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PFO and Stroke: What Should Be Done?

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Abstract

Purpose of review—The role of a patent foramen ovale (PFO) as a risk factor for ischemic stroke has been established in recent years. However, the best therapeutic option to prevent recurrent events is still controversial, with antithrombotic treatment or transcatheter PFO closure being favored by different clinicians. Also, associated conditions that may guide the therapeutic choices are being investigated

Recent findings—The stroke risk associated with a PFO, mainly considered of importance in younger patients, has also been recognized and better defined in patients over the age of 55 years. The study of potential cofactors that may increase the possibility of paradoxical embolization through the PFO has made some progress, and holds promises of allowing more informed and rational treatment choices in the future. More data have become available on the efficacy of transcatheter PFO closure.

Summary—The approach to patients with PFO and ischemic stroke has been better defined in recent years. However, a better understanding of factors that increase the stroke risk in subjects with a PFO and the results from randomized treatment trials comparing medical treatment with PFO closure are needed to further advance the field.

Keywords

foramen ovale; stroke; cardiac embolism; coagulation

Introduction

In the past 20 years, the role of a patent foramen ovale (PFO) as a risk factor for ischemic stroke has been established, especially for those strokes that lack an apparent cause (cryptogenic strokes). Therapeutic strategies have been developed to decrease the risk of recurrent events in patients with PFO, but controversies exist on whether antithrombotic treatment or closure of the PFO should be preferred. Also, given the high prevalence of PFO in the general population, the identification of subjects at higher risk of stroke before the stroke occurs would be of great importance.

This review will briefly summarize the evidence on the relationship between PFO and ischemic stroke, the possible role of associated factors in enhancing the stroke risk, and the therapeutic strategies adopted to decrease it.

PFO and ischemic stroke

The present section will review the frequency of PFO in the population, the modalities for its detection and its role as risk factor for stroke.

Frequency of PFO in the general population

A PFO is a normal component of the fetal circulation, and is supposed to close early after birth. In approximately one out of four subjects, however, the closure is incomplete, leaving a small communication between the left and the right atrium. This communication is referred to as a PFO, and is usually insignificant from a hemodynamic standpoint, but represents a conduit for shunting of the blood between the atria. The prevalence of PFO in the general population has been reported to be between 15% and 35% in autopsy studies[1-4], and tends to decrease with age[3]. Another abnormality of the interatrial septum possibly associated with stroke is an atrial septal aneurysm (ASA), a discrete protrusion of a redundant atrial septum into either atrial chamber. An ASA is found in a 1-4% of the population, and approximately 60% of ASA are associated with a PFO[5-13].

Detection of PFO in vivo

A PFO is usually identified by transthoracic echocardiography (TTE) with injection of contrast material, usually aerated saline solution (Figure 1). If present, an ASA can also be identified with this test in most cases (also Figure 1). Transesophageal echocardiography (TEE), a semi-invasive test that requires conscious sedation, is used when further assessment is necessary. TEE is the most sensitive technique for PFO detection, and in most cases it may allow the direct visualization of the separation between the two septal components (Figure 2), thus allowing its measurement to be used as an indication of shunting potential. The use of Valsalva maneuver or cough to increase the right atrial pressure and therefore make a right-to-left shunt visible increases the sensitivity of both TTE and TEE (Figure 1 B).

PFO, ASA and risk stroke risk

A PFO is a conduit for paradoxical embolization, which is the embolization in the systemic arterial circulation of a thrombus originating in the venous system. Among ischemic strokes, approximately 40% are cryptogenic[14]. The association between PFO and cryptogenic stroke was first reported in case-control studies in patients younger than 55 years[15-20], which showed an over four-fold increase in prevalence of PFO in patients with cryptogenic stroke compared with controls (approximately 45% vs. 11%; $p<0.001$)[21]. The association between PFO and stroke in older patients has been more controversial [18-20;22] and was questioned in a meta-analysis that evaluated case-control studies published until 2000 [23]. More recently, the association between PFO and ischemic stroke in patients over the age of 55 has been confirmed by a large TEE study[24]. In that study, PFO was significantly more frequent in patients with cryptogenic stroke than in those with stroke of determined cause in both the younger subgroup (43.9% vs. 14.3%; odds ratio 4.70, 95% confidence interval 1.89 to 11.68; $p<0.001$) and the older subgroup (28.3% vs. 11.9%; odds ratio 2.92, 95% confidence interval 1.70 to 5.01; $p<0.001$). After adjustment for other stroke risk factors, PFO remained strongly associated with cryptogenic stroke in both the younger (odds ratio 3.70, 95% confidence interval 1.42 to 9.65; $p=0.008$) and the older group (odds ratio 3.00, 95% confidence interval 1.73 to 5.23; $p<0.001$)[24]. In aggregate, the studies conducted in patients over age 55 show a significantly higher prevalence of PFO in cryptogenic stroke patients than in controls (25%

vs. 14%; $p < 0.001$), although the difference is less pronounced than the one seen in younger patients[21].

Although the risk of stroke related with a PFO has been established by the case-control studies mentioned earlier, such risk appears rather low in the general population. The only two studies that prospectively followed stroke-free subjects with and without a PFO reached similar conclusions, with a slight, non-significant increase in risk of stroke and death in subjects with PFO compared with those without it (hazard ratio 1.46, 95% confidence interval 0.74-2.88 in one study [25], hazard ratio 1.64, 95% confidence interval 0.87-3.09 in the other [26]). The apparent discrepancy of these results with those of the case-control studies may be explained in different ways. The average follow up duration of the two prospective population studies (5 and 6.5 years, respectively) may have not been long enough for the effect of PFO to be fully manifested. Alternatively, other associated factors may come into play that enhance the risk of events associated with PFO in stroke patients. Some of the cofactors that may increase the risk of paradoxical embolization through a PFO are described in the next section.

Possible cofactors for paradoxical embolization

Anatomical variants of the PFO and the right atrium, and the coexistence of thrombotic or pre-thrombotic conditions have been identified as possible cofactors in increasing the risk of stroke from a PFO.

Anatomical characteristics

The size of the PFO (separation of septum primum and secundum as assessed by TEE or intracardiac ultrasound) may affect its embolic potential. Larger PFOs (over 2 mm separation) were observed more often in cryptogenic stroke patients than in those with stroke of determined stroke in the PFO in Cryptogenic Stroke Study (PICSS)[27]. Patients with larger PFOs have been found to have more often brain MRI findings suggestive of embolism than those with smaller PFOs[28]. A prominent Eustachian valve (the structure that directs the blood from the inferior vena cava towards the PFO) is more commonly seen in patients with suspected paradoxical embolism[29].

Deep venous thrombosis and hypercoagulable states

Since the embolic potential of a PFO is believed to be related to the occurrence of paradoxical embolization through it, the presence of venous thrombi or of conditions predisposing to thrombosis might enhance the likelihood of paradoxical embolization to occur. Also, the identification of one of these conditions might affect the ensuing treatment choices, making systemic anticoagulation the preferred option over other therapeutic modalities. The association of deep venous thrombosis with PFO in patients with cryptogenic stroke has been reported[30], but not confirmed in other studies[31;32]. Pelvic vein thrombi were found more frequently in young patients with cryptogenic stroke than in those with defined causes of stroke [33], but the occurrence of pelvic vein thrombosis is not routinely investigated in most stroke patients, making its real prevalence and clinical relevance difficult to evaluate.

An association between prothrombotic states and PFO in patients with cryptogenic stroke has been reported. Factor V Leiden and prothrombin G20210A mutations have been observed more often in patients with PFO and cryptogenic stroke [34-37]. In a recent study, the prevalence of at least one of these two prothrombotic genotypes was significantly higher in young cryptogenic stroke patients than in age-matched controls (10.3% vs. 2.5%; $p = 0.008$), with prothrombin G20210A mutation being far more frequent than factor V Leiden (8.2% vs. 2.1%) [38]. The association of either genotype with PFO increased the stroke risk in that study by 4.7-fold. An association between PFO size and presence of antiphospholipid antibodies has

been suggested[39]. Common risk factors for venous thrombosis, such as recent surgery, trauma, or use of oral contraceptives, may also increase the risk of paradoxical embolization through a PFO[40].

Prevention of recurrent stroke

Since paradoxical embolization from a thrombus present in the venous system is the putative mechanism of the association between PFO and stroke, antithrombotic strategies have been adopted to reduce the risk of recurrent events in patients with a PFO. The alternate therapeutic option, which is PFO closure, was initially accomplished surgically, but the use of catheter-deployed devices has recently become the norm when PFO closure is performed, eliminating the need for open heart surgery. The following section will summarize the available data on the efficacy of medical treatment and transcatheter PFO closure.

Antithrombotic treatment

Oral anticoagulation with warfarin or treatment with antiplatelet drugs, especially aspirin, are commonly prescribed in stroke patients with a PFO. The combined rate of recurrent stroke, death and transient ischemic attack (TIA) for medical treatments was 4.86 events/100 person-years in a pooled analysis of published studies[41]. In several studies that have included patients treated medically, the rate of recurrent events was not significantly different between patients with a PFO and those without it[27;42-44]. In PICSS, which was the only randomized, double-blinded study of warfarin and aspirin treatment in patients with noncardioembolic stroke and a PFO, there were no significant differences in the rates of recurrent stroke or death among cryptogenic stroke patients with or without PFO over a 2-year follow-up (14.3% vs. 12.7%; hazard ratio 1.17, 95% confidence interval 0.60 to 2.37; $p=0.65$)[27]. Although the comparison between treatment types was not the main objective of the study, no significant differences in the rates of recurrent stroke or death were observed between patients treated with warfarin (9.5%) or aspirin (17.9%; hazard ratio 0.52, 95% confidence interval 0.16 to 1.67; $p=0.28$). In another study, there was no difference in recurrent events rate between patients with and without a PFO in patients treated with aspirin (annual rates: 1.5% vs. 1.8%), but patients with combined PFO and ASA had a much higher event rate (annual rate: 3.7%). This observation lead the Authors to believe that aspirin treatment may not be sufficiently protective in patients with PFO plus ASA, a circumstance not supported by PICSS, in which the annual event rates were similar in patients with PFO (7.4%), PFO plus ASA (8.0%), or neither (7.7%). In the 2006 AHA/ASA guidelines for the prevention of stroke in patients with ischemic stroke or TIA, antiplatelet treatment was recommended in most stroke patients with a PFO[45]. Warfarin was considered a reasonable alternative for high-risk patients with a coexisting venous thrombosis or hypercoagulable state[45].

Percutaneous PFO closure

The closure of a PFO has recently received great interest, as a potentially curative approach to the problem of recurrent events in stroke patients with a PFO. An example is provided in Figure 3. A pooled analysis of studies published until 2004 reported a combined rate of recurrent stroke, death or transient ischemic attack (TIA) of 2.95 events/100 person-years, slightly lower than that of medical treatment[41]. Complications have included death, major hemorrhage, cardiac tamponade and fatal pulmonary emboli, which occurred in approximately 1.5% of the patients in a meta-analysis of 1,355 patients [46]. Other complications such as atrial arrhythmias, device arm fractures, device embolization, device thrombosis, EKG changes, and artero-venous fistula formation were reported in 7.9%[46]. As the experience with device placement has grown and newer, better devices have entered the market, rates of recurrent events and complication have decreased. In a recent study conducted in 247 patients with presumed paradoxical embolization, acute complications from device placement were reported

in 4 (1.6%), and seven recurrent strokes or TIAs were observed during a mean follow up of 14 months (2.8%)[47]. In a multicenter European study recently published, peri-procedural complications occurred in 11.5% of patients, but only 0.2% of them were considered major. Recurrent stroke or TIA rate was rather high in that study, at 3.0% over a median follow up of less than a year[48]. In another recently published study, PFO closure was shown to be effective even in patients over the age of 55 years, in whom the frequency of thromboembolic events at 18 months was 1.8%, compared to 1.3% for younger patients[49].

In summary, transcatheter PFO closure has been performed with increasing frequency for the prevention of recurrent events in stroke patients with PFO, showing good efficacy and relatively low incidence of complications. However, long-term follow up in patients treated with these devices is not yet available, and neither is a reliable comparison with the results of antithrombotic medical treatments. The current status of knowledge on the relative merit of the two strategies will be outlined in the next section.

PFO closure vs. antithrombotic treatment

Although at least two randomized clinical trials comparing PFO closure with antithrombotic treatment are ongoing, no results on this comparison are available to date. The comparisons attempted so far have been based on meta-analyses from studies that have looked at one or the other treatment strategy. These meta-analyses have pointed at a slight difference in efficacy favoring PFO closure over medical treatment[46;50], but the results were obtained from studies with substantial differences in design, definitions and patient populations. The latter circumstance may have been the result of selection bias for one on the other treatment. In general, patients referred for PFO closure were younger and more likely to have had a previous stroke or TIA, while patients treated medically, on the other hand, were generally older and had higher frequencies of other stroke risk factors, such as diabetes and smoking history[46]. Given the dearth of results from randomized trials, the choice of one treatment modality over the other has so far been largely empirical. Supporters of PFO closure quote its apparent greater efficacy and the possibility to avoid long-term antithrombotic treatment[51]; supporters of medical treatment, on the other hand, mention the non-significant difference in event rates between patients with and without PFO when they are placed on effective antithrombotic therapy, and the need for randomized treatment comparisons before a drastic shift in the therapeutic paradigm may be considered[52]. In the 2006 AHA/ASA guidelines for the prevention of stroke in patients with ischemic stroke or TIA, the available evidence was deemed insufficient to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure was considered a reasonable choice in patients with recurrent events despite medical therapy[45].

Conclusion

Although significant progress has been made in the elucidation of the role of a PFO as a risk factor of stroke, more work remains to be done. Recent advancements have been the clarification of the role of a PFO in older patients, the refinement of devices and techniques for transcatheter PFO closure and the acquisition of more data on its safety and efficacy. More investigation is needed on the identification of possible associated conditions that may enhance the PFO-related stroke risk, and perhaps allow for a more rational choice among preventive strategies. From a therapeutic standpoint, antiplatelet treatment is currently preferred in most stroke patients with a PFO, with the possible exception of patients with an associated ASA, for whom the possibility that anticoagulation may be more effective requires more study. Systemic anticoagulation is indicated in the case of associated venous thrombosis or hypercoagulable states. The possibility that PFO closure may improve on the already effective medical treatment options needs to be evaluated in appropriately designed randomized clinical

trials. At this time, PFO closure appears to be an appropriate choice to reduce the risk of recurrent events in patients who fail medical therapy, or have contraindications to it.

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Figure 1.

Example of positive contrast study by transthoracic echocardiography with contrast injection in a patient with PFO and ASA. A: Contrast material fills the right ventricle and right atrium; the ASA is seen between the two atria (lower chambers) B: When the ASA moves toward the left atrium as a consequence of Valsalva maneuver, microbubbles are seen shunting from the right atrium to the left atrium and then into the left ventricle.

Figure 2.
Example of a PFO plus ASA by TEE. The septal separation is visualized.

Figure 3.
Example of a PFO closure device deployed between the atria.