博士論文

The prevalence and risk factor analysis of atrioventricular block after atrial septal defect closure

（心房中隔欠損閉鎖後の房室ブロック

発生頻度とリスク因子の検討）

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Abstract

Objective: Secundum atrial septal defect (ASD) is a common congenital heart defect. There is limited data on both early and late AV block post ASD closure. We sought to determine the incidence and risk factors of AV block associated with ASD closure.

Methods: A retrospective analysis of all patients who underwent either surgical or device ASD closure at the Royal Children's Hospital Melbourne between 1996 and 2010 was performed. Baseline demographics, procedural details and follow-up data were collected from medical records.

Results: A total of 378 patients were identified; 242 in the device group and 136 in the surgical group. Fourteen patients (3.7%) had AV block (one with second degree and 13 with first degree) at a median follow-up of 28 months; 11/242 (4.5%) in the device group and 3/135 (2.2%) in the surgical group (p=0.39). Six patients had new onset AV block after ASD closure. In the device subgroup, patients with AV block at follow-up had a larger indexed device size compared to those without (22 [15- 31] vs 18[7- 38], p=0.02). Multivariate analysis revealed the presence of AV block either pre- or post-procedure to be the only variables associated with late AV block.

Conclusion: Late AV block in patients with repaired ASD is rare and most likely independent of the technique used. In the device subgroup, the only risk factors identified to be associated with late AV block was the presence of either pre- or post-procedural AV block so long term follow up should be provided.

Abbreviations

ASD= atrial septal defect

ASO= Amplatzer Septal Occluder

AVNRT= atrioventricular nodal re-entrant tachycardia

AVSD= atrioventricular defect

CS= coronary sinus

ECG= electrocardiogram

ePTFE= expanded polytetrafluoroehylene

IVC= inferior vena cava

LA= left atrium

Qp/Qs= pulmonary-to-systemic blood flow ratio

RA= right atrium

RV=right ventricle

SND= sinus node dysfunction

SVC= superior vena cava

SVT= supraventricular

TEE= transesophageal echocardiogram

TGA= transposition of the great arteries

VSD= ventricular septal defect

VT= ventricular tachycardia

Table of Contents

1 Introduction

1.1 Clinical features of atrial septal defect

1.1.1 Prevalence of atrial septal defect

Atrial septal defect (ASD) is a very common congenital heart defect with an incidence of approximately 0.6/100 births. ASDs occurs as an isolated anomaly in 5% to 10% of all congenital heart defects. It is the second most common congenital heart disease following ventricular septal defect (VSD) which accounts for 15% to 20% of all congenital heart defects. It is more common in females than in males with a male: female ratio of 1:2. Approximately 30% to 50% of children with congenital heart defects have an ASD as part of the cardiac defect[1-3].

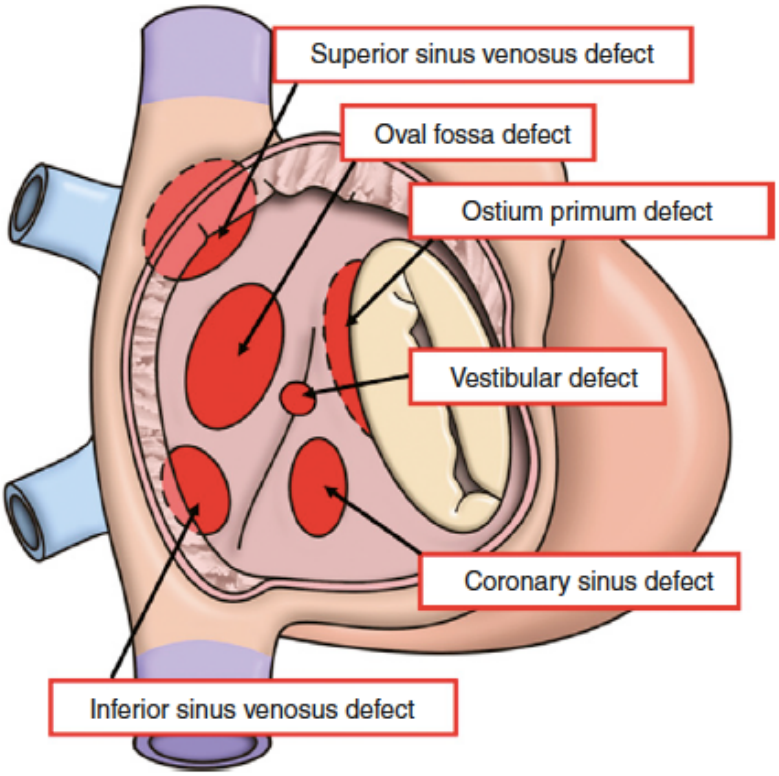
1.1.2 Types of interatrial communication

Based on the location of the interatrial communication, it can be divided into the so-called primum and secundum types, sinus venosus defects and those found at the mouth of the coronary sinus and the rare vestibular defect (Figure 1). The so-called secundum ASDs result from deficiency of the primary atrial septum, which forms the floor of the fossa ovalis. The secundum ASD is the most common type of ASD, accounting for 50% to 70% of all ASDs. Isolated ostium primum ASDs occurs in about 15% of all ASDs, or 30% if those that occur as part of complete atrioventricular septal defect (AVSD) are included. Sinus venous ASD occurs in about 10% of all ASDs. This type of defect is most commonly located at the entry of the superior vena cava (SVC) into the right atrium (RA) (superior sinus venosus defect) and rarely at the entry of the inferior vena cava (IVC) into the RA (inferior sinus venosus defect). The superior sinus venosus defects are very commonly associated with anomalous drainage of the right

upper pulmonary vein into the RA, and the inferior sinus venous defect is often associated with anomalous drainage of the right pulmonary veins into the IVC (an entity known as Scimitar Syndrome). In coronary sinus ASD, there is a defect in the roof of the coronary sinus (CS) and the left atrium (LA) blood shunts through the defect and the coronary sinus ostium into the RA, which results in similar clinical features to other types of ASDs.

Figure 1: A cartoon showing the various types of interatrial communication.

From: Anderson Pediatric Cardiology (3e 2010), page 516



1.1.3 Associated anomalies

Certain cardiac and vascular abnormalities have been reported to occur more frequently in patents with an ASD than in the general population. As mentioned above, anomalous connection of pulmonary veins is a relative common associated finding and is the phenotypic feature of the sinus venous ASD. Mitral valve prolapse occurs in approximately 20% of patients with either secundum or sinus venosus ASDs [4].

The association of Down Syndrome with ostium primum defects is well known. However, the incidence of Down Syndrome in those having surgery for an isolated secundum ASD is not particularly high. Holt-Oram Syndrome is a rare disease characterized by abnormalities in the bones of the upper limb, congenital heart disease, and/or an abnormality in the cardiac conduction system. It is an autosomal dominant genetic condition which is associated with an abnormality in the TBX5 gene. Around 75% of those affected have congenital heart disease, most commonly an ASD followed by VSD. Cardiac conduction disturbances can be present even in the absent of congenital heart disease. The degree of conduction disease is highly variable from asymptomatic first degree atrioventricular (AV) block to symptomatic complete heart block requiring permanent pacemaker implantation.

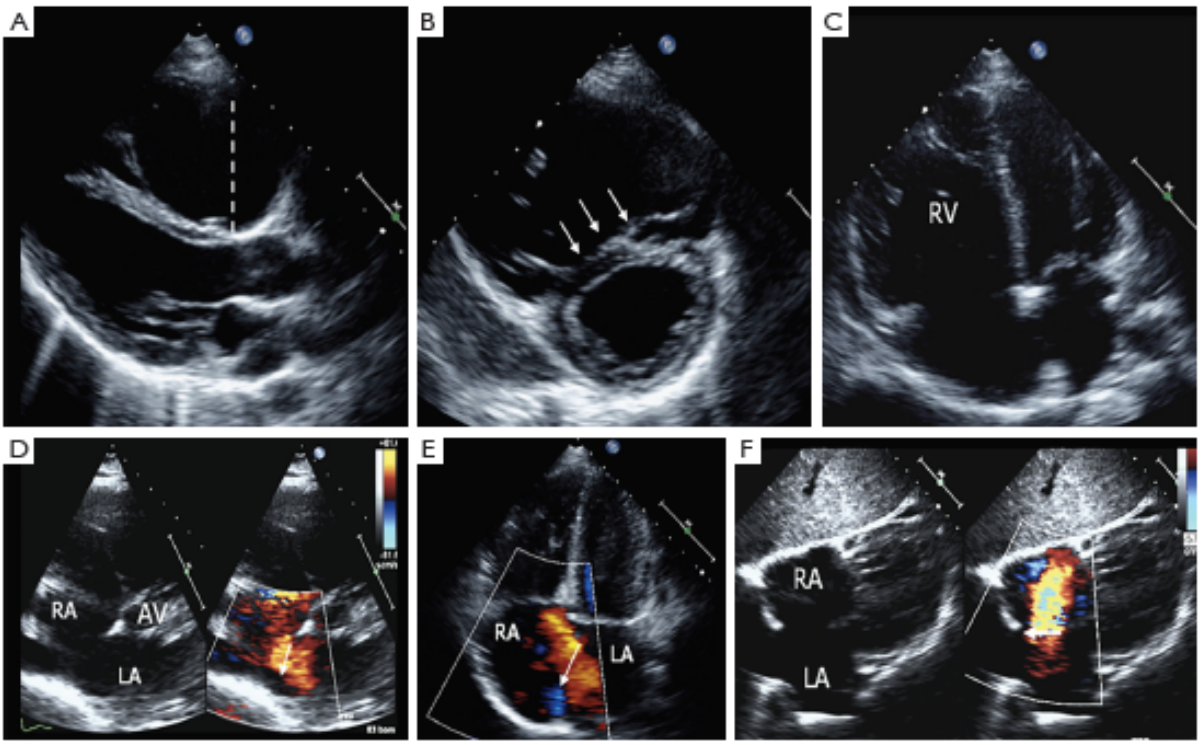
1.1.4 Pathophysiology

The pathophysiology of an ASD is related to the magnitude and direction of shunting of blood across the interatrial communication. Substantial left-to-right shunt results in a high ratio of pulmonary to systemic flow. The amount of shunting is mainly determined by the size of the defect and the relative resistance to inflow of the ventricles which is greatly influenced by pulmonary vascular resistance. A large left-to-right shunt at the atrial level leads to enlargement of both the RA and the right ventricle (RV). Diagnosis is made with an echocardiogram (Figure 2).

Despite increased blood flow to the lungs, pulmonary arterial pressure is rarely elevated in children. The incidence of pulmonary hypertension in children is no more than 5% in most studies, but increase to 20% of those aged from 20 to 40 years, and is found in half of the patients older than 40 years [5-8]. Chronic RV volume overload caused by an atrial septal defect is generally well tolerated in children. Congestive heart failure rarely occurs before the fourth or fifth decade of life, but has been reported to be present in approximately one-third of patients greater than 40 years of age [9,10].

Figure 2. Typical echocardiographic images of an ASD

Modified from Rana et al. J Thorac Dis. 2018;10(Suppl24): S2899-2908[11]



A,B,C demonstrates RV dilatation and volume overload state.
(A) Parasternal long axis view: the dotted line shows a severely dilated RV
(B) Parasternal short axis view: the arrows depict interventricular flattening at end diastole, demonstrating increased RV pressure due to RV volume overload
(C) Apical four chamber view: dilated RV
(D) –(F) Parasternal short axis, apical four chamber and subcostal view showing 2D with color Doppler across the atrial septum
RA: right atrium; LA: left atrium; RV: right ventricle; AV: aortic valve

1.1.5 Course and prognosis

An isolated atrial septal defect is usually well tolerated and symptoms are minimal or absent during childhood. Occasionally, infants with isolated and uncomplicated atrial septal defects may be symptomatic and experience congestive heart failure. Secondary pulmonary hypertension eventually appears in some patients and is an important factor in the development of both cyanosis and congestive heart failure. Dyspnea and fatigue with exertion become more prevalent in adulthood and are experienced by the majority of patients over 50 years of age. Approximately two-thirds of patients older than 40 years of age will have complications such as congestive heart failure, pulmonary hypertension, atrial arrhythmias or paradoxical embolization [10,12].

Earlier reports have indicated that spontaneous closure of an ASD occurs in about 14% to 55% of the patients in the first 4 years of life [13,14]. Spontaneous closure becomes increasingly uncommon after 2 years of age. The defect may also decrease in size in some patients. In patients with an ASD less than 3mm in size diagnosed before 3 months of age, spontaneous closure occurs in 100% of patients by 18 months of age. In patients with an ASD between 2 and 8mm in size, spontaneous closure occurs in more than 80% of the patients before 18 months of age. As ASD larger than 8mm in size rarely closes spontaneously [4].

1.1.6 Management of atrial septal defects

In infants with congestive heart failure, medical management is recommended due to its high success rate and the possibility of spontaneous closure of the defect. Classically, a left-to-right shunt with a pulmonary-to-systemic blood flow ratio (Qp/Qs) of ≥ 1.5:1 is an indication for surgical closure. Current indications for ASD closure are listed in Table 1. The level of evidence and strength of recommendation of particular options are weighed and graded according to predefined scales as outlined in Table 2 and Table 3.

Closure is usually delayed until 2 to 4 years of age due to the possibility of spontaneous closure. In the rare occasion where congestive heart failure is not tolerated despite medical management, closure is performed during infancy. There are also previous reports that premature infants with an ASD are at higher risk of developing pulmonary hypertension, and a close follow-up is warranted in this at-risk patient population [8]. In patients with pulmonary hypertension requiring oxygen or other medical therapy, closure may be considered during infancy.

Table 1. Indications for intervention in ASD: Guideline from the European Society of Cardiology [15]

Indications	Class[a]	Level[b]
Patients with significant shunt (signs of RV volume overload) and PVR<5WU should undergo ASD closure regardless of symptoms	I	B
Device closure is the method of choice for secundum ASD closure when applicable	I	C
All ASDs regardless of size in patients with suspicion of paradoxical embolism should be considered for intervention	IIa	C
Patients with PVR> 5WU but <2/3 SVR or PAP<2/3 systemic pressure and evidence of net L-R shunt (Qp:Qs>1.5) may be considered for intervention	IIb	C
ASD closure must be avoided in patients with Eisenmenger physiology	III	C

The definition of classes of recommendations and levels of evidence as outlined in Tables 2 and 3. ASD: atrial septal defect; LR shunt: left-to-right shunt; PAP: pulmonary artery pressure; PVR: pulmonary avascular resistance; Qp:Qs: pulmonary to systemic flow ratio; SVR: systemic vascular resistance; WU: Wood units

Table 2. Definition of classes of recommendations and level of evidence

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful.

Table 3. Levels of evidence

Level of evidence A	Data derived from multipile randomized clinical trials or meta-analysis.
Lvel of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion or the experts and/or small studies, retrospective studies, registries.

1.2 Surgical closure of atrial septal defects

Open heart repair of ASD has excellent results with a near-zero operative mortality [16-18]. The mortality rate is less than 0.5%, however, there is a greater risk for small infants and those with increased pulmonary vascular resistance.

The surgical approach consists of either direct suture of patch closure, depending on the size of the defect. In a sinus venous defect, a patch is always necessary so as to close the interatrial communication and at the same time redirect the anomalously draining pulmonary veins into the left atrium. Perioperative complications including cerebrovascular accident, postoperative arrhythmias and post-pericardiotomy syndrome may develop but are rare.

Long-term result of surgical repair is excellent. Survival of patients undergoing surgery is comparable with the general population [19].

1.3 Catheter device closure of atrial septal defects

As an alternative to surgical repair, patients with an ASD within the oval fossa are now increasingly submitted to closure by means or interventional catheterization. In 1976, King and Mills performed the first successful percutaneous ASD closure, but it was not until 1990 that percutaneous closure became clinically widely available[20].

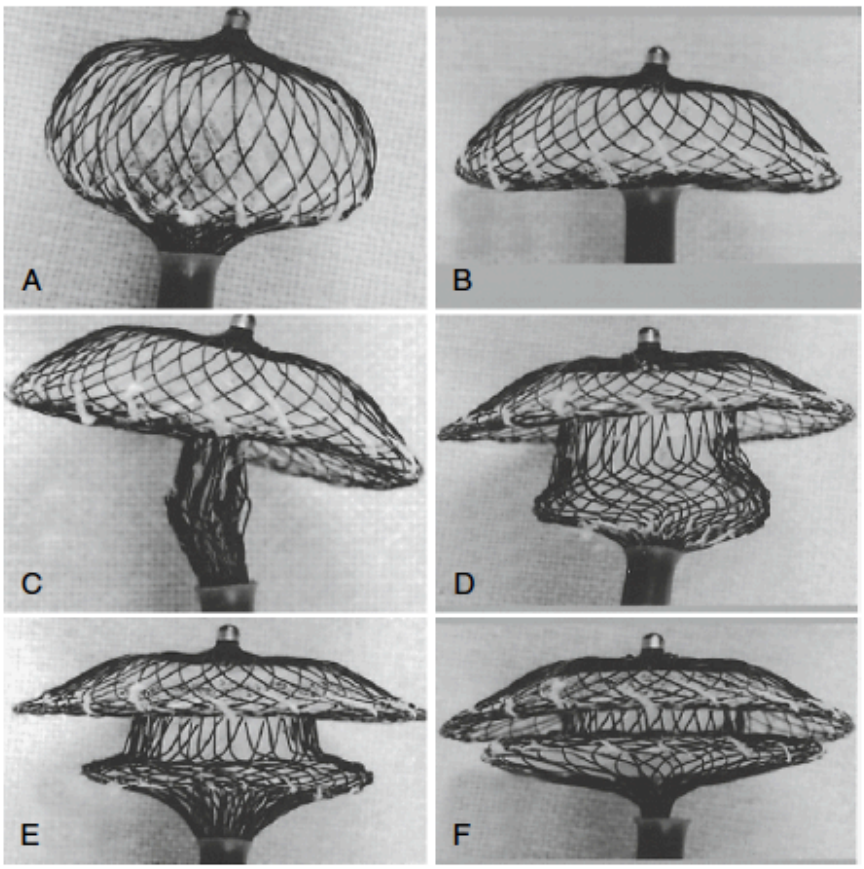
1.3.1 Types of devices

There has been development of multiple devices. The CardioSEAL, StarfLex device (CSD), and Angel Wings device are designed to close the defect by means of a membrane placed on one or both sides of the rims of the oval fossa. These devices have arms that stabilize the membrane against the atrial wall. Use of these devices has been associated with a higher risk of left atrial thrombus which can result in stroke.

The Amplatzer Septal Occluder (ASO, St Jude Medical, Inc, Saint Paul, MN, USA) is a self-centering device composed of a nitinol wire mesh with polyester fabric sewn into the discs. The device consists of two self-expandable discs with a connecting waist that dictates the device diameter. The dumbbell-shaped nitinol plug stents the defect, sitting like a peg within it (Figure 3). The device has a high success rate due to ease of deployment and is repositionable before final deployment. The deployed device conforms to the shape of the surrounding structure. The ASO is available in various sizes ranging from 4mm to 38 mm are available in increments of 1-2 mm. The ASO device has the widest usage and has the most outcome data for all ASD closure devices over the last 20 years[21]. The most serious risk is device erosion, which is associated with oversizing the device or rim deficiency. The mechanism is thought to be friction between the left atrial disk wire mesh and the aortic or atrial wall.

Figure 3. The stages of deployment of the nitinol Amplatzer Septal Occluder.

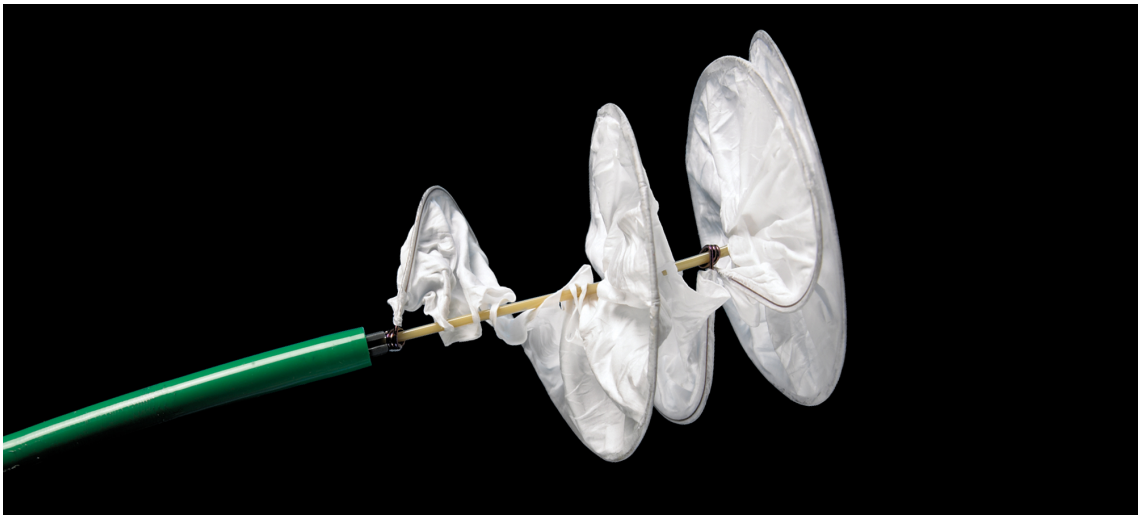
From: Pediatric Cardiology (Elsevier, 3rd edition, 2010) page 544



The Gore Helex septal occluder (HELEX, W. L. Gore & Associates, Flagstaff, Arizona) was FDA (US food and drug administration) approved for ASD closure in 2006. The device consists of a corkscrew type nitinol wire frame covered by a protective Gore-Tex (expanded polytetrafluoroethylene; ePTFE) coating (Figure 4). The device sizes available range from 15mm to 35 mm in increments of 5 mm. There have been no reported erosions for the Gore Helex device, consistent with the softer material of ePTFE compared with a metal mesh. The Gore Helex device is retrievable but requires a moderate learning curve to deploy the disks and understand the subtleties of its construction. The Gore Helex device has been upgraded to the Gore septal occluder (GSO, WL Gore&Associates, Inc) with a flexible petal design, platinum core instead of solid nitinol, delivery handle and a porous coating. These factors play an important role in delivery and conformation to the surrounding structures. Both the Gore Helex device and GSO have a softer disk with less frictional forces, which is a safety feature against device erosion.

Figure 4. The Gore HELEX Septal Occluder

From the Gore medical website

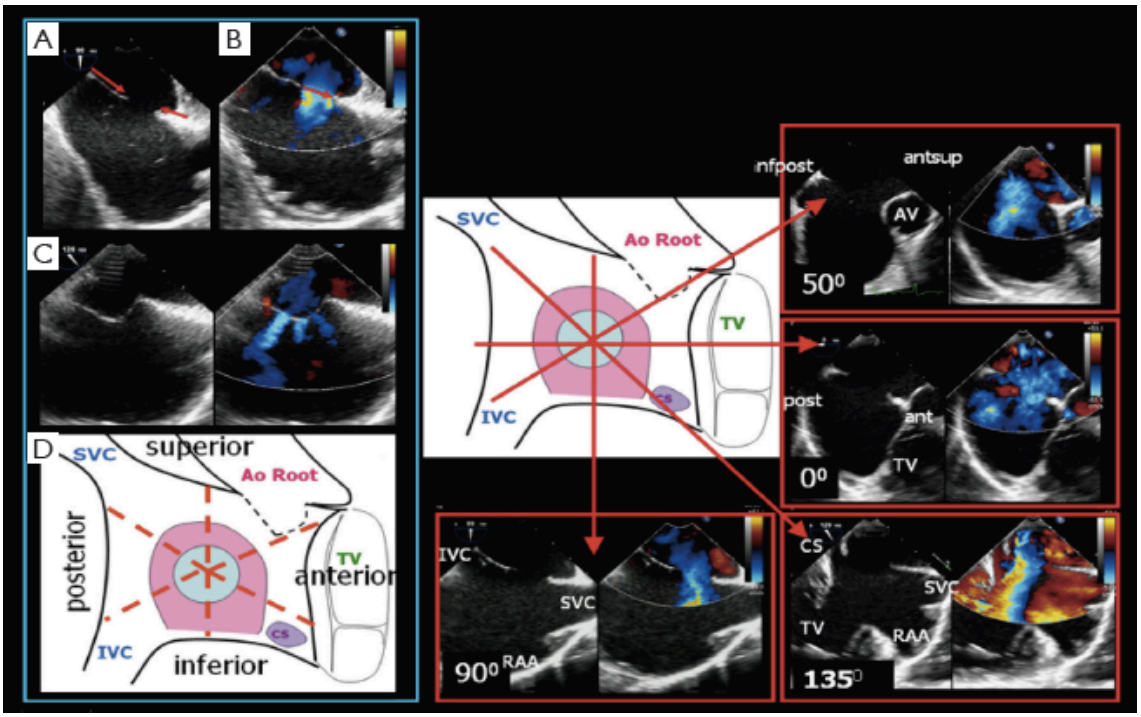


1.3.2 Indications for device closure

Device closure may be indicated in a secundum ASD measuring 5mm or more in diameter, and a significant left-to-right shunt with clinical evidence of right ventricular volume overload (i.e. Qp/Qs ≥ 1.5:1 or RV enlargement). Not all atrial septal defects are suitable for closure and careful selection of patients is mandatory. In addition to the absolute size of the defect, the rims of tissue bordering the defect play an important role in determining the suitability for closure. Typically, the adequacy of the rims is assessed by either transthoracic echocardiography of transesophageal echocardiography. Transthoracic echocardiography is often diagnostic although the resolutions are limited particularly in adults, and a detailed transesophageal echocardiography is necessary to confirm the anatomy and asses suitability for device closure (Figure 5).

Figure 5. Assessment of the atrium septum with transesophageal echocardiogram

Modified from Rana et al. J Thorac Dis. 2018;10(Suppl24): S2899-2908[11]



(A) SVC and IVC rims
(B) Largest ASD diameter
(C) Fenestrated FO with multiple small ASDs
(D) The rims described by the structure in close proximity of the defect
0 degree: Evaluation of SVC, posterior, aortic, IVC and CS rims
45-135 degree: Assessment of size and shape of defect using 2D and Color Doppler imaging, evaluation of SVC, IVC rims, aortic, and posterior rims
45-50 degree: Evaluation of anterior and posterior rims; the case example demonstrates an absent aortic rim
SVC: superior venous cava; IVC inferior venous cava; ASD: atrial septal defect; FO: foramen oval; CS: coronary sinus; TV: tricuspid valve; AV: anterior valve; RAA: right atrial appendage

The treatment strategy for large ASD in small children remains controversial. In most cases, such patients undergo medical therapy or surgical closure as transcatheter closure with a large device is considered as a high-risk procedure. The results remain conflicting with some reporting a higher risk when the device/weight ratio>1.5, and others reporting an acceptable complication rate[22,23].

1.3.3 Results of catheter intervention

Results of catheter intervention are comparable to those with surgical repair [23-28]. Since the initial reports of interventional closure, device closure has become the treatment of choice of atrial septal defects in the fossa oval. Advantages of device closure include complete avoidance of cardiopulmonary bypass with its inherent risk, avoidance of pain and residual thoracotomy scars and a rapid recovery post-procedure.

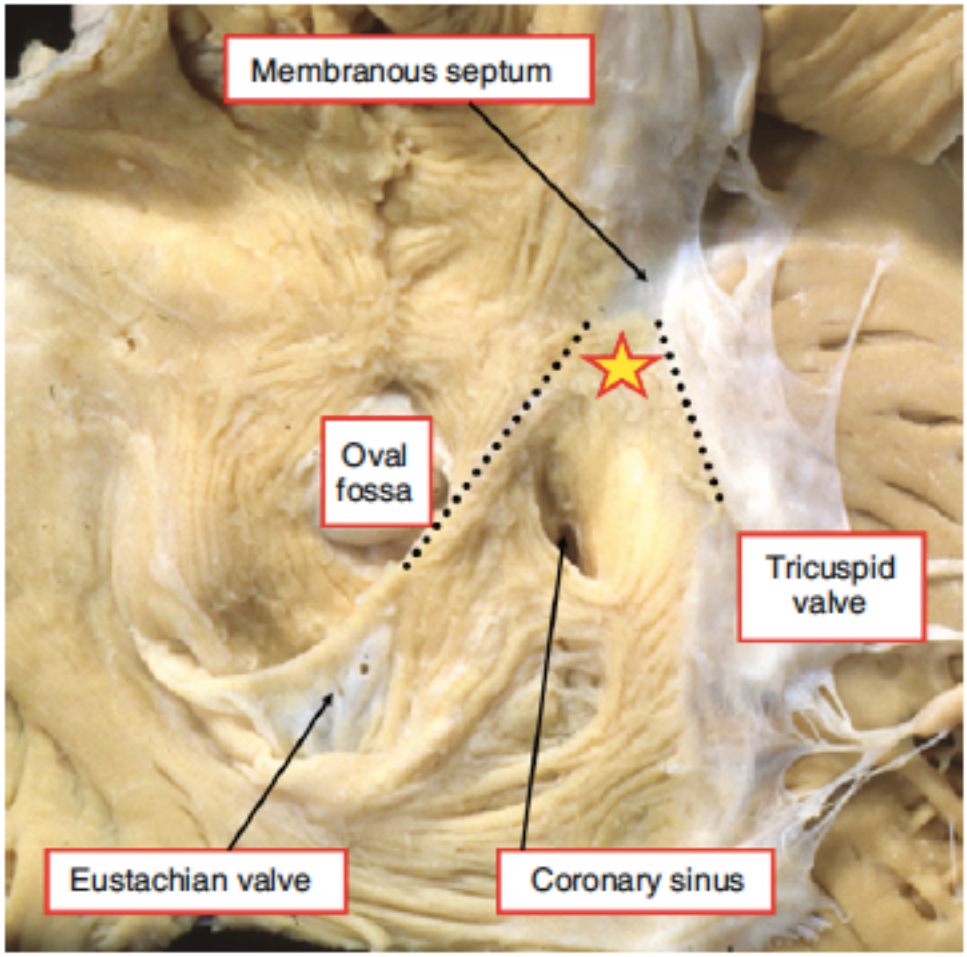
1.4 The conduction system

1.4.1 The anatomy of the conduction system

The conduction system is a small area of specialized myocardium that originate and disseminate the cardiac impulse. The cardiac impulse is generated in the sinus node. The sinus node is a cigar-shaped structure located subepicardially within the terminal groove, positioned inferior to the crest of the atrial appendage. The impulse from the sinus node is conducted throughout the atrial myocardium and is then carried through towards the atrioventricular (AV) node. The AV node is contained within the triangle of Koch. This important landmark is delineated by the tendon of Todaro, the attachment of the septal leaflet of the tricuspid valve and the orifice of the coronary sinus. The location of the AV node and triangle of Koch in relation to the oval fossa is shown in Figure 6. From the apex of the triangle of Koch the AV conduction penetrates the central fibrous body as the bundle of His (otherwise described as the penetrating atrioventricular bundle. The bundle then reaches the crest of the muscular septum beneath the non-facing leaflet of the aortic valve where it branches to the left bundle branch and right bundle branch. The sinus node artery arises from the initial course of either the right or the circumflex coronary artery. The artery to the AV node courses anteriorly through the paraseptal space into the triangle of Koch.

Figure 6. Anatomy of the AV conduction system

From: Anderson Pediatric Cardiology (3e 2010), page 31[14]



The hinge of the septal leaflet of the tricuspid valve and the tendon of Todaro (dotted lines) delineates the triangle of Koch. The atrioventricular node is situated at the apex of the triangle (star). Note the location of the oval fossa in relation to the AV conduction system.

1.4.2 Types of atrioventricular block

Atrioventricular (AV) block is defined as a delay or block in the transmission of cardiac impulses from the sinus node through the specialized conduction system. The traditional electrocardiographic categorization of AV block is presented in Table 4. From a therapeutic standpoint, the level at which the block is located is more important than the electrocardiographic classification. Block at the AV node is usually associated

with a junctional escape rhythm which tends to be reliable with an adequate heart rate responding to autonomic interventions. In contrast, block within the His-Purkinje system is associated with an idioventricular escape rhythm characterized by a wide QRS complex. This tends to be considerably slower and less reliable than a junctional escape rhythm, and is relatively unaffected by autonomic maneuvers.

Table 4. Electrocardiographic definition of atrioventricular block

Modified from: Management of Cardiac Arrhythmias (Humana Press) page 218[29]

Type	ECG
First degree	PR prolongation
Second degree, Mobitz type I	Gradual PR increase before dropped beat
Second degree, Mobitz type II	Dropped beat with no PR increase
High-grade	More than 2 consecutive P waves not conducted
Third degree	No P waves conducted

1.4.3 Treatment for atrioventricular block

The treatment for AV block is permanent pacing. The general indications for pacemaker implantation in children are similar to those in adults, there are several important considerations in young patients. The clinical significance of bradycardia is age dependent and there are significant technical challenges which may complicate device implantation. In small patients as well as patients with complex congenital heart disease, an epicardial pacemaker implantation may be necessary. There is also a need to consider long-term prognosis in these patients, as most patients will have a longer life-expectancy than those of the adult patients.

The prognosis of congenital heart disease patients with permanent postsurgical AV block who do not receive permanent pacemakers is very poor [30]. Therefore, advanced second- or third-degree AV block that persists for at least 7 days and that is not expected resolve after cardiac surgery is considered a Class I indication for pacemaker implantation [31]. In patients whom AV conduction returns, the prognosis is generally favorable [32]. However, there have been reports of late-onset complete AV block years after surgery for congenital heart disease in patients with transient postsurgical AV block [33]. Unexplained syncope in patients with a history of transient postsurgical complete AV block and residual bifascicular conduction block is a Class II1 indication for permanent pacemaker implantation due to the possibility of intermittent complete AV block. The joint ACCF/AHA/HRS recommendations for permanent pacing in children with AV block are shown in Table 5.

Table 5. Recommendations for permanent pacing in children with post, adolescents, and patients with congenital heart disease

Modified from the 2012 ACCF/AHA/HRS guidelines for device-based therapy of cardiac rhythm abnormalities [30]

Indications	Class[a]	Level[b]
Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output	I	C
SND with correlation of symptoms during age-inappropriate bradycardia		B
Postoperative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery	I	B
Patients with congenital heart disease and sinus bradycardia for the prevention of recurrent episodes of intra-atrial reentrant tachycardia	IIa	C
Sinus bradycardia with complex congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 seconds.	IIa	C
Congenital heart disease and impaired hemodynamics due to sinus bradycardia or loss of AV synchrony.	IIa	C
Unexplained syncope in the patient with prior congenital heart surgery complicated by transient third-degree AV block with residual fascicular block after careful evaluation to exclude other causes of syncope.	IIa	B

Transient postoperative third-degree AV block that revers to sinus rhythm with residual bifascicular block	IIb	C
Asymptomatic sinus bradycardia after biventricular repair of congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 seconds.	IIb	C
Transient postoperative AV block with return of normal AV conduction in the otherwise asymptomatic patient	III	B
Asymptomatic bifascicular block with or without first-degree AV block after surgery for congenital heart disease in the absence of prior transient complete AV block	III	C
Asymptomatic type I second-degree AV block	III	C

The definition of classes of recommendations and levels of evidence as outlined in Tables 2 and 3. ACCF: American College of Cardiology Foundation; AHA: American Heart Association; HRS: Heart Rhythm Society; AV: atrioventricular; SND: sinus node dysfunction

1.5 Arrhythmias in congenital heart disease

1.5.1 Postoperative arrhythmia in patients with congenital heart disease

Development of postoperative arrhythmias during the follow-up period has been reported in patients after repair of CHD [34-39]. In particular, patients with ASDs, singe ventricle physiology who have been palliated with a Fontan operation, and transposition of the great arteries (TGA) repaired with an atrial switch operation are well known to develop late arrhythmias during follow up. The most common conduction abnormalities in these patients are sinus node dysfunction (SND) and atrial arrhythmias. The mechanism of arrhythmia appear to be multifactorial, with surgical factors such as atriotomy incisions, cardiopulmonary bypass cannulation sites, and multiple surgical suture lines all contributing to traumatic injury of the sinus node, interruption of the sinus node artery, and establishment of reentry circuits.

1.5.2 ASD and arrhythmias

Long-standing left-to-right shunt can result in the development of atrial arrhythmias, particularly atrial flutter and fibrillation[40-42]. They presumably result from chronic stretching of the atriums, and occur most commonly in adults aged greater than 40 years[43]. Atrial arrhythmias rarely occur in childhood. However, electrophysiological studies have demonstrated a high incidence of subclinical sinus node dysfunction, along with conduction disturbances, in children prior to operative intervention[44] .

1.5.3 Arrhythmias following surgical closure of atrial septal defects

Arrhythmias including SND, supraventricular tachycardia, and atrioventricular conduction disturbances occur occasionally after surgical repair of atrial septal

defects[45,46]. Implantation of permanent pacemaker devices may be required in a small number of patients. The incidence of tachyarrhythmias, particularly atrial flutter or fibrillation, increases with age at surgical repair. Patients with sinus venosus defects appear to be more at risk for bradyarrhythmia's more than those with defects within the oval fossa[46]. Approximately one-third of patients with sinus venosus defects have had persistent sinus node dysfunction after surgery. In contrast, less than one-sixth of patients with oval fossa defects have post-operative SND. It is presumed that these post-operative arrhythmias result from intra-operative damage to nodal or conduction tissue.

1.5.4 Arrhythmias following device closure of atrial septal defects

Arrhythmias have also been reported as complications in patients undergoing device closure of an ASD. In particular, the close proximity of the AV node to the device placed in the fossa ovalis places these patients at a risk of developing AV block as a complication. Most previously reported data have been on AV block presenting soon after device closure, with most resolving within a short period of time.

2 Aim

Transcatheter device closure of VSDs is known to be associated with late AV block which raises the concerns of the effect of an ASD device on AV conduction, particularly since ASD in itself is known to be associated with AV conduction disease. Permanent pacemaker implantation is the only treatment option for patients with complete AV block and this can have a significant impact on the patient's long-term prognosis.

The prevalence of AV block after ASD closure have been addressed in several large cohorts of a predominantly adult population. The prevalence is reported to be rare and usually transient. Chessa and colleagues reported results from a cohort of 417 patients (mean age 26.6± 19 years) who had device closure of an ASD using either a CardioSEAL/STARFlex or an ASO device[47]. There were 11 patients (2.6%) who experienced arrhythmic problems, out of which one patient had complete AV block immediately after device implantation. The device (18mm ASO) was removed and there was complete recovery of AV conduction three hours later. Another single centre cohort of 610 patients(predominantly adult) who underwent ASD and PFO closure with a device reported two patients who developed complete AV block; one patient with pre-procedure intermittent 2nd degree AV block and one 16-year-old patient with previously repaired double outlet right ventricle who had a device closure of a residual ASD two weeks after right ventricular-pulmonary artery conduit[48].

Wang and colleagues reported the results of ASD device closure in 706 pediatric patients (median age 4.6 years). 653 patients had closure using a modified ASO which

is a device made in China. The incidence of AV block was 0.85% (6/706 patients) [49]. All six patients with AV block had a modified ASO. All AV block occurred within 24 hours after the procedure. There was one patient with first degree AV block, 2 patients with second degree AV block, one patient with advanced AV block and two patients with complete AV block. The 2 patients with complete AV block both had device removal; 1 patient recovered to sinus rhythm immediately after device removal, but 1 patient had persistent AV conduction disturbance at follow-up although the details are not described in the paper. They identified younger age, larger ASD size, larger device size and larger device diameter to septum diameter ratio to be associated with AV block.

A study of 162 pediatric patients who underwent an ASD closure with an ASO reported a rate of 6.2 % (10/162 patients) for new-onset or aggravation of AV block[50]. In all patients, AV block occurred within one week of procedure with spontaneous resolution or improvement observed in all patients. Device size ≥ 19mm or indexed device size ≥ 0.18 mm/cm was the major predisposing factor.

As described above, the prevalence of AV block in the pediatric population appears to be quite rare in typically transient, however the data is limited to specific devices, mainly the ASO. Long-term follow-up data specifically regarding AV conduction remains unknown. There is also lack of data comparing the prevalence of AV block following device closure to the contemporary surgical closure group, which is important information to determine whether a patient should undergo surgical closure instead of device closure.

The aim of this study was to determine the prevalence and risk factors of AV block following ASD device closure in comparison to the contemporary surgical closure group.

3 Methods

This study was a single center retrospective observational study. The study was approved by the Royal Children's Hospital Human Research Ethics Committee (Reference number 30192B), and the procedures followed were in accordance with institutional guidelines for retrospective record review and protection of patient confidentiality. The need for patient consent was waived given the retrospective nature of the study.

3.1 Subjects

A retrospective review of all patients who underwent either transcatheter device closure or surgical closure of a secundum ASD at the Royal Children's Hospital (Melbourne, Australia) between January 1996 and December 2010 was performed. The start date of data collection was when transcatheter device ASD closure was started at the institution. Patients with the following conditions were excluded: 1) the presence of associated congenital cardiac anomalies requiring surgical repair, 2) Primum ASD; 3) Sinus venosus ASD (including partial anomalous pulmonary venous drainage); 4) Holt-Oram Syndrome. Sinus venosus ASDs were excluded from the study as these patients do not meet the criteria for a transcatheter device closure due to concomitant pulmonary venous drainage abnormalities and requires a different surgical to secundum ASDs procedure (the so-called Warden procedure) predisposing them to a higher risk of post-operative SND. Patients with Holt-Oram Syndrome were excluded as these patients are known to be at risk of cardiac conduction disease regardless of the presence of an ASD. Patient demographics, procedural details, and follow-up data were collected from

the medical records and departmental database. The details of the data collected are listed in Table 5.

Table 6. List of data collected

Baseline demographics
Gender
Down Syndrome
Number of ASDs, ASD size
Pre-procedure PR interval and HR
Procedural details
Age, BW, BH at procedure
Type of procedure
Device type, device size, number of device, BH/device ratio
Surgical technique
Post procedure PR interval and HR, other arrhythmias
Follow-up details
Age at last follow-up, follow-up duration
Follow-up PR interval and HR, other arrhythmias

ASD: atrial septal defect; HR: heart rate; BW: body weight; BH: body height

3.2 Electrocardiographic evaluation

The electrocardiogram (ECG) at three time points were reviewed; (1) immediately prior to ASD closure, (2) immediately post ASD closure, and (3) latest follow-up. For each ECG, the PR and RR intervals were manually measured by one experienced paediatric cardiologist (Hiroko Asakai). A PR interval exceeding the upper limits of normal for a given age and heart rate was defined as first-degree AV block[51]. The presence of any AV conduction disturbances, SND, and tachyarrhythmias including atrial tachycardia, SVT, and ventricular tachycardia (VT) were noted. Although first degree AV block is a physiological finding which does not require treatment, this was also included in the analysis as the progression from normal conduction to first degree AV block may reflect a change in the AV conduction capabilities. It was also thought to be important whether the patients with first degree AV block will further progress to second degree or third degree AV block over time.

3.3 Catheter devices and implantation techniques

Over the study period, two different devices were used; the Amplatzer Septal Occluder (ASO; AGA Medical Corp., Golden Valley, Minnesota) and the GORE® HELEX® septal occluder (HELEX, W. L. Gore & Associates, Flagstaff, Arizona). All procedures were performed by two interventional pediatric cardiologists (Dr. Geoffrey Lane and Dr. Lucas Eastaugh). All procedures were performed under general anaesthesia. A standard right heart catheterization was performed, taking recordings of pressures and blood samples to measure oxygen saturations. Heparin (100 IU/kg) and antibiotic prophylaxis were given routinely. A transesophageal echocardiogram (TEE) was performed to evaluate the number, position, and size of ASDs and surrounding rims.

The defects were balloon-sized using a stop-flow technique with either the Meditech Occlusion Balloon Catheter (Boston Scientific Corp., Watertown, Massachusetts) or Amplatzer Sizing Balloon (AGA Medical Corp., Golden Valley, Minnesota). The device selected was dependent upon physician preference and anatomical factors; a HELEX device was more likely to be used for defects with deficient retroaortic rims or multi-fenestrated defects. Device size selection was based on manufacturer recommendations; the ASO device size was up to 1-2 mm larger than the stop-flow balloon diameter and the HELEX device was chosen with a disc size 1.75-2 times greater. The technique for implantation of each device type was performed as recommended by the manufacturer and involved the initial deployment of one disc on the LA side of the defect followed by deployment of the second disc on the RA side. TEE guidance was used to confirm cessation of flow across the ASD and the balloon size on x-ray was compared to that on ultrasound to determine the most accurate defect size. The cardiac rhythm was also closely monitored to ensure no new ECG changes were present prior to final release of the device. Patients were usually observed overnight with cardiac monitoring and discharged the following day.

3.4 Surgical techniques

Standard surgical ASD closure was performed under general anaesthesia. All surgeries were performed by the pediatric cardiac surgical team over the study period (Dr.Christian Brizard, Dr.Yves d'Udekem and Dr. Igor Konstantinov). The RA was opened after a sternotomy. The ASD was closed either by direct suture or by using a pericardial patch depending on the size of the defect. Patients were discharged home after an average of four days in hospital.

3.5 Statistical analysis

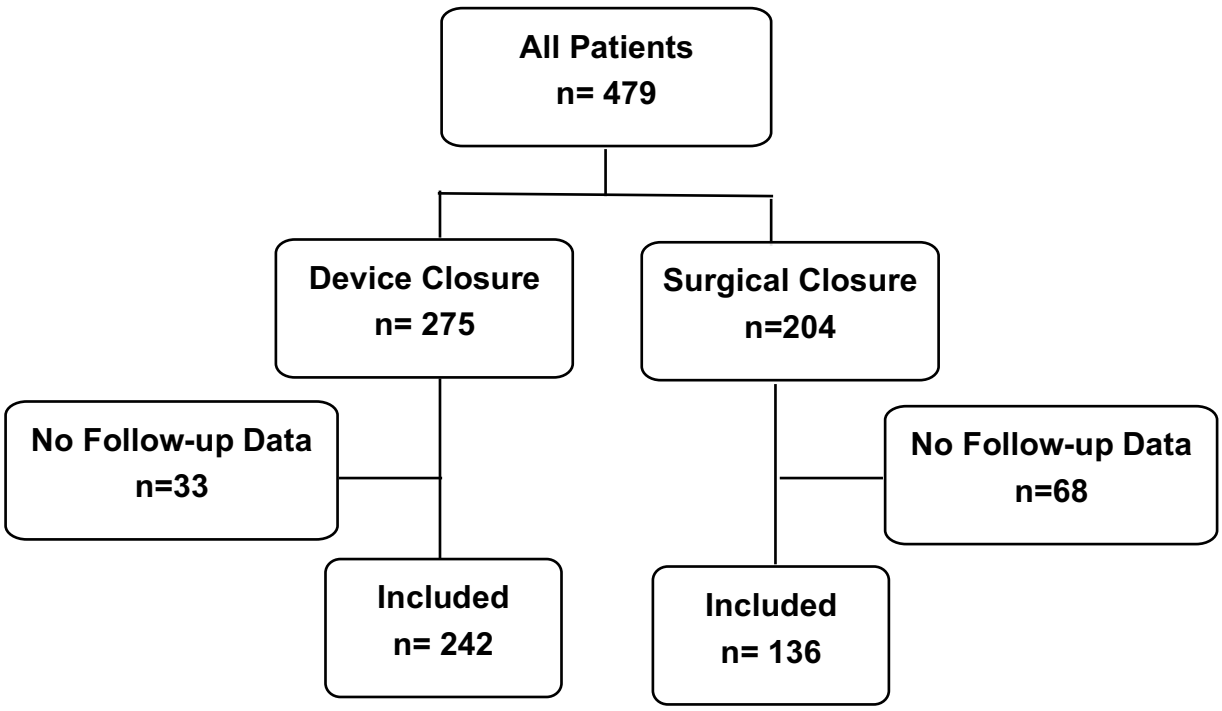
The primary outcome was the presence of AV block at latest follow-up. Continuous variables were summarized as median and range (minimum to maximum) and categorical variables were summarized as number of cases and percentage. Comparison between the two groups were performed using a Fisher's exact test or Mann-Whitney Test as appropriate. In the device subgroup, risk factors associated with follow-up AV block was analysed by univariable conditional logistic regression. All variables entered into the univariable analysis were selected on clinical grounds. Of these, variables with a p-value < 0.20 under univariable modelling were considered for entry into the multivariable model. All statistical analyses were performed using the statistical package SPSS (IBM, ver.20)

4 Results

4.1 Demographics and baseline characteristics

Between January1996 and December 2010, a total of 479 patients underwent ASD closure at our institution; 275 patients (57%) had transcatheter device closure (device group) and 204 patients (43%) had surgical closure (surgical group). Follow-up data was available in 378 patients; 242 (65%) in the device group and 136 (35%) in the surgical group (Figure 7). One hundred and one patients were either discharged from follow-up or had been referred back to the local cardiologists. The patients without follow-up data at our institution were excluded from the study.

Figure 7. Flowchart of patient inclusion



The baseline patient characteristics are described in Table 7. Thirty-one patients (8.2%) had first degree AV block prior to ASD closure; 21/242 (8%) in the device group and 10/36 (7%) in the surgical group. Not surprisingly, the surgical group had larger ASDs and were treated at a younger age and smaller bodyweight. In the device group, there were 190/242 (78.5%) patients who had an ASO device and 52/242 (21.5%) patients who had a HELEX device.

4.2 Atrioventricular block at follow-up

The median duration of follow-up was 28 months (range 1-193 months). The device group had a longer follow-up than the surgical group (37 months [1-193] vs 18[1-172] months, p=0.005). The median age at follow-up was 9 years (range 1-21 years); 10 (1-21) years in the device group and 7 (1-20) years in the surgical group (p=0.001) (Table 7).

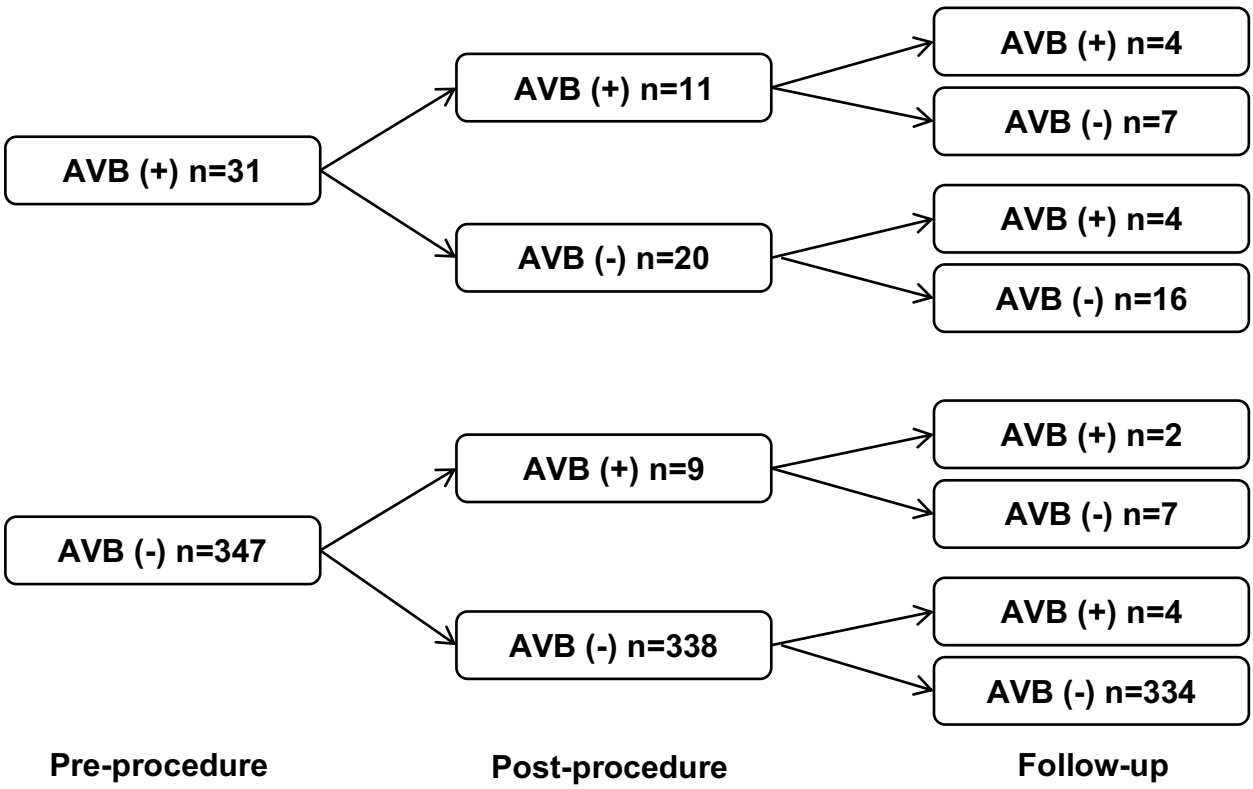
Table 7. Baseline patient demographics, procedural and follow-up data

	Total	Catheter	Surgical	
	n=378	n=242	n=136	p value
Demographics				
Male gender	146/378 (39%)	90/242 (37%)	56/136 (41%)	NS
Down Syndrome	18/378 (5%)	12/242 (5%)	6/136 (4%)	NS
ASD Single	341/378 (90%)	220/242 (90%)	121/136 (89%)	NS
Multiple	37/378 (10%)	22/242 (10%)	15/136 (11%)	
ASD size (mm)	14 (4-30)	13 (4-27)	18 (6-30)	<0.0001
Pre-procedure AVB	31/378 (8%)	21/242 (8%)	10/136 (7%)	NS
Procedure variables				
Age at procedure (yrs)	4 (0-18)	5 (0-18)	4 (0-17)	0.016
BW at procedure (kg)	18(4.5-95)	19 (5.8-78)	15.5 (4.5-95)	0.001
BH at procedure (cm)	107(58-179)	110 (60-179)	104 (58-178)	0.013
Post procedure AVB	20/378 (5%)	15/242 (6%)	5/136 (4%)	NS
Follow-up variables				
Age at FU (yrs)	9 (1-21)	10 (1-21)	7 (1-20)	0.007
Duration of FU (mths)	28 (1-193)	37 (1-193)	18 (1-172)	0.007
AVB at FU	14/378 (4%)	11/242 (5%)	3/136 (2%)	NS
Other arrhythmias at FU	3/378 (0.8%)	2/242 (0.8%)	1/136 (0.7%)	NS

Values are expressed as median and range for continuous variables and number of patients for categorical variables. ASD: atrial septal defect; AVB: atrioventricular block; BW: body weight; BH: body height; FU: follow-up; yrs: years; mths: months

There were 14 patients (3.7%) who had AV block at follow-up; 11/242 (4.5%) in the device group and 3/135 (2.2%) in the surgical group (p=0.39) (Table 7). Of these, 6 patients had new onset of AV block after ASD closure; 5 in the device group and 1 in the surgical group. There was only one patient with second degree AV block and the 13 other patients had first degree AV block. None of the patients had any symptoms or hemodynamic compromise requiring ASD device removal or permanent pacemaker implantation. The change in prevalence of AV block throughout the study period in the entire cohort is shown in Figure 8.

Figure 8. Prevalence of AV block



AVB: atrioventricular block

The clinical details of all 14 patients who had AV block at follow-up are described in Table 8. Patient 6 did not have the original ECG tracings hence the PR interval was not recalculated, however the patient was included in the AV block group due to an ECG reporting and clinical notes from the time of the ECG analysis. More than half of the patients (8/14, 57%) had first degree AV block prior to ASD closure, which was a significantly higher prevalence compared to 23/364 (6%) in patients who did not have AV block at follow up ($p<0.05$). Other baseline characteristics as well as procedural variables did not differ between the patients with AV block and without AV block at follow-up (Table 9).

Table 8. Details of patients with AV block at follow-up

Pt	ASD			Pre-ECG		Procedure Details					Post-ECG		Follow-up		
		#	Size	PR	HR	Age	BW	Procedure Type	D size	BH/D ratio	PR	HR	Age	PR	HR
1	M	1	8	*NA	NA	1	10	d-ASO	11	0.15	*160	68	16	240	68
2	F	1	22	*184	80	13	41	d-ASO	32	0.22	164	63	18	180	63
3	F	1	23	*200	83	9	34	d-ASO	32	0.24	*180	85	10	200	85
4	F	1	10	*180	78	6	21	d-ASO	24	0.24	*200	82	18	210	82
5	M	1	15	*160	170	3	19	d-ASO	19	0.22	*180	104	4	160	104
6	F	1	14	120	102	5	18	d-ASO	17	0.16	NA	NA	11	NA	NA
7	M	2	13	160	90	5	19	d-ASO	18	0.16	160	75	10	180	75
8	F	1	13	*160	110	2	16	d-Helex	25	0.28	NA	NA	10	180	53
9	M	1	10	140	118	4	16	d-Helex	24	0.23	150	92	4	160	107
10	F	2	12	144	100	2	10	d-Helex	25	0.31	*180	120	12	192	100
11	M	1	15	176	120	15	75	d-Helex	35	0.2	*184	84	19	180	80
12	F	1	25	*188	104	9	35	s-patch	-	-	130	116	17	186	94
13	F	1	21	156	103	5	17	s-patch	-	-	150	102	17	200	50
14	F	1	8	*160	94	6	18	s-direct	-	-	NA	NA	7	160	98

ASD size and device size is described in mm, age in years

ASD: atrial septal defect; M: male; F: female; AVB: atrioventricular block; #: number of ASDs; PR: PR interval (msec); HR: heart rate (bpm); BW: bodyweight; s-ASO: d-: device; s-: surgery, D size: device size; BH/D: body height/device size ratio

*PR interval classified as first degree atrioventricular block

There was only one patient with other significant arrhythmias at follow-up. This patient was known to have supraventricular tachycardia (SVT) prior to ASD closure and underwent a catheter ablation for atrioventricular nodal re-entrant tachycardia (AVNRT) during the follow-up period. Interestingly, out of the 31 patients who had AV block prior to ASD closure, 23 patients (74%) had resolution of AV block at follow-up (Figure 8).

4.3 Atrioventricular block in the device closure subgroup

Of the 242 patients who underwent device closure, 11/242 (4.5%) had AV block at follow-up. Ten patients had first-degree AV block and one patient had second-degree AV block. Six patients had pre-procedural AV block, and five patients developed AV block post device closure, with three patients developing AV block only at follow-up. The patients who had AV block at follow-up had a larger indexed device size (device size/body height ratio, mm/m) (22 [15- 31] vs 18 [7- 38], p=0.02). Device type, number of devices deployed, and device size were similar amongst the group with AV block at follow-up and without AV block at follow-up (Table 9).

Table 9. Comparison between patients with and without AV block at follow-up

		Total	AVB (+)	AVB (-)	
		n=378	n= 14	n=364	p-value
Demographics					
Male gender		146/378 (38.6%)	5/14 (36%)	141/364 (39%)	NS
Down Syndrome		18/378 (4.8%)	2/14 (14%)	16/364 (4%)	0.097
Multiple ASDs		37/378 (9.8%)	2/14 (16.7%)	35/364 (9.6%)	NS
Size of ASD (mm)		14 (4-30)	13.5 (8-25)	14 (4-30)	NS
Pre-procedure AVB		31/378 (8%)	8/14 (57%)	23/364 (6%)	<0.0001
Procedure variables					
Age at procedure (yrs)		4 (0-18)	5 (1-15)	4 (0-18)	NS
BW at procedure (kg)		18(4.5-95)	18.5 (10-75)	18 (4.5-90)	NS
BH at procedure (cm)		107(58-179)	106 (73-179)	107 (58-178)	NS
Catheter closure		242/378 (64%)	11/14 (79%)	231/364 (64%)	NS
Device details					
Device type	ASO	190/242 (79%)	7/11 (64%)	183/231 (79%)	NS
	Helex	52/242 (21%)	4/11 (36%)	48/231 (21%)	
Number of devices	One	236/242 (97%)	11/11 (100%)	225/231 (97%)	NS
	Two	6/242 (3%)	0/11 (0%)	6/231 (3%)	
Device size (mm)		20 (8-35)	24 (11-35)	20 (8-35)	0.076
BH/device (cm/mm)		0.18 (0.07-0.38)	0.22 (0.15-0.31)	0.18 (0.07-0.38)	0.022
Post procedure AVB		20/378 (5%)	6/14 (43%)	14/364 (4%)	<0.0001
Follow-up variables					
Age at follow-up (yrs)		9(1-21)	11.5(4-19)	9(1-21)	0.037
Follow-up Duration (mths)		28(0-193)	70(6.4-189)	27(0-193)	0.018

Continuous values are expressed as median and range.
ASD: atrial septal defect; BW: body weight; BH: body height; AVB: atrioventricular block; yrs: years; mths: months; NS: not significant

With univariate analysis, pre-procedural and post-procedural AV block as well as indexed device size appeared to be associated with follow-up AV block, however, with multivariate analysis, the presence of AV block either prior to or post procedure were the only variables associated with follow-up AV block (Table 10).

Table 10. Risk factors associated with follow-up AV block in the device closure group

	Univariate analysis				Multivariate analysis			
		CI		P value		CI		P value
Risk Factors	**OR**	**lower**	**upper**		**OR**	**lower**	**upper**	
Demographics								
Male gender	1.43	0.43	4.83	0.54				
Down Syndrome	4.87	1.93	25.60	0.10	1.23	0.10	15.27	0.88
Multiple ASDs	2.34	0.47	11.61	0.28				
Pre-procedure AVB	18.60	5.00	68.50	0.00	7.92	1.32	47.35	0.02
Procedure variables								
ASO device	2.18	0.61	7.75	0.22				
Multiple device	0.97	0.95	1.00	1.00				
Device size (mm)	1.09	1.00	1.20	0.06	1.00	0.86	1.15	0.94
BH/device (m/mm)	1.12	1.01	1.23	0.03	1.15	0.97	1.35	0.10
Post procedure AVB	29.60	7.50	115.40	0.00	9.84	1.52	63.46	0.02

ASD: atrial septal defect; AVB: atrioventricular block; ASO: Amplatzer Septal Occluder; BH: body height

5 Discussion

5.1 Device closure vs surgical closure

Both device closure and surgical closure are safe procedures with very low mortality and complication rate. A comparison of the US Food and Drug Administration Manufacturer and User Facility Device Experience database and the Society of Thoracic Surgery congenital cardiac surgery database demonstrated the overall mortality for device and surgical closure to be equivalent (0.093% vs 0.13 %, p=0.649) [25]. However, in a large multicentre non-randomized trial of 442 patients including both children and adults, the complication rate was lower and the length of hospital stay was shorter in device closure than for surgical repair[18]. Arrhythmias and conduction abnormalities were the most common complications, seen in 17/442(3.9%) in the device group and 9/154 (5.9%) in the surgical group. However, most of these arrhythmias were transient with only one paediatric case requiring a permanent pacemaker implantation for AV block. In our cohort, the prevalence of post-procedural AV block was 5 % in the device group and 2% in the surgical group, which is comparable to the reported prevalence. However, the follow-up period was shorter in the surgical group and this may have influenced the difference in the prevalence.

5.2 Device closure and atrioventricular block

Transcatheter device closure of ASDs has become an alternative to surgical closure requiring cardiopulmonary bypass. Although considered a highly effective and low risk procedure, complications such as device erosion, embolization/malposition, and arrhythmias have been previously reported[18,47,52-56]. In particular, AV block following device closure is an important risk factor as it may cause long term effect on patient care. AV block related to device closure is reported to be rare[47,50,57-59], and most have been transient [50,60]. However, there are several case reports of complete AV block post device closure requiring removal of the device and surgical closure of the ASD[61,62].

In a cohort of 417 adult patients (mean age 26.6± 19 years) who had device closure of an ASD using either a CardioSEAL/STARFlex or an ASO device, Chessa and colleagues reported a complication rate of 8.6% (36/417) out of which 11/417 (2.6%) were arrhythmic problems[47]. Six patients had atrial fibrillation requiring electrical cardioversion, 2 patients had atrial fibrillation with spontaneous resolution, 2 patients had SVT with spontaneous resolution, and one patient had complete AV block immediately after device implantation. The device (18mm ASO) was removed and there was complete recovery of AV conduction three hours later. There were 2 cases of late complications at 12 to 18 months after device implantation, both of which were not arrhythmia related.

In a large single centre cohort of 610 patients (including adults) who underwent ASD and PFO closure with a device, there were two patients who developed complete AV block; one patient with pre-procedure intermittent 2nd degree AV block and one 16-year-old patient with previously repaired double outlet right ventricle who had a device

closure of a residual ASD two weeks after right ventricular-pulmonary artery conduit. This was the only paediatric case (<21 years of age) with post-procedure arrhythmia. The incidence of short-term post-procedure arrhythmia in the adult patients (>21 years of age) was 5.6% (31/557) [48].

Wang and colleagues reported an incidence of AV block to be 0.85% (6/706 patients) in patients who had device closure[49]. All AV block occurred within 24 hours after the procedure. They identified younger age, larger ASD size, larger device size and larger device diameter to septum diameter ratio to be associated with AV block. In particular, all patients with 2nd degree or higher AV block were under the age of 3.5 years. Patients with first degree AV block recovered with time and no patients developed progressive AV block during follow-up. The 2 patients with complete AV block both had device removal; 1 patient recovered to sinus rhythm immediately after device removal, but 1 patient had persistent AV conduction disturbance at follow-up although the details are not described in the paper.

Suda and colleagues reported a rate of 6.2 % (10/162 patients) for new-onset or aggravation of AV block following ASD closure with ASO [50]. In all patients, AV block occurred within one week of procedure with spontaneous resolution or improvement observed in all patients. Device size ≥ 19mm or indexed device size ≥ 0.18 mm/cm was the major predisposing factor. In this current study, indexed device size was identified to be associated with follow-up AV block in the univariable analysis. Although this was not statistically significant in the multivariable analysis, this may be

due to insufficient sample size as well as the inclusion of periprocedural AV block in the analysis.

The mechanism of AV block after device closure remains uncertain. The location of the ASD and the rim characteristics may be an important factor, however these details were not collected in this current study. It can be postulated that a larger device can potentially pressure and damage the AV node itself.

5.3 **Atrioventricular block at follow-up**

There are several reports of changes in Holter monitor findings pre and post device closure of ASD. Hill and colleagues analysed ambulatory Holter monitoring pre- and immediately post ASD closure with ASO in 41 patients[58]. There were 3/41 patients (7%) who demonstrated changes in AV conduction, with one patient who developed complete AV dissociation requiring a pacemaker implantation. Overall, there was no change in PR interval pre- and post-procedure. Hessling and colleagues performed 24-hour Holter monitoring before and one year after ASD closure using an ASO in 23 paediatric patients[63]1. There were no AV conduction disturbances observed in this study. In an adult study, the PR interval increased post ASD device closure after a mean follow-up period of 4 years [59].

In this study, of the six patients who developed AV block at follow-up, 4 patients had new-onset AV block only at follow-up and not during the immediate post-procedure period. There may be a different mechanism of the development of AV block during the follow-up period. Whereas direct pressure or damage to the AV node will likely result in AV block in the immediate post-procedure period, scar and long-term endothelialisation and fibrosis may play a role in the slow development of AV node during the follow-up period.

5.4 **Resolution of AV block following ASD closure**

Interestingly, resolution of arrhythmias following ASD closure has also been reported[44,53,64]. Wilson and colleagues reported 227 adults and children who underwent ASD closure with ASO in a single centre in New Zealand[53]. There were 26 patients who had pre-procedure arrhythmias; atrial fibrillation/atrial flutter(n=15), SVT (2), atrial tachycardia (2), long QT syndrome (1), frequent ectopy (3) and ablated arrhythmias (3,

2 with AVNRT and 1 with WPW). All were adults with a median age of 52 years old, except for a 5-year old with long QT syndrome. Of these patients, 16/26(62%) had resolution of arrhythmias following ASD closure. Of the 10 patients with persistent arrhythmias, 8 had atrial fibrillation/atrial flutter and 2 had atrial tachycardia. Schenck and colleagues studied 18 patients who underwent ASD closure with the Bard Clamshell Septal Umbrella with a Holter and ECG, and demonstrated that there was improvement of first degree AV block in 2/3 patients[44].

Similarly, in this current cohort, close to 75% of the patients who had pre-procedural first degree AV block had resolution at follow-up. The mechanism of arrhythmias including AV block in ASDs are thought to be due to chronic stretching of the atrium. Therefore, it can be postulated that the resolution of atrial volume overload with ASD closure leads to improvement of AV conduction.

5.5 Study limitations

This study is limited to a single-center non-randomized cohort of patients who underwent ASD closure. The device closure and surgical closure groups were not comparable in age and size of the ASD. The disparity is mainly due to patient selection as patient with large ASDs and/or younger age would most likely be not suitable for device closure and would have had surgical closure. A substantial number of patients were excluded due to lack of follow-up data, which may have resulted in potential selection bias. There may be interobserver variability in the ECG analysis as it was performed by a single cardiologist.

6 Summary

The prevalence of AV block in patients with repaired ASD is low and rarely requires medical management. However, there are rare cases of late onset AV block. The presence of either pre-procedural or post-procedural AV block were the only risk factors identified to be associated with follow-up AV block in the device subgroup. Previously reported risk factors such as device size and indexed device size were not identified to be significantly associated with late AV block. In patients with perioperative AV block a close longer-term is warranted.

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8 References

1. Dickinson DF, Arnold R, Wilkinson JL. Congenital heart disease among 160 48 liveborn children in Liverpool 1960 to 1969. Implications for surgical treatment. *Heart*. 1981;46:55–62.

2. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *JAC*. 2002;39:1890–1900.

3. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. *Circulation*. 1971;43:323–332.

4. Park MK. Pediatric Cardiology for Practitioners. 5 ed. Mosby Elsevier; 2008.

5. Schwerzmann M, Pfammatter J-P. Approaching Atrial Septal Defects in Pulmonary Hypertension. *Expert Review of Cardiovascular Therapy*. 2015;13:693–701.

6. Nashat H, Montanaro C, Li W, Kempny A, Wort SJ, Dimopoulos K, Gatzoulis MA, Babu-Narayan SV. Atrial septal defects and pulmonary arterial hypertension. *J Thorac Dis*. 2018;10:S2953–S2965.

7. Dalvi B, Jain S, Pinto R. Device Closure of Atrial Septal Defect with Severe Pulmonary Hypertension in Adults: Patient Selection with Early and Intermediate Term Results. 2019;93:309–315.

8. Vyas-Read S, Guglani L, Shankar P, Travers C, Kanaan U. Atrial Septal Defects Accelerate Pulmonary Hypertension Diagnoses in Premature Infants. *Frontiers in Pediatrics*. 2018;6:1–10.

9. Engelfriet P, Meijboom F, Boersma E, Tijssen J, Mulder B. Repaired and Open Atrial Septal Defects Type II in Adulthood: An Epidemiological Study of a Large European Cohort. *International Journal of Cardiology*. 2008;126:379–385.

10. Geva T, Martins JD, Wald RM. Atrial Septal Defects. *Lancet*. 2014;383:1921–1932.

11. Rana BS. Echocardiography guidance of atrial septal defect closure. *J Thorac Dis*. 2018;10:S2899–S2908.

12. Takaya Y, Taniguchi M, Akagi T, Nobusada S, Kusano K, Ito H, Sano S. Long-Term Effects of Transcatheter Closure of Atrial Septal Defect on Cardiac Remodelling and Exercise Capacity in Patients Older than 40 Years with a Reduction in Cardiopulmonary Function. *Journal of Interventional Cardiology*. 2013;26:195–199.

13. Helgason H, Jonsdottir G. Spontaneous Closure of Atrial Septal Defects. *Pediatric Cardiology*. 1999;20:195–199.

14. Anderson RH, Baker EJ, Penny D, Redington AN, Rigby ML, Wernovsky G. Paediatric Cardiology. 3rd ed. Churchill Livingstone Elsevier; 2009.

15. Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJM, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E, ESC Committee for Practice Guidelines (CPG), Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA,

Tendera M, Vardas P, Widimsky P, Document Reviewers:, McDonagh T, Swan L, Andreotti F, Beghetti M, Borggrefe M, Bozio A, Brecker S, Budts W, Hess J, Hirsch R, Jondeau G, Kokkonen J, Kozelj M, Kucukoglu S, Laan M, Lionis C, Metreveli I, Moons P, Pieper PG, Pilossoff V, Popelova J, Price S, Roos-Hesselink J, Uva MS, Tornos P, Trindade PT, Ukkonen H, Walker H, Webb GD, Westby J. Endorsed by the Association for European Paediatric Cardiology (AEPC). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010): The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC). *European Heart Journal*. 2010;31:2915–2957.

16. Murphy JG, Gersh BJ, McGoon M, Mair DD, Porter C-BJ, Ilstrup DM, McGoon DC, Puga FJ, Kirklin JW, Danielson GK. Long-term outcome after surgical repair of isolated atrial septal defect. *the New England Journal of Medicine*. 1990;323:1645–1650.

17. Horvath KA, Burke RP, Collins JJ, Cohn LH. Surgical Treatment of Adult Atrial Septal Defect: Early and Long- Term Results. *JAC*. 1992;20:1156–1159.

18. Du Z-D, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K. Comparison Between Transcatheter and Surgical Closure of Secundum Atrial Septal Defect in Children and Adults. *Journa of the American College of Cardiology*. 2002;39:1836–1844.

19. Brida M, Diller G-P, Kempny A, Drakopolou M, Shore D, Gatzoulis MA, Uebing A. Atrial Septal Defect Closure in Adulthood is Associated with Normal Survival in the Mid to Longer Term. *Heart*. 2019;0:1–6.

20. Rome JJ, Keane JF, Perry SB, Spevak PJ, Lock JE. Double-umbrella closure of atrial defects. Initial clinical applications. *Circulation*. 1990;82:751–758.

21. Bissessor N. Current perspectives in percutaneous atrial septal defect closure devices. *MDER*. 2015;8:297–7.

22. McElhinney DB, Quartermain MD, Kenny D, Alboliras E, Amin Z. Relative Risk Factors for Cardiac Erosion Following Transcatheter Closure of Atrial Septal Defects. *Circulation*. 2016;133:1738–1746.

23. Houeijeh A, t SH, Bouvaist HLN, Hadeed K, Petit JRM, Godart FO, Fraisse A. Transcatheter closure of large atrial septal defects (ASDs) in symptomatic children with device/weight ratio >1.5. *International Journal of Cardiology*. 2018;267:84–87.

24. Butera G, Carminati M, Chessa M, Youssef R, Drago M, Giamberi A, Po EG, Bossone E, Frigiola A. Percutaneous Versus Surgical Closure of Secundum Atrial Septal Defect: Comparison of Early Results and Complications. *American Journal of Cardiology*. 2006;151:228–234.

25. DiBardino DJ, McElhinney DB, Kaza AK, Mayer JEJ. Analysis of the US Food and Drug Administration Manufacturer and User Facility Device Experience database for adverse events involving Amplatzer septal occluder devices and comparison with the Society of Thoracic Surgery congenital cardiac surgery database. *The Journal of Thoracic and Cardiovascular Surgery*. 2009;137:1334–1341.

26. Kutty S, Hazeem AA, Brown K, Danford CJ, Worley SE, Delaney JW, Danford DA, Latson LA. Long-Term (5- to 20-Year) Outcomes After Transcatheter or Surgical Treatment of Hemodynamically Significant Isolated Secundum Atrial Septal Defect. *AJC*. 2012;109:1348–1352.

27. El-Said H, Hegde S, Foerster S, Hellenbrand W, Kreutzer J, Trucco SM, Holzer R, Burch G, Mirani A, Nicolas R, Porras D, Bergersen L, Moore J. Device Therapy for Atrial Septal Defects in a Multicenter Cohort. *Cathet Cardiovasc Intervent*. 2014;85:227–233.

28. Abaci A, Unlu S, Alsancak Y, Kaya U, Sezenoz B. Short and Long Term Complications of Device Closure of Atrial Septal Defect and Patent Foramen Ovale: Metaanalysis of 28,142 Patients from 203 studies. *Cathet Cardiovasc Intervent*. 2013;82:1123–1138.

29. Management of Cardiac Arrhythmias. Humana Press; 2007.

30. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NAM, Ferguson TB, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD. 2012 ACCF/AHA/HRS Focused Update IncorporatedInto the ACCF/AHA/HRS 2008 Guidelines forDevice-Based Therapy of Cardiac Rhythm Abnormalities. *JAC*. 2013;61:e6–e75.

31. Weindling SN, Saul PJ, Gamble WJ, Mayer JE, Wessel D, Walsh EP. Duration of Complete Atrioventricular Block After Congenital Heart Disease Surgery. *The American Journal of Cardiology*. 1998;82:525–527.

32. Krongrad E. Prognosis for patients with congenital heart disease and postoperative intraventricular conduction defects. *Circulation*. 1978;57:867–870.

33. Gross GJ, Chiu CC, Hamilton RM, Kirsh JA, Stephenson EA. Natural history of postoperative heart block in congenital heart disease: Implications for pacing intervention. *Heart Rhythm*. 2006;3:601–604.

34. Brandenburg ROJ, Holmes DRJ, Brandenburg RO, McGoon DC. Clinical Follow-Up Study of Paroxysmal Supraventricular Tachyarrhythmias After Operative Repair of a Secundum Type Atrial Septal Defect in Adults. *The American Journal of Cardiology*. 1983;51:273–276.

35. Hayes CJ, Gersony WM. Arrhythmias After the Mustard Operation for Transposition of the Great Arteries: A Long-Term Study. *Journal of american college of cardiology*. 1986;7:133–137.

36. Martin RP, Radley-Smith R, Magdi YH. Arrhythmias Before and After Anatomic Correction of Transposition of the Great Arteries. *Journal of american college of cardiology*. 1987;10:200–204.

37. Driscoll DJ, Offord KP, Heldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to Fifteen-Year Follow-up After Fontan Operation. *Circulation*. 1992;:469–496.

38. Gelatt M, Hamilton RM, McCrindle BW, Connelly M, Davis A, Harris L, Gow RM, Williams WG, Trusler GA, Freedom RM. Arrhythmia and Mortality After the Mustard Procedure: A 30-year Single-Center Experience. *Journal of american college of cardiology*. 1996;29:194–201.

39. Fishberger SB, Wernovsky G, Gentles TL, Gauvreau K, Burneett J, Mayer JEJ, Walsh EP. Factors that Influence the Development of Atrial Flutter after the Fontan Operation. *J Thorac Cardiovasc Surg*. 1997;:80–86.

40. Williams MR, Perry JC. Arrhythmias and Conduction Disorders Associated with Atrial Septal Defects. *J Thorac Dis*. 2018;10:S2940–S2944.

41. Houck CA, Evertz R, Teuwen CP, Roos-Hesselink JW, Duijnhouwer T, Bogers AJJC, de Groot NMS. Time course and interrelationship of dysrhythmias in patients with surgically repaired atrial septal defect. *Heart Rhythm*. 2018;15:341–347.

42. Loomba RS, Chandrasekar S, Sanan P, Shah PH, Arora RR. Association of Atrial Tachyarrhythmias with Atrial Septal Defect, Ebstein's Anomaly and Fontan Patients. *Expert Review of Cardiovascular Therapy*. 2014;9:887–893.

43. Morton JB, Sanders P, Vohra JK, Sparks PB, Morgan JG, Spence SJ, Grigg LE, Kalman JM. Effect of Chronic Right Atrial Stretch on Atrial Electrical Remodeling in Patients With an Atrial Septal Defect. *Circulation*. 2003;107:1775–1782.

44. Schenck MH, Sterba R, Foreman CK, Latson LA. Improvement in noninvasive electrophysiologic findings in children after transcatheter atrial septal defect closure. *The American Journal of Cardiology*. 1995;76:695–698.

45. Berger F, Vogel M, Kramer A, Alexi-Meskishvili V, Weng Y, Lange PE, Hetzer R. Incidence of Atrial Flutter/Fibrillation in Adults With Atrial Septal Defect Before and After Surgery. *The Annals of Thoracic Surgery*. 1999;68:75–78.

46. Walker RE, Mayer JE, Alexander ME, Walsh EP, Berul CI. Paucity of Sinus Node Dysfunction Following Repair of Sinus Venosus Defects in Children. *The American Journal of Cardiology*. 2001;87:1223–1226.

47. Chessa M, Carminati M, Butera G, Bini RM, Drago M, Rosti L, Giamberti A, Pome G, Bossone E, Frigiola A. Early and Late Complications Associated with Transcatheter Occlusion of Secundum Atrila Septal Defect. *Journal of the american College of Cardiology*. 2002;39:1061–1065.

48. Johnson JN, Marquardt ML, Ackerman MJ, Asirvatham SJ, Reeder GS, Cabalka AK, Cetta F, Hagler DJ. Electrocardiographic changes and arrhythmias following percutaneous atrial septal defect and patent foramen ovale device closure. *Cathet Cardiovasc Intervent*. 2011;78:254–261.

49. Wang L, Li J, Yao R, Song S, Guo Z. Long-term follow-up of patients with P-R prolongation after catheter ablation of slow pathway for atrioventricular node re-entrant tachycardia. *Archives of Medical Research*. 2004;35:442–445.

50. Suda K, Raboisson M-J, Piette E, Dahdah NS, Miró J. Reversible atrioventricular block associated with closure of atrial septal defects using the amplatzer device. *Journal of the american College of Cardiology*. 2004;43:1677–1682.

51. Rijnbeek P. New normal limits for the paediatric electrocardiogram. *European Heart Journal*. 2001;22:702–711.

52. Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. *Journal of the american College of Cardiology*. 2005;45:505–507.

53. Wilson NJ, Smith J, Prommete B, O'Donnell C, Gentles TL, Ruygrok PN. Transcatheter Closure of Secundum Atrial Septal Defects with the Amplatzer Septal Occluder in Adults and Children—Follow-up Closure Rates, Degree of Mitral Regurgitation and Evolution of Arrhythmias. *"Heart, Lung and Circulation."* 2008;17:318–324.

54. Berger F, Vogel M, Alexi-Meskishvili V, Lange PE. Comparison of Results and Complications of Surgical and Amplatzer device Closure of Atrila Septal Defects. *Journal of Thoracic and Cardiovascular Surgery*. 1999;118:674–680.

55. Hijazi ZM. Catheter Closure of Atrial Septal and Ventricular Septal defects Using The Amplatzer Devices. *"Heart, Lung and Circulation."* 2003;:63–72.

56. Sadiq M, Kazmi T, Rehman AU, Latif F, Hyder N, Qureshi SA. Device Closure of Atrial Septal Defect: Medium-Term Outcome with Special Reference to Complications. *Cardiology in the Young*. 2012;22:71–78.

57. Nehgme RA, Huddleston AR, Cheatham JP. Progression to Late Complete Atrioventricular Block Following Amplatzer Device Closure of Atrial Septal Defect in a Child. *Pediatric Cardiology*. 2008;30:367–370.

58. Hill SL, Berul CI, Patel H, Rhodes J, Supran S, Cao Q-L, Hijazi ZM. Early ECG Abnormalities Associated with Transcatheter Closure of Atrial Septal Defects Using the Amplatzer. *Journal of Interventional Cardiac Electrophysiology*. 2000;:469–474.

59. Cottens D, Van De Bruaene A, Troost E, Willems R, Moons P, Budts W. Influence of percutaneous transcatheter closure of an atrial septal defect on the atrioventricular conduction. *Acta Cardiol*. 2011;66:309–314.

60. Wang Y, Hua Y, Li L, Wang X, Qiao L, Shi X, Hua J, Qu Y, Mu D. Risk Factors and Prognosis of Atrioventricular Block After Atrial Septum Defect Closure Using the Amplatzer Device. *Pediatric Cardiology*. 2013;35:550–555.

61. Al-Anani SJ, Weber H, Hijazi ZM. Atrioventricular block after transcatheter ASD closure using the Amplatzer septal occluder: Risk factors and recommendations. *Cathet Cardiovasc Intervent*. 2009;75:767–772.

62. Clark JB, Chowdhury D, Pauliks LB, Weber HS. Resolution of Heart Block After Surgical Removal of an Amplatzer Device. *ATS*. 2010;89:1631–1633.

63. Hessling G, Hyca S, Brockmeier K, Ulmer HE. Cardiac Dysrhythmias in Pediatric Patients Before and 1 Year After Transcatheter Closure of Atrial Septal Defects Using the Amplatzer Septal Occluder. *Pediatric Cardiology*. 2003;24:259–262.

64. Vecht JA, Saso S, Rao C, Dimopoulos K, Grapsa J, Terracciano CM, Peters NS, Nihoyannopoulos P, Holmes E, Gatzoulis MA, Athanasiou T. Atrial Septal Defect Closure is Associated with a Reduced Prevalence of Atrial Tachyarrhythmia in the Short to Medium Term: a Systematic Review and Meta-analysis. *Heart*. 2010;96:1789–1797.