

ATRIAL SEPTAL DEFECTS

OSTIUM SECUNDUM ASD

Epidemiology

Secundum ASDs account for approximately 7% of all congenital malformations.¹⁻³ Females predominate (70%). Secundum ASD is the most common cardiac manifestation of Holt-Oram syndrome (triphangeal thumbs, ASD or VSD) due to mutation of TBX5. Familial forms associated with gene mutations are rare, and usually coexist with conduction disturbances.¹

Pathophysiology

The pathophysiology of ASD is complex and multifactorial.² Conventionally, an ASD must be at least 10 mm in diameter for a significant left-to-right shunt (although most ASDs are not circular). A left-to-right atrial shunt is considered significant when the Qp/Qs ratio is greater than 1.5 or if it causes dilation of the right heart chambers. The RV is more compliant than the LV and as a result left atrial blood is shunted to right atrium causing increased pulmonary blood flow and dilatation of the pulmonary arteries. However, as opposed to VSD, pulmonary hypertension is uncommon even with large defects, although when it develops it results in pulmonary pressures that approach systemic levels.² Once a patient has reached adulthood with normal PA pressures he seldom develops pulmonary hypertension later. Left ventricular hypertrophy and mitral stenosis increase left-to-right shunting, whereas pulmonary stenosis, tricuspid stenosis and pulmonary hypertension reduce a left-to-right shunt and may also cause a right-to-left shunt.

Presentation

Spontaneous closure of ASDs (<1 cm) may occur within the first year of life. Patients with small defects are asymptomatic. Patients with moderate/large ASDs often have no symptoms until the third or fourth decade of life despite substantial left to right shunting. The age at which symptoms appear is variable and not exclusively related to the size of the shunt. SOB is the most common initial presenting symptom. Atrial fibrillation or flutter due to atrial dilatation occurs at >40 years of age and is symptomatic. Eisenmenger's syndrome occurs rarely, only with large ASD in adults (<10%).² Occasionally, a paradoxical embolus or transient ischemic attack may be the first clue to the presence of an ASD. Rarely, cyanosis may be seen, especially with inferior sinus venosus defects. Patients with unexplained RV

volume overload should be investigated to rule out obscure ASD, partial anomalous venous connection, or coronary sinoseptal defect. Morbidity and mortality are higher in men than in women.⁴

Physical Examination

The absence of clinical signs does not necessarily exclude a hemodynamically important ASD.

Dilated pulmonary artery may be palpable in the second left interspace.

Right ventricular lift may be felt on held expiration or in the subxiphoid area on deep inspiration.

Soft systolic ejection murmur is heard at the upper left sternal border (pulmonary flow).

Wide and fixed split of S₂, the auscultatory hallmark of an ASD, is not always present.

Tricuspid diastolic rumble heard at the lower left sternal border reflects a large shunt.

Loud P₂ and **tricuspid regurgitation** may be heard with pulmonary hypertension.

Investigations

ECG SR, AF, or atrial flutter with right axis deviation and RV hypertrophy (incomplete RBBB). Inverted P waves in the inferior leads suggest an absent or deficient sinus node, as may be seen in a sinus venosus defect. First-degree heart block suggests a primum ASD but may be seen in older patients with a secundum ASD.

Chest radiography May be normal even with significant ASD. The central pulmonary arteries may also be characteristically enlarged, with pulmonary plethora and peripheral vascular pattern of shunt vascularity (well visualized small pulmonary arteries in the periphery of both lungs).

Transthoracic echocardiography The functional importance of the defect can be estimated by the size of the right atrium and ventricle, the presence/absence of paradoxical septal motion (right ventricular volume overload), ventricular septal orientation in diastole (volume overload) and systole (pressure overload), and an estimation of the shunt ratio.⁵ Pulmonary artery systolic pressures may be estimated from the Doppler velocity of tricuspid regurgitation.

Transesophageal echocardiography may be needed to confirm the type of ASD and to delineate the pulmonary venous return, and to guide device closure of ASDs.

Cardiac Magnetic Resonance is the gold standard for the assessment of right ventricular size and function, and pulmonary venous return. It is also important for diagnosis of sinus venosus defects.² In patients who cannot have an MRI, computed tomographic scanning and angiography can offer similar information.

Maximal exercise testing may be useful to document exercise capacity in patients with symptoms that are discrepant with clinical findings or to document changes in oxygen saturation in patients with mild or moderate pulmonary arterial hypertension.

Pulse oximetry at rest and during exercise to determine the direction and magnitude of the shunt (Table 1).

Cardiac Catheterization Not necessary any more unless in order to test vasoreactivity in pulmonary hypertension. Oximetry is now rarely used for shunt detection and Qp/Qs calculation. Coronary angiography is needed pre-operatively in patients >40 years old.

Therapy

Small defects (<1cm) may be left alone, but some patients develop right heart dilation later in life due to increased LVEDP and left-to-right shunting. Patients with an ASD have increased mortality compared with the general population regardless of closure in childhood or adulthood. Early surgical or device closure of significant secundum ASD, especially in childhood, is beneficial and seems to improve survival.⁶⁻⁸ ASD closure is now recommended for many patients with a significant left-to-right shunt and pulmonary vascular resistance ≤ 2 Wood units or $>2-5$ Wood units.⁵

Closure Indications

Indications for ostium secundum ASDs are presented in Tables 2 and 3 and Figures 1 and 2.⁵

⁹ Main indications for closure are:

- Qp/Qs > 1.5
- RV overload/enlargement

Closure Contraindications

- Irreversible pulmonary arterial hypertension more than 2/3 of SVR (see VSD). There have been case reports of such patients being managed with intravenous epoprostenol or oral bosentan in a way that ASD closure subsequently became possible.¹⁰ A calculated PVR > 8 Woods units generally precludes closure.²

Device closure is the treatment of choice for secundum ASDs.^{5, 9, 11} Unsuitable anatomy includes inadequate atrial septal rims to allow stable device deployment (<5 mm), proximity of the defect to the AV valves, the coronary sinus, or the vena cavae, and very large secundum ASD (>35 mm). Complications are device embolization (<1%) and cardiac

perforation (<0.1%). Small residual shunts seen on transesophageal echocardiography after the end of the procedure are of no clinical significance. Late complications such as mitral valve dysfunction, obstruction of the pulmonary veins, new-onset migraine, and erosion or perforation of the atrial wall or aorta are very rare. After closure, aspirin and clopidogrel are prescribed for 6 to 12 months and, compared to aspirin alone, may reduce the incidence of migraine.¹² Device erosion, which may present with chest pain or syncope, should warrant urgent evaluation. Cardiac erosion occurs in 0.043-0.3% of cases and is mainly seen with deficiency of any rim (or of the aortic rim), device >5 mm larger than ASD diameter, and the weight:device size ratio.¹³

Surgical closure is required for patients with secundum ASD whose anatomy is unsuitable for device closure. Perioperative mortality is <1%. Surgical repair, particularly before the 25 years of age, has been shown to result in normal long-term survival, and reduce the incidence of arrhythmias such as atrial flutter and fibrillation, and RV failure and stroke.⁸ Patients over age 40 years remain at risk of atrial arrhythmias and systemic thromboembolism despite complete closure of the ASD, but surgery is also preferable to medical treatment.¹⁴ Age and preprocedural arrhythmia are risk factors for late arrhythmia.¹⁵

Effect on arrhythmias

Surgical repair of ASD before the 25 years of age has been shown to reduce the incidence of arrhythmias such as atrial flutter and fibrillation (AF), but patients over age 40 years may remain at risk of atrial arrhythmias.^{14, 16} Up to 68% of patients who present with pre-operative AF may remain in AF after surgical ASD closure,⁸ whereas in patients over 40 years old, post-operative AF develops in 8% to 23% over the next 7 to 10 years.^{14, 16} Arrhythmia and neurologic events remain long-term risks after ASD closure (device or surgical), especially if the patient had pre-existing arrhythmia.¹⁵ Resolution of paroxysmal atrial arrhythmias has been reported in 45% to 67% of patients after device closure,¹⁷⁻²⁰ but in other series, patients with pre-existing persistent AF remain in AF after device closure of their ASD.⁷ New-onset AF occurs in 6-7% of patients after transcatheter closure and 12% of patients with underlying ASD.^{7, 20} A history of previous arrhythmia and age > 40 years at closure, are associated with increased incidence of AF. In a meta-analysis of 25 studies, percutaneous ASD closure was not associated with a reduction in atrial arrhythmia prevalence in this meta-analysis. A weak benefit was seen in patients ≥40 years of age, not present in patients ≥60 years.²¹ If ASD does not require closure on hemodynamic grounds, closure is unlikely to abolish flutter or AF.

Endocarditis prophylaxis

It is not recommended for unrepaired ASDs. Revised indications are discussed in General Principles as well as in the Chapter on endocarditis.

Pregnancy

Pregnancy is well tolerated by most women with repaired atrial septal defect (WHO risk class I).²² In unrepaired ASDs, thromboembolic complications, pre-eclampsia and growth restriction may occur more frequently, but pregnancy is usually well tolerated in the absence of severe pulmonary arterial hypertension (Table 3). Thus, in ASD diagnosed during pregnancy closure can be deferred for 6 months after delivery. For a suitable secundum defect, catheter device closure can be performed during pregnancy if necessary with transesophageal or intracardiac echocardiographic guidance. The recurrence rate in offsprings is estimated in 2-6%.⁹

SINUS VENOSUS DEFECT

Partial anomalous pulmonary venous return to the SVC or the right atrium is very common with **superior sinus venosus defect** (5-10% of all ASDs). Diagnosis is often more difficult than for other forms of ASD and catheter closure is not possible. Unexplained RA or RV dilatation, especially in the presence of dyspnea, should raise the possibility of the disease.²³ The **inferior sinus venosus defect** near the IVC is very rare. ***Surgical closure*** may be required for patients with sinus venosus ASD. Indications for closure are presented in Table 1. In high-frequency units, covered stent correction is also offered as an alternative to surgery in patients with a sinus venosus atrial septal defect. The success rate of stent implantation is 97.4%, with major complications in 1.3% and repeat catheter interventions for residual leaks in 1.8%.²⁴

PATENT FORAMEN OVALE

The prevalence of a patent foramen ovale (PFO) ranges from 15% to 25% in autopsy studies, to 20% to 40% with transesophageal echocardiography in patients with a history of cerebral events. The average PFO size ranges from 1 to 19 mm but increases with each decade of life; the mean diameter in the first decade is 3.4 mm and in the tenth decade is 5.8 mm.²⁵ A common association is *atrial septal aneurysm*, where part or all of the atrial septum shows aneurysmal dilatation, protruding into either atria (prevalence 1-5%) for at least 15 mm during the cardiorespiratory cycle. Under normal physiological conditions, the left atrial pressure is higher than the right one and pushes the thin septum primum against the septum secundum and, except for very brief periods in each cardiac cycle, seals the potential opening of the PFO. Actions, such as the release of a Valsalva maneuver, can transiently reverse the normal left-to-right pressure gradient and cause an exaggerated transient leftward shift of the free edge of the septum primum with apparent enlargement of the orifice of the PFO.

Transesophageal echocardiography can diagnose PFO by injecting saline contrast, preferable in the femoral vein than the upper extremities, and detect microbubbles in the left atrium immediately after arriving in the right atrium. If bubbles appear in the left atrium before or <5 beats after they appear in the right atrium, then the possibility of anomalous venous connection to the left atrium or pulmonary arteriovenous malformations must be considered.²⁵ PFO is a potential risk factor for several clinical syndromes including paradoxical systemic embolism such as ischemic stroke and myocardial infarction, and decompression sickness in divers.

PFO and Cryptogenic Stroke

Approximately 15% of ischaemic strokes are cryptogenic, defined as embolic strokes of undetermined source.^{26, 27} Patent foramen ovale is found in up to half of young adults with cryptogenic stroke but, as discussed, is also found in up to 25% of healthy persons.²⁸ No cause can be established in approximately 25% of patients with ischaemic stroke.²⁸ The size of the PFO and interatrial shunt, the presence of an atrial septal aneurysm and Chiari strands (congenital remnants of the right valve of the sinus venosus), as well as Eustachian valve that virtually extends the vena cava to the foramen ovale, may all contribute to the relative risk for stroke. Atrial septal aneurysm is found in 7-15% of stroke patients and seems to be associated with embolism,²⁹ but the issue is debatable. In an analysis of the CLOSE and DEFENSE-PFO trials, the presence of atrial septal aneurysm was a more important correlate of stroke recurrence than shunt size.³⁰ In the PICCS trial, the presence of PFO in cryptogenic stroke patients, either on aspirin or warfarin, did not increase the chance of adverse events

regardless of PFO size or the presence of atrial septal aneurysm.³¹ Cryptogenic stroke due to tiny emboli (a few millimeters in size) can form anywhere in the venous system and occur with increasing frequency after 50 years of age. Paradoxical embolism does not necessarily require clinically apparent deep vein thrombosis since thrombi may emerge from the inferior vena cava or within the PFO tunnel. A classification has been proposed using the PASCAL algorithm.³² PASCAL combines the Risk of Paradoxical Embolism score, based on clinical characteristics, with key cardiac anatomic features of the PFO such as large right-to-left shunt and atrial septal aneurysm. Additional risk factors do exist, such as stroke occurring at awakening in patients with sleep apnoea, circumstances that promote venous thrombotic events (e.g. prolonged travel, dehydration, or hypercoagulable state), a history of migraine with aura, and decompression illness, and anatomic features including the presence of a Eustachian valve or Chiari network.²⁷ Patients with PFO are vulnerable to ischaemic stroke for an extended period of time after surgery.³³

However, a definitive causal relationship between PFO and cryptogenic stroke has not been convincingly established for the majority of affected patients, and concurrent etiologies are identified for more than one third of recurrent ischemic events in patients with cryptogenic stroke.³⁴ Approximately 7.5% of patients with embolic stroke of undetermined source develop atrial fibrillation over the next 19 months.³⁵ An index to identify stroke-related vs incidental PFO in cryptogenic stroke has been developed and is based on the absence of risk factors such as hypertension, diabetes, and smoking, the presence of cortical infarct on imaging, and young age (especially less than 40-30 years).³⁶ Pacemaker and ICD implantation increases the risk of stroke in patients with PFOs.³⁷ The annual risk of recurrent cryptogenic stroke with or without PFO is estimated 6%-8% without any treatment. With either medical treatment or PFO closure, the annual risk decreases to approximately 2%-4%,²⁵ and warfarin has not been found superior to aspirin in this respect.^{38 39} In a Danish registry, the 4-year risk of ischemic stroke after routine PFO closure for cryptogenic stroke was comparable to that observed in clinical trials, but remained higher than in the general population.⁴⁰ Rivaroxaban has been found superior to aspirin in reducing the risk of recurrent stroke in both patients with and without a PFO, without increased risk of bleeding.⁴¹ Silent paroxysmal AF is an important cause of cryptogenic stroke and its presence should be ruled out in patients with cryptogenic stroke.^{42, 43} Non-stenotic complicated carotid plaques, as defined by intra-plaque haemorrhage, a ruptured fibrous cap, or the presence of a mural thrombus are also a cause of cryptogenic stroke.⁴⁴ Of note, however, routine anticoagulation in patients with acute ischaemic or embolic stroke of undetermined aetiology is not recommended.^{45, 46}

PFO and Migraine

There has been evidence that migraine headaches improve in selected patients who are subjected to PFO closure. Three randomised trials to test this hypothesis have failed to confirm it and (MIST, PRIMA, and PREMIUM),⁴⁷⁻⁴⁹ and new-onset migraine can be a complication of transcatheter ASD closure.¹² However, in a pooled analysis of patient-level data from the PRIMA and PREMIUM trials demonstrated that PFO closure significantly reduced the mean number of monthly migraine days and monthly migraine attacks, and resulted in a greater number of subjects who experienced complete migraine cessation.⁵⁰ The issue remains controversial, but routine closure is not recommended for migraine in the 2021 European Position Paper.⁵¹

Indications for PFO Closure

The optimal therapy for prevention of recurrent stroke or transient ischemic attack in patients with cryptogenic stroke and patent foramen ovale remains controversial (Table 5). Treatment choices include medical therapy with antiplatelet agents or vitamin K antagonists or percutaneous device closure. Percutaneous device closure is technically easy and the Amplatzer occlude appears to be the safest device so far.⁵² There has been increasing, although not definitive, evidence to support PFO closure in patients with cryptogenic stroke or TIA. The initial three RCTs comparing closure with antiplatelet or anticoagulation therapy (CLOSURE, PC, RESPECT)⁵³⁻⁵⁵ failed to detect any benefit by means of recurrent stroke. More recent trials (Gore-REDUCE, CLOSE, RESPECT-extended follow-up, and DEFENSE-PFO)⁵⁶⁻⁵⁹ demonstrated prevention of stroke with PFO closure, in two of them using various devices,^{56, 58} at the expense of an increased incidence of AF (approximately 5%). Recent meta-analyses have verified these results.⁶⁰⁻⁶³ A European Position Paper in 2019 performed a study-level meta-analysis of RCTs with an average 3.8 years of follow-up. The incidence of recurrent stroke was 2% in the closure arms, and the number needed to treat with PFO closure to prevent one stroke overall was 37 (95% CI: 26 to 68), and 21 in patients with high-risk PFO features (95% CI: 16 to 61). Results on TIA and on death were neutral.⁶⁴ However, patients >60 years old were usually excluded in these RCTS. In a multicenter study including consecutive patients aged 67±5 years, who had a PFO closure following a presumed PFO-related ischemic event, PFO closure was safe and associated with a relatively low incidence of recurrent ischemic events after a median follow-up of 3 years compared with historical cohorts without PFO closure. However, a higher risk of recurrent cerebrovascular events was observed in older patients compared to a control group of their younger counterparts with PFO closure.⁶⁵ PFO closure is associated with a low rate of ischemic events (stroke, 1%) at >10 years of follow-up, and dual antiplatelet therapy <12

months is probably adequate.⁶⁶ Procedural complications have a 2.6% incidence in RCTs. Device thrombosis is a late complication which is seen in 1.0-2.0%. The most frequent undesirable event following transcatheter percutaneous closure is AF with an up to 4-7% incidence, compared to 1.0-1.5% of those who did not.^{64, 67} In a report of the Danish national registry, in those undergoing closure, the AF incidence was 5.2 within 3 months and 2.7% from then until 5 years. In those with a PFO that was not closed, the 5-year risk was 3.1% and in matched control individuals the risk was 1.2%. Thus, there was a four-fold risk in the first 3 months and no increased rate after that.⁶⁸ Flecainide has failed to prevent atrial arrhythmia after PFO closure.⁶⁹

PFO device closure has been recommended by the ACCP (2C) in patients with recurrent events despite aspirin therapy or in the presence of DVT.⁷⁰ In 2016, the FDA approved the Amplatzer device for PFO closure to prevent recurrent stroke. The AHA/ASA 2014 guidelines on stroke and TIA give a weak (IIb-C) recommendation for closure only in the setting of PFO and DVT.⁷¹ The 2019 European Position Paper recommends percutaneous closure in carefully selected patients aged from 18 to 65 years with a confirmed cryptogenic stroke, TIA, or systemic embolism and an estimated high probability of a causal role of the PFO as assessed by clinical, anatomical and imaging features.⁶⁴ PFO closure in patients with PFO-associated stroke is also recommended in patients less than 60 years by the SCAI,⁷² and the UK National Clinical Guideline (<https://www.strokeguideline.org/app/uploads/2023/04/National-Clinical-Guideline-for-Stroke-2023.pdf>)..

Closure should also be considered in the platypnea orthodeoxia syndrome [dyspnea (platypnea) and arterial desaturation in the upright position with improvement in the supine position (orthodeoxia)],⁷³ and in scuba divers for prevention of decompression illness,⁷⁴ and in patients with multiple paradoxical emboli.⁷⁵ The presence of antiphospholipid antibodies in patients with a PFO does not significantly increase risk of subsequent cerebrovascular events.⁷⁶ The role of PFO in fat embolism following long bone fracture is also investigated, and the potential value of pre-operative closure in these patients remains to be determined.⁷⁷ PFO screening is also recommended in decompression sickness cases with no obvious risk factors or with high but non-modifiable risk for decompression sickness.⁵¹

Anticoagulation following PFO closure depends on the device used and the thrombotic and bleeding risks. Usually 1-6 months of aspirin plus clopidogrel are recommended.⁷⁸ A biodegradable PFO closure device fully degraded within 24 months after implantation is under study.⁷⁹

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