Incidence and risk factors of post-operative arrhythmias and sudden cardiac death after atrioventricular septal defect (AVSD) correction: Up to 47 years of follow-up

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Abstract

Background

Atrioventricular septal defect (AVSD) has an incidence of 4-5.3 per 10.000 live births and is associated with Down syndrome (DS). Data on arrhythmias and sudden cardiac death (SCD) after AVSD correction is scarce.

Aim

To analyse the incidence of post-operative arrhythmias and SCD after AVSD correction and explore risk factors.

Methods

This is a retrospective multicenter study including patients after biventricular AVSD correction. Univariate and multivariate analyses were performed to explore risk factors.

Results

A total of 415 patients were included with a mean follow-up duration of 9 years (range; <30 days – 47 years).

Early post-operative SVTs were documented in 33 patients (8%) and late post-operative SVTs in 15 patients (3.6%). Non-syndromic AVSD (p=0.022, HR=2.64; 95% CI= 1.15-6.04) and cAVSD (p=0.005, HR= 3.7; 95% CI= 1.39-7.51) were independent risk factors for early post-operative SVTs and significant more late post-operative SVTs occurred in non-syndromic patients (p=0.016, HR=6.38; 95% CI= 1.42-28.71) and in pAVSD (p=0.045, HR=3.703; 95% CI= 1.03-13.32). Fifteen patients (3.6%) received a pacemaker. Non-syndromic AVSD (p=0.008, HR=15.82; 95% CI= 2.04-122.47), pAVSD (p=0.017, HR=6.26; 95% CI= 1.39-28.28) and re-operation (p=0.007, HR=4.911; 95% CI= 1.54-15.64) were independent risk factors for postoperative pacemaker implantation.

Late life-threatening ventricular arrhythmias and SCD occurred in 0.5% and 1.7% respectively.

Conclusion

There is good long-term survival after AVSD correction and incidence of SCD is low. Non-syndromic

AVSD and cAVSD are independent risk factors for early post-operative SVTs. Non-syndromic AVSD patients have significant more early 3rd degree AVB and late post-operative SVTs. Non-syndromic patients with partial AVSD who have undergone reoperation have a significant higher risk of pacemaker implantation.

Introduction

Atrioventricular septal defect (AVSD) represents a spectrum of cardiac anomalies characterized by incomplete development of the atrioventricular septum along with abnormalities of the atrioventricular (AV) valves. The incidence of AVSD is 4-5.3 per 10.000 live births and it is associated with several syndromes, in particular Down syndrome (DS) [1]. Surgical repair can be accomplished with good long-term survival, with an estimated overall survival after 15 years of 88.6% [2].

In patients with an AVSD, the AV node and bundle of His are displaced inferiorly [3], predisposing the conduction system for injury during surgical repair [4]. Furthermore, functional properties of the conduction tissues can be suboptimal and may result in complete heart block [5]. In recent ACC/AHA guidelines regular evaluation of the status of AV conduction with ECG and periodic Holter monitoring in patients with repaired or palliated AVSD is recommended [5].

An incidence of early and late post-operative supraventricular arrhythmias is reported in 9.6% and 11.7% respectively in patients with a partial AVSD [6] and the reported incidence of pacemaker implantation after AVSD correction ranges from 1.3% to 5.0%[6-11]**.** There is little data on the incidence of ventricular arrhythmia and sudden cardiac death (SCD) in AVSD patients [12]. Although clinical differences between isolated AVSD and AVSD in the setting of syndromal heart disease are overt [1], the difference between DS and non-syndromic patients with regard to conduction and rhythm disorders is not well established. Literature suggests that non-syndromic AVSD patients tend to have more post-operative arrhythmias, although to date there is no clear evidence about differences in post-operative arrhythmias or the need for permanent pacemaker implantation [13].

The aims of the current study were 1. To analyse the incidence of post-operative arrhythmias, especially late ventricular arrhythmias and SCD, after surgical repair of AVSD and 2. To explore potential factors, including DS and type of AVSD, contributing to the risk of rhythm- and conduction disorders after surgical repair of AVSD.

Methods

Study Population and Design

This is a retrospective multicenter study including all AVSD patients who underwent biventricular correction between June 1958 and January 2014. Patients were recruited from a surgical database of the Center of Congenital Heart Disease Amsterdam-Leiden (CAHAL) that includes all patients who have undergone surgical procedures at the Leiden University Medical Center (LUMC) and the Amsterdam Academic Medical Center (AMC), the Netherlands. Patients with an unbalanced AVSD who underwent univentricular repair and patients with heterotaxy syndrome were excluded from the study.

Data was obtained during follow-up by analyses of medical files, electronic records, 24-hour Holter recordings, catheterisation reports, echocardiographic findings and electrocardiograms (ECGs). The majority of patients underwent routine follow-up at the paediatric or adult Cardiology departments of the LUMC or AMC, some patients underwent routine follow-up at their local hospital. Data, as far as obtainable, of these visits were collected.

Informed consent for retrospective observational studies is not mandatory according to Dutch law, provided the results are reported anonymously.

Pre-operative, peri-operative & post-operative data

Collected data consisted of gender, type of AVSD, associated cardiovascular anomalies, chromosomal abnormalities, ECG features and documented arrhythmias or conduction disorders. Treatment of all arrhythmias consisting of anti-arrhythmic drug treatment, electrical cardioversion, catheter ablations and pacemaker or implantable cardiac defibrillator (ICD) implantation were registered.

Atrioventricular septal defect was subdivided in complete AVSD (cAVSD; both atrial and ventricular shunting) and partial AVSD (pAVSD; atrial or ventricular (intermediate AVSD) shunting). Down syndrome was confirmed by chromosomal analysis.

Collection of ECG-derived data included rhythm, heart rate, PR interval and QRS duration. Paediatric

ECGs were scored according to normal values matched by age and heart rate [14]**.** An experienced researcher, supervised by a Paediatric Cardiologist and a Cardiologist specialized in grown-up congenital heart disease, examined the ECGs.

Peri-operative data consisted of type of surgical repair (single/double patch) and rhythm after cardiopulmonary bypass. As early surgical era may negatively influence survival and risk for reoperation**,** AVSD repairs were divided into two surgical eras: 1958 to 1995 and 1996 to 2014 [2].

Post-operative data consisted of post-operative arrhythmias and conduction disorders, early and late mortality and cause of death.

Early mortality was defined as mortality within 30 days after surgery or longer when death occurred with the patient still in hospital. Cause of death was classified as cardiac or non-cardiac. Sudden cardiac death (SCD) was defined as unexpected death within 1 hour of cardiac symptom onset or unwitnessed death.

Rhythm & Conduction disorders

Arrhythmias documented during the early post-operative period (<30 days) were defined as early onset post-operative arrhythmias and arrhythmias documented during the late post-operative period (>30 days) as late post-operative arrhythmias. Arrhythmias were classified as either tachy-arrhythmias or brady-arrhythmias.

Tachy-arrhythmias

Supraventricular tachycardia was subdivided in atrial flutter (AFL), atrial fibrillation (AF), atrial tachycardia (AT), junctional ectopic tachycardia (JET), atrioventricular re-entrant tachycardia (AVRT) and AV nodal re-entrant tachycardia (AVNRT).

Ventricular arrhythmias included ventricular tachycardia (VT) and ventricular fibrillation (VF).

Brady-arrhythmias

Sino-atrial node (SAN) dysfunction was reported as sinus bradycardia (SB), sick sinus syndrome (SSS), SA exit block and atrial or junctional escape rhythm. Rhythm was scored from ECGs and 24-hour Holter reports.

Atrioventricular block (AVB) was categorized as 1st and 2nd degree AVB and complete AVB. Second degree AVB was further subdivided in type 1 Wenkebach and type 2 Mobitz block.

Bundle branch block was subdivided in right or left bundle branch block (RBBB, LBBB) and left anterior fascicular block (LAFB).

Pacemaker/ICD implantation

Pacemaker implantation was subdivided in early post-operative period (<30 days) and late post-operative period (>30 days) implantation. The indications for pacemaker and ICD therapy were documented.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistical software (version 20, IBM Corp., Armonk, New York, USA). Descriptive statistics were used to describe post-operative arrhythmias and the incidence of ICD and pacemaker implantation.

Univariate Cox regression analyses were performed to evaluate the effect of multiple variables, DS (DS versus non-syndromal), type of AVSD (pAVSD versus cAVSD), gender (male versus female) and surgical era (before 1996 versus after 1996), on the incidence of arrhythmias and pacemaker implantation. The variables DS and type of AVSD were further entered into a stepwise multivariate cox regression model to assess their independent value. Some variables were analysed in a time-dependent Cox model. A P-value of < 0.05 was considered statistical significant.

Results

Patient Characteristics

Overall, 428 patients underwent biventricular correction at our institute. Patients with other syndromes than Down syndrome (n=13) were excluded from further analysis since the numbers of events were too low for risk stratification, but an overview of arrhythmia's that occurred in these patients is provided in **appendix 1.**

Therefore, 415 patients were included for further analysis with a mean follow-up duration of 9 years (range; <30 days – 47 years) **(Figure 1A)**. Among these, 238 (57%) had a cAVSD and 253 (61%) were diagnosed with DS **(Table 1)**. In patients with a cAVSD, DS was present in 206 patients (87% of all cAVSD patients). The two most common additional cardiac malformations were patent ductus arteriosus (30%) and atrial septal defect type 2 (25%). Other additional cardiac anomalies are listed in **Table 1**.

Holter monitoring was available in 44 patients (11% of all patients), consisting of 17 patients with DS (7% of all patients with DS) and 27 non-syndromic patients (17% of all non-syndromic patients).

Overall mortality was 10.3%. In-hospital mortality occurred in 5.5% and late mortality in 4.8%. The main causes of late cardiac mortality were sudden cardiac death (1.7%) and heart failure (0.5%).

Eighty-nine patients underwent 128 re-operations. Left atrioventricular valve pathology was the most common indication for reoperation, in 53.0%.

Tachy-arrhythmias

Among the included 415 patients, at least one episode of a SVT was documented in 48 patients (11.6%), further subdivided in AF (n=7), AFL (n=8), AVNRT (n=1), AVRT (n=1), JET (n=12), unspecified SVT (n=29), and VT or VF in 6 patients (1.9%) **(Table 2)**. Some patients experienced more than one type of arrhythmia.

According to analyses of both early and late SVTs, significantly more SVTs occurred in non-syndromic patients(P=0.049, HR=1.79; 95% CI= 1.00-3.20). There were no statistically significant associations between the occurrence of SVT and gender (p=0.221, HR=1.45; 95% CI= 0.80-2.64), type of AVSD (pAVSD vs. cAVSD, p=0.719, HR=0.89; 95% CI= 0.50-1.61) or surgical era (before 1996 vs. after 1996, p=0.899, HR=1.04; 95% CI= 0.55-1.99). In **Figure 1B** the time free interval of SVT is shown for both types of AVSD; DS and non-syndromic.

Early post-operative supraventricular arrhythmias

The majority of SVTs occurred within 30 days after surgical correction (n= 33, 8.0%). In this group, there were no significant differences between patients with DS and non syndromic patients (p=0.576, HR=1.22; 95% CI= 0.61-2.43). Likewise, there was no significant association between the occurrence of early post-operative arrhythmia and gender (p=0.065, HR=2.01; 95% CI= 0.96-4.22), type of AVSD (p=0.072, HR=0.50; 95% CI= 0.23-1.06) or surgical era (p=0.992, HR=1.00; 95% CI= 0.50-2.02). However, in a multiple Cox regression model with DS and type of AVSD, significant more early post-operative SVTs occurred in patients with a cAVSD (p=0.005, HR= 3.70; 95% CI= 1.39-7.51) and in non-syndromic patients (p=0.022, HR=2.64; 95% CI= 1.15-6.04).

Electrical cardioversion was performed in 5 patients in the early post-operative period. All other patients were treated with anti-arrhythmic drugs.

Late post-operative supraventricular arrhythmias

Late post-operative SVTs were documented in 15 patients (3.6%). Significant more late SVTs occurred in non-syndromic patients as compared to patients with DS (p=0.016, HR=6.38; 95% CI= 1.42-28.71) and in pAVSD compared to cAVSD (p=0.045, HR=3.703; 95% CI= 1.03-13.32). No significant associations between the occurrence of late post-operative arrhythmia and gender or surgical era could be demonstrated. Tetralogy of Fallot was not a risk factor for post-operative arrhythmias.

Patients experiencing an arrhythmic event in the early post-operative period, included in the model as a time-dependent covariate, were not at risk for an event later in life (p=0.486, HR=0.04; 95% CI= 0.00-296.47). After correction for the presence of DS, no association between type of AVSD and the occurrence of late post-operative SVTs could be demonstrated (p=0.762, HR=1.28; 95% CI= 0.260-6.238).

Electrical cardioversion was performed in 6 patients in the late post-operative period. Other patients were treated with anti-arrhythmic drugs. Four patients underwent catheter ablation for AVRT (n=2) and AF (n=2). All patients who underwent catheter ablation were non-syndromic patients with a pAVSD.

Post-operative ventricular arrhythmias

Three VF and 3 VT episodes were documented in 6 patients (1.4%). Two events occurred in patients with DS and 3 patients had cAVSD. None of these patients had AVSD – Tetralogy of Fallot. Descriptive analyses showed 3 events occurring in the early post-operative period after primary correction and 2 events occurring in the early post-operative period after re-operation. Two of these patients did not survive. Since the number of ventricular events is small, no conventional Cox regression analyses were performed. Late life-threatening VT occurred in 2 patients (0.5%, both non-syndromic). One VT episode occurred in a patient with a good ventricular function 20 months after his second re-operation for subvalvular aortic stenosis.

Brady-arrhythmias

Sinoatrial node dysfunction was reported as SB in 25 patients (6.0%), SSS in 1 patient (0.2%) and brady-tachy syndrome in two patients (0.5%). No significant associations between the occurrence of sinoatrial node dysfunction and gender, type of AVSD or DS could be demonstrated.

First degree AVB was present in 97 patients (23.4%), 43 patients had DS and 45 patients had a cAVSD. After correction for the AVSD type 1st degree AVB occurred significantly more in non-syndromic

patients (p=0.008, HR=2.02; 95% CI= 1.21-3.40). No significant difference in gender could be demonstrated (p=0.551, HR=0.886; 95% CI= 0.59-1.32).

Second degree AVB type Wenkebach was reported in 5 patients (1.2%), 2 patients had DS and 4 patients pAVSD. Second-degree AVB type Mobitz was reported in 13 patients (3.1%), 5 patients with DS and 9 patients with pAVSD. At least one episode of early complete AVB was documented in 41 patients (9.9%), 20 patients with DS and 17 patients with a pAVSD. After correction for the type of AVSD significantly more early post-operative complete AVB occurred in non-syndromic patients (p=0.016, HR=2.57; 95% CI= 1.19-5.56). Late complete AVB occurred in 3 patients (0.7%).

Complete RBBB and complete RBBB in combination with LAFB was reported in 44.8% and 26.7% respectively. Complete RBBB occurred significantly more frequent in cAVSD, also after correction for the presence of DS (p=0.010, HR=1.71; 95% CI= 1.14-2.56). Isolated LAFB and complete LBBB were present in 8.9% and 1.2% respectively.

Permanent pacemaker/ICD implantation

Fifteen patients (3.6%) required permanent pacemaker implantation and no ICD or cardiac resynchronisation therapy devices were implanted **(Table 3)**. Down syndrome was present in only one patient. The indication for permanent pacemaker implantation was complete AVB in 9 patients. In 4 patients complete AVB occurred <30 days after primary correction, in 4 other patients it occurred <30 days after a re-operation. One patient spontaneously developed complete AVB 5 years after surgery. Non-DS (p=0.008, HR=15.82; 95% CI= 2.04-122.47), pAVSD (p=0.017, HR=6.26; 95% CI= 1.39-28.28) and re-operation (p=0.007, HR=4.911; 95% CI= 1.54-15.64), as a time-dependent covariate, were all independently related to the postoperative need for permanent pacemaker implantation. There were no statistically significant associations between permanent pacemaker implantation and gender (p=0.545, HR=0.731; 95% CI= 0.27-2.02) or surgical era (p=0.795, HR=0.832; 95% CI= 0.21-3.34).

Discussion

To our knowledge this is the largest study investigating the incidence and risk factors for rhythm and conduction disorders, SCD and pacemaker implantation after AVSD correction with a follow-up of up to 47 years. Key findings of this study are; 1) In 11.6% of the patients SVT is reported, 8% in the early post-operative period and only 3.6% in the late post-operative period during a mean follow-up period of 9 years. 2) Late life-threatening ventricular arrhythmia and SCD occurred in only 0.5% and 1.7% respectively. 3) Although different forms of conduction disorders are encountered frequently, pacemaker implantation was reported in only 3.6%. 4) Non-syndromic AVSD patients have a significant higher risk of early and late post-operative SVT's, 1st degree AVB and early complete AVB. 5) Partial AVSD, re-operation and non-syndromic AVSD are risk factors for post-operative pacemaker implantation after AVSD correction.

Post-operative arrhythmias after AVSD correction

In the current study, early post-operative SVTs were documented in 8% and late post-operative SVTs in only 3.6%, which is lower than reported by El-Najdawi et al. respectively in 9.6% and 11.7% [6]**.** The incidence of early post-operative SVTs in children with congenital heart defects (CHD) is reported in 9% - 15% and therefore an AVSD or correction of an AVSD does not seem to convey an additional risk for early post-operative SVTs [15]**.** However, significant more late SVTs were documented in patients with a pAVSD compared to cAVSD. This might due to insufficiency of the left AV valve, which mostly occurs in patients with a pAVSD, and its effect on the atria [29]**.** In adults with CHD SVTs, including AF and AFL, are reported in 15%, and these are related to the severity of the underlying cardiac defect, its surgical treatment, age and the development of heart failure [16-18]. In our study population late AF and AFL occurred in only 2.4%, unfortunately there is no data on late AF and AFL after AVSD correction in the current literature to compare this finding. However, this is lower than

the reported incidence after repair in other CHD populations, such as tetralogy of Fallot and secundum atrial septal defect [16]. The lower incidence of late post-operative AF and AFL in our population might due to a relatively short mean follow-up duration.

Ventricular arrhythmia in the early post-operative period after surgical correction or reoperations occurred in 1.2%. This is lower than the incidence of early post-operative ventricular arrhythmias in patients with CHD, which is reported in 2.1% in children and 5.0% in adults [19, 20].

Sudden cardiac death and late ventricular arrhythmias

Heart failure and SCD are the major causes of late death in postoperative patients with CHD [21]**.** Large cohort studies indicate that late SCD can occur in CHD patients with different underlying defects [22]. In our cohort SCD and heart failure were the main causes of late death. We found a low incidence of life threatening ventricular arrhythmias and SCD beyond the early postoperative period. Although there is no other literature data in AVSD patients for comparison, our results are in contrast to the higher incidences of ventricular arrhythmia and SCD in large CHD cohort studies [12, 22]. Our findings indicate that postoperative AVSD patients form a low risk group for SCD.

Conduction disorders and pacemaker implantation after AVSD correction

Atrioventricular conduction disturbances varying from 1st degree to complete AVB are described in patients with an AVSD [9, 23, 24]**.** Late complete AVB is reported in 0.5% of the patients by Lin et al [25], which is in line with our results. Although 1st degree AVB and bundle branch blocks were encountered quite frequently in our population, second degree and spontaneous complete AVB in the late post-operative period are rare. Only 3.7% of the patients in our population required pacemaker implantation. This is an average of what is reported in the literature after AVSD correction [6-11] and is in a similar range of pacemaker implantation incidence after mitral valve surgery in adults with acquired heart disease: 2.6% - 6% [26-28]. Significant less pacemakers were

implanted in patients with DS as compared to non-syndromic patients in our study. Lange et al. reported a pacemaker implantation rate of 5.1% in patients with DS and 6.3% in non-syndromic patients after AVSD correction [11].

Re-operation and pAVSD were associated with a significant higher risk of pacemaker implantation. Left AV valve pathology is the main indication for re-operation in AVSD patients [2, 29-31]. Extensive abnormalities of the AV valves are more frequently seen in patients without DS, and more often in combination with a pAVSD [11, 32, 33]. This renders repair of the AV valves more challenging and increases the risk of recurrence of left AV valve pathology and reoperation and therefore risk of damage to the AV-node necessitating PM-implantation. Several studies have shown a lower risk for reoperation in patients with DS and a cAVSD [11, 32, 34].

Influence of Down syndrome

Data on the influence of DS on cardiac conduction and arrhythmias is scarce [35]. According to our results, non-syndromic patients had a significant higher risk of early and late post-operative SVTs. Our findings are in line with the results published by Dunlop et al., but contradictory to the early post-operative outcomes published by Desai et al., who reported no difference in SVTs in patients with and without DS [13, 36].

There is no data about possible differences in the development of the conduction system between DS AVSD vs. non-syndromic AVSD. However, development of the AV node and the ventricular conduction system in DS AVSD is different compared to normal [37]. Furthermore, an aberrant development of the AV septum in DS, even in the absence of AVSD is observed [38, 39], suggesting structural differences in the AV node area as compared to non-syndromic hearts. Whether this relates to the findings in the current study is as yet unclear.

Another factor influencing the lower incidence of documented arrhythmias in DS might also relate to underreporting of complaints by DS patients, either due to their mild to moderate impaired mental functioning or due to communication problems. Furthermore, not all patients had a Holter recording,

as in our cohort, the performance of a Holter recording was at the discretion of the physician. This may have influenced our diagnostic work-up in patients with Down-syndrome [40].

Study limitations

This study has limitations inherent to any retrospective study. Data collection was limited to data available in medical and electronic files. As stated above, incidence of arrhythmias might be underestimated in DS patients, influencing our results. Patients who are doing well after surgery, or complain less, were potentially monitored less rigorously. This may result in less additional diagnostics as Holter monitoring, and thus in underreporting of events. Not al arrhythmias were documented on ECG and not all patients had ECGs in their medical file, this may result in less accurate description of the arrhythmias. Furthermore, some events may occur later during follow-up and therefore may be missed in the current study.

Clinical application & conclusions

There is a good long-term survival after biventricular AVSD correction and the incidence of life-threatening ventricular arrhythmias and SCD is low. Furthermore, post-operative arrhythmias do not have a high incidence after AVSD correction. On the other hand, conduction disorders of some degree are encountered frequently, but there is a low incidence of pacemaker implantation. Rhythm and conduction disorders may occur at any time during follow-up. Non-syndromic patients have a significant higher risk for early and late post-operative SVT and early complete AVB. Risk factors for post-operative pacemaker implantation are pAVSD, re-operation and non-syndromic AVSD. In our study cohort Holter recordings seem to be underutilized, especially in DS patients. Periodic Holter monitoring should be performed, according to the American guidelines [5], after AVSD correction to prevent potential underreporting.

Reference list

[1] Calkoen EE, Hazekamp MG, Blom NA, Elders BB, Gittenberger-de Groot AC, Haak MC, et al. Atrioventricular septal defect: From embryonic development to long-term follow-up. Int J Cardiol. 2016;202:784-95.

[2] Hoohenkerk GJ, Bruggemans EF, Rijlaarsdam M, Schoof PH, Koolbergen DR, Hazekamp MG. More than 30 years' experience with surgical correction of atrioventricular septal defects. Ann Thorac Surg. 2010;90:1554-61.

[3] Feldt RH, DuShane JW, Titus JL. The atrioventricular conduction system in persistent common atrioventricular canal defect: correlations with electrocardiogram. Circulation. 1970;42:437-44.

[4] Thiene G, Wenink AC, Frescura C, Wilkinson JL, Gallucci V, Ho SY, et al. Surgical anatomy and pathology of the conduction tissues in atrioventricular defects. J Thorac Cardiovasc Surg. 1981;82:928-37.

[5] American College of Cardiology/American Heart Association Task Force on Clinical Data S, Buxton AE, Calkins H, Callans DJ, DiMarco JP, Fisher JD, et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). Circulation. 2006;114:2534-70.

[6] El-Najdawi EK, Driscoll DJ, Puga FJ, Dearani JA, Spotts BE, Mahoney DW, et al. Operation for partial atrioventricular septal defect: a forty-year review. J Thorac Cardiovasc Surg. 2000;119:880-9; discussion 9-90.

[7] Buratto E, McCrossan B, Galati JC, Bullock A, Kelly A, d'Udekem Y, et al. Repair of partial atrioventricular septal defect: a 37-year experience. Eur J Cardiothorac Surg. 2015;47:796-802.

[8] Ginde S, Lam J, Hill GD, Cohen S, Woods RK, Mitchell ME, et al. Long-term outcomes after surgical repair of complete atrioventricular septal defect. J Thorac Cardiovasc Surg. 2015;150:369-74.

[9] Gunther T, Mazzitelli D, Haehnel CJ, Holper K, Sebening F, Meisner H. Long-term results after repair of complete atrioventricular septal defects: analysis of risk factors. Ann Thorac Surg. 1998;65:754-9; discussion 9-60.

[10] Jacobs JP, Jacobs ML, Mavroudis C, Chai PJ, Tchervenkov CI, Lacour-Gayet FG, et al. Atrioventricular septal defects: lessons learned about patterns of practice and outcomes from the congenital heart surgery database of the society of thoracic surgeons. World J Pediatr Congenit Heart Surg. 2010;1:68-77.

[11] Lange R, Guenther T, Busch R, Hess J, Schreiber C. The presence of Down syndrome is not a risk factor in complete atrioventricular septal defect repair. J Thorac Cardiovasc Surg. 2007;134:304-10.

[12] Koyak Z, de Groot JR, Bouma BJ, Zwinderman AH, Silversides CK, Oechslin EN, et al. Sudden cardiac death in adult congenital heart disease: can the unpredictable be foreseen? Europace. 2016.

[13] Dunlop KA, Mulholland HC, Casey FA, Craig B, Gladstone DJ. A ten year review of atrioventricular septal defects. Cardiol Young. 2004;14:15-23.

[14] Park M. How to Read Pediatric ECGs. 4th ed2006.

[15] Rekawek J, Kansy A, Miszczak-Knecht M, Manowska M, Bieganowska K, Brzezinska-Paszke M, et al. Risk factors for cardiac arrhythmias in children with congenital heart disease after surgical intervention in the early postoperative period. J Thorac Cardiovasc Surg. 2007;133:900-4.

[16] Koyak Z, de Groot JR, Mulder BJ. Interventional and surgical treatment of cardiac arrhythmias in adults with congenital heart disease. Expert Rev Cardiovasc Ther. 2010;8:1753-66.

[17] Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation. 2007;115:534-45.

[18] Roos-Hesselink JW, Karamermer Y. Significance of postoperative arrhythmias in congenital heart disease. Pacing Clin Electrophysiol. 2008;31 Suppl 1:S2-6.

[19] Koyak Z, Achterbergh RC, de Groot JR, Berger F, Koolbergen DR, Bouma BJ, et al. Postoperative arrhythmias in adults with congenital heart disease: incidence and risk factors. Int J Cardiol. 2013;169:139-44.

[20] Delaney JW, Moltedo JM, Dziura JD, Kopf GS, Snyder CS. Early postoperative arrhythmias after pediatric cardiac surgery. J Thorac Cardiovasc Surg. 2006;131:1296-300.

[21] Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, et al. Mortality in adult congenital heart disease. Eur Heart J. 2010;31:1220-9.

[22] Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, et al. Sudden cardiac death in adult congenital heart disease. Circulation. 2012;126:1944-54.

[23] Craig B. Atrioventricular septal defect: from fetus to adult. Heart. 2006;92:1879-85.

[24] Okada Y, Tatsuno K, Kikuchi T, Takahashi Y, Shimokawa T. Complete atrioventricular septal defect associated with tetralogy of fallot: surgical indications and results. Jpn Circ J. 1999;63:889-92.

[25] Lin A, Mahle WT, Frias PA, Fischbach PS, Kogon BE, Kanter KR, et al. Early and delayed atrioventricular conduction block after routine surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2010;140:158-60.

[26] Gordon RS, Ivanov J, Cohen G, Ralph-Edwards AL. Permanent cardiac pacing after a cardiac operation: predicting the use of permanent pacemakers. Ann Thorac Surg. 1998;66:1698-704.

[27] Berdajs D, Schurr UP, Wagner A, Seifert B, Turina MI, Genoni M. Incidence and pathophysiology of atrioventricular block following mitral valve replacement and ring annuloplasty. Eur J Cardiothorac Surg. 2008;34:55-61.

[28] Meimoun P, Zeghdi R, D'Attelis N, Berrebi A, Braunberger E, Deloche A, et al. Frequency, predictors, and consequences of atrioventricular block after mitral valve repair. Am J Cardiol. 2002;89:1062-6.

[29] Sojak V, Kooij M, Yazdanbakhsh A, Koolbergen DR, Bruggemans EF, Hazekamp MG. A single-centre 37-year experience with reoperation after primary repair of atrioventricular septal defect. Eur J Cardiothorac Surg. 2016;49:538-44; discussion 44-5.

[30] Birim O, van Gameren M, de Jong PL, Witsenburg M, van Osch-Gevers L, Bogers AJ. Outcome after reoperation for atrioventricular septal defect repair. Interact Cardiovasc Thorac Surg. 2009;9:83-7.

[31] Stulak JM, Burkhart HM, Dearani JA, Cetta F, Barnes RD, Connolly HM, et al. Reoperations after repair of partial atrioventricular septal defect: a 45-year single-center experience. Ann Thorac Surg. 2010;89:1352-9.

[32] Al-Hay AA, MacNeill SJ, Yacoub M, Shore DF, Shinebourne EA. Complete atrioventricular septal defect, Down syndrome, and surgical outcome: risk factors. Ann Thorac Surg. 2003;75:412-21.

[33] De Biase L, Di Ciommo V, Ballerini L, Bevilacqua M, Marcelletti C, Marino B. Prevalence of left-sided obstructive lesions in patients with atrioventricular canal without Down's syndrome. J Thorac Cardiovasc Surg. 1986;91:467-9.

[34] Formigari R, Di Donato RM, Gargiulo G, Di Carlo D, Feltri C, Picchio FM, et al. Better surgical prognosis for patients with complete atrioventricular septal defect and Down's syndrome. Ann Thorac Surg. 2004;78:666-72; discussion 72.

[35] Caro M, Conde D, Perez-Riera AR, de Almeida AP, Baranchuk A. The electrocardiogram in Down syndrome. Cardiol Young. 2015;25:8-14.

[36] Desai AR, Branco RG, Comitis GA, Maiya S, Vyas DB, Vaz Silva P, et al. Early postoperative outcomes following surgical repair of complete atrioventricular septal defects: is down syndrome a risk factor? Pediatr Crit Care Med. 2014;15:35-41.

[37] Blom NA, Ottenkamp J, Deruiter MC, Wenink AC, Gittenberger-de Groot AC. Development of the cardiac conduction system in atrioventricular septal defect in human trisomy 21. Pediatr Res. 2005;58:516-20.

[38] Gittenberger-de Groot AC, Bartram U, Oosthoek PW, Bartelings MM, Hogers B, Poelmann RE, et al. Collagen type VI expression during cardiac development and in human fetuses with trisomy 21. Anat Rec A Discov Mol Cell Evol Biol. 2003;275:1109-16.

[39] Calkoen E, Adriaanse B, Haak M, Bartelings M, Kolesnik A, Niszczota C, et al. How Normal is a 'Normal' Heart in Fetuses and Infants with Down Syndrome? Fetal Diagn Ther. 2016;39:13-20.

[40] Valkenburg AJ, Tibboel D, van Dijk M. Pain sensitivity of children with Down syndrome and their siblings: quantitative sensory testing versus parental reports. Dev Med Child Neurol. 2015;57:1049-55.

Tables

Table 1. Patient characteristics

	Total n=415	**cAVSD n=238**	**pAVSD n=177**	**p-value cAVSD vs. pAVSD**
Gender M/F	193/222	113/125	80/97	0,645
Isolated AVSD	165	35	130	< 0,001
Down Syndrome	253	206	47	< 0,001
Additional cardiac anomalies:				
PDA	126	111	15	< 0,001
ASD type II	104	74	30	0,001
VSD	41	2	39	< 0,001
PLSCV	27	16	11	0,836
ToF	18	17	1	0,001
CoA	10	5	5	0,634
BPV	9	7	2	0,107
BAV	4	2	2	0,765
AS	0	-	-	
SubAS	2	-	2	0,100
SupraAS	2	-	2	0,100
Mean age at repair (yrs)	3,03 ± 5,88	0,75 ± 1,37	6,11 ± 7,89	< 0,001
Early surgical era (1958-1995)	161	76	85	0,001
Late surgical era (1996 – 2013)	254	162	92	0,001
Double patch technique	229	221	8	< 0,001
Single patch technique	184	15	169	< 0,001
Unknown	2			

AS= Aortic stenosis, ASD= Atrial septal defect, BAV= Bicuspid aortic valve, BPV= Bicuspid pulmonary valve, cAVSD= Complete atrioventricular septal defect, CoA= Coarctation aortae, F= Female, M= Male, pAVSD= Partial atrioventricular septal defect, PDA= Patent ductus arteriosis, PLSVC= Persistent left superior vena cava, ToF= Tetralogy of Fallot, VSD= Ventricular septal defect, yrs.= Years

Table 2. Early and late post-operative arrhythmias

		cAVSD (n=23)		pAVSD (n=25)	
		DS (n=18)	**NS (n=5)**	**DS (n=3)**	**NS (n=22)**
Overall post-operative arrhythmias	**SVT (n=48)**	18	5	3	22
	VT/VF (n=6)	2	1	0	3
Early post-operative arrhythmias	**SVT (n=33)**	16 (88,9%)	4 (80%)	3 (100%)	10 (45,5%)
Late post-operative arrhythmias	**SVT (n=15)**	2 (11,1%)	1 (20%)	0 (0%)	12 (54,5%)

cAVSD= Complete atrioventricular septal defect, DS= Down syndrome, NS= Non-syndromic, pAVSD= Partial atrioventricular septal defect, SVT= Supraventricular tachycardia, VF= Ventricular fibrillation, VT= Ventricular tachycardia

Commented [RK1]: In response to R3Q4

Table 3. Pacemaker implantations after AVSD correction

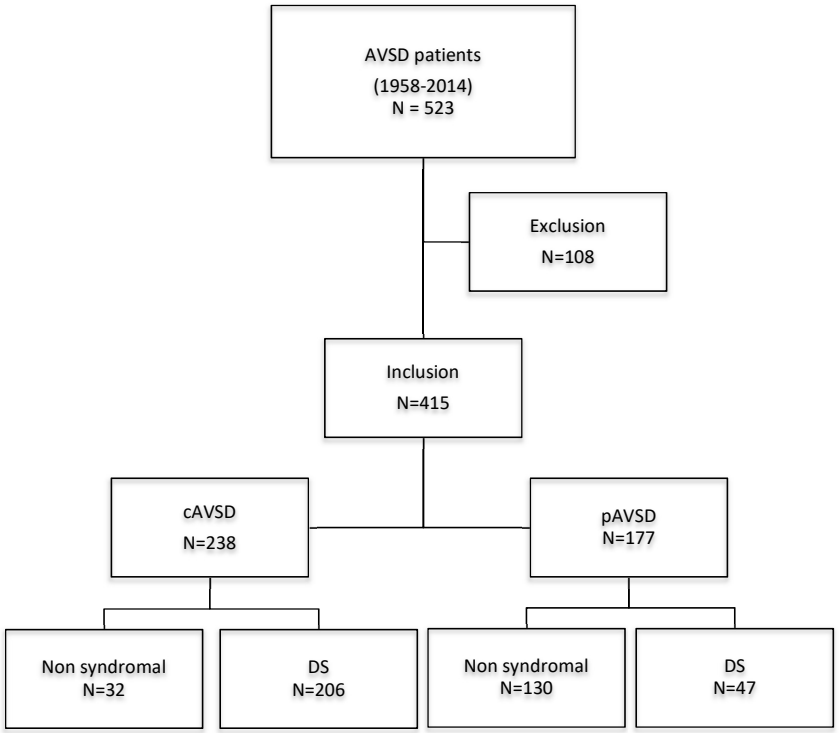
AVB= Atrioventricular block, cAVSD= Complete atrioventricular septal defect, DS= Down syndrome, F=

Gender	**Type of AVSD**	**DS**	**PM indication(s)**	**Re-operation (N=)**	**Time to PM implantation**
F	pAVSD	No	Complete AVB	Yes (3)	< 30 Days after re-operation
F	pAVSD	No	Complete AVB	No	5 Years after correction
M	pAVSD	No	AF with slow ventricle reponse	Yes (1)	20 Years after correction
F	cAVSD	Yes	SSS	No	19 Years after correction
M	pAVSD	No	2nd AVB Mobitz	No	26 Years after correction
M	pAVSD	No	2nd AVB Mobitz	No	1 Year after correction
M	pAVSD	No	Complete AVB	Yes (2)	< 30 Days after re-operation
F	cAVSD	No	Complete AVB	No	< 30 Days after correction
F	pAVSD	No	Complete AVB	Yes (2)	< 30 Days after re-operation
M	pAVSD	No	Complete AVB	Yes (5)	< 30 Days after re-operation
M	pAVSD	No	Complete AVB	Yes (2)	< 30 Days after correction
F	pAVSD	No	Complete AVB , 2nd AVB Mobitz, SSS	No	< 30 Days after correction
F	pAVSD	No	Brady-tachy syndrome	No	32 Years after correction
M	pAVSD	No	Complete AVB	Yes (4)	< 30 Days after correction
M	pAVSD	No	Brady-tachy syndrome	No	35 Years after correction

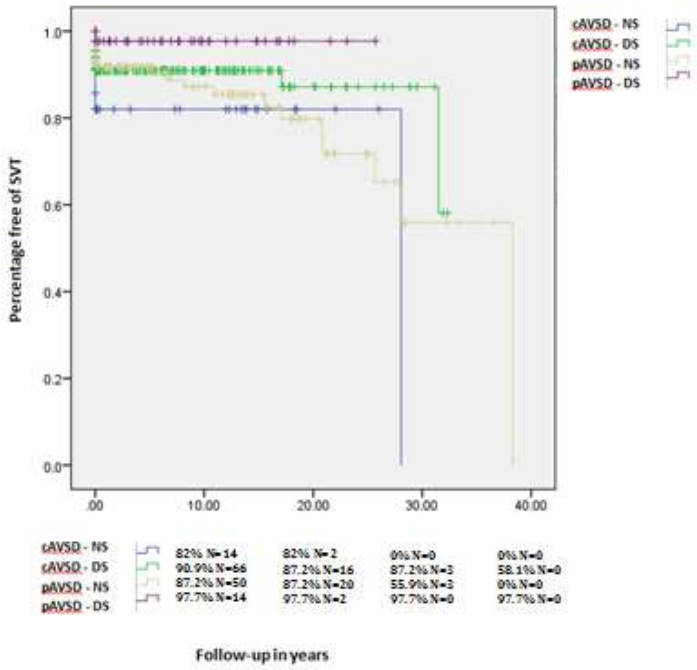
Female, M= Male, pAVSD= Partial atrioventricular septal defect, PM= Pacemaker, SSS= Sick sinus syndrome

Figures

Figure 1A + 1B Inclusion of patients and time free of SVT


AVSD patients
(1958-2014)
N = 523
Exclusion
N=108
Inclusion
N=415
cAVSD
N=238
pAVSD
N=177
Non syndromal
N=32
DS
N=206
Non syndromal
N=130
DS
N=47

1A Inclusion of patients



1B Time free of SVT in 4 different groups; cAVSD-DS (green), cAVSD-ND (blue), pAVSD-DS (purple) and pAVSD-ND (yellow). Percentage free of SVT and the remaining cases are provided above.
Significant less SVT occurred in the pAVSD-DS (p=0.017) and cAVSD-DS (p=0.011) group compared to cAVSD-ND group.

cAVSD= Complete atrioventricular septal defect, DS= Down syndrome, NS= Non-syndromic, pAVSD= Partial atrioventricular septal defect, SVT= Supraventricular tachycardie

Appendix 1

Supplemental data

Table 1 Type of syndrome and incidence of SVT/VT/VF/ PM-implantation

Type of syndrome	**N=**	**SVT**	**VT/VF**	**PM**
Non-sydromic	162	27	4	14
Down syndrome	253	21	2	1
Other syndromes:	13	4	2	1
22q11 deletion	1	1	-	-
3p deletion	1	-	-	-
Bardet-Biedl syndrome	1	-	1	-
CHARGE syndrome	2	1	-	1 (SSS/ 3rd degree AVB)
Ellis van Creveld syndrome	2	-	-	-
Mohr syndrome	1	-	-	-
Noonan syndrome	2	1	-	-
Unknown syndrome	3	1	1	-