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PATENT FORAMEN OVALE AND STROKE

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SUMMARY

The presence of a patent foramen ovale has been found to be associated with an increased risk of ischemic stroke of otherwise unknown origin (cryptogenic stroke). The present article will review the evidence regarding this association, the technical aspects of PFO detection, and the preventive options to decrease the risk of recurrent cerebral events.

Frequency of PFO in the population

The foramen ovale is a normal component of the fetal circulation that usually closes after birth because of the fusion between the two embryologic components of the atrial septum, the septum primum and septum secundum. In many individuals, a small communication persists into adult life, and is referred to as a patent foramen ovale (PFO). The frequency of a PFO in the population has been reported at 15% to 35% in autopsy studies [1–3] and appears to decrease with age[3]. In-vivo studies that have used transesophageal echocardiography (TEE) have reported a prevalence of PFO in the population very similar to that of the autopsy studies (24.3%)[4]. The prevalence of PFO has been described as similar across different race-ethnic groups[5].

Detection of PFO

In its most common variety, a PFO is a virtual conduit located at the site of confluence of the septum primum and septum secundum, which opens whenever the pressure in the right atrium exceeds the pressure in the left atrium. Therefore, the diagnostic techniques for PFO detection are based on the direct visualization of the opening or of its functional consequence, the right-to-left shunt. The assessment is usually performed at rest and during maneuvers, such as the Valsalva maneuver or cough, which increase the pressure in the right-sided chambers of the heart and may therefore unmask a shunt not visible under resting conditions. The diagnostic techniques most commonly used for PFO detection are TEE, transthoracic echocardiography (TTE) and transcranial Doppler (TCD), performed with contrast injection to allow the visualization of any right-to-left shunt. The contrast material may be aerated and agitated saline solution or a polygelatine agent. For screening purposes, TTE or TCD are generally used. TEE is the gold standard for the diagnosis due to its higher diagnostic accuracy, but, due to its semi-invasive nature, is usually reserved to cases in which a better anatomic definition of the PFO is needed. With contrast TTE, the study is considered positive when any microbubble is seen in the left-sided chamber within three cardiac cycles after the contrast material fills the right-sided chambers (Figure 1). Contrast

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TTE has been shown to have lower sensitivity for PFO detection than TEE (50–60%) [6–9]. Recent advances in imaging technique have led to an improved sensitivity of TTE (80–90%) [10, 11]. Probably due to the lower sensitivity of TTE for small shunts, the prevalence of PFO by contrast TTE in the general population has reported to be lower than by TEE (14.9% vs. 24.3%)[4, 12].

Contrast TCD is also used to detect a PFO (Figure 2). The sensitivity of TCD has been shown to be slightly lower than that of TEE in some studies[7, 13], but essentially equivalent to it in others [14, 15].

TEE is considered the gold standard for the diagnosis of PFO. Its sensitivity and specificity have been reported to be essentially 100%[16]. TEE also allows the direct visualization of the PFO opening in most patients (Figure 3), and therefore the direct measurement of the separation between septum primum and secundum as an indicator of PFO size. Also, TEE allows the direct visualization of the pulmonary veins, therefore resulting in a more accurate distinction between PFO and intrapulmonary shunt than possible by TTE or TCD.

Major complications resulting from the performance of TEE are rare (0.2% in a published series) [17].

Atrial Septal Aneurysm (ASA)

An atrial septal aneurysm (ASA) is a protrusion of a segment of atrial septum into either atrial chamber. A protrusion of at least 10 mm with base of at least 10 mm is generally considered diagnostic of ASA[5, 18]. The prevalence of ASA in the population appears to be low (approximately 1–4%) [4, 12, 19]. When present, an ASA is associated with a PFO in over 60% of cases[18, 20, 21]. TEE can identify the presence of an ASA very accurately (Figure 4). TTE can also detect an ASA, although with lower sensitivity than TEE[18, 20].

PFO, ASA and stroke risk

In the past twenty years, the association between PFO and cryptogenic strokes, which represent up to 40% of ischemic strokes[22], has been established. The present section will review the evidence supporting this association.

Case-control studies

The relationship between PFO and cryptogenic stroke was first described in patients younger than 55[23] or 40[24] years of age. The hypothesized stroke mechanism is paradoxical embolization, or the embolization to the systemic arterial circulation of thrombus originated in the venous circulation. Paradoxical embolization, whose occurrence is documented by the occasional detection of thrombus lodged in the PFO (figure 5), often remains a presumptive rather than a certain diagnosis.

The association between PFO and cryptogenic stroke in younger patients was confirmed in multiple studies with TTE or TEE [25–29]. Overall, younger stroke patients have a to 4-fold increase in PFO prevalence compared to stroke-free control subjects of same sex and age (Table 1A). The association has been more controversial in elderly subjects, in whom it has been invoked [27] or negated[30] [31]. Recently, a TEE study reaffirmed its existence in the older age group after adjustment for other stroke risk factors (odds ratio 3.00, 95% confidence interval 1.73 to 5.23; $p<0.001$)[29]. The strength of the association was in fact similar to that observed in younger patients (odds ratio 3.70, 95% confidence interval 1.42 to 9.65; $p=0.008$) [29]. Combined results from studies in the elderly suggest the existence a 2-fold increase in PFO prevalence in stroke patients compared to controls (Table 1B).

Therefore, the association between PFO and cryptogenic stroke appears to exist in all age groups, although it may be stronger in younger individuals.

ASA has also been linked to an increased risk of ischemic stroke. ASA was significantly more frequent in patients with cryptogenic stroke than in controls (15% vs 4%; $p<0.05$)[20]. However, a coexisting PFO is very often seen in patients with ASA (60–70% of cases), and the PFO size tends to be larger in them [21, 32]. Therefore, the associated stroke risk may reflect the frequent coexistence of a PFO. However, the coexistence of the two abnormalities may be a stronger stroke risk factor than either condition alone. In a meta-analysis, the odds ratio for stroke was 1.83 for PFO alone and 2.35 for ASA alone, but 4.96 for their combination [31]. In stroke patients below age 55 treated with aspirin, the 4-year recurrent stroke rate was markedly higher (15.2%) in those with combined PFO and ASA than in those with isolated PFO (2.3%) or no PFO (4.2%)[33]. Patients with PFO and ASA were shown to have more often multiple acute brain lesions, a hallmark of embolic mechanism, than patients with PFO alone (53% vs. 17%; $p=0.01$) [34]. Other potential stroke mechanisms from an ASA include in situ thrombus formation, which is probably rare [18]; a predisposition to the development of atrial arrhythmias, which remains controversial [35, 36]; and left atrial dysfunction, a precursor of thrombus formation [37].

Stroke Risk in the General Population

The above data were obtained from case-control studies, therefore on individuals that had already had an event compared to stroke free-subjects of similar sex and age. This approach, although effective, suffers from an inherent risk of incomplete matching of cases and controls with regard to pertinent variables, and may therefore lead to biased results. Prospective studies do not suffer from those limitations, and two such studies examined the role of a PFO in the general population. In the Stroke Prevention: Assessment of Risk in a Community (SPARC) study, the stroke risk from cardiac embolic sources was investigated by TEE [4]. The prevalence of PFO was 24.3%. Over a median follow-up of approximately five years, PFO was found not to be independently associated with increased risk of cerebrovascular events (hazard ratio 1.46, 95% confidence interval 0.74–2.88). In the population-based Northern Manhattan Study (NOMAS), the presence of a PFO was sought by contrast TTE in 1,100 stroke-free individuals [12]. PFO prevalence was lower (14.9%), reflecting the lower sensitivity of TTE. Over a mean follow up of almost seven years, PFO was not independently associated with ischemic stroke (hazard ratio 1.64, 95% confidence interval 0.87–3.09). Therefore, the two studies, although on different populations and using different diagnostic tests, obtained remarkably similar results, with a slight, non-significant increase in stroke risk in individuals with PFO. Both studies hinted at an increased stroke risk from an ASA, but numbers were too small to allow any conclusions. The presence of both PFO and ASA did not increase the stroke risk in NOMAS, while the information was not available in SPARC. In general, these studies did not support the concept of an increased stroke risk from a PFO, although the possibility exists that a significant effect might have been observed with larger sample sizes or longer follow up durations.

Possible associated factors

Since the results of the population-based prospective studies did not confirm the result of the case-control studies, it appears that co-factors may exist that increase the risk associated, and may be more frequently present in stroke patients. This section will review some of the potential cofactors.

Anatomical variants—The size of the PFO (intended as the separation between septum primum and septum secundum on TEE) has been linked with stroke risk in multiple studies [38, 39].

The degree of shunt through the PFO (inferred from the count of microbubbles in the left atrium) has also been associated with stroke risk, although this has not been confirmed in recent studies[40].

The role of a prominent Eustachian valve (the remnant of the valve that directs the blood from the inferior vena cava to the fossa ovalis of the atrial septum) as a co-factor in the stroke risk has been controversial. [39, 41]. An example of thrombus on Eustachian valve is presented in Figure 6. A Chiari's network (a web-like network of threads and fibers variably connecting the Eustachian valve to other atrial structures) is more frequently seen in patients with a PFO, ASA [21] and unexplained arterial embolism[42].

Hemodynamic factors—Conditions that increase the right atrial pressure have the potential to increase the degree of right-to-left shunt through the PFO, and therefore the likelihood of paradoxical embolization. Pulmonary embolism, right ventricular infarction and severe tricuspid regurgitation have been associated with increased shunting through a PFO.

Deep venous thrombosis (DVT)—The presence of a DVT can enhance the risk of paradoxical embolization through a PFO. An increased prevalence of DVT in cryptogenic stroke patients with a PFO was reported[43] but not confirmed[44]. The diagnostic technique used is also important, as pelvic vein thrombi, a potential source for paradoxical embolism [45], may be diagnosed by venography or MRI venogram, but are difficult to assess by ultrasound techniques.

Prothrombotic states—Blood hypercoagulability may facilitate thrombus formation in the vascular system, providing the substrate for paradoxical embolization. G20210A and factor V Leiden mutations have been reported in patients with cryptogenic stroke and PFO[46, 47]. One of these prothrombotic genotypes, more often G20210A mutation, was more frequently observed in young cryptogenic stroke patients than in age-matched controls (10.3% vs. 2.5%; p=0.008), and increased the stroke risk by over 4-fold[48]. The combination of PFO and antiphospholipid antibodies did not significantly increase the stroke risk stroke in a multicenter study [49]. Recent surgery, trauma, or use of oral contraceptives may be associated with blood hypercoagulability and consequent greater potential for paradoxical embolization [50].

Prevention of recurrent events

The efforts to prevent recurrent events has focused on decreasing the likelihod of thrombosis or closing the PFO.

Antithrombotic treatment

The most frequently used antithrombotic drugs have been vitamin K inhibitors (such as warfarin) and antiplatelet agents, especially aspirin. From various meta-analyses, the rate of recurrent stroke or transient ischemic attack (TIA) whilst on these treatments was 4 events/100 person-years [51], and almost 5 events/100 person-years when death was also included [52]. In most studies, the treatment was not randomized. The only trial with randomized treatment assignment was the Patent Foramen Ovale in Cryptogenic Stroke study (PICSS), a TEE-based substudy of the Warfarin Aspirin Recurrent Stroke Study (WARSS), which randomized patients with non-cardioembolic stroke to aspirin 325 mg or warfarin (target INR 1.4 to 2.8) [53]. In PICSS, 630 patients underwent TEE early after stroke. Over 2 years of follow-up, no significant differences in rates of recurrent stroke and death were observed between patients with and without a PFO (hazard ratio 0.96, 95% confidence interval 0.62 to 1.48), even in patients with cryptogenic stroke (hazard ratio 1.17, 95% confidence interval

0.60 to 2.37) [54]. Similar results had been previously obtained in two studies in which the treatment was not randomized (La Sapienza study, 86 cryptogenic stroke patients treated with aspirin, warfarin, both or neither)[55] or consisted of only aspirin (PFO/ASA French study, 581 stroke patients below age 55)[33]. No significant differences in annual rates of stroke or death was reported between stroke patients with and without a PFO (3.7% vs. 4.5% in La Sapienza study; 1.5% vs. 1.8% in the PFO/ASA French study). The French study documented a higher annual event rate (3.7%) for patients with both PFO and ASA, raising the question that aspirin may not be sufficient protection in those patients. In PICSS, however, the combination of PFO and ASA did not carry an increased risk of recurrent events compared with neither condition (hazard ratio 1.04, 95% confidence interval 0.51 to 2.12). This finding was confirmed by the CODICIA study on 200 stroke patients with PFO treated with warfarin or aspirin[40]. The presence of larger shunt was also not found to significantly affect the risk of recurrent events in PICSS [54] or CODICIA[40].

It therefore appears that antithrombotic treatment reduces the risk of recurrent events in stroke patients with a PFO to the level of stroke patients without it. By combining the data of PICSS, La Sapienza and PFO/ASA studies, the hazard ratio of PFO for recurrent stroke and death is 0.95[56]. Whilst conclusive data are not available on the relative efficacy of warfarin and aspirin treatment, the event rates observed in PICSS did not suggest a definite advantage for either treatment.

PFO closure

Surgery

Surgical PFO closure was initially performed in selected cryptogenic stroke patients, and has become infrequent since the introduction of percutaneous closure devices. A low incidence of recurrent cerebrovascular events was reported after surgical closure in younger patients [57, 58], but not in older ones[57]. A meta-analysis on 161 patients (mean age 43 years) reported an annual risk of recurrent stroke or death of 0.85% (95% CI, 0.10 – 3.07%)[52].

PFO closure is sometimes performed prophylactically in patients undergoing open heart surgery for other indications, but this practice is questioned. A study on over 13,000 cardiac operations showed no significant differences in perioperative stroke (2.3% vs. 2.3%; p=0.84) and in-hospital death (3.4% vs. 2.6%; p=0.11) between patients with or without a PFO; however, patients who had their PFO surgically closed experienced a 2.5-fold increase in the risk of in-hospital stroke compared with those who did not (2.8% vs. 1.2%; p=0.04), and showed no long-term survival benefit over a mean follow-up of 5.6 years[59].

Transcatheter closure

The introduction of percuteaneous closure devices has offered a less invasive alternative for closing a PFO. An example of PFO closure is shown in Figure 7. Data on the efficacy of these devices have come from case series and non-randomized studies. In a pooled analysis of studies published until 2004[52], the combined rate of recurrent stroke, death or TIA for PFO closure was 2.95 events/100 person-years. As devices have been improved, the incidence of recurrent events has decreased. In 131 patients, no recurrent embolic events were reported over a mean follow–up of 30 months[60]. Complications from device implantation have also decreased. In a meta-analysis of 1,355 patients, major complications such as death, major hemorrhage, cardiac tamponade and fatal pulmonary emboli were reported in approximately 1.5%[61]. Other complications such as atrial arrhythmias, device arm fractures, embolization or thrombosis, EKG changes, and arterio-venous fistula formation were observed in 7.9%[61]. In a multicenter European study on 430 patients, peri-procedural complications occurred in 11.5% of patients, 0.2% of which defined as major[62].

Transcatheter PFO closure may cause microembolization to the brain. Transient microembolic signals were detected by TCD in 28 of 29 patients during the procedure [63]. Repeat brain MRI documented new microembolic lesions after PFO closure in 3 of 35 subjects (8.6%)[64].

Atrial fibrillation is relatively frequent after PFO closure, with an annual incidence of 2.5%, which appears not related to device type or size [65].

Antithrombotic treatment versus PFO closure

Several randomized trials comparing PFO closure and antithrombotic treatment are ongoing, but the first results are not expected for at least another year [66]. So far, the patient populations in studies that have looked at PFO closure and studies that have examined antithrombotic treatment have differed. In general, patients in PFO closure studies tended to be younger and have higher frequency of previous thromboembolic events, whereas patients in the medical treatment studies tended to have higher frequencies of traditional stroke risk factors such as diabetes and cigarette smoking [61]. In 308 cryptogenic stroke patients with PFO treated medically (158 patients) or with PFO closure (150 patients), recurrent stroke or TIA tended to be less frequent in the closure group (7.8% vs. 22.2%; $p = 0.08$; 95% CI 0.23 to 1.11), especially in patients with multiple cerebrovascular events at baseline [67]. As treatment was not randomized, patients with larger PFOs or multiple cerebrovascular events were more frequently assigned to PFO closure.

Because of the lack of data from randomized clinical trials, the treatment choice has been empirical. Supporters of PFO closure deem the available data strong enough not to withhold a potentially life-saving treatment while awaiting the results of randomized clinical trials[68]. Supporters of medical treatment argue that such treatment has been proven to essentially eliminate the PFO-related risk of stroke, and that a therapeutic paradigm shift such as PFO closure in stroke patients should only be entertained after evidence of its superiority has been proven by randomized trials[69]. The 2006 AHA/ASA guidelines for the prevention of stroke in patients with ischemic stroke or TIA deemed the available evidence insufficient to recommend PFO closure in patients with a first stroke[70]. Aspirin treatment was considered adequate in most stroke patients, with warfarin treatment recommended instead in case of coexisting DVT or prothrombotic state. The guidelines recommended to consider PFO closure in patients with recurrent cryptogenic stroke despite medical therapy[70].

Conclusion

Although the association between PFO and increased risk of stroke has been established, the role of a PFO as a stroke risk factor in the general population has not been confirmed. No preventive treatment is therefore necessary in individuals with an incidentally detected PFO. In stroke patients, treatment with antiplatelet agents (aspirin) appears to confer sufficient protection against recurrent events. Systemic anticoagulation should be preferred in patients with coexisting deep venous thrombosis or prothrombotic conditions. While awaiting the results of randomized trials, PFO closure appears indicated in patients with contraindications to medical treatment, or who experience recurrent events whilst on it. Further research is necessary to establish the optimal preventive treatment in patients with the more infrequent combination of ASA and PFO. Finally, a better understanding of co-factors that may increase the PFO-related stroke risk may allow a more rational and targeted approach to preventing recurrent embolic events.

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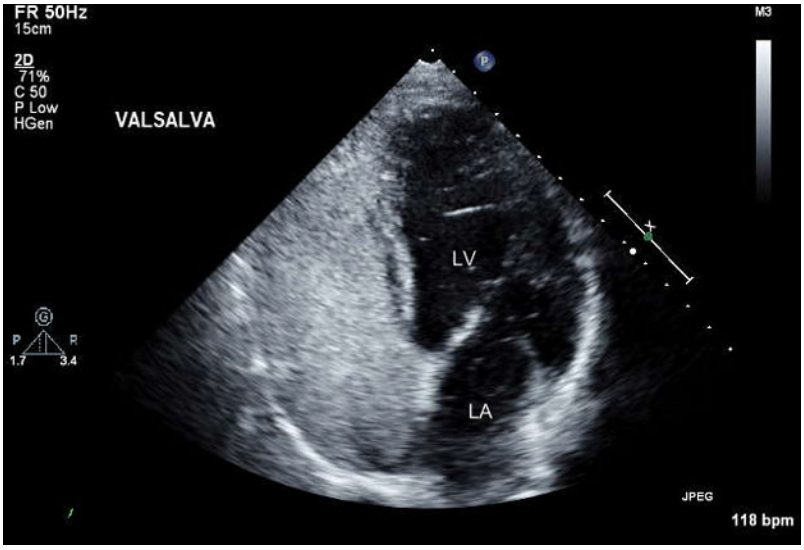

Figure 1.
Example of PFO detection by transthoracic echocardiography (TTE) with contrast injection. Microbubbles are visualized filling the right-sided chambers and into the left atrium (LA) and left ventricle (LV).

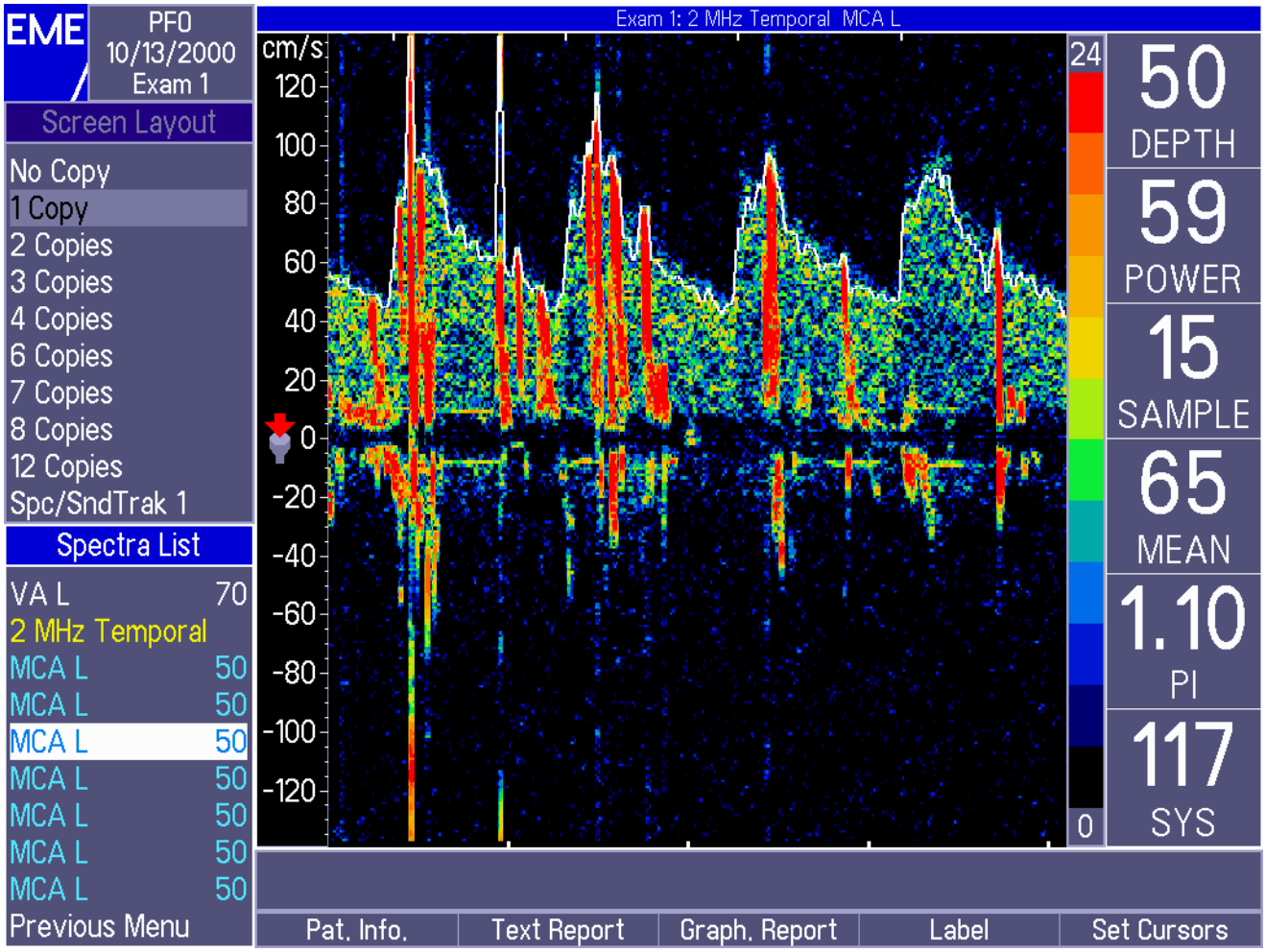

Figure 2.
Detection of microbubbles by transcranial Doppler (TCD) in the middle cerebral artery of a patient with a PFO. Microbubbles are visualized as spikes superimposed to the normal blood flow

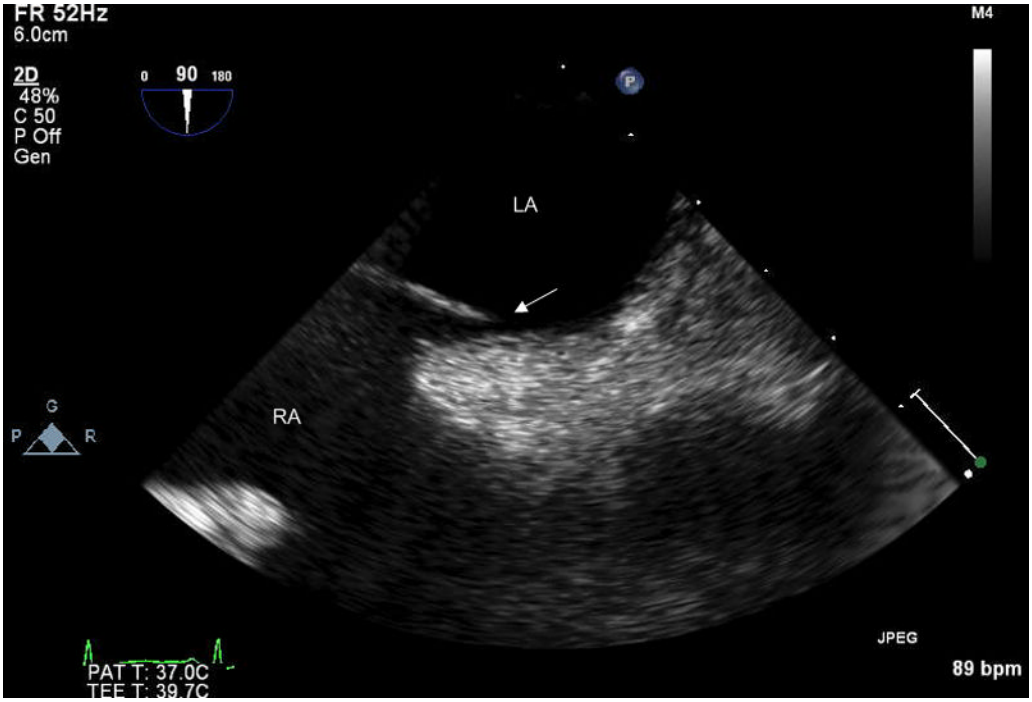

Figure 3.
Direct visualization of PFO by TEE. A separation (arrow) is seen between septum primum and septum secundum.
LA = left atrium; RA = right atrium

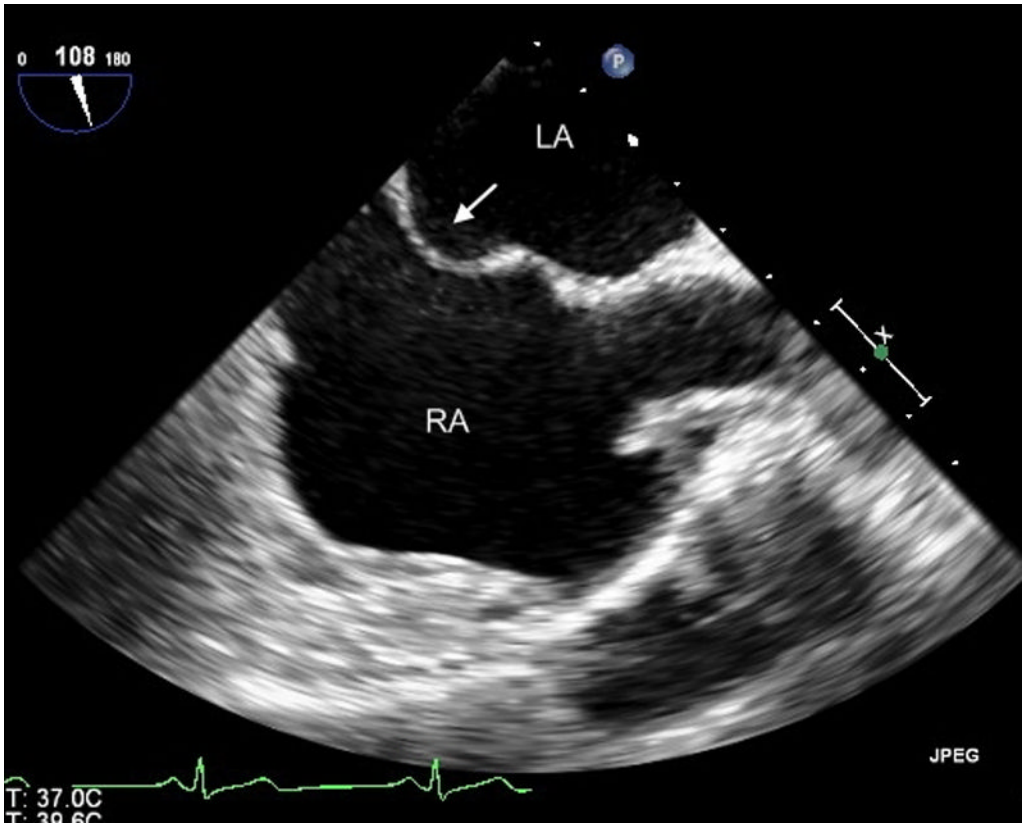

Figure 4.
Visualization of atrial septal aneurysm (ASA) by TEE. Protrusion of the atrial septum towards the right atrium is visible (arrow).
LA = left atrium; RA = right atrium

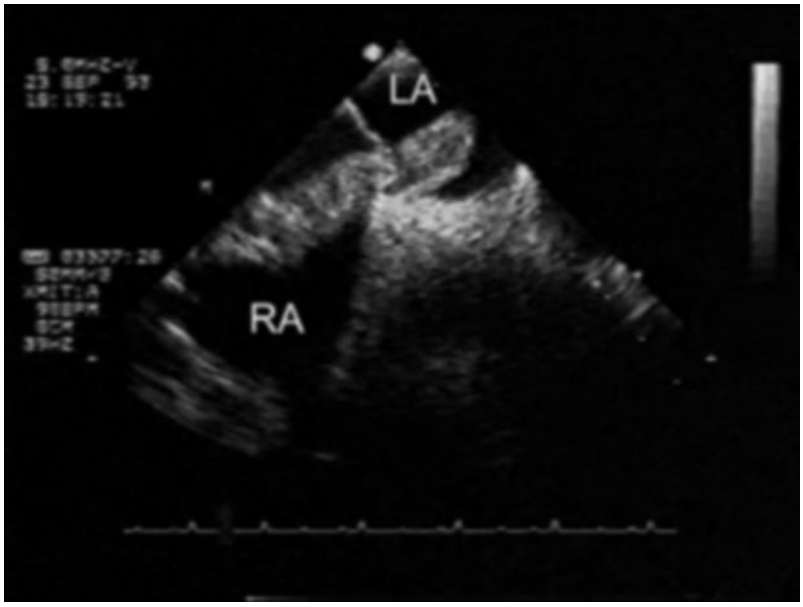

Figure 5.
Visualization by TEE of large thrombus crossing the PFO (arrows).
LA = left atrium; RA = right atrium

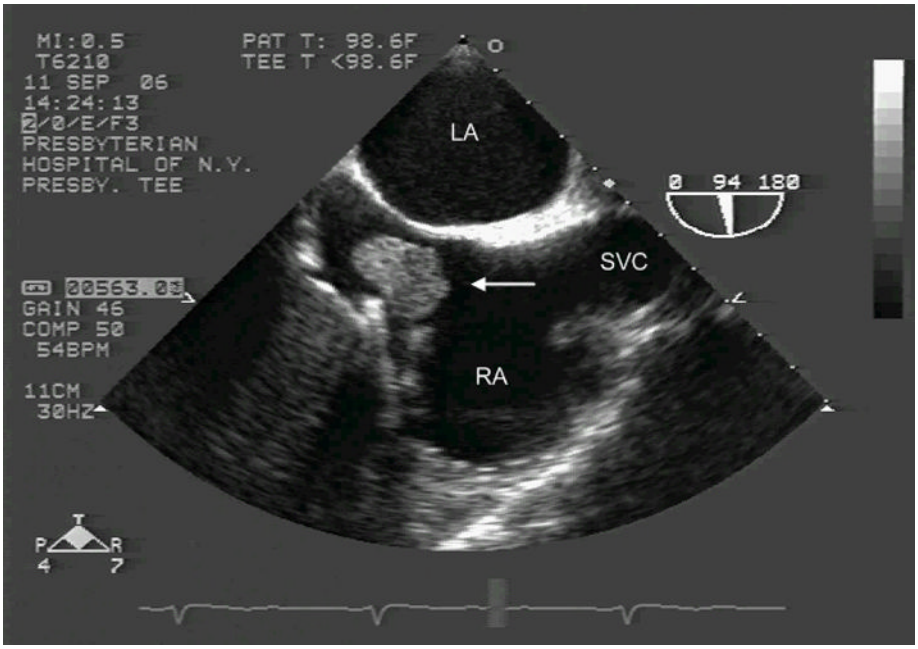

Figure 6.
Visualization by TEE of large thrombus (arrow) on the Eustachian valve.
LA = left atrium; RA = right atrium; SVC = superior vena cava

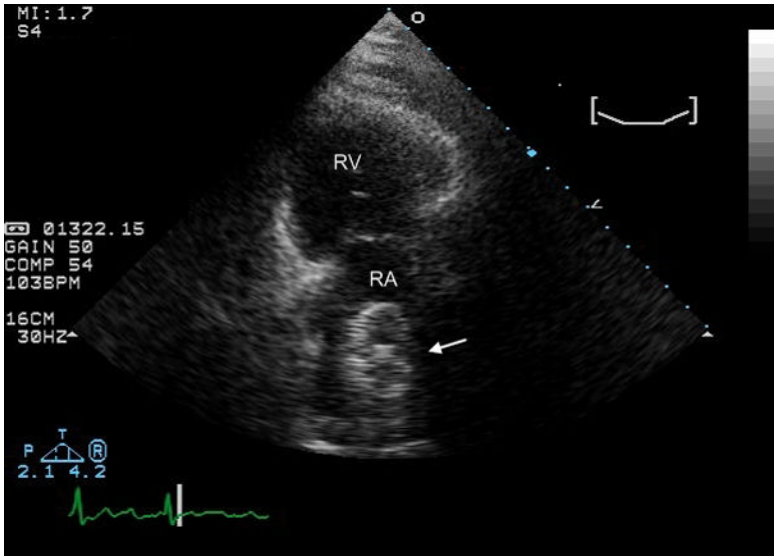

Figure 7.
Visualization by TTE (long axis view) of a PFO closing device.
RV = right ventricle; RA = right atrium

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TABLE 1A

Relationship of Cryptogenic Stroke with PFO in Younger Patients

Study	N (patients)	Age	PFO (Cryptogenic)	PFO (Control)	P-Value
Lechat[23]	26	<55	54% (14/26)	10% (10/100)	<0.001
Webster[24]	34	<40	56% (19/34)	15% (6/40)	<0.001
Cabanes[25]	64	<55	56% (36/64)	18% (9/50)	<0.001
De Belder[26]*	39	<55	13% (5/39)	3% (1/39)	-
Di Tullio[27]	21	<55	47% (10/21)	4% (1/24)**	<0.001
Hausmann[28]	18	<40	50% (9/18)	11% (2/18)	<0.05
Handke [29]	82	<55	44% (36/82)	14% (7/49)**	<0.001
TOTAL			45% (129/284)	11% (36/320)	<0.001

*Includes different stroke subtypes

**Controls were patients with stroke of known cause

TABLE 1B

Relationship of Cryptogenic Stroke with PFO in Older Patients

Study	N (patients)	Age	PFO (Cryptogenic)	PFO (Control)	P-Value
De Belder[26]*	64	>55	20% (13/64)	5% (3/56)	<0.001
Di Tullio[27]	24	>55	38% (9/24)	8% (6/77)**	<0.001
Hausmann[28]	20	>40	15% (3/20)	23% (23/98)	NS
Jones[30]	57	>50	18% (10/57)	16% (29/183)	NS
Handke[29]	145	>55	28% (41/145)	12% (28/232)**	<0.001
TOTAL			25% (76/310)	14% (89/646)	<0.001

*Includes different stroke subtypes

**Controls were patients with stroke of known cause

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