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Chapter 1.2

Atrioventricular septal defect: from embryonic development to long-term follow-up

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* Equal contributions

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ABSTRACT

Atrioventricular septal defect (AVSD) covers a spectrum of heart anomalies with a common atrioventricular connection and has an incidence of 4–5.3 per 10,000 live births. About half of the AVSDs occur in patients with Down syndrome. This review provides a bench to bedside overview of AVSD. Developmental aspects, nomenclature, anatomy, and classification of AVSD are discussed. Furthermore, an overview of genetic and maternal risk factors for AVSD is provided, and available literature on (fetal) diagnosis, surgical techniques and follow-up is presented. Special attention is given to differences in developmental, anatomical and prognostic factors of AVSD between non-syndromic and Down syndrome patients.
INTRODUCTION

The term atrioventricular septal defect (AVSD) covers a spectrum of heart anomalies with a common atrioventricular (AV) junction [1]. With an incidence of 4–5.3 per 10,000 live births, AVSD comprises 7% of all congenital heart diseases (CHD) and is often associated with Down syndrome [2–5]. Despite intensive investigation, the morphogenesis of AVSD is still not fully understood. Furthermore controversy remains in nomenclature and long-term follow-up data are scarce. Recent developments in knowledge on heart development provide new insights in (epi)genetic factors in AVSD development.

The aim of the current review is to give a complete bench to bedside overview, from embryonic development to clinical aspects of AVSD. Special attention is given to the difference between non-syndromic and syndromic, in particular Down syndrome, patients.

NOMENCLATURE AND TYPES OF AVSD

An overview of nomenclature is presented in Figure 1. Controversies exist on nomenclature and subdivision of the varying morphology of AVSDs, and several different descriptions are currently used. The terms ‘atrioventricular canal defect’ and ‘endocardial cushion defect’ are used as synonyms for AVSD.

In this review we will use the classification as agreed upon by the International Paediatric and Congenital Cardiac Code (www.IPCCC.net) [6, 7]. Complete AVSD according to the IPCCC includes an ostium primum defect of the atrial septum and a non-restrictive defect in the inlet portion of the ventricular septum, with one AV annulus and a common AV valve. The common AV valve classically is composed of two (a superior and an inferior) leaflets bridging across the ventricular septum, as well as a left lateral (mural) leaflet, a right antero-superior and a right inferior leaflet (Figure 1). In complete AVSD shunting takes place at both the atrial and ventricular level. In an AVSD with an isolated atrial component (also known as ASD primum, ostium primum defect or partial AVSD) the bridging leaflets are attached to the ventricular septum. Although there is one annulus, the attachment of the bridging leaflets to the ventricular septum results in two orifices and shunting can take place only above this level, at the atrial level (Figure 1). Less common is an AVSD with an isolated ventricular component (also known as partial AVSD), where the partially fused bridging leaflets are attached to the atrial septum and shunting is just at the ventricular level. This type of AVSD is in the clinical setting mostly referred to an inlet VSD (Figure 1). Fourthly, the IPCCC defines an intermediate (or transitional) AVSD with an ostium primum defect and a (often restrictive) VSD just below the AV valves, but with two remaining separate AV orifices due to fusion of the bridging leaflets (Figure 1). Of note, some authors distinguish between a transitional AVSD, being an AVSD with two annuli and an inlet VSD and an intermediate AVSD,
being an AVSD with 1 annuli and 2 orifices [8]. This difference is not acknowledged by the IPCCC that equally classifies the 2 forms. We support the latter, as we do not consider AVSD to have 2 annuli, but rather a common annulus and a common AV valve that can have 2 orifices in case of attachment of the valve to either the ventricular (most common) or atrial septum. Fifth, the IPCCC describes an AVSD with ventricular imbalance, with an unequal position of the common AV valve above the (unbalanced) ventricles with a variable degree of ventricular hypoplasia. The imbalance may occur in the setting of either a complete, partial or intermediate/transitional AVSD.

Another defect at the level of the AV septum is the so-called Gerbode defect. This malformation is on the spectrum between an AVSD and a membranous VSD being a defect in the membranous part of the AV septum allowing shunting between the left ventricle (LV) and right atrium (RA). According to Gerbode [8] shunting can take place either directly (supra-annular) through the membranous septum or indirect (infra-annular) via a perimembranous VSD and a defect in the tricuspid valve. In the IPCCC the Gerbode defect is classified as a subtype of VSD [9], however as the defect is present in the AV septum one could also argue that the anomaly could be designated a form of AVSD.

The Rastelli classification, originally described in 1966 [10], subdivides complete AVSD based on the anatomy of the superior (anterior) common/bridging leaflet. A completely split leaflet (i.e., the superior bridging leaflet is divided), with the superior bridging leaflet almost completely adherent to the left ventricle and firmly attached on the ventricular septum by multiple chordal insertions is designated as Rastelli type A. Type A is the most frequently found [11]. A divided (split) superior leaflet, with the superior bridging leaflet attached over the ventricular septum by an anomalous papillary muscle of the right ventricle is designated Rastelli type B. Rastelli type C indicates a large, non-divided, superior leaflet without chordal attachment to the interventricular septum, also known as the ‘free floating’. Type C is often seen in association with other cardiac defects [12]. From classes A to C ventricular shunting increases. The Rastelli classification was originally designed to predict the outcome of surgery. However, due to the lack of correspondence between the classification and surgical outcome and enormous variability in leaflets [13,14], the use of the Rastelli classification is currently largely omitted in literature.

A mitral cleft in an otherwise normal mitral valve (isolated mitral cleft) should not be considered the same as the ‘cleft’ in the left part of the common AV valve in AVSD. An isolated cleft is a cleft in the aortic (anterior) mitral leaflet, whereas a ‘cleft’ in the setting of AVSD is a gap between the superior and inferior bridging leaflets, clearly distinguishing the anatomy of the left AV valve in AVSD from a normal mitral valve anatomy [15–17]. Although anatomically features are different from the cleft in AVSD, an isolated mitral cleft is frequently seen in families with AVSD and, like AVSD, is associated with Down syndrome [18], therefore a developmental relationship between an isolated mitral cleft and a cleft seen in AVSD has been suggested [18].

Distribution numbers of AVSD-types vary in the literature, which may be due to an inconsistent use of nomenclature. The majority (56%–75%) of AVSDs are complete AVSDs [2,4,19]. Subtype
distribution of AVSD differs between patients with and without chromosomal abnormalities, with complete AVSD more frequently seen in syndromic patients [4,5,20] (Table 1). Unbalanced AVSD occurs in 6%–10% of complete AVSDs [5,21,22] and is more frequently seen in non-syndromic patients (Table 1).

The spectrum of AVSD can thus range from partial AVSD to intermediate AVSD and complete AVSD. Abnormalities are also found in the membranous septum of relatives of patients with AVSD [23] and in patients with Down syndrome without AVSD [24,25], indicating that the AV septum may be abnormal without overt deficiency. Some authors have even suggested the occurrence of AVSD without shunting, i.e., an AVSD-valve morphology (common valve with linear insertion), where the common valve is attached to both the atrial and the ventricular septum [26]. The observed variability in anatomy may relate to the complex development of the AV septum and AV valves during embryology.

**Figure 1.** Schematic presentation of nomenclature of different types of AVSD.

The defect can occur at atrial, ventricular or atrioventricular level. Black arrows indicate the defects, but do not necessarily represent blood flow direction. RA = right atrium, LA = left atrium, RV = right ventricle, LV = left ventricle. In the complete AVSD the five leaflets are shown: superior bridging leaflet (1), left lateral (mural) leaflet (2), inferior bridging leaflet (3), right inferior leaflet (4) and right antero-superior leaflet (5).
Table 1. Studies that report differences between non-syndromic (NS) patients with AVSD and patients with AVSD and Down syndrome (DS) in incidence of type of AVSD, associated (cardiac and non-cardiac) defects and outcome. Ao = aorta, papill. = papillary, IVC = inferior vena cava, LAVR = left atrioventricular valve repair. * Indicates a study only in patients with complete AVSD.

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<tr>
<td></td>
<td>25%</td>
<td>3%</td>
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<tr>
<td></td>
<td>11%</td>
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<tr>
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EMBRYONIC AND FETAL DEVELOPMENT: (ABNORMAL) ATRIOVENTRICULAR SEPTATION

Normal development

Cardiac septation takes place in the first 9 weeks of pregnancy. The primary heart tube forms from a myocardial progenitor population from the splanchnic mesoderm. Additionally, a second pool from the splanchnic mesoderm, the so-called second heart field population, situated dorsal to the primary heart tube, will contribute cells to the arterial and venous side of the heart.
The heart tube initially consists of an inner endocardial layer and outer myocardial layer, separated by cardiac jelly. Cells from the endothelium migrate into this jelly mesenchyme, a process known as endothelial to mesenchymal transformation (EMT) [27]. As a result four endocardial cushions are formed at the AV junction: inferior, superior and two lateral cushions (purple in Figure 2A), that will contribute to the AV valves during later development. Besides endocardial cushion formation, AV septation requires growth of the muscular atrial septum primum toward the AV canal with on its lower rim a cushion-like structure, known as the mesenchymal cap (green in Figure 2A). Initially, the septum primum will not connect to the AV canal, leaving an opening, the ostium primum. Subsequently, the mesenchymal cap fuses with the superior and inferior AV endocardial cushions. To complete AV septation, the mentioned structures fuse with the so-called dorsal mesenchymal protrusion (DMP) or vestibular spine (yellow in Figure 2A), a mesenchymal (second heart field) protrusion at the base of the atrial septum [28,29] (Figure 2). During development the DMP will partly myocardialize, and a remnant of the DMP will form the tendon of Todaro, which is the continuation of the Eustachian valve of the inferior vena cava and the Thebesian valve of the coronary sinus [30].

Figure 2. Anatomical structures involved in normal and abnormal atrioventricular septation during development.

Panel A shows the three main structures involved in AV-septation: endocardial cushions (EC, light purple), mesenchymal cap (MC, green) and dorsal mesenchymal protrusion (DMP, yellow). Modified after Webb et al. [28]. Panel B shows an early stage (E10.5) embryonic heart, with a common AV canal, guarded by two endocardial cushions. In panels C and D (caudal section) the three structures are shown in a wild type 12.5 day old mouse embryo, where only a small ostium primum can be seen at this developmental stage. Panel E shows the situation after AV septation has been completed in human. The ostium primum had been closed. In the Pdgfr-α knock-out embryo the MC and DMP are less well formed as schematically shown in F. Panel G shows an early (E10.5) embryo and subsequent sections show a 13.5 day old Pdgfr-α−/− embryo (E-F) with a dotted circle showing the reduced volume of the MC, the * showing the atrial defect and the # the ventricular defect. In Panel J, a complete AVSD is shown. Developmental stages are given as days/weeks after conception. Right atrium (RA), LA = left atrium, RV = right ventricle, LV = left ventricle, RCV = right cardinal vein, LCV = left cardinal vein, PV = pulmonary vein, VS = ventricular septum, AS = atrial septum. Black bars in panels B–D and G–I indicate 200 um and in panels E and J 1 mm. Panel J is published with permission from Calkoen et al. [25].
The endocardial cushions, mesenchymal cap and DMP thus all contribute to the membranous septum. The membranous septum will eventually contain an atrioventricular part, situated between the left ventricle and right atrium and an interventricular part, situated between the left and right ventricles. Initially however, only the AV part is present, but with detachment of the tricuspid valve the interventricular membranous septum develops [31]. The superior and inferior endocardial cushions also contribute to the septal leaflet of the tricuspid valve, and the anterior (aortic) leaflet of the mitral valve [32]. The right lateral cushions will form the lateral (anterior and posterior) leaflets of the tricuspid valve and the left lateral cushion forms the lateral (posterior) leaflet of the mitral valve [32]. Next to cells derived from the endocardium, also epicardial derived cells contribute to the formation of the annulus fibrosis and the parietal leaflets of the mitral and tricuspid valves [33,34].

Abnormal development

Early studies on AVSD development with transgenic mouse models focused mainly on malformation of the endocardial cushions. Attention has shifted in the past decades to the DMP as well as the mesenchymal cap. Also abnormal looping may play a role. Several examples are listed below. The trisomy 16 (Ts16) mouse which is suggested to be a model for Down syndrome, develops, among other cardiac malformations, a complete AVSD. The pathogenesis of complete AVSD in the Ts16 mouse model is attributed to insufficient looping, fused but smaller endocardial cushions [35], as well as aberrant mesenchymal cap and DMP development [36].

Heterozygous mutations in the genes GATA4 [37] and NR2F2 [38] in mouse can result in partial (ASD1) or complete AVSDs, suggested to be caused by deficient endocardial cushion formation. Wnt [39], (SHF specific) Shh [40] and Pdgfr-a [41] knock-out mice all have a diminished DMP development leading to a partial or complete AVSD. In general, in mutant mouse studies little attention is addressed to difference in origin of partial, intermediate or complete AVSD. Also, the significance of knowledge of the “culprit” anatomical deficiency (i.e., due to a defect in either endocardial cushion, mesenchymal cap, DMP, or a combination) in terms of outcome/prognosis of the resulting AVSD, is currently unclear. In human embryos with AVSD no abnormal development of the endocardial cushions is described to date [42], whereas a diminished DMP development was observed in fetuses with Down syndrome and an AVSD [43]. In addition, abnormalities in fetal blood flow may affect septation and valve formation [44–46].

Abnormal AV septation may also affect formation of the AV conduction system. During normal development both an anterior and posterior node are present and a fusion of both nodes in order to form the definitive AV node was suggested [47]. A study in human embryos with Down syndrome showed that the posterior and anterior AV-node fail to fuse in AVSD and that the (posterior) AV node remains at a more posterior position in AVSD hearts comparable to normal hearts at earlier developmental stages [48].
ANATOMY OF THE AV VALVES AND CONDUCTION SYSTEM IN AVSD

It is important to realize that the leaflets, chordae and papillary muscles of the AV valves of all AVSD types, even after surgical correction, are different compared to the normal tricuspid and mitral valves [49]. Basically, in all types of AVSD, there is a common valve, in which the leaflets are to a variable extent fused with each other and/or with the atrial or ventricular septum. The posterior (lateral) leaflet of the normal mitral valve covers about 2/3 of the circumference of the valve, whereas the left posterior (lateral) leaflet in a corrected AVSD heart only covers 1/5. The right half of the inferior leaflet in AVSD is comparable with the normal posterior tricuspid leaflet. The size of the right anterior leaflets depends on the superior bridging leaflet. The different valve leaflet division causes a different position of the papillary muscles as compared to normal hearts, which can cause regurgitation or stenosis [50] and influences the direction of the inflow of blood into the LV [51].

Another feature that may contribute to valvular dysfunction later in life is dysplasia of the common AV valve, especially of the lateral leaflet [52]. Al-Hay et al. [53] reported marked differences in valve dysplasia in patients with Down syndrome (3%) versus non-syndromic patients (24%), although this was not confirmed by a recent study (nonsyndromic 10% and Down syndrome 13%) [54].

Right bundle branch block, first degree AV block and more rarely 2nd and 3rd degree AV block are all described in patients with AVSD even before surgical correction [55,56]. Several studies in human hearts have described the morphology and position of the cardiac conduction system in AVSD [50,57]. The AV node is positioned more posteriorly and inferiorly compared to the normal position in the triangle of Koch (Fig. 3). This aberrant position, especially when it is combined with a significant defect of the ventricular septum, necessitates the presence of a long non-branching (His) bundle, in order to reach the top of the ventricular septum [57]. Knowledge on the anatomy of the conduction system in AVSD contributes to reduction of surgically induced AV block [50].

SYNDROMES, GENES AND MATERNAL RISK FACTORS INVOLVED IN HUMAN AVSD

Several syndromes are associated with AVSD. In a recently studied large cohort, 49% of patients with an AVSD had Down syndrome [5]. In live born children with Down syndrome the incidence of AVSD is as high as 25% [58]. In patients with heterotaxia syndrome AVSD is often found; in right isomerism (or asplenia syndrome), the prevalence of complete AVSD is 90% [59]. In left isomerism (or polysplenia syndrome), the prevalence of partial AVSD is 60–70% [60], indicating that the morphogenesis of at least some cases of AVSD may be related to the loss of normal right/left asymmetry in the body. Genes involved in regulation of normal body asymmetry including PITX2, NODAL, ZIC3, CFC1, and NKX2.5 are also associated with AVSD. Other regularly encountered

The high incidence of Down syndrome in AVSD patients makes genes located on chromosome 21 suspect for involvement in the morphogenesis of AVSD. However not all patients with trisomy 21 develop an AVSD, suggesting a multigenic influence. The most frequently described associated gene in both patients with and without Down syndrome is CRELD1 on chromosome 3. The penetrance of AVSD in Down syndrome is incomplete; therefore CRELD1 is seen as a risk factor [64,65]. Interestingly CRELD+/- mice do not have septal defects. When they are however crossed onto the ‘Down syndrome mice’ Ts65Dn, they do develop septal defects [66].

Table 2 gives a summary of other reported humane genes associated with AVSD. Several syndromes associated with AVSD have mutations in genes related to Sonic Hedgehoc (SHH) [63]. SHH acts on the outflow tract formation via contribution of endocardial cushion cells as well as on AV septation via DMP contribution [40]. These studies all suggest that a single gene can contribute
to the arterial pole of the heart causing outflow tract defects and the venous pole of the heart (DMP), causing AVSD [67], which could also explain frequent co-occurrence of AVSD with for example tetralogy of Fallot. This may also relate to recent findings that genes involved in the VEGF-A pathway are not only associated with outflow tract defects, but also AVSD [64].

Table 2. Genes involved in human development of AVSD.

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<td>[64]</td>
<td>Endocardial cushions (Vegf path)[148]</td>
</tr>
<tr>
<td>FRZB</td>
<td>2</td>
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<td>DSCAM</td>
<td>21</td>
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<td>Cell-cell adhesion of cushion fibroblasts[150]</td>
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<td>CRELD1</td>
<td>3</td>
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<td>Left right asymmetry (Vegf path)</td>
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<td>GJA1/Cx43</td>
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<td>Left right asymmetry</td>
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<td>NR2F2/Coup-TFII</td>
<td>15</td>
<td>[38]</td>
<td>Endocardial cushion (EMT)</td>
</tr>
</tbody>
</table>
Besides genetic risk factors there are several maternal risk factors reported. In infants without Down syndrome a strong association between complete AVSD and maternal diabetes was found (odds ratio 21) [4]. Moreover, a recent study found an association between complete AVSD and pregestational diabetes, gestational diabetes and obesity (BMI N 30 kg/m²) [68]. In another study, correlation between heavy smoking and AVSD was seen [62], however this study did not correct for diabetes. These findings indicate that epigenetic and genetic factors are likely to contribute to the genesis of AVSD.

ASSOCIATED ANOMALIES

Non-syndromic AVSD patients often have associated cardiac anomalies [7,69]. In patients with chromosomal anomalies associated cardiac defects are rare (8%) [5,70], with the exception of tetralogy of Fallot cooccurring more often with AVSD in patients with Down syndrome than in non-syndromic patients [71] (Table 1). In patients with an AVSD the aorta is in a more anterior position, possibly due to improper wedging of the outflow tract during development. Moreover the ventricular septum is shorter in AVSD patients [72]. This together leads to a longer outlet than inlet part. The anterior position of the aorta can be seen on a chest x-ray or ventricular angiography and is described as a “gooseneck”. There is a correlation between different arrangements of the outflow tract and Rastelli subtypes [73]. The combination of the more anterior placed aorta and a narrow sub-aortic outflow tract [74] might lead to the most frequent associated cardiac anomalies: subaortic stenosis and coarctation of the aorta [5].

Taking syndromic and non-syndromic patients together, in 5% of patients with a complete AVSD a double outlet right ventricle (DORV) is seen [75]. Double orifices of the left AV valve and a single papillary muscle (i.e., parachute valve) are observed in AVSD patients in respectively 14% and 1% [76]. AVSD is commonly observed in heterotaxy syndrome, and can also occur concomitant with Ebstein’s anomaly, anomalous pulmonary venous return and transposition of the great arteries. 75% of patients with an AVSD have anomalies in other organs than the heart. Reported congenital anomalies occur in both non-syndromic and syndromic patients (Table 1) [5,20,22,64,70].

DIAGNOSIS

Prenatal diagnosis

In utero prevalence of AVSD has been reported as high as 18% of CHD affected individuals. The discrepancy with the prevalence in live births is possibly due to a high number of fetal demises and elective termination, most frequently in cases with aneuploidy [77]. AVSD can be detected with fetal echocardiography as early as 12 weeks of gestation specialized centers [78].
The detection rate in routine screening, using the four-chamber view, is, however, reported to be as low as 27% [79]. Recent data show, however, that detection rate as high as 67% for balanced AVSD and 93% for unbalanced AVSDs can be achieved in national organized screening programs, using distinct protocols and adequate training of the ultrasonographers [80]. To improve detection rate, additional tools as the atrial to ventricular ratio [81] and level of linear insertion [82] have been suggested. Recent reports from the United States and Europe report elective termination of pregnancy of respectively 32% [83] and 31% [5] of cases, however in these studies the incidence of Down syndrome and associated CHD in the terminated fetuses were not specifically reported. Heterotaxia, unbalanced ventricles and a syndrome other than Down syndrome were detected as negative prognostic factors for late survival when an AVSD was detected at 20 weeks' gestation [83]. When pregnancy is not terminated, fetuses with Down syndrome have a better survival compared with nonsyndromic fetuses [84]. As the incidence of associated cardiac anomalies, extra-cardiac abnormalities and aneuploidy (40%–50% Down syndrome) is high in AVSD patients, third level ultrasound and invasive testing should be offered, including array comparative genomic hybridization to detect the presence of copy number

**Figure 4.** Diagnosis of AVSD.

(A) Prenatal ultrasound with an oblique plane through the thorax at 12 weeks pregnancy. (B) Section of a complete AVSD heart of fertilization age 14 weeks stained with troponin I with black scale bar indicating 1 mm. (C) The common valve seen from the left ventricle in a specimen of a 13 week old AVSD heart. D and E) Echocardiography of a 5-week-old patient with a complete AVSD during diastole (D) and systole (E). (F) A specimen of an uncorrected partial AVSD (ASD1). RV = right ventricle, LV = left ventricle, A = atrium, RA = right atrium, LA = left atrium, Ao = Aorta, SBL = superior bridging leaflet, IBL = inferior bridging leaflet, ML = mural leaflet. Modified after Jansen et al. [78].
variations [85]. No studies are performed that investigate the advantage of prenatal diagnosis of AVSD above postnatal diagnosis on postnatal morbidity and mortality, but the association with other defects makes prenatal detection important to provide parents all necessary information to aid the decision to continue the pregnancy.

**Postnatal diagnosis.**

Clinical presentation depends on the type of AVSD with the associated level and degree of shunting. Mild central cyanosis can be present in the newborn due to bidirectional shunting because of the high pulmonary resistance at birth. Due to the left to right shunt at atrial and ventricular level in complete AVSD and, if present, the AVV regurgitation, the child will develop congestive heart failure and if uncorrected, eventually Eisenmenger’s syndrome [86]. Cases with a partial AVSD (ASD1) can remain asymptomatic for years. With physical examination the AVV regurgitation can be heard as a holosystolic murmur and the increased diastolic flow as a mid-diastolic rumble. On electrocardiography the posterior and inferior displacement of the conduction system results in a left and superior QRS axis. First degree AV block can be present due to enlargement of the right atrium, or displacement of the AV-node Also higher degree AV block including complete heart block can be observed. On chest x-ray ventricular enlargement and the “goose neck” appearance reflecting the more anterior position of the aorta can be detected. Echocardiography is the main diagnostic modality of AVSD and can assess the presence and size of atrial and ventricular shunting, AVV morphology and orientation, size of left and right ventricle, number and location of papillary muscles, left and right outflow tract obstruction, additional septal defects and associated anomalies [87].

Three-dimensional echocardiography can have additive value in surgical planning, because AVV and LVOT morphology can be assessed with more detail, as is reviewed by Kutty and Smallhorn [88]. Although intra-operative transoesophageal echocardiography is influenced by differences in hemodynamics during surgery and does not always correspond with post-operative echocardiography [89], it can decrease the incidence of re-operation due to left AVV regurgitation [90]. Small studies reported the use of MRI in pre-operative assessment of AVSD, to visualize morphology and quantify ventricular size pre-operatively [91]. Angiography is not suggested in clinical decisions making prior to AVSD correction [87].

**TREATMENT**

Before surgical repair digoxin, diuretics and angiotensin-converting enzyme inhibitors may be used to treat congestive heart failure and food supplements may be necessary to achieve weight gain [87,92].

Surgical repair of a complete AVSD was first described by Lillehei et al. [93] in 1955. Three techniques have been described (Figure 5) [87]: 1) the single-patch technique where one piece
of prosthetic material is used to close the atrial or ventricular shunt (Figure 5A), 2) the twopatch technique where one patch is used to close the VSD and one other patch used to close the ASD (Figure 5B), and 3) the modified single-patch technique in which the common valve is sutured to the ventricular septum and the ASD is closed with a patch (Figure 5C). Partial AVSDs are closed with the single-patch technique. Complete AVSDs are mostly closed with the double-patch technique. An intermediate AVSD can be closed by the double-patch technique or modified singlepatch. Recent studies report the modified single-patch technique for closure of a complete AVSD, with the benefit of a shorter cardiac pulmonary bypass and aortic cross-clamp time and low mortality and low incidence of left AVV (LAVV) regurgitation [94]. Choice of techniques varies from patient to patient and depends on the extent of the atrial and ventricular defects. In all three techniques besides insertion of a patch 1) the “cleft” of the left AVV is suture-closed, to prevent AVV regurgitation [95–97]; 2) the anterior and posterior right leaflets of the RAVV are approximated; and 3) the two left lateral commissures of the LAVV are approximated (Figure 5 lower planes). As AVSD can cooccur with tetralogy of Fallot and DORV, combined repair is often performed with desirable results [75]. Patients with an unbalanced AVSD, where a biventricular repair is not possible, are a high risk group [97]. Decisions to perform a univentricular repair can be made based on the so-called AV valve index, (i.e., the LAVV area/total AV valve area), with an index between 0.4 and 0.6 considered as a balanced AVSD [98].

Because morbidity of AVSD repair in small infants is low in the current era [99–101] and pulmonary vascular obstructive disease needs to be prevented [102], repair of complete AVSD currently is advised to be performed around 3 months of age [87]. However timing of surgery is influenced by many factors, as co-occurrence of other heart defects. Correction in children below 5 kg was suggested a risk factor for late LAVV regurgitation [99], however, correction at an age above 6 months has also been considered a risk factor for reoperation [103]. In studies including patients corrected after the year 2000, the mean age at correction of complete AVSD ranged between 3.6 months [19] and 7.2 months [7]. Patients with intermediate AVSD usually undergo surgery around 1 year of age [104]. Patients with partial AVSD (ASD1) without severe LAVV regurgitation, can be asymptomatic and controversy exists when repair is indicated and what the optimal age for repair of partial AVSD is. The median age of surgical correction reported in recent studies varied from 1.8 [104] to 7.9 years [105]. In a study by Minich et al. [104] surgical correction of partial AVSD before 4 years of age is associated with significant catch-up growth and less LAVV regurgitation [104], whereas Bowman et al. [105] report that older age at surgical correction results in less morbidity and mortality. The guidelines of the European Society of Cardiology (ESC) for Grown-up Congenital Heart Disease (GUCH) [106] recommend surgical correction of partial AVSD in case of significant overload of the RV (Class I, level of evidence C).
Figure 5. Different surgical techniques for correction of an AVSD.

Single patch correction (A), double patch correction (B) and modified single patch (C) where the valve is attached to the ventricular septum are shown. In all techniques closure of the so-called cleft in the left atrioventricular valve (LAVV) is performed (1) and often approximation of the septal parts of the right atrioventricular valve (RAVV) (2) and approximation of the 2 left lateral commissures of the LAVV (3) are performed. RA = right atrium, LA = left atrium, RV = right ventricle, LV = left ventricle.

Figure 6. 4D-Flow MRI with streamline visualization.

Disturbed inflow and regurgitation after AVSD correction. Compared to a control heart (A and B) in patients with a corrected AVSD eccentric regurgitation (arrow in C) can be seen and more laterally directed inflow (arrow in D). Streamlines with color coding representing velocity magnitude. RV = right ventricle, LV = left ventricle, RA = right atrium, LA = left atrium.
FOLLOW-UP

Early postoperative outcome

Early hospital mortality (thirty-day mortality) of biventricular AVSD correction has decreased in the last decades [107] and in current era (2000–2014) ranges between 0% [54,101,108,109] and 10.7% [110]. According to some studies early mortality is associated with a younger age at operation [56,95], whereas others report AVSD correction to be save at younger age [99–101]. Weight below 3.5 kg showed to be a risk factor for mortality [111]. Controversy in literature exists as to whether the presence of Down syndrome influences early postoperative outcome of AVSD correction (Table 1). On the one hand patients with Down syndrome have a higher incidence of pulmonary hypertension, pulmonary vascular obstructive disease and respiratory disease, which can complicate anesthesia. On the other hand extensive abnormalities of the AV valves, complex co-occurring cardiac anomalies (as in heterotaxia [20]), left ventricular outflow tract obstruction and right ventricular dominance are more frequently seen in patients with a normal karyotype [53,112,113]. While an early study suggested that patients with Down syndrome are of higher risk and should be treated differently [114], more recent studies do not show difference in early hospital mortality between Down syndrome and non-Down syndrome patients [53, 71,112,115–117] or even a lower in-hospital mortality and complication incidence in patients with Down syndrome [111] (Table 1).

Late follow-up

The overall 10 year survival after surgical AVSD correction also decreased in the last decades [107] ranging between and 70% [118] and 100% [108], largely dependent on era of surgery and complexity of the cardiac anatomy [20,118]. Surgery related postoperative arrhythmias, including complete heart block leading to pacemaker implantation (incidence ranging between 0.5% [19] an 7.5% [109]), are more frequently seen after repair of complete AVSD.

After correction of the AVSD, the need for reoperation ranges from 1.8% [119] to 28.9% [120] of all patients. In most cases reoperation is performed for the indication of LAVV regurgitation [53,121–123]. Other indications for reoperation are sub-aortic stenosis [122–124], a residual atrial septal- or ventricular septal defect [122,123], left ventricular out- flow tract obstruction [123] and right AVV regurgitation [122]. According to several studies patients with Down syndrome have a lower risk of reoperations compared to patients without Down syndrome (Table 1). This may be due to less LAVV abnormalities and less dysplastic mural leaflets [52,53] as compared to non-Down patients. LAVV regurgitation is equally found in patients with corrected partial and complete AVSD [95]. The guidelines of the ESC for adults (GUCH) [106] suggest surgical correction of moderate to severe LAVV regurgitation in symptomatic patients or asymptomatic patients with enlarged left ventricle and/or reduced EF% (Class I recommendation). Furthermore, surgical correction should be considered in asymptomatic patients with moderate to severe LAVV regurgitation who have signs of volume overload of the LV and a substrate of regurgitation
that is very likely to be amenable for surgical repair (Class 2a recommendation) [106]. However guidelines are based on level B and C evidence, as data from large randomized cohorts are lacking. Decision making for surgical correction is especially challenging due to the difficulty to quantify LAVV regurgitation reliably with echocardiography, which is due to presence of dynamic, eccentric regurgitation jets (Figure 6C). 4DFlow MRI enables characterization and more reliable quantification of these jets [125].

Rhodes et al. [126] report that after increase of LAVV regurgitation in the first 3 years after re-operation, regurgitation stays stable. The longterm effect of chronic regurgitation on exercise capacity, cardiac function and arrhythmias requires further investigation. Surgical correction of LAVV regurgitation can be performed by LAVV repair or LAVV replacement [127]. Survival is higher after valve repair than after replacement [121,128,129]. Furthermore, valve replacement has the disadvantage of the need for anti-coagulants, increased risk of infection and during pregnancy a higher risk of cardiac and neonatal complications [130]. In a study by Hoohenkerk et al. [121] a second re-operation (mostly replacement) in patients who underwent a LAVV repair was performed in 33%. The incidence of heart block after LAVV repair is reported as high as 37.5% [131]. Because of the occurrence of LAVV regurgitation, residual shunts, subaortic stenosis and arrhythmias the guidelines of the ESC for GUCH [106] suggest lifelong follow-up at least every 2–3 years in a GUCH center, although this does not seems to be general practice currently as low follow-up rates at out-patient clinics have been reported [132].

The majority of studies on AVSD follow-up focus on survival and reoperation, and little is known about systolic and diastolic function after AVSD correction. Takahashi et al. [133] extensively studied the LAVV, AV annuli and papillary muscles after AVSD correction using 3D echocardiography. They observed a larger annular area, more prolapse of the mural leaflet and a lateral displacement and angulation of the anterolateral papillary muscle in corrected AVSD patients with moderate regurgitation as compared to healthy control hearts. The abnormal valvular structure is a possible explanation of the lateral inflow direction in corrected AVSD patients (Fig. 6D) [51]. Whether the disturbed inflow direction leads to less efficient cardiac pumping remains to be investigated.

**Pregnancy**

According to the ESC GUCH guidelines closure of a significant partial AVSD before pregnancy should be considered. In patients with severe pulmonary hypertension pregnancy is contraindicated [106]. Patients with a corrected AVSD with AVV regurgitation who have no indication for surgery tolerate pregnancy well [106]. However in 17% of pregnancies of women with a corrected AVSD increase of the LAVV regurgitation is observed, in 23% deterioration of the NYHA class is observed and in 19% arrhythmias were recorded [134]. These cardiac complications were more frequently seen in patients after surgical correction of complete AVSD compared with patients after partial AVSD correction. Recurrence of AVSD in the offspring of mothers with an AVSD is reported to be 10%–12.5% [134,135].
AVSD is a spectrum of cardiac anomalies with a common AV junction with a variety in septal defect(s) and valve abnormalities, which can be divided in partial (atrial or ventricular shunt), intermediate and complete AVSD. More consistent use of nomenclature will improve communication between anatomists, (pediatric) cardiologists and surgeons and enable better comparison of studies. Recent studies concerning AVSD development focus on the role of abnormal DMP, endocardial cushions and mesenchymal cap with the atrial and ventricular septum. Whether the range of defects found is a result of a sliding scale in maldevelopment of the different structures involved in AV septation and/or of differences in which gene is disturbed, remains to be investigated.

Recent genetic studies suggest CRELD and genes in the VEGF-A and SHH pathway to be important culprit genes for AVSD development. Early detection rate of AVSD is increasing due to improvement of early fetal echocardiography. Although correction of AVSD in early life has a good prognosis, re-operation due to regurgitation of the LAVV is often required. Because indications for surgical re-operation are debatable, improvement of quantification techniques is necessary to measure complex regurgitation in corrected AVSD patients. Quantification of LAVV regurgitation is challenging with echocardiography, while velocity encoded MRI might allow for reliable quantification and can contribute to surgical decision making for correction of the LAVV regurgitation. The corrected LAVV differs from the normal mitral valve in many aspects, and this might not only result in regurgitation of the LAVV, but also in abnormal inflow. Future studies focusing on the impact of valve abnormalities on intra-cardiac flow patterns and efficiency will add to knowledge of pathophysiological mechanisms and may contribute to identification of prognostic factors for valve and chamber dysfunction. The disturbance of the cardiac conduction anatomy in AVSD patients is known, but future studies are required to report types of arrhythmia and conduction disorders and risk factors. Furthermore little is known about diastolic and systolic function as well as exercise capacity, long after AVSD correction. As pregnancy in corrected AVSD patients is related to cardiac complications and recurrence of congenital heart disease in offspring, careful follow-up during pregnancy is warranted.

Anatomy and associated cardiac defect are different between patients with Down syndrome and non-syndromic patients. Although, the current available literature is not consistent enough to consider Down syndrome a risk or protective factor for outcome, most recent studies suggest a better outcome in Down syndrome patients than nonsyndromic patients. Long-term follow-up will have to establish the impact of AVSD correction on cardiac function and the possible differences in outcome of AVSD repair in non-syndromic patients and patients with Down syndrome.
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