Atrial septal defects

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Atrial septal defects are the third most common type of congenital heart disease. Included in this group of malformations are several types of atrial communications that allow shunting of blood between the systemic and the pulmonary circulations. Most children with isolated atrial septal defects are free of symptoms, but the rates of exercise intolerance, atrial tachyarrhythmias, right ventricular dysfunction, and pulmonary hypertension increase with advancing age and life expectancy is reduced in adults with untreated defects. The risk of development of pulmonary vascular disease, a potentially lethal complication, is higher in female patients and in older adults with untreated defects. Surgical closure is safe and effective and when done before age 25 years is associated with normal life expectancy. Transcatheter closure offers a less invasive alternative for patients with a secundum defect who fulfil anatomical and size criteria. In this Seminar we review the causes, anatomy, pathophysiology, treatment, and outcomes of atrial septal defects in children and adult patients in whom this defect is the primary cardiac anomaly.

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Introduction

Atrial septal defects belong to a group of congenital cardiac anomalies that allow communication between the left and right sides of the heart. These interatrial communications include several distinct defects in the cardiac terminations of the systemic and pulmonary veins (sinus venosus and coronary sinus defects) and in the interatrial septum (atrial septal defects). Patent foramen ovale is a normal communication during fetal life and is commonly encountered after birth. In this Seminar we review the anatomy, pathophysiology, and recent developments in the management of interatrial communications in children and adults. We focus on haemodynamically important atrial septal defects in patients who do not have major associated congenital cardiac anomalies.

Incidence and causes

Defects of the atrial septum are the third most common type of congenital heart disease, with an estimated incidence of 56 per 100 000 livebirths.[1] With improved recognition of clinically silent defects by echocardiography, recent estimates are about 100 per 100 000 livebirths.[2] About 65–70% of patients with a secundum defect, roughly 50% of those with a primum atrial septal defect, and 40–50% of those with a sinus venosus defect are female.

Most atrial septal defects are sporadic with no identifiable cause. Reports of familial clusters of secundum defects have noted different modes of inheritance, most notably autosomal dominant.[3,4] Abnormalities in genes essential to cardiac septation have been associated with atrial septal defects,[5] including mutations in the cardiac transcription factor gene *NKX2-5*,[6–8] *GATA4* and *TBX5*,[4,9–11] *MYH6* located on chromosome 14q12,[12] and other mutations.[13–15] The association between secundum defects and conduction abnormalities, especially atrioventricular block, has been linked to mutations in *NKX2-5*.[16–19] The risk of a secundum defect is increased in families with history of congenital heart disease, especially when an atrial septal defect is present in a sibling.[3]

Secundum defects are often encountered in genetic syndromes such as Holt-Oram, Ellis van Creveld, Noonan, Down, Budd-Chiari, and Jarcho-Levine, to mention only a few.[20–27] In Holt Oram syndrome (*NKX2-5* mutation), an atrial septal defect is seen in 66% of cases. In patients with trisomy 21, secundum and primum defects are the most frequent lesions, accounting for 42% and 39% of major congenital heart disease, respectively.[28]

Exposure to several substances has been associated with atrial septal defects, including fetal alcohol syndrome,[29] first trimester maternal cigarette consumption,[30,31] and some antidepressants.[32–34] Other maternal risk factors include diabetes, increased dietary glycaemic index in women without diabetes,[35,36] and advanced maternal age (≥35 years).[37,38]

Developmental considerations

Knowledge of the development of the atrial septum and its neighbouring systemic and pulmonary veins forms the basis for the classification of interatrial communications. Atrial septation involves septum primum, septum secundum, and the atrioventricular canal septum. Figure 1 shows key elements of atrial septation.[39–43]

Normal development of the atrial septum results in formation of the fossa ovalis, which includes two anatomical elements: first, muscular boundaries contributed by septum secundum; and second, the valve of the fossa ovalis, which attaches on the left atrial aspect of septum secundum—septum primum. The atrial component of the atrioventricular canal septum lies

Search strategy and selection criteria

We searched PubMed for articles in English with the term "atrial septal defect" in the title from Jan 1, 2003, to April 24, 2013. We also searched for multiple combinations of the terms "atrial septal defect" AND relevant terms such as "pregnancy", "pulmonary hypertension", "Eisenmenger syndrome", "arrhythmias", "outcomes", "surgery", "device", "percutaneous", "gene". We also retrieved relevant articles from the reference list of key articles. Whenever possible, we prioritised articles published in the past 5 years, but cited older references when appropriate.

anterior and inferior to the fossa ovalis, separating it from the tricuspid and mitral valve annuli—the atrioventricular canal septum (figure 2). The tissue that separates the right pulmonary veins from the superior vena cava and from the posterior and inferior aspects of the right atrial free wall is termed sinus venosus.[44–46] The tissue that separates the coronary sinus from the left atrium is termed coronary sinus septum.[47]

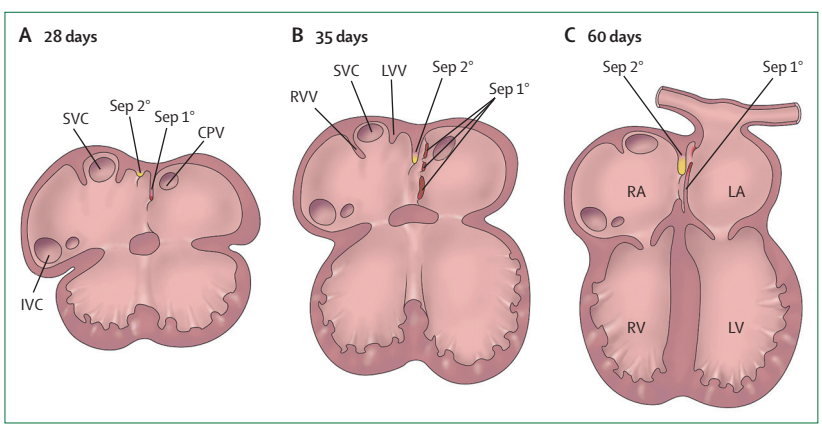

Figure 1: **Development of the atrial septum**
(A) At 28 days after gestation, septum primum (Sep 1°)—the first septum to appear in the developing atria—develops as a crescent-shaped structure. Its leading edge is covered by a layer of mesenchymal cells called mesenchymal cap (shown in red). The space between the developing septum primum and the developing endocardial cushions is called foramen primum or ostium primum. Septum secundum (Sep 2°; limbus of the fossa ovalis) is a crescent-shaped muscular infolding of the atria wall that appears shortly thereafter to the right of septum primum. (B) At 35 days, both septum primum and septum secundum continue to develop. The openings within septum primum are called foramina secundi. (C) At 60 days, the atrial septum is nearly fully formed and the foramina secundi close by way of coalescing fenestrations within septum primum. The foramen ovale remains patent throughout pregnancy. Modified from Geva,[39] with permission from Wiley-Blackwell Publishing. CPV=common pulmonary vein. IVC=inferior vena cava. LA=left atrium. LV=left ventricle. LVV=left venous valve. RA=right atrium. RV=right ventricle. RVV=right venous valve. SVC=superior vena cava.

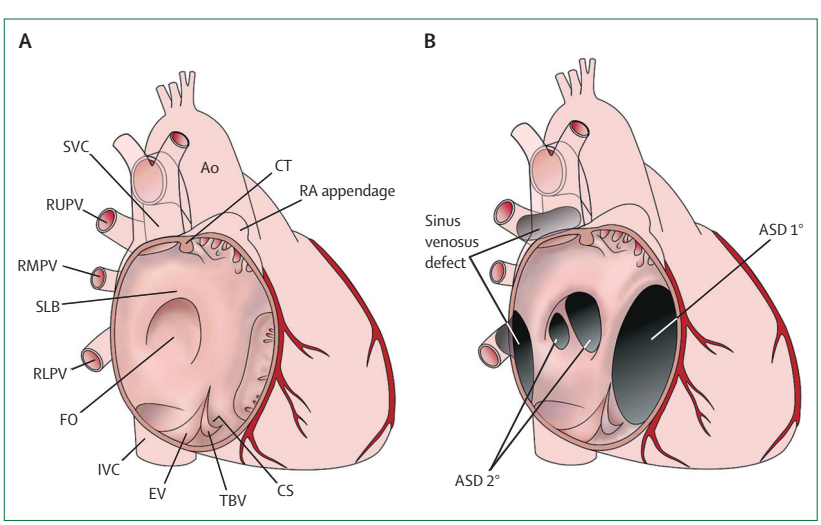

Figure 2: **Anatomy of the atrial septum and neighbouring structures**
(A) Right atrial aspect of the normal atrial septum. (B) Types of interatrial communications. Modified from Geva,[39] with permission from Wiley-Blackwell Publishing. ASD=atrial septal defect. Ao=aorta. CS=coronary sinus. CT=crista terminalis. EV=Eustachian valve. FO=foramen ovale. IVC=inferior vena cava. RA=right atrial. RLPV=right lower pulmonary vein. RMPV=right middle pulmonary vein. RUPV=right upper pulmonary vein. SLB=superior limbic band (septum secundum). SVC=superior vena cava. TBV=Thebesian valve.

Anatomy

Patent foramen ovale

Patent foramen ovale is the space between a well developed (valve-competent) septum primum and a normally formed septum secundum (figure 3). It is a normal interatrial communication during fetal life, characterised by streaming of oxygen-rich flow from the ductus venosus and, to a lesser extent, from the inferior vena cava, through the foramen ovale to the left atrium. After birth, left atrial pressure normally exceeds right atrial pressure and, septum primum apposes septum secundum, and the foramen ovale narrows. A patent foramen ovale is seen in almost all newborn babies, but its frequency decreases with advancing age.[48–50] Complete anatomical closure of the foramen ovale occurs in 70–75% of adults.[51]

Secundum atrial septal defect

Secundum atrial septal defect is a defect within the fossa ovalis usually due to one or several defects within septum primum (figure 2B). Septum secundum is well-formed in most patients. Most secundum defects are not confluent with the vena cavae, right pulmonary veins, coronary sinus, or the atrioventricular valves. With the exception of patent foramen ovale, secundum atrial septal defect is the most common cause of an atrial-level shunt. The size of secundum defects varies from several millimetres to 2–3 cm. Large defects are usually associated with substantial deficiency, or even complete absence, of septum primum.

Primum atrial septal defect

Primum atrial septal defect is one of several variants of common atrioventricular canal defects (also termed atrioventricular septal defect) with an interatrial communication located between the anterior-inferior margin of the fossa ovalis and the atrioventricular valves. The defect is characterised by a common atrioventricular orifice with two distinct atrioventricular valve annuli completed by valve tissue adhering to the crest of the ventricular septum. The atrioventricular tissue occludes the space that accounts for the ventricular septal defect component in the complete form of the malformation (figure 2B). In addition to the septal defect, the atrioventricular valves in this anomaly are almost always abnormal, including a cleft in the anterior mitral leaflet. Unlike other types of atrial septal defects, the position and course of the conduction axis is abnormal as in complete atrioventricular canal defect.

Sinus venosus defect

This defect is a communication between one or more of the right pulmonary veins and the cardiac end of the superior vena cava (superior vena cava type) or the posterior-inferior atrial wall just above the inferior vena cava-right atrial junction (inferior sinus venosus defect; figure 2B).[44,46] About 4–11% of atrial septal defects are sinus venosus defects.[52] The most common location of the

defect (around 87%[43]) is between the right upper pulmonary vein and the superior vena cava, resulting from deficiency of the tissue that separates these two veins.[44,45] The left atrial orifice of the right upper pulmonary vein allows for communication between the left atrium and the cardiac end of the superior vena cava. Less frequently, the defect involves the posterior or inferior aspects of the right atrium with or without involvement of the right lower and middle pulmonary veins (figure 2B).[44,46]

Coronary sinus defect

This uncommon atrial communication results from partial or complete unroofing of the tissue separating the coronary sinus from the left atrium, allowing a shunt through the defect and the coronary sinus orifice. The association of a coronary sinus septal defect and persistent left superior vena cava is termed Raghib syndrome.[53]

Common atrium

Common atrium is present when septum primum, septum secundum, and the atrioventricular canal septum are absent, which is often seen in patients with heterotaxy syndrome. Remnants of atrial septal tissue can sometimes be recognised.

Pathophysiology

In most patients an atrial septal defect results in left-to-right shunt. The direction and magnitude of blood flow through an atrial communication are determined by the size of the defect and by the relative atrial pressures, which relate to the compliances of the left and right ventricles. Both the size of the defect and the compliances of the ventricles can change over time.[54] At birth, pulmonary vascular resistance is high and right ventricular compliance is low, changing gradually to a high compliance–low resistance circulation. The usual haemodynamic findings in secundum atrial septal defect include left-to-right shunt mostly during late ventricular systole and early diastole, increasing during atrial contraction and expiration. Most defects smaller than 10 mm in diameter are associated with a fairly small shunt and minimum or no enlargement of the right heart structures. In larger defects the pulmonary-to-systemic flow ratio can exceed 1·5 and triggers a cascade of changes in the myocardium and in the pulmonary vasculature. The initially predominant volume overload and later pressure overload on the right heart leads to chamber enlargement with diastolic septal shift towards the left ventricle and adverse interventricular interaction resulting in decreased left ventricular compliance and a shift from a circular to a D-shape short-axis geometry.[55] These changes result in decreased left ventricular diastolic filling, increased pulmonary-to-systemic flow ratio through the defect, and diminished systemic output. Left ventricular systolic dysfunction can develop late in patients with a large atrial septal defect.[56] Factors that decrease left-to-right flow include anatomical (eg, valve or vessel stenosis) or functional (eg, pulmonary vascular disease) reasons.

A longstanding shunt results in impaired right atrial reservoir and pump functions,[57] right ventricular dilatation, myocardial cell hypertrophy and fibrosis, and cellular injury manifesting as increased serum concentrations of cardiac troponin-I.[58] The pulmonary vascular bed remodels with myointimal cell proliferation, increased medial smooth muscle, and increased collagen leading to arteriolar narrowing and pulmonary hypertension. Mild increase in pulmonary artery pressure is common in young patients with a large atrial septal defect, but a few (6–19%), mostly female patients, will develop pulmonary vascular disease over time.[59,60]

Natural history

Defect size

The natural history of isolated atrial communications varies according to anatomical type, size, and patient-specific factors. Sinus venosus and primum defects are usually associated with a haemodynamically significant shunt, do not decrease in size, and usually need surgical closure. By contrast, the natural history of secundum defects vary widely. Spontaneous closure occurs frequently in young patients with small defects. Hanslik and colleagues,[61] in a study of 200 consecutive patients (median age at presentation 5 months; median follow-up 4·5 years), reported spontaneous closure in 56% of patients with an initial defect size of 4–5 mm, 30% in

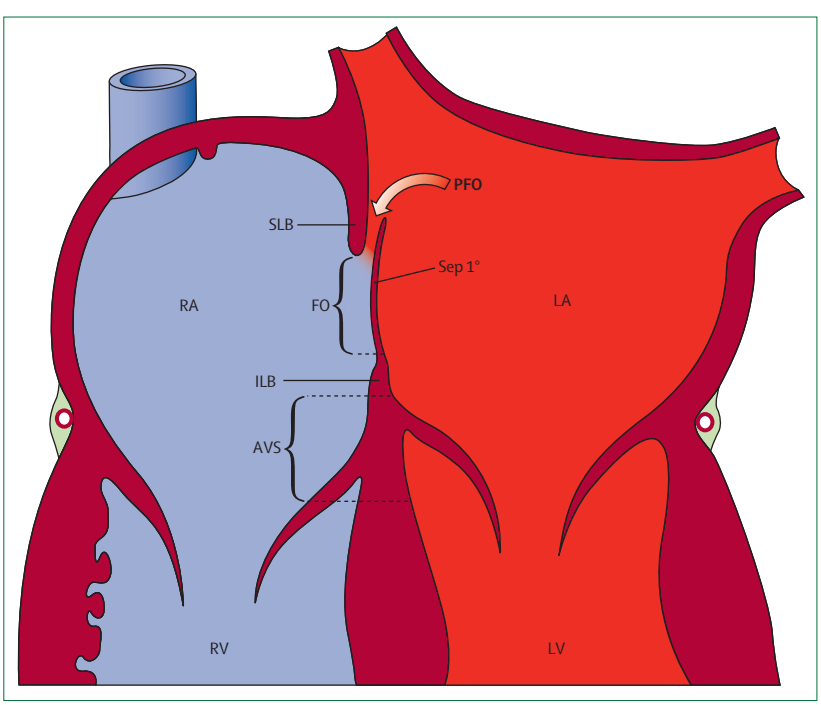

Figure 3: **Atrial septal components and patent foramen ovale**
Arrow indicates patent foramen ovale (PFO). Modified from Geva,[39] with permission from Wiley-Blackwell Publishing. AVS=atrioventricular septum. FO=fossa ovalis. ILB=inferior limbic band. LA=left atrium. LV=left ventricle. RA=right atrium. RV=right ventricle. Sep 1°=septum primum. SLB=superior limbic band (septum secundum).

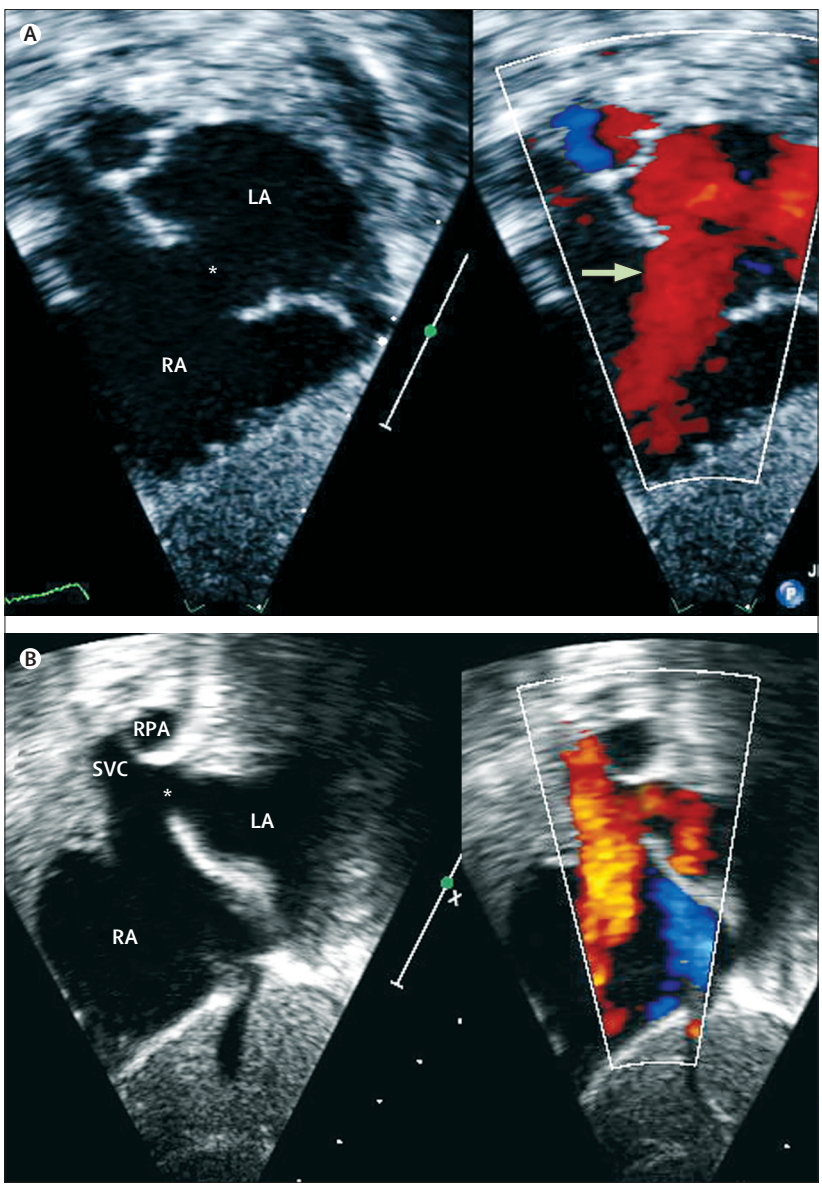

Figure 4: **Echocardiographic imaging of atrial defects**
(A) Secundum atrial septal defect in the centre of the fossa ovalis (*). Note the left-to-right flow imaged by colour Doppler (arrow). (B) Superior vena cava (SVC)-type sinus venosus defect located above the fossa ovalis between the SVC and the right upper pulmonary vein as it enters the left atrium (LA). RA=right atrium. RPA=right pulmonary artery.

6–7 mm defects, 12% in 8–10 mm defects, and in none of those with a larger defect. In that study, 39% of patients diagnosed at younger than 1 year had spontaneous closure by contrast with only 19% of those diagnosed later.

In patients whose secundum defect does not close spontaneously, defect size can increase or decrease with age.[61–64] In general, 70% of initially small (≤4 mm) defects decrease in size, 12% remain unchanged, and 18% increase. By contrast, in those with an initial defect size greater than 8–12 mm, only 9% decreased in size, 15% remain unchanged, and 76% increased. Notably, most reports of change in defect size have reported absolute values. Whether changes in defect size are proportional to increase in heart size or to somatic growth is unclear.

Clinical presentation

Most patients remain asymptomatic throughout most of childhood. Even those with a large left-to-right shunt might not have overt symptoms until adulthood. Incidental diagnosis by an echocardiogram obtained because of a heart murmur or an abnormal finding on a chest radiogram or an electrocardiogram is common. Rarely an isolated atrial septal defect is found in an infant with tachypnoea, slow weight gain, or recurrent respiratory infections.[65,66] In such cases, a careful search for associated non-cardiac anomalies and pulmonary hypertension should be done.[67] In the second decade of life, none or subtle symptoms of shortness of breath with exertion or palpitations are common. By contrast, most adult patients with a large defect present with symptoms, including fatigue, exercise intolerance, palpitations, syncope, shortness of breath, peripheral oedema, manifestations of thromboembolism, and cyanosis.

Exercise capacity

Exercise intolerance is uncommon in young children with an isolated atrial septal defect.[68] Nonetheless, pulmonary function is often impaired in this age group.[69] The frequency of exercise intolerance increases insidiously with age. Exercise capacity and peak oxygen consumption are decreased in most adults with unrepaired secundum defect, often at 50–60% of predicted values in healthy controls.[70]

Arrhythmias

Major arrhythmias are uncommon in children with atrial septal defects. The most common arrhythmias are atrial flutter and fibrillation, incidences of which increase with age. Among the 211 adult patients with atrial septal defects reported by Berger and colleagues,[71] only one patient younger than 40 years had atrial flutter compared with 15% of the patients aged 40–60 years; 16% and 19% had atrial flutter and fibrillation, respectively, in those older than 60 years. In addition to tachyarrhythmias, atrioventricular block associated with genetic mutations (eg, *NKX2-5*) has been reported.[16,72]

Pulmonary hypertension

Pulmonary hypertension is uncommon in children with an isolated atrial septal defect. In adults with large defects, mild or moderate pulmonary hypertension is common and tends to increase with age and in those living at high altitude.[73–75] Pulmonary vascular obstructive disease with or without right-to-left atrial-level shunting (Eisenmenger syndrome) is present in 5–10% of adults with untreated atrial septal defects, with a female-to-male ratio of roughly 2.[59,60] Patients with atrial septal defect and severe pulmonary hypertension are diagnosed at a

median age of 51 years, which is several decades older than those with an underlying ventricular septal defect.[76] The pathophysiology of pulmonary vascular obstructive disease is not fully understood and contributing factors such as Down syndrome, other genetic predisposition, upper airway obstruction, pulmonary emboli or in-situ pulmonary artery thrombosis, and drug use such as anorexigenic agents (eg, fenfluramine) should be explored, especially in patients with fairly small defects.

Life expectancy

The availability of surgical closure of atrial septal defects since 1952 hampers the evaluation of its natural history in the modern era. Nonetheless, evidence clearly suggests that untreated large secundum defects are associated with a reduced lifespan. Campbell reported a low annualised mortality rate in the first two decades of life (0·6% and 0·7% per year, respectively), increasing to 4·5% per year in the fourth decade and 7·5% per year in the sixth decade.[77] This finding is supported by a subsequent study comparing early versus late defect closure.[78]

Diagnosis

Clinical

On physical examination, most young patients with an isolated secundum atrial septal defect are acyanotic and can have few or no symptoms. The precordium is often hyperdynamic to palpation. The second heart sound is characteristically widely split without respiratory variations. The intensity of the pulmonary component of the second heart sound (P_2) corresponds to the pulmonary artery pressure with a loud sound indicating pulmonary hypertension. A soft systolic ejection murmur is usually heard over the pulmonary area in the left upper sternal border. A diastolic rumble over the left lower sternum corresponds to increased flow through the tricuspid valve. A holosystolic flow murmur over the apex indicative of mitral regurgitation should raise suspicion for a primum atrial septal defect or mitral valve prolapse. Signs of right heart failure are rare, but can be encountered in adults with pulmonary hypertension.

Electrocardiography

Characteristic electrocardiographic features of atrial septal defect include a tall P wave indicative of right atrial enlargement, incomplete right bundle branch block pattern, and right axis deviation. The rhythm is typically sinus, but in adult patients can be atrial flutter or fibrillation. Right ventricular hypertrophy is evident in patients with pulmonary hypertension. Left axis deviation with a superior axis is suggestive of primum defect.

Chest radiography

Enlargement of the right heart structures are evident on chest radiography in patients with haemodynamically significant atrial septal defects. Right atrial and pulmonary artery enlargement are best seen in the anterior-posterior projection whereas right ventricular enlargement is best seen in the lateral projection. Similarly, left atrial dilatation (associated with mitral regurgitation in primum defects) is evident in the lateral projection. The pulmonary vasculature is prominent. Discrepancy between enlarged central pulmonary arteries and relative paucity of peripheral vasculature suggests pulmonary vascular obstructive disease.

Echocardiography

Transthoracic echocardiography is the primary diagnostic method for determining the presence, location, size, and haemodynamic characteristics of atrial septal defects. Two-dimensional imaging with colour Doppler flow mapping depicts the location and size of the defect and the direction of flow (figure 4). Spectral Doppler further documents the direction of flow and allows determination of flow velocity. Three-dimensional imaging allows en-face views of the defect from the right and left atrial perspectives, allowing appreciation of the defect's shape and change in size during the cardiac cycle (figure 5).[79] The haemodynamic burden associated with the defect is determined by assessments of right atrial, right ventricular, and pulmonary artery size. Right ventricular and pulmonary artery pressures can be estimated by Doppler determination of the velocities of the tricuspid and pulmonary valve regurgitation jets. The former estimates the peak systolic pressure difference between the right ventricle and right atrium whereas the latter estimates the early and late pressure differences between the main pulmonary artery and right ventricle, which correlate with the mean and diastolic pulmonary artery pressures. The geometry of the interventricular septum is another indicator of right ventricular volume and pressure overloads. Right ventricular volume overload manifests as diastolic septal flattening (deviation towards the left ventricle) and pressure overload manifests as septal flattening during systole.

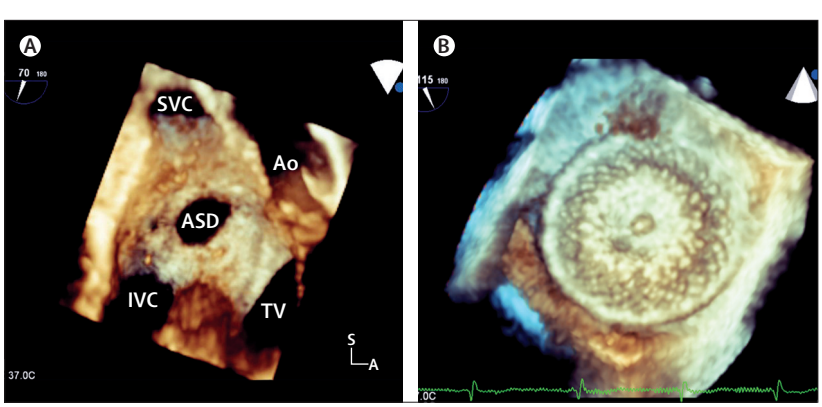

Figure 5: **Three-dimensional imaging of a secundum atrial septal defect imaged by a transoesophageal echocardiogram before (A) and after (B) device closure**

(A) En-face view of the defect as seen from the right atrium. (B) En-face view of the occluding device as seen from the left atrium. Images are from different patients. Ao=ascending aorta. ASD=atrial septal defect. IVC=inferior vena cava. SVC=superior vena cava. TV=tricuspid valve.

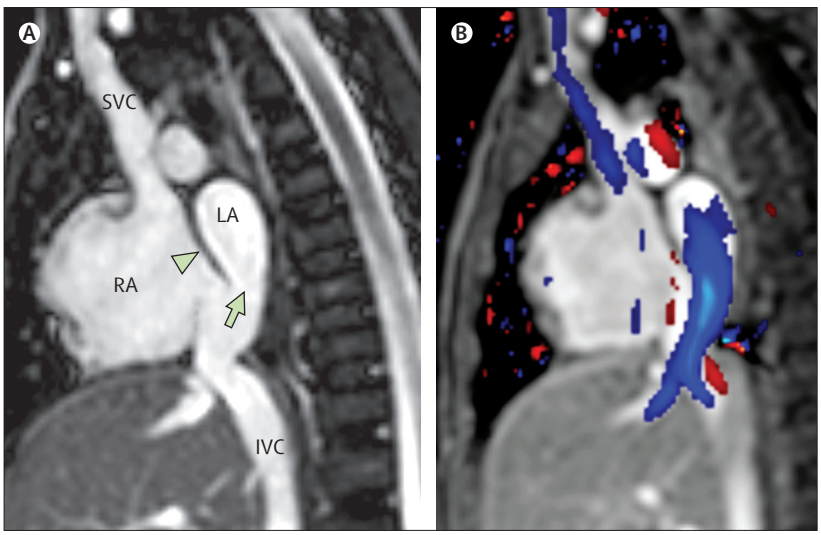

Figure 6: **Inferior sinus venosus defect imaged by cardiac MRI**
(A) Cine steady-state free precession image in an oblique sagittal plane showing the defect in the posterior-inferior atrial junction (arrow), just above the entrance of the inferior vena cava (IVC) to the right atrium (RA). Note that the fossa ovalis is intact (arrow head). (B) Phase velocity mapping in the same orientation showing flow from the left atrium (LA) to the right atrium through the defect. SVC=superior vena cava.

The diagnostic sensitivity of transthoracic echocardiography is excellent in young patients, but lower in those with restricted acoustic windows due to obesity, large body habitus, and previous thoracic surgery. Transoesophageal echocardiography provides an excellent alternative approach in these patients and is also used for guidance of transcatheter closure.

Contrast echocardiography with injection of agitated saline through a peripheral venous cannula during imaging of the atria and ventricles can assist in the diagnosis of atrial septal defect, especially in patients with restricted acoustic windows.[80] In the presence of a left superior vena cava, injection of agitated saline in a left arm venous cannula can diagnose a coronary sinus septal defect with appearance of the contrast in the left atrium before it appears in the right atrium.

MRI and CT

Advances in cardiac MRI techniques allow anatomical delineation of atrial septal defects and quantitative assessment of their haemodynamic consequences.[81,82] Specifically, cine steady-state free precession imaging is currently the gold standard technique for measurements of ventricular volumes and function whereas phase velocity flow mapping allows accurate quantification of the pulmonary-to-systemic flow ratio.[83] Magnetic resonance angiography allows imaging of associated pulmonary and systemic venous anomalies. In patients with isolated secundum or primum defects, cardiac MRI is seldom necessary. Exceptions include those in whom the location of the defect or its haemodynamic burden is in question. In contrast, cardiac MRI is an important diagnostic method in sinus venosus defects (figure 6).[46,84] The posterior location of these defects and the frequently associated anomalous pulmonary venous drainage hamper the ability of transthoracic echocardiography to adequately evaluate these defects as patients' body size increases.

High-resolution contrast CT is capable of anatomical delineation of atrial septal defects. However, the risk of cancer related to ionising radiation limits its application to only carefully selected patients in whom other modalities are insufficient.[85]

Diagnostic catheterisation

Cardiac catheterisation is seldom done solely for diagnostic purposes. Most catheterisations are done with the intention to close the defect percutaneously. A diagnostic procedure typically precedes device placement, including determination of pressures and pulmonary and systemic flow ratios. In selected patients, angiography is done to delineate associated anomalies not shown by non-invasive imaging. In adult patients at risk of coronary artery disease and in those with pulmonary hypertension, diagnostic catheterisation is indicated for detailed evaluation.

Treatment

Indications and contraindication for defect closure

Closure of an atrial septal defect is indicated in the presence of a haemodynamically significant shunt that causes enlargement of right heart structures, irrespective of symptoms (class I, level of evidence B).[86,87] Before the advent of non-invasive imaging, a haemodynamically significant shunt was classically defined by a pulmonary-to-systemic flow ratio greater than 1·5, which is the magnitude of shunt needed for a right-sided volume overload and pulmonary overcirculation. Other indications include suspicion of paradoxical embolism in the absence of other causes (class IIa, level of evidence C) or in the rare instance of documented orthodeoxia-platypnoea (dyspnoea and hypoxaemia accompanying a change to a sitting or standing from a recumbent position) irrespective of shunt size.[86] A small defect without evidence of volume overload on the right heart and without other indications should be followed up expectantly, keeping in mind the possibility of increase in shunt later in life.

Pulmonary hypertension is not an absolute contraindication for defect closure. American and European practice guidelines[86,87] state that an atrial septal defect can be closed if the pulmonary vascular resistance is lower than two-thirds of the systemic vascular resistance (at baseline or after pulmonary vasodilator acute challenge or targeted pretreatment course) and there is evidence of a pulmonary-to-systemic flow ratio greater than 1·5 (class IIB, level of evidence C). A calculated pulmonary vascular resistance greater than 8 Woods units generally precludes closure, as does a resting interatrial right-to-left shunt such as Eisenmenger syndrome.[88] Closure can also be contraindicated in other conditions in which the defect serves as a decompressing route for blood flow

(pop-off valve), including severe obstructive or restrictive right or left heart lesions.[87,89] Patients with pulmonary hypertension need careful evaluation in an experienced centre, including possible balloon occlusion of the defect with haemodynamic assessment.

Timing of defect closure

A haemodynamically significant atrial septal defect should be closed electively once the diagnosis is confirmed. Although there is no lower limit of age for defect closure, many clinicians choose to refer asymptomatic children for the procedure at age 3–5 years. At the other end of the age spectrum, evidence indicates that with the exception of the contraindications noted above, defect closure is safe and effective in improving symptoms, even in elderly patients.[74,89–91]

Treatment strategies for defect closure

Sinus venosus, primum, and coronary sinus septal defects need surgical closure. Secundum defects can be closed by either surgery or by a percutaneous route using an occluding device delivered by a catheter. Transcatheter closure might not be feasible in some large secundum defects or small infants.

Surgery

Since the pioneering reports of Murray who first closed an atrial septal defect without direct visualisation in 1948 and Lewis and Taufic who used hypothermia and inflow occlusion to close an atrial septal defect under direct vision in 1952,[92,93] more than 50 years of experience have resulted in a safe and effective operation with almost no mortality and little morbidity. The defect is closed under direct vision using cardiopulmonary bypass, either by direct suture or with a pericardial or a synthetic patch. Access to the heart is accomplished through median sternotomy, submammary incision, lateral thoracotomy, transxiphoid, and other approaches. A small skin incision improves the cosmetic results and video-assisted thoracoscopic techniques have been shown to be feasible.[94]

Results of secundum defect closure in the modern era are excellent with near-zero mortality for isolated defects. Morbidities such as arrhythmias, bleeding, pneumothorax, and pericardial and pleural effusions are usually transient. Arrhythmia and prolonged stay in the intensive care unit (>3 days) are more common in adults, especially elderly patients.[91] The long-term results of surgical closure of secundum defects are excellent for patients operated on when younger than 25 years with an actuarial survival curve that is indistinguishable from that of the general population—98% versus 99% in those operated on when younger than 12 years and 93% versus 97% in those operated on between the ages of 12 and 24 years. By contrast, those operated on at age 25–41 years (84% *vs* 91%) and older than 41 years (40% *vs* 59%) had lower survival than healthy individuals.[78]

Transcatheter closure

Since King and colleagues[95] reported the first transcatheter device closure of a secundum defect in 1976 the field has evolved substantially with a range of occluding devices and delivery systems now available (table). Improvements in device design and ease of use coupled with avoidance of cardiac surgery have led many centres to adopt transcatheter closure of secundum defects as their first choice.[86,87,96] Secundum defects larger than 36–40 mm in maximum diameter, inadequate margins to anchor the device, and interference of the device with atrioventricular valve function or with systemic or pulmonary venous drainage are generally regarded as relative contraindications.[97,98] The device is typically introduced through a sheath in the femoral vein and its deployment is guided by a combination of fluoroscopy and echocardiography. Echocardiographic guidance can be accomplished through a transoesophageal approach (real-time two-dimensional and three-dimensional), intracardiac ultrasound, or transthoracic imaging.[99,100] Most practitioners prescribe antiplatelet drugs after device implantation, but data to support the practice are lacking.

Current results of device closure of secundum defects show a good safety and efficacy profile. A retrospective multicentre review of 478 patients undergoing implantation of an Amplatzer septal occluding device (St Jude Medical, Plymouth, MN, USA) at a median age of 6 years showed technical success in 96% with an occlusion rate at 24 h of 99·6%.[101] A study in 650 adult patients at a mean age of 45 years showed similarly good early results.[102] Results of a prospective multicentre cohort evaluating the Helex device (W L Gore & Associates, Flagstaff, AZ, USA) showed a procedural success rate of 93% and closure rate of 98·1%.[103]

Complications occur in inverse relation to institutional procedural volume.[104] The rates of minor and major complications have been reported at roughly 5% and 1%, respectively.[101,102,105] Meta-analysis of 142 case series showed major periprocedural complications in 1·6% (95% CI 1·4–1·8), with device embolisation necessitating surgery (0·7%) and pericardial tamponade (0·1%) being the most common.[106] The most common minor complications were atrial arrhythmias, vascular complications, and transient heart block. Late complications included atrial arrhythmias (1·5%), stroke (0·4%), device thrombosis (0·2%), device erosion through the atrial wall or aortic root (0·1%), device embolisation (0·1%), and death (0·1%). Cardiac erosion by the device was the focus of several reports[107–109] and a review by the US Food and Drug Administration.[110] New-onset or worsening migraine headache have been reported in some patients, some of whom were later found to have an allergy to nickel, which is a component of some devices.[111] Antiplatelet treatment with clopidogrel was found in that report to be helpful in amelioration of the headaches.

Although several studies have compared costs, clinical outcomes, efficacy, and rates of complications between transcatheter and surgical closure of secundum

	Company	Design	Maximum size of defect	Advantages	Disadvantages	Regulatory status
Amplatzer septal occluder	St Jude Medical, Plymouth, MN, USA	Nitinol mesh of self-centring double disc with polyester patch inside	40 mm	Easy to use; versatile; easily withdrawn and redeployable; small delivery sheath (8/9 Fr for 18 mm device); largest experience worldwide	Avoid in nickel allergy; late erosions (rare); stiffer delivery cable (distorts anatomy before release) and framework (distorts atrial anatomy)	FDA and CE mark approval
Gore Helex septal occluder	W L Gore & Associates, Flagstaff, AZ, USA	Nitinol helix spiral guide covered with ePTFE membrane	18 mm	Flexible, compliant (no erosion, conforms to atrial septal anatomy); low profile; metal almost completely covered by ePTFE; retrievable at any stage (even after release); experience worldwide	Not self-centred; slightly more challenging deployment; care with deficient rims; more device embolisation and residual shunt; needs larger sheath (12 Fr for closure of 18 mm defect)	FDA and CE mark approval
Figulla atrial septal defect occluder	Occlutech, Helsingborg, Sweden	Nitinol mesh of self-centring double disc with Dacron patch inside	40 mm	Same as Amplatzer device, but left atrial component flat and latest generation has tilting of attachment with delivery cable (allows better positioning before release)	Same as Amplatzer device, but needs slightly larger sheaths (10 Fr for 18 mm device); less published experience	CE mark approval
Cera atrial septal defect occluder	Lifetech Scientific, Shenzhen, China	Nitinol mesh of self-centring double disc with polyester patch inside	42 mm	Same as Amplatzer device, but has a flat left atrial component and latest generation has tilting with delivery cable (allows better positioning before release)	Same as Amplatzer device, but needs slightly larger sheaths (10 Fr for 18 mm device); scarce published experience	CE mark approval
Ultrasept atrial septal defect occluder	Cardia, Eagen, MN, USA	Nitinol double disk self-centring frame covered with polyvinyl alcohol	34 mm	Low profile, flexible (conforms to atrial anatomy), retrievable and re-deployable, less metal, which is covered	Requires only slightly larger delivery sheath than Amplatzer device (9 Fr for 18 mm device); no published experience with newest design, only personal communications	CE mark approval

See appendix for images of devices. FDA=US Food and Drug Administration. CE=Conformité Européenne. ePTFE=expanded polytetrafluoroethylene.

***Table*: Examples of devices for transcatheter closure of atrial septal defect**

See Online for appendix

defects,[91,112–114] no prospective randomised trial has been published at the time of writing. In general, these studies have shown no major advantage of one approach compared with the other with each having specific advantages and disadvantages.[114] The aforementioned discussion emphasises the importance of long-term follow-up after defect closure.

Clinical and haemodynamic results of defect closure

Patients commonly report subjective improvement in symptoms after closure of atrial septal defects.[70,89] In young children, somatic growth rate can increase.[115] Some studies have shown an increase in exercise capacity in adults after defect closure,[116] but in asymptomatic children the change has been minimum or none.[68] Conversely, studies on respiratory symptoms and pulmonary function in children have shown a significant improvement after closure.[117,118]

The haemodynamic response to defect closure includes reduction in right atrial and right ventricular size.[119–122] Most of the decrease occurs immediately with some further remodelling 1–2 years later.[119] A younger age at closure and a lesser degree of chamber enlargement before repair are associated with a higher likelihood of normalisation of right ventricular size.[119] Persistent enlargement of the right heart has been reported in up to a third of patients, mostly in adults with severely dilated chambers.[121] Echocardiographic indices of right ventricular function before and after defect closure have shown mixed results with some measures showing an improvement from before to after closure, whereas others show either no change or a decrease.[120,123,124] Left ventricular filling improves in children and young adults.[120] However, in adults with pre-existing decreased left ventricular compliance, the acute increase in preload associated with defect closure can lead to worsening left atrial and pulmonary venous hypertension and heart failure symptoms.[125] Pulmonary artery pressure decreases to normal except in some patients with moderate to severe pulmonary hypertension.[126]

A salutary effect of defect closure on atrial arrhythmias has been shown in meta-analysis of 26 studies spanning four decades, including 1841 surgical closures and 945 transcatheter closures.[127] Considering all studies, the incidence of atrial arrhythmias decreased in the short term (odds ratio 0·66, 95% CI 0·57–0·77). However, when only studies with at least 5 years of follow-up were considered, the beneficial effect was lost. Other studies have identified persistent rhythm and conduction abnormalities associated with delayed closure.[128,129] These observations have led the American Heart Association and the European Society of Cardiology to consider a Maze antiarrhythmic procedure in selected adult patients.[86,87]

Adults with atrial septal defects

Unrepaired defects

An isolated atrial septal defect can occasionally go undiagnosed for decades. It accounts for 25–30% of congenital heart disease cases diagnosed in adulthood.[130] Although many young adults have no subjective symptoms, exercise testing usually unveils subnormal exercise capacity.[131] With advancing age, however, overt symptoms of fatigue, exercise intolerance, shortness of breath, palpitations, and manifestations of heart failure become prevalent and survival rate is reduced.[77] Onset of ischaemic heart disease and other comorbidities associated

with decreased left ventricular compliance (eg, essential hypertension, aortic valve stenosis, ageing) lead to increased left-to-right shunting across the defect, which further aggravate the symptoms and lead to clinical deterioration. Atrial flutter and fibrillation are important causes of morbidity, seen in 21% of adults older than 40 years with a rising frequency over time.[132]

Repaired defects

Irrespective of technique, closure of atrial septal defects after age 40 years confers morbidity and mortality benefits compared with medical therapy alone.[132,133] Studies have shown improvements in symptoms and exercise capacity, decrease in right atrial and right ventricular size, and improvement in pulmonary hypertension in most but not all patients.[74,75,121,134,135] Although these benefits are less pronounced after age 60 years,[74,75] symptomatic improvement and increase in 6 min walking distance coupled with a low procedural risk provide the rationale for defect closure in elderly patients.[74,89,136] In view of the risk of unmasking left ventricular diastolic dysfunction by closing an atrial communication, test occlusion in the catheterisation laboratory is recommended before closure of the defect. The risk of atrial tachyarrhythmias, especially atrial flutter and fibrillation, remains high after defect closure in adulthood. Risk factors include atrial arrhythmia before closure and age at closure older than 40 years.[137,138]

Pregnancy

Maternal complications are uncommon in isolated atrial septal defects not complicated by pulmonary hypertension.[139] Yap and colleagues[140] found similarly low rates of maternal complications in women with repaired and unrepaired defects, including arrhythmias (4%) and transient ischaemic attack (1%). None of the 98 women with 188 pregnancies had a stroke, heart failure symptoms, or endocarditis. Pre-pregnancy history of arrhythmia and maternal age older than 30 years were risk factors for maternal cardiac complications. By comparison with the general population, women with unrepaired atrial septal defects had an increased risk of pre-eclampsia, fetal loss, and low birthweight. By contrast, the outcome for offspring of women with a repaired defect was similar to that of the general population.

Pregnancy should be avoided in women with an atrial septal defect and severe pulmonary hypertension. In a contemporary study maternal mortality was prohibitively high (28%) in women with congenital heart disease and pulmonary hypertension, despite use of pulmonary vasodilator therapy in more than half of the patients.[141] Maternal deaths tended to occur shortly after delivery and were often caused by heart failure, thromboembolism, pulmonary hypertensive crisis, and sudden cardiac death.

Contributors

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Declaration of interests

We declare that we have no competing interests.

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