 y. In REDUCE (Søndergaard et al. 2017), patients were eligible if they were 18-59 y of age. In contrast with previous trials, the CLOSE and REDUCE trials (Mas et al. 2017; Søndergaard et al. 2017) have imposed the exclusion of patients with identifiable causes of stroke other than PFO (intracranial small vessel disease, atherosclerosis arterial disease, coagulopathies, arterial or venous thromboembolism).

The DEFENSE trial (Lee et al. 2018) reported a further advance, studying patients with cryptogenic stroke and high-risk PFO anatomic criteria such as atrial septal aneurysm, hypermobility (phasic septal excursion into either atrium of ≥10 mm) and moderately large size (maximum separation of the septum primum from the secundum of ≥2 mm), who randomly underwent PFO device closure using the Amplatzer PFO occluder or medical therapy alone. The DEFENCE trial not only breaks the spear in favor of PFO device closure over medical therapy in reducing the risk of recurrent crypto-genic stroke but also suggests greater effectiveness of device closure in patients with high-risk anatomic PFO features. Albeit this trial reported a PFO size cutoff value of ≥2 mm, the presence of a large PFO (≥3 mm) has been previously related to increased recurrence of ische-mic stroke (Lee et al. 2010), and a distinction between small (≤1.9 mm), medium (2−3.9 mm) and large (≥4 mm) PFOs has been proposed (Aggeli et al. 2018).

There are many commercially available PFO and ASD closure devices on the world market. Based on extended follow-up results of the RESPECT and REDUCE trials, the U.S. Food and Drug Administration approved the Amplatzer PFO Occluder on October 28, 2016, and the Gore Cardioform Septal Occluder on March 30, 2018, for PFO closure in the United States (Collado et al. 2018).

In addition to cryptogenic stroke, other potential indications for PFO closure (Table 1) are platypnea-−orthodeoxia syndrome (POS), decompression sickness, migraine with auras and obstructive sleep apnea. The relationship between PFO and these clinical conditions and benefits of device closure remain unclear (Collado et al. 2018), and further data from clinical trials are needed. POS is a condition in which dyspnea and oxygen desaturation occur in the upright position and resolve in the supine position, and is due to intracardiac right-to-left shunting through a PFO, an atrial septal defect or pulmonary arteriovenous malformations. Most of the cases with PFO are patients with additional pulmonary diseases such as chronic lung disease and pneumonec-tomy. Closure in POS could be considered in cases of severe symptomatic hypoxia in the absence of pulmo-nary hypertension (Mojadidi et al. 2019; Shah et al. 2016). In divers, albeit the incidence of decompression sickness is rare, the presence of PFO could cause venous bubbles to go into the arterial circulation and lead to cerebral or myocardial infarction. In these cases, percu-taneous closure should be individualized based on the presence of symptoms, the presence of high-risk ana-tomo-functional features along with PFO (large right-to-left shunt), the type and frequency of dives and the patient's desire to continue with this activity (Wilmshurst et al. 2015). The relationship between migraine headache and PFO is not equally defined. Migraine is a complex disease that occurs as the result of the combination of susceptibility and trigger factors. According to the "microthrombi hypothesis," in the pres-ence of PFO, microthrombi or emboli originating in the venous circulation penetrate into the systemic and cere-bral circulation and trigger a migraine attack. The PFO Premium trial did not provide evidence to support the use of PFO closure as a preventive therapy for migraine, but in the same trial the 8.5% of patients who experienced complete remission of migraine over a 1-y period raised the hypothesis that an atrial shunt may play a causative role for a subset of patients with migraine (Tobis et al. 2017). A strong association has also been reported between the presence of a PFO with atrial septal aneu-rysm and the occurrence of migraine with aura in a large patient population referred for TEE (Snijder et al. 2016). Lastly, in patients with OSA, increases in right-to-left shunting across a PFO may result in increased burden of

hypoxia. PFO closure could result in improvement in apneas and symptoms in selected OSA patients and have an impact on cardiovascular events in this group through hypoxia-mediated or other unrecognized mechanisms (Rimoldi et al. 2015; White et al. 2013). This may have a role particularly in patients intolerant of standard care, including continuous positive airway pressure.

Varying anatomies

A thorough understanding of the embryology of the atrial septum is needed to better understand the variable anatomy concerning the favorable outcome of the PFO percutaneous procedure (Amin 2014; Bartel and Müller 2013; Faletra et al. 2014; Karsenty 2018; Ostermayer et al. 2015; Rana et al. 2010a, 2010b; Tanaka et al. 2013; Vettukattil et al. 2013).

The development of the normal atrial septum occurs following the initial looping of the heart after 28 d of gestation. The *septum primum* is a thin sickle-shaped membrane that arises craniodorsally on the posterosuperior wall of the primitive single atrial chamber and grows down to the endocardial atrioventricular cushions, leaving an *ostium primum* below its free edge. It fuses with the endocardial cushions at about 35 d, obliterating the ostium primum. The *ostium secundum* is an opening that appears at about 33 d in the upper part of the septum primum before the ostium primum closes. It forms by apoptosis (programmed cell death) as a number of small perforations that coalesce. This structure replaces the ostium primum as the conduit for right-to-left shunting of oxygenated blood from the umbilical vein to bypass the fetal pulmonary circulation. The *septum secundum* begins to develop at about 33 d by an infolding of the superior walls of the two atria after integration of the pulmonary veins in the left atrium. It is a thick muscular septum that arises to the right of the septum primum and grows from the roof of the atrium covering the right atrial side of the septum except for an area inferiorly. It covers and obliterates the foramen secundum in the septum primum, but in the lower interatrial septum, directly in the path of the blood coming from the inferior vena cava, it remains as an incomplete partition which results in an oval-shaped pathway, the *foramen ovale.*

This septal region is called the *fossa ovalis* (an evident depression on the right side of the interatrial septum) and is composed only of the septum primum. The fossa ovalis is considered a "true atrial septum," as a transseptal puncture at this level leads to the left atrium, differently from the septum secundum that consists of infolded tissue and is considered a "false atrial septum," as a puncture at this level would lead outside the heart. The atrial septal tissue between the fossa ovalis and the surrounding structures is called a *rim*. By convention, there are six anatomically named rims (Silvestry et al. 2015): aortic (superior/anterior), superior vena cava

(SVC)(superior), right upper pulmonary vein (superior/posterior), atrioventricular valve (inferior/anterior), IVC (inferior/posterior) and posterior atrial wall (posterior). A deficient rim is considered a rim of less than 5 mm in multiple TEE views, assessed in at least three sequential views in 15˚ increments (Silvestry et al. 2015).

The two septa eventually fuse together in the areas where they overlap, including around the edges of the fossa ovalis (limbus of fossa ovalis), but at the anterosuperior edge of the fossa ovalis (adjacent to the aortic root) they remain unfused and form the "valve of the foramen ovale." This "flap valve" is a tunnel that permits the right-to-left shunting of blood that is necessary for normal fetal circulation. The walls of the tunnel are the septum primum on the left side and the septum secundum on the right. The thin and compliant septum primum is similar to a door closing against the foramen ovale on the septum secundum. At birth, the increase in pulmonary blood flow causes the left atrial pressure to surpass the right atrial pressure, leading to closure of the PFO. Although the primum and secundum septa covering the PFO tunnel usually fuse shortly after birth, PFO may persist in a large minority of the population.

Patent foramen ovale is anatomically different from secundum ASD as it presents with a complete coverage of the foramen ovale that effectively separates the two atria under normal physiologic conditions. On the basis of its topography, variations in PFO anatomy can result from both different degrees of overlapping of the foramen ovale and mobility of the septum primum. Larger-width PFOs (Tanaka et al. 2013), longer PFO tunnels (Rana et al. 2010b) and the presence of atrial septal aneurysm (ASA) (Figs. 1 and 2) often require larger device size (Fig. 3) to ensure proper closure. For the Amplatzer PFO Occluder,

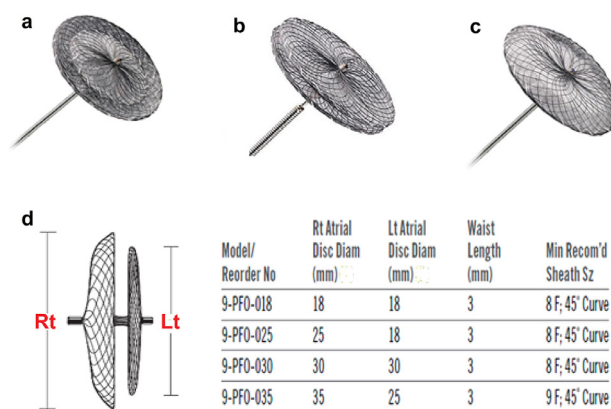| Model/ Reorder No	Rt Atrial Disc Diam (mm)	Lt Atrial Disc Diam (mm)	Waist Length (mm)	Min Recom'd Sheath Sz
9-PFO-018	18	18	3	8 F; 45˚ Curve
9-PFO-025	25	18	3	8 F; 45˚ Curve
9-PFO-030	30	30	3	8 F; 45˚ Curve
9-PFO-035	35	25	3	9 F; 45˚ Curve

Fig. 3. Amplatzer occluders (images granted by Abbott). (a) Patent foramen ovale septal occluder. (b) Multi-fenestrated septal occluder. (c) ASD septal occluder. (d) Family of Amplatzer PFO occluders. The right (Rt) and left (Lt) numbers indicate the diameters of the right and left discs. The French size indicates the minimal inner lumen of the required sheath (1 F = 0.3 mm).

the device size corresponds to the right atrial disc (Fig. 3). According to the instructions for use, a minimum distance of 9 mm should be present between the PFO and aortic root or SVC to safely implant the Amplatzer PFO occluder and minimize risk of erosion or SVC obstruction. However, this occluder was implanted in patients with smaller aortic rims with no sequelae, probably because there are other factors, in addition to the simple contact of the edge of the device, that can lead to complications (Amin 2014). Use of a relatively larger and soft occluder can also allow the left and right discs to embrace aortic root and avoid the disc edge abraded aortic root. The Gore Cardioform Septal Occluder device sizing recommendations include a complete TEE color Doppler assessment to determine if there is adequate space for the selected device size without affecting the function of neighboring structures, such as mitral and tricuspid valves, pulmonary veins and coronary sinus.

Atrial septal aneurysm is essentially a description of the size and mobility of the fossa ovalis tissue (septum primum) and is defined on echocardiography as 15 mm of total septal tissue excursion or a 10-mm protrusion into either atrium from the septal midline with a base that extends ≥10 mm (Ostermayer et al. 2015; Silvestry et al. 2015). ASAs pose a higher risk of recurrent neurologic events and are usually associated with larger PFOs (Lee et al. 2018; Mas et al. 2017; Saver at al. 2017; Søndergaard et al. 2017). Most interventionalists in this situation stabilize the septum by covering a larger area than needed in order to cover the PFO with a stiffer device such as Amplatzer PFO.

In long PFO tunnels (Figs. 1 and 2), traditional double-disc occluders tend to distort the septal anatomy, and in these cases some interventional cardiologists propose placement of the device using transseptal puncture. This seems to overcomplicate a procedure that should be relatively simple. The technique is also associated with high incidence of residual shunting (Collado et al. 2018). To collapse the PFO tunnel, most operators tend to use stronger devices like Amplatzer, which is often more effective.

"Spiral septum" (Vettukattil et al. 2013), also described as "double atrial septum" or "malalignment of the primary atrial septum," consists of a wide separation between the flap valve and the margins of the fossa ovalis. Although uncommon, spiral spatial configuration of the flap valve relative to the rims of the fossa in PFOs or ASDs, best seen on 3D-TEE interrogation (Fig. 2), predisposes to embolization of devices used for percutaneous closure (Rana et al. 2010a; Vettukattil et al. 2013). If the space between the flap valve and the rim is extensive anterosuperiorly, a larger device could be required to close the defect.

A PFO double orifice in the LA can be produced by a strand tissue of the septum primum tethered to the septum secundum at the point of its atrial opening. In these cases it is advisable to be sure that both orifices are covered by a device placed through one of the openings.

Excessive thickness of septum secundum is caused by adipose tissue contained within this septal structure that derives from infolding of atrial walls. A thickness ≥10 mm may cause problems with device position (Rana et al. 2010b), the disc cannot be arranged flush against the fossa ovalis, and a small size or softer type of device should be considered.

Redundant Eustachian valve or, more rarely, Chiari network, caused by excessive tissue attached to Eustachian ridge and facing the IVC orifice, may interfere with device placement, as passing the guidewire may be difficult and the valve can get caught in the device during deployment (Rana et al. 2010b). A voluminous Eustachian ridge can also limit the space available over the fossa ovalis on the right atrial side and cause a PFO device to sit away from the fossa, making it necessary to evaluate the impact of the structure on the choice of device size.

A septum with multiple defects (Fig. 1) most likely represents either a fenestrated secundum defect in conjunction with a PFO ("hybrid defect") or an isolated fenestrated secundum defect. In most cases, these can be effectively closed with a single device such an Amplatzer Cribriform occluder. A single device of adequate size through the largest defect is usually sufficient. A two-device strategy is more appropriate for multiple true secundum ASDs (Bartel and Müller 2013).

Therefore, because of these variable anatomic aspects of PFO with respect to size, redundancy of the atrial septum, thickness of the septum secundum, length of the tunnel and relationship to adjacent structures, a single device cannot be suitable for the best treatment in all PFOs. Appropriate devices for specific morphologic variants can improve the success rate of the procedure and decrease the risk of residual shunts and complications. In the future, new devices and/or new techniques may be available on the market. PFO closure with bioabsorbable devices, closure with radiofrequency without a permanent implant and "device-less" closure with Noble Stitch are currently under investigation (Rigatelli and Zuin 2018). Noble Stitch (Noble's Medical Technology, Fountain Valley, CA, USA) makes use of the transcatheter suture technology adapted from vascular access suturing devices. It involves engaging and puncturing each septum separately, where a suture is captured by the needle and pulled through the septum. It has been reported to be technically feasible (Ruiz et al. 2008) but cannot be applied to all PFO anatomies. Moreover, some concerns persist about closure rate and complications.

INTRA-PROCEDURAL GUIDANCE

During a PFO closure procedure, TEE is used in combination with fluoroscopy (Bartel and Müller 2013; Bechis et al. 2017; Faletra et al. 2014; Karsenty et al.

2018; Silvestry et al. 2015). Both 2-D-TEE and 3-D-TEE enable display of the long segments of the catheters and wires and their relationship to adjacent and surrounding anatomic structures, helping the manipulation of the device. Echocardiography allows the echocardiologist and the interventionist to assess closure device sizing and deployment, to image atrial septum from oblique and lateral perspectives visualizing left and right disc expansion, to obtain information on the adequacy of closure and to make eventual modifications before final implantation.

"Simple" PFOs do not necessarily require continuous echocardiographic monitoring. When the device is deployed but still connected to the delivery cable, one short inspection by TEE under conscious sedation is quite adequate to check for proper device position (Fig. 2), to perform the so-called "wiggle maneuver" and to observe the release of the device from the cable. During the "wiggle maneuver," the occluder is pushed and pulled before release to make sure that neither the right nor the left disc slips into the contralateral chamber. In some cases, TTE may be an alternative, depending on the choice of the echocardiologist. For "complex" PFOs, continuous TEE guidance is preferred.

Real-time 3-D-TEE offers improved spatial orientation with respect to the characteristics of complex PFOs, multi-fenestrated ASAs or ASDs. The "3-D zoom" mode is useful during the procedure to observe the position of guide wires, sheaths and devices in real time (Bartel and Müller 2013; Faletra et al. 2014). The spatial relationship between any interatrial communication and the occluder can be easily represented at any time and from each side. The device has to be retrieved and redeployed if it is seen to impinge on a native structure such as the aortic root, because late perforation of the aortic wall or atrial wall are well-defined possibilities. The major advantage of 3-D-TEE in comparison with conventional TEE or intracardiac echocardiography (ICE) is its capability to demonstrate the dynamic morphology of interatrial communications. Compared with ICE, 3-DTEE has the advantages of lower costs and the potential to supply *en face* views from the LA and RA (Fig. 2), which make device alignment during implantation and confirmation of proper device position easier.

Post-procedure follow-up

Patent foramen ovale transcatheter closure is a minimally invasive procedure with a high success rate, excellent long-term outcomes and low complication rate. However, there are still some complications (Fig. 4). Anatomic knowledge of atrial and interatrial structures, careful manipulation of catheters and wires and clear communication between the interventional cardiologist and echocardiologist are of primary importance to abate these risks.
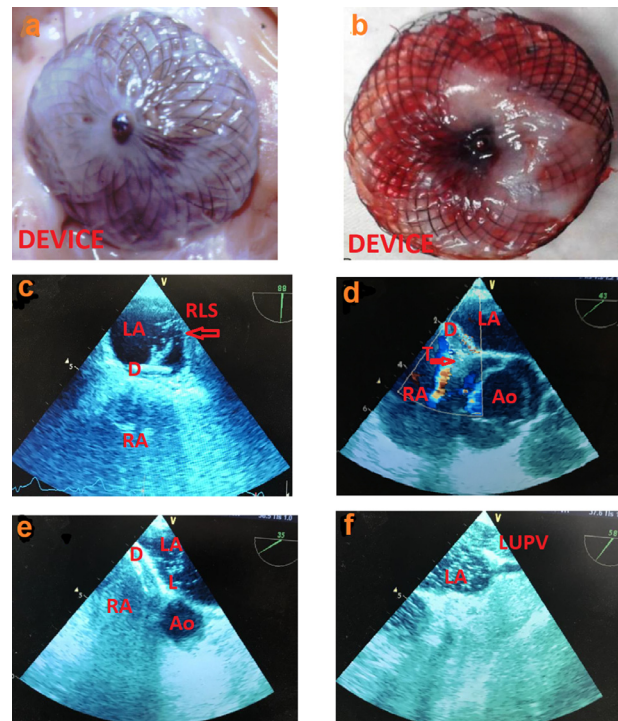

Fig. 4. Representative images of potential outcomes or complications on post-procedure follow-up. (a) Surgical view showing a complete endothelialization of an implanted Amplatzer device (Abbott courtesy). (b) Surgical view revealing a limited endothelialization of an implanted Amplatzer device (from Amedro et al. 2017, with permission). (c) Peripheral contrast injection revealing residual right-to-left shunting at 6-mo follow-up, possibly caused by incomplete device endothelialization. (d) Right-sided device-attached thrombus (T) at 6-mo follow-up. Thrombus resolution occurred after 2 mo of warfarin therapy. (e) Malalignment of the atrial septal device (D) with the superior limbus (L) of the fossa ovalis. (f) Residual intrapulmonary shunting in a patient with persistent post-procedure right-to-left shunting. Bubbles enter the LA from the left upper pulmonary vein. D = device; L = limbus; LA = left atrium; LUPV = left upper pulmonary vein; RA = right atrium; RLS = right-to-left shunting; T = thrombus.

Periprocedural complications are generally benign and reversible compared with late complications (Collado et al. 2018; Yared et al. 2009). Table 2 lists the incidences of post-procedural adverse outcomes reported in the literature and the potential role of TEE in diagnosing those events. Figure 5 summarizes the role of TEE in the indications for PFO closure and post-procedure follow-up.

Whereas predisposing factors for embolization of ASD closure devices (inadequate rim and undersized device) are reported, PFO closure-device embolization is such a rare complication that data on its incidence, etiology and management are sparse (Goel et al. 2013; Yared et al. 2009). Accurate pre-procedure and intra-procedure imaging and appropriate device selection are needed to avoid this potentially serious complication. Morphologic features associated

Table 2. Potential outcomes or complications on post-procedure follow-up and role of TEE

Event	Etiology	Incidence (%)	References	Role of TEE
Device embolization	Morphologic predispositions to closure-device malpositioning	0.7−0.9	Goel et al. 2013 Saver et al. 2017 Yared et al. 2009	Diagnosis
Device thrombosis	More common with devices containing uncoated metal arms	0.4−2	Krumsdorf et al. 2004 Saver et al. 2017 Yared et al. 2009	Diagnosis
Infective endocarditis	There is a risk as long as the device has not been endothelialized	~0.4	Amedro et al. 2017 Krantz and Lawton 2014	Diagnosis
Device erosion	Deficient rims in vulnerable areas could increase device mobility and cause excessive friction between device and atrial or aortic wall	0.01−0.02	Amin et al. 2014 Collado et al. 2018 Yared et al. 2009	Diagnosis
Pulmonary embolism	The rate of venous thromboembolism (including pulmonary embolism and DVT events) is higher in PFO-closure groups than in medical therapy groups	0.4−2.4	Collado et al. 2018 Mookadam et al. 2010 Saver et al. 2017 Yared et al. 2009	Important role in the diagnosis
Atrial fibrillation/flutter	More common in patients with pre-existent atrial dysfunction	3−14	Collado et al. 2018 Lee et al. 2018 Mas et al. 2017 Saver et al. 2017 Søndergaard et al. 2017 Vitarelli et al. 2018	Guiding management
Residual RLS	Cardiac or extracardiac	6−11	Collado et al. 2018 Greutmann et al. 2009 Mojadidi et al. 2014a, 2014b Shah et al. 2018 Susuri et al. 2017 Wintzer-Wehekind et al. 2019	
Cardiac shunts From within the device (incomplete endothelialization)		~4	Greutmann et al. 2009 Shah et al. 2018 Susuri et al. 2017	Diagnosis
From around the device (fenestrated septum)		~2	Greutmann et al. 2009 Shah et al. 2018 Susuri et al. 2017	Diagnosis
Extracardiac vascular shunts Intrapulmonary shunt		~4	Abushora et al. 2013 Greutmann et al. 2009 Sinha et al. 2016	Important role in the diagnosis
Persistent LSVC		~1	Sheikh and Mazhar 2014 Thaiyananthan et al. 2009	Important role in the diagnosis
Hepatopulmonary syndrome		/	Rollan et al. 2007 Scott-Herridge et al. 2016	Important role in the diagnosis

DVT = deep vein thrombosis; LSVC = left superior vena cava; PFO = patent foramen ovale; RLS = right-to-left shunting; TEE = trans-esophageal echocardiography.

with device embolization were the presence of a hypermobile septum primum and a thick septum secundum (Goel et al. 2013). No device embolizations occurred in recent trials (Lee et al. 2018; Mas et al. 2017, Saver at al. 2017; Søndergaard et al. 2017).

The incidence of device thrombosis was reported to be 2% after ASD/PFO closure (Yared et al. 2009). Some patients may have minor cerebrovascular accidents or transient ischemic attacks (Krumsdorf et al. 2004). Thrombus appears to be more common with devices containing uncoated metal arms than with the polyester fabric-coated device such as the Amplatzer. Most thrombi were detected by TEE within the first month after device implantation. Patient compliance with antiplatelet therapy is required to prevent thrombosis.

Infectious endocarditis (IE) is a very rare but serious sequela of device implantation. The majority of the reported cases are in patients who had a true ASD rather than PFO (Amedro et al. 2017; Krantz and Lawton 2014). Despite advances in diagnostic and therapeutic techniques, morbidity and mortality rates in IE remain high. For patients with fever and prosthetic devices in which endocarditis is suspected, TEE is the test of choice and should be performed promptly. TEE can reveal mobile vegetations on the left or right atrial aspect of the PFO device (Krantz and Lawton 2014). Although the use of antibiotic prophylaxis in the prevention of infective endocarditis has been controversial (Thornhill et al. 2018), in patients whose devices might be incompletely endothelialized a short therapy aimed at IE prophylaxis
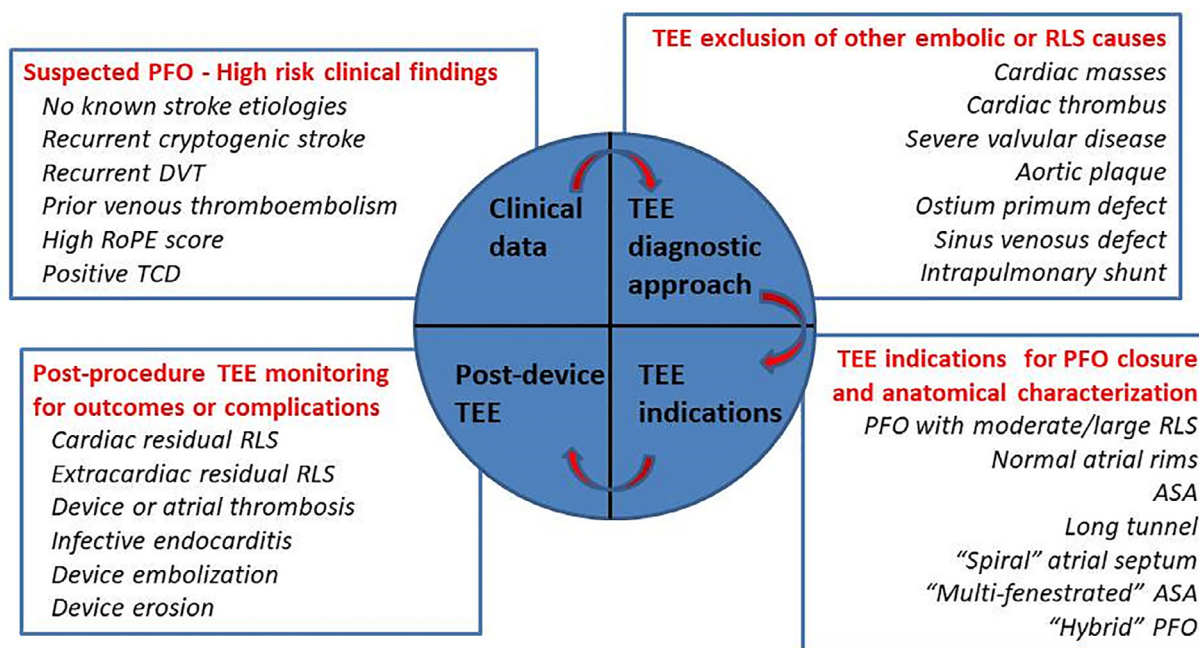
Fig. 5. Schematic summarizing the role of TEE in the indications for PFO closure and post-procedure follow-up. ASA = atrial septal aneurysm; DVT = deep vein thrombosis; PFO = patent foramen ovale; RLS = right-to-left shunting; RoPE = Risk of Paradoxical Embolism; TCD = transcranial Doppler; TEE = transesophageal echocardiography.

would be appropriate during high-risk events causing transient bacteremia.

Erosion (and later pericardial effusion and/or perforation) can occur as soon as 48 h after the procedure, but also long after device implantation (Collado et al. 2018; Yared et al. 2009). Although death from such mechanical complications is rare, the risk of erosion is estimated to be 0.01%−0.02% (Collado et al. 2018). Because it has been reported to occur in the first 3 mo but also 3 y after the initial procedure, this time range and possible lack of symptoms suggest the need for long-term monitoring for potential complications. Some echocardiographic findings have been identified that increase the risk of erosion in ASD closures and can also be applied to PFO closures, such as absent aortic rim, scanty posterior rim and atrial septal malalignment (Amin 2014).

The rate of venous thromboembolism (which comprised events of pulmonary embolism and deep vein thrombosis) was higher in the PFO closure group than in the medical therapy group in the Respect trial (Saver et al. 2017). The rate of venous thromboembolism in the latter two groups exceeded that in healthy populations. The higher rate of venous thromboembolism in the PFO closure group could be explained by the lower intensity of anti-thrombotic therapy compared with the medical therapy group, including the less common use of anticoagulant agents. The propensity for venous thromboembolic events was particularly strong in the subgroup of patients who had previous and clinically manifest deep vein thrombosis. The important role of TTE and TEE in managing patients with pulmonary embolism has been reported (Mookadam et al. 2010). Right ventricular dysfunction, significant pulmonary hypertension and free-floating right heart thrombus are echocardiographic markers identifying patients at higher risk for morbidity and mortality.

The overall incidence of new-onset atrial fibrillation (AF) post-PFO closure varies from 3%−14% (Collado et al. 2018). The mechanical irritation caused by the device can be one of the causes as it may behave as an electrical obstruction and lead to new LA or RA re-entry circuits. Moreover, it can cause a local inflammatory response as a result of a foreign body reaction and provoke arrhythmias, especially in older patients. However, potential mechanisms promoting AF development include not only the local stretch or irritation derived from the device itself but also intrinsic factors related to the patient and particularly pre-existent atrial enlargement and dysfunction (Vitarelli et al. 2018). Diagnosis and treatment of AF after PFO closure should be done expeditiously under TEE guidance, because these patients have a higher incidence of LA thrombi compared with those without AF.

Residual shunts are usually diagnosed during post-procedure TCD or TTE/TEE with color Doppler echocardiography or by agitated saline contrast injection, both at rest and with the Valsalva maneuver (Greutmann et al. 2009; Shah et al. 2018; Wintzer-Wehekind et al. 2019).

Although there remains some controversy over the relative sensitivity of TCD and TEE in detecting PFO shunting (Yamashita and Oshima 2017), TEE allows a more complete assessment of residual shunts (Shah et al. 2018; Vitarelli et al. 2014) by detecting a leak through the defect/device, additional fenestrations or bubble entry through pulmonary veins. In a recent study using an Amplatzer PFO occluder (Shah et al. 2018), the incidence of residual RLS was 19.5% at a mean of 4 mo of follow-up, which decreased to 8.4% at 11 ± 2 mo. Interatrial shunting may occur from around the device or from within the device. Residual right-to-left shunts, seen immediately after device closure of PFO, often disappear or decrease after endothelialization of the device. However, in some patients, persistent shunting may be seen many months post-procedure. Serial TEE evaluations can be used in these cases to follow the degree of shunting and possible appearance of symptoms. The management of significant residual post-procedure RLS is controversial. The therapeutic possibilities are anti-aggregant or anti-coagulant therapy, percutaneous closure with an additional device and surgical treatment. Closure rate may improve over time as the device endothelializes, but a second device may be necessary (Susuri et al. 2017) if the residual PFO shunt is associated with clinical events such as recurrent ischemic stroke.

Defining the mechanism for RLS, either a residual defect or an additional RLS pathology not detected earlier, is important. In some patients with persistently positive results on bubble studies, other anatomic lesions may coexist and represent a potential risk factor for recurrent paradoxical embolization (Shah et al. 2018). Most of these conditions can be treated with transcatheter interventions.

Pulmonary arteriovenous malformations (PAVMs) constitute one such anomaly that has been reported to be responsible for cryptogenic stroke. Nearly half of the patients with PAVMs present with hereditary hemorrhagic telangiectasia (HHT), an autosomal-dominant condition, but there are also isolated cases of PAVM unrelated to HHT. The incidence of PAVM in the general population is reported as 1:5000, whereas other studies in patients after PFO closure have reported a variable rate on the basis of the finding of persistent RLS (Shah et al. 2018). Despite some potential pitfalls, intrapulmonary shunt can be detected by contrast TEE (Abushora et al. 2013; Sinha et al. 2016) as direct visualization of bubbles entering the left atrium from one or more pulmonary veins. Chest computed tomography (CT) or pulmonary angiography complements the diagnosis.

A persistent left superior vena cava (PLSVC) is the most common anomalous systemic venous return anomaly (Sheikh and Mazhar 2014; Thaiyananthan et al. 2009). In most patients, it drains into the right atrium through the coronary sinus (CS), but can communicate with the left atrium in the absence of an intact CS roof. Its presentation may range from asymptomatic to right heart dilation or even resting cyanosis, but should also be considered as an alternative diagnosis in patients presenting with paradoxical embolization. A left antecubital vein saline contrast injection during TEE can be used to diagnose a PLSVC draining into the coronary sinus. Cardiac CT or magnetic resonance imaging can confirm the diagnosis and help to define the extent of the defect and associated other congenital anomalies.

Hepatopulmonary syndrome (HPS) is considered in patients with the triad of liver disease, impaired oxygenation and intrapulmonary microvascular dilations. The prevalence of HPS among patients with chronic liver disease in the literature is approximately 24% (Rollán et al. 2007; Scott-Herridge et al. 2016). Although the pathophysiology of HPS is incompletely understood, it has been hypothesized that the inability of the liver to clear or inhibit nitric oxide, endothelin-1 and tumor necrosis factor α may play a role in the formation of pulmonary arteriovenous malformations. TEE can be effective in ruling out an intracardiac shunt and also to show late transfer of agitated saline contrast from the right-sided circulation into the left atrium. When the diagnosis of liver cirrhosis is not initially suspected, the TEE finding may lead to abdominal ultrasound imaging and liver biopsy to confirm the diagnosis.

Future directions

Transcatheter structural heart disease intervention is a rapidly growing field, and both the implementation of new devices and the application of new sophisticated imaging techniques are evolving. Proper devices for specific anatomic varieties will refine the success of the procedure and reduce the rate of residual shunts and/or complications. The communication among echocardiographers and interventionists is vital, and the role of the echocardiographer is crucial, especially when 2-D and 3-D imaging data are combined. Advancements in technology have improved the balance between spatial and temporal resolution in 3-D echocardiography. The full potential of 3-D echocardiography is not yet completed, and new techniques under development, such as 3-D printing and virtual reality simulations (Lang et al. 2018), could help in demonstrating how different atrial devices work in a dynamic interventional model and create dynamic displays using multiple 3-D images throughout the cardiac cycle. Future studies will aid in understanding the role of these advanced technologies in routine clinical care.

CONCLUSIONS

In young patients with PFO and cryptogenic stroke ("PFO-mediated stroke") the combined assessment of high-risk clinical and TEE data helps in the indications for transcatheter device implantation. Guidelines should

be updated to reflect the superiority of device treatment over medical therapy and include anatomo-functional TEE findings. Some clinical questions related to imaging findings remain to be solved. What should be done in patients >60 or in young patients with anatomically low-risk PFO? And primarily, in patients with high-risk PFO echocardiographic anatomy, should we always wait for the first stroke before deciding to close? Further studies are needed to clarify these points.

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