Clinical Implications and Procedural Complications in Patients with Patent Foramen Ovale Concomitant with Atrial Septal Aneurysm

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Abstract
Atrial septal aneurysm (ASA) is defined as excursion of the atrial septum exceeding 10 mm beyond the atrial septum into the right or left atrium, or a combined total excursion of 15 mm on the right and left sides during the cardiac cycle. According to previous studies, 20–40% of patent foramen ovale (PFO) cases are accompanied by ASAs. ASA is associated with the presence of PFO, left atrial dysfunction, cryptogenic stroke, migraine, and arterial embolism, thus making closure of PFO in patients with concomitant ASA necessary but challenging. The anatomy of ASAs associated with PFO has crucial effects on complications after the closure procedure; therefore, several factors must be considered. Herein, we review the clinical implications of concomitant PFO and ASA; discuss the complications occurring after the closure procedure; and provide practical guidance for the closure of concomitant PFO and ASA.

Keywords: atrial septal aneurysm; patent foramen ovale; clinical implications; closure; complications

Introduction
Atrial septal aneurysm (ASA) was first reported in an autopsy in 1934 [1] and diagnosed in patients in 1981 [2]. ASA was initially described as an important anatomical characteristic associated with stroke recurrence in patients with cryptogenic stroke and patent foramen ovale (PFO). ASA is defined as an excursion of the atrial septum plane exceeding 10 mm beyond the atrial septum into the right or left atrium, or a total excursion of 15 mm on the right and left sides during the cardiac cycle, characterized by increased mobility of the atrial septum [3–5]. ASA is associated with several cardiac abnormalities such as PFO and atrial septal defects (ASDs). Approximately 20–40% of patients with PFO also have ASAs [6]. Moreover, ASA is predictive of the presence of PFO [7, 8]. The incessant motion of the septum primum in ASA impedes the fusion of the septum primum with the septum secundum after birth. PFO and ASA have synergistic effects in patients with cryptogenic stroke and other clinical conditions. The complications occurring after the closure procedure, and guidance for closure in patients with concomitant PFO and ASA, had not been clearly described.

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Herein, we discuss the epidemiology and classification of ASA; the clinical implications of concomitant PFO and ASA; complications occurring after the closure procedure; and guidance for the closure of concomitant PFO and ASA.

**Epidemiology and Classification of ASA**

According to transthoracic echocardiography (TTE) findings, the prevalence of ASA is 2.2–2.5% in the general population, and that of PFO with ASA is 1.7% [7, 9]. Moreover, TTE has indicated an ASA prevalence of 1.0% in children: 71.1% of cases are limited to the fossa ovalis, and 28.9% of cases involve the entire septum primum; the prevalence of isolated ASA is 35.6%, and that of ASD or PFO is 54.4% [10]. The prevalence of ASA in adults is 2.4%, and that of isolated ASA is 7–19.0%; 39% of cases are associated with mild to moderate mitral valve regurgitation, 16% are associated with aortic valve regurgitation, 16% are associated with supraventricular arrhythmia, 8–33.3% are associated with PFO, 4–19.5% are associated with ASD [4, 11, 12], and 20.6% are associated with mitral valve prolapse. Familial occurrence of ASA has also been reported [13]. Transesophageal echocardiography (TEE) is superior to TTE in detecting ASA [4]. A total of 13% (3/23) to 62.5% of ASAs diagnosed through TEE are missed through TTE [4, 14, 15]. ASAs are classified into five types according to the excursion of the atria (Table 1) [16], among which type 5 is the most severe. Moderate to severe ASA (3RL, 4LR, 5) is associated with left atrial dysfunction in patients with PFO [17]. In one study, in the single device strategy group, in which patients with PFO received a single device type regardless of anatomy, 14 small residual shunts occurred in those with ASA 3RL or 4LR and a long channel [18].

Previous studies have revealed that 20–40% of patients with PFO also have ASAs [6]. Furthermore, ASA predicts the presence of PFO (Figure 1) [7, 8]. In screening for ASA, its strong association with a PFO should prompt an additional bubble test or even to a TEE with a bubble test.

**Clinical Implications of ASA**

**ASA and Left Atrial Dysfunction**

Left atrium systolic function is diminished in ASA; however, left atrial appendage function is enhanced in a compensatory manner [19]. ASA is associated with left atrial dysfunction in patients with PFO. Furthermore, after PFO closure, left atrial function has been found to improve to normal levels in control participants, even in the presence of incomplete ASA coverage [17, 20]. ASA has the same abnormal left atrial function as atrial fibrillation, thus potentially contributing to arterial embolic events in patients with PFO and large ASAs [17]. Both left and right atrial functions (measured according to reservoir strain and peak contraction strain) are impaired in patients with isolated ASA [21]. Atrial dysfunction may be associated with the development of atrial arrhythmias, and may be both a cause and a consequence of atrial fibrillation in patients with ASA.

**ASA and Cryptogenic Stroke**

The association between ASA and cryptogenic stroke has been debated for many years [22]. ASA is an independent risk factor for embolism [8]. Similarly to PFO, ASA is common in patients with cryptogenic stroke [15]. Approximately 7.9% of patients with cerebral ischemic events have ASA [7]. During a mean follow-up of 79.7 ± 28.0 months,

<table>
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<tr>
<th>Types</th>
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<tr>
<td>1R</td>
<td>ASA protrudes toward the right atrium</td>
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<tr>
<td>2L</td>
<td>ASA protrudes toward the left atrium</td>
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<tr>
<td>3RL</td>
<td>ASA has a bidirectional excursion with a major excursion toward the right atrium</td>
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<tr>
<td>4LR</td>
<td>ASA has a bidirectional excursion with a major excursion toward the left atrium</td>
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<td>5</td>
<td>ASA has a bidirectional excursion with the same excursion toward both atria</td>
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isolated ASA has been associated with an elevated incidence of stroke (adjusted HR 3.66, 95% CI 0.88 to 15.30) [9]. A hypermobile interatrial septum (“aneurysmal”) has been considered a risk factor for recurrent stroke [23, 24].

In patients with cryptogenic stroke or TIA, the prevalence of PFO with ASA is 35.2% in younger patients (<50 years) and 18.6% in older patients [25]. Furthermore, both PFO and ASA are significantly associated with cryptogenic stroke, and show synergistic effects in both younger and older patients [26–29]. PFO with concomitant ASA increases the risk of initial and recurrent stroke (OR = 4.96 and OR = 23.93, respectively). The change in volume and pressure of the right atrium causes the PFO to open during the cardiac cycle, thus allowing the thrombus to enter the arterial system from the venous system [30]. PFO with ASA is also a strong predictor of elevated risk of recurrent stroke in patients with cryptogenic stroke [24]. In patients with PFO related stroke, ASA is a more important predictor of recurrent stroke than shunt size [31].

In one study, greater mobility of the interatrial septum and protrusion of the ASA have been observed in the severe right-to-left shunt group than in the mild and moderate groups. According to multivariate analysis, interatrial septum mobility is a predictor of severe right-to-left shunt [32]. The maximum ASA distance is positively associated with the risk of cryptogenic stroke [33]. ASA excursion ≥10 mm is associated with elevated risk of stroke [26].

The concomitant presence of PFO and ASA is also associated with the severity of cerebral white matter lesions [34].

ASA and Atrial Arrhythmias

Premature atrial contraction, premature ventricular contraction, and paroxysmal atrial fibrillation are more common in patients with rather than without ASA [35, 36]. Among these conditions, premature supraventricular contraction is the most universal arrhythmia [36]. The prevalence of atrial arrhythmia in ASA is 24–26%, and that of atrial fibrillation is
≥14% [4, 37]. Two studies have reported longer dispersion and duration of P-waves in the ASA group than the control group [36, 38]. Prolonged dispersion and duration of P-waves indicate prolongation of the right and left atrial contraction times, which are common features of atrial arrhythmias, including paroxysmal atrial fibrillation. P-wave dispersion is frequently used to clinically assess the risk of atrial fibrillation [39]. Another study has shown elevated inter- and intra-atrial electromechanical delays of both atria in patients with ASA than in controls. Subgroup analysis indicated greater interatrial electromechanical delay, ASA size, and P-wave dispersion in patients with ASA with rather than without arrhythmia [40]. Therefore, both P-wave dispersion and atrial electromechanical delay may provide new perspectives for evaluating the risk of atrial arrhythmia in patients with ASA.

Atrial fibrillation is the most common complication after device closure, both within 30 days and during follow-up, with an incidence of 1.3–7.4% [41–43]. However, the incidence of atrial fibrillation in patients with concomitant PFO and ASA remains unclear.

**ASA and Migraine**

A higher prevalence of PFO has been found in patients with rather than without migraine, particularly those with migraine with aura (MA) [44, 45]. Similarly, a significantly higher prevalence of PFO with ASA has been observed in patients with rather than without MA. PFO with ASA is significantly associated with MA [46, 47]. Moreover, ASA is associated with earlier age of onset in patients with MA [48]. The presence of ASA in PFO with migraine is also associated with elevated risk of ischemic lesions and larger PFO size [47].

**ASA and Arterial Embolism**

In addition, several studies have reported an association between ASA and arterial embolism [15, 49, 50]. ASA is an independent predictor of embolic events [8]. The presence of ASA tends to aggravate turbulent blood flow in the left atrium, thus predisposing patients to arterial embolism. A retrospective study has indicated that ASA (particularly left-to-right or right-to-left shunts) is associated with previous clinical events compatible with cardiogenic embolism. In 24% of patients with preexisting cardiogenic embolism, ASA appears to be the only source of embolism [4]. In another study, in 86% of patients with ASA together with cerebral ischemia, TEE did not indicate other sources of cardioembolism except an associated PFO; moreover, ASA (with or without PFO) was the only potential source of embolism detected by TEE [7]. Three pathogenic mechanisms may be involved in arterial embolism in patients with ASA. First, paradoxical embolism, i.e., thrombi from the venous system, may gather in the ASA, pass through the PFO, and induce embolization in the arterial system. ASA facilitates paradoxical embolism through the following postulated mechanisms: ASA predisposes the atrial septum to retraction, thus causing a larger right-to-left shunt; and ASA may enhance the right-to-left shunt by redirecting the flow from the inferior vena cava toward the PFO [51]. In addition, ASA prolongs the overall gaping time of a PFO. A marked ASA may briefly open the PFO with every heartbeat. Second, although rare and mostly asymptomatic, thrombi may develop locally in the left atrium or ASA, and lead to pulmonary or systemic embolization [52–54]. Systemic embolism requires an atrial shunt in this situation. Third, atrial arrhythmias are common in the ASA and may cause embolism [35].

**Association between ASA and Other Cardiac Abnormalities**

ASA is associated with other cardiac abnormalities, such as ASD and mitral valve prolapse [4, 55]. Approximately 20.6% of patients with ASA have concurrent mitral valve prolapse. A similar inherent deficiency in connective tissue has been suggested to result in redundancy of the atrial septum and the mitral (and/or tricuspid) valve [56]. A higher incidence of mitral valve prolapse has been observed in stroke patients with an ASA than in patients without stroke or an ASA [55, 57]. ASA is also associated with the severity of myxomatous degeneration [55]. ASA can cause intracardiac platypnea-orthodeoxia syndrome, particularly in patients with aortic abnormalities (such as root dilation, aneurysm, and elongation) [58, 59]. Mild to moderate mitral and aortic valve regurgitation are also common (39%) in patients with ASA [11]. Larger diameters of the
aortic root and of the ascending aorta have been observed in patients with rather than without ASA [60]. Moreover, mitral valve regurgitation is independently and positively associated with ASA [60].

**Need for Closure of Concomitant PFO and ASA**

Isolated ASA without other complications does not require special treatments [61]. However, closure of the PFO is necessary in patients with concurrent ASA in some conditions, because the presence of ASA indicates high-risk PFO, similarly to straddling thrombus, large-shunt PFO, and long tunnel PFO [62]. In the RESPECT and REDUCE studies, the benefit of PFO closure was greater among patients with rather than without ASA [63, 64]. This finding has been confirmed in other meta-analyses [65–67]. Combined analysis of RESPECT and REDUCE data has indicated similar risk of recurrent stroke in patients with PFO without ASA after closure and patients treated medically (3.1% vs 4.2%, \( P = 0.37 \)); however, the risk of recurrent stroke in PFO with ASA after closure was significantly lower than that observed in patients treated medically (1.2% vs 9.0%, \( P < 0.001 \)) [68]. PFO closure with the percutaneous method has been found to decrease the maximal excursion of the atrial septum in patients with ASA and PFO [69], and to improve left atrial function [17, 20].

**Complications Occurring after the Closure Procedure of Concomitant PFO and ASA**

Closure of the PFO, regardless of the special anatomy of the atrial septum, culminates in misalignment of the device, residual shunt, impingement of adjacent structures, thrombus formation, and atrial fibrillation [70–72]. The anatomy of the atrial septum associated with PFO has crucial effects on complications related to the closure procedure [18].

The success of the device and the peri-procedural complications are similar in PFO with versus without ASA [69]. The presence of a mobile ASA predisposes the atrial septum to retraction, thereby resulting in a larger right-to-left shunt, and additionally weakens device stability after PFO closure [73]. Therefore, the presence and detailed structure of the ASA are important factors in the selection of devices for PFO closure. Operators usually choose an oversized device to cover the ASA, a stiff metallic device to stabilize the atrial septum, or an ASD occluder. However, an oversized and stiff metallic device might delay endothelialization and is likely to lead to detrimental changes in the geometry of the atrial septum, thus increasing the risk of residual shunt, misalignment, arrhythmia, device thrombosis, and aortic and atrial erosion [74]. An oversized device may cause cardiac perforation caused by its strut [75]. An incomplete floppy or frank aneurysmal floor of the fossa ovalis may also be likely to be associated with secundum ASD, thus complicating the closure procedure [37, 76, 77].

ASA is also a predictor of thrombus formation after percutaneous closure of a PFO or ASD [72]. Moreover, PFO with ASA has a lower closure rate than PFO alone [78, 79]. The risk of severe residual shunts is elevated in patients with ASA [80]. The closure rates of PFO with ASA are 84.1%, 90.1%, and 98.5%, and those of PFO alone are 95.4%, 97.4%, and 99.5% at 6 months, 1 year, and 2 years, respectively [78]. Compared with PFO alone, concomitant PFO and ASA are more likely to have residual shunts at 6 months (27% vs. 8%, \( P = 0.01 \)) [74]. The presence of ASA is a predictor of residual shunt after PFO closure at 6 months and 12 months of follow-up (RR = 24.7, 95% CI 8.2–74.4, \( P < 0.001 \)) [81]. In univariate logistic analysis, a residual shunt has been associated with the presence of ASA but not long tunnel PFO, large PFO, or large device size [82]. Residual shunts are more common after PFO closure in patients with ASA for several reasons. First, a 35-mm occluder is frequently used in patients with ASA and might prolong endothelialization. Second, 35-mm occluders are relatively likely to detrimentally alter the geometry of the atrial septum, thus leading to misalignment [74]. Residual shunt after percutaneous closure is a severe problem. A moderate to large residual shunt is associated with higher risk of recurrent stroke or TIA [83]. Complete PFO closure without a residual shunt at 6 months is significantly associated with a >50% improvement in migraine burden [84]. In one study, three of four patients with recurrent decompression sickness had a residual shunt [85].
The device is fully protective only with complete endothelialization. The risk of recurrence of peripheral and cerebral thromboembolic events is higher in patients with PFO with ASA rather than PFO alone.

Iatrogenic ASD induced by device erosion has been detected at follow-up in two patients with PFO concurrent with ASA [86]. Because of the paper-thin septum primum, the presence of ASA predisposes the septum primum to erosion. ASD induced by erosion is rare, but requires attention because of the risk of paradoxical embolism in certain situations, in which implantation of a second device is effective.

Other techniques used for the closure of concomitant PFO and ASA have their own drawbacks. Transseptal puncture may lead to aortic puncture, tamponade, and pericardial effusion, and the implantation of multiple devices does not prevent device misalignment or impingement of adjacent structures.

Finally, large ASAs frequently show leaks next to the occluder and may later require a second occluder [78].

**Guidance for the Closure of Concomitant PFO and ASA**

The crucial step in device closure in patients with PFO concomitant with ASA is choosing the appropriate device, according to the stability of the ASA, the size of the PFO, and other complicated situations (such as ASD). When a simple PFO is concomitant with a stable ASA, a regular PFO occluder is appropriate; for a large PFO or an unstable ASA, a 30-mm or 35-mm PFO occluder or even an ASD occluder is recommended to overcome the residual shunt; for PFO concomitant with ASA with two perforations, more than one device for closure is required; for PFO concomitant with ASA with multiple perforations, device closure is not recommended, and surgery or lifelong anticoagulant serve as alternatives [87].

Device choice according to the ASA classification is also prudent [18]. For example, the asymmetric low-weight nitinol soft device Premere Occlusion System is used for 1R, 2L ASA; the standard symmetric full nitinol device Amplatzer PFO occluder is used for unidirectional and mild ASA (2RL or 2LR); the moderately stiff symmetric mixed nitinol/tissue device Biostar Occluder (NMT) or the Gore septal occluder is used for unidirectional and moderate ASA (3RL or 3LR); and the stiff symmetric full nitinol device ASD Cribriform occluder is used for bidirectional moderate ASA (3RL or 3LR), in all cases of large ASA (4RL or 4LR or 5).

TEE and intracardiac echocardiography are necessary to investigate the structure and severity of ASA in detail. To overcome the residual shunt after PFO closure in patients with ASA, the Amplatzer ASD occluder should be considered because of their self-centering characteristics [20, 88, 89]. The safety and efficiency of these devices have been verified in 160 patients with a low residual shunt rate (complete closure rate of 93.7% at 6 months), even with incomplete ASA coverage. The authors of that study have also suggested that a diameter ratio of the device and interatrial septum <0.8 is sufficient to cover ASA while minimizing the risk of erosion and interference of the atrioventricular valves [20].

In cases of percutaneous closure of PFO concomitant with ASA, the “stretching capability” of the PFO tunnel balloon sizing determined by the balloon is critical. When the “stretch diameter” of the PFO tunnel exceeds 13 mm, self-centering devices are superior to non-self-centering devices, because of their lower residual shunt rates [90].

**Conclusions**

The presence of ASA is associated with left atrial dysfunction, cryptogenic stroke, migraine, arterial embolism, and other cardiac abnormalities, thus complicating PFO closure. Because the benefit of PFO closure is greater in patients with rather than without ASA, PFO closure is necessary in certain patients with concurrent ASA. The anatomy of the ASA associated with PFO has critical effects on related complications after the closure procedure. The crucial step in device closure in patients with PFO concomitant with ASA is the choice of an appropriate device.

**Conflicts of Interest**

All authors have no conflicts of interest to disclose.
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