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LUND
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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Thoracic Surgery at Lund University to be publicly defended on the 16 of May at 09.00 in Segerfalk Salen, BMC, Lund

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Abstract

Background: Atrioventricular septal defect (AVSD) is a complex congenital heart malformation accounting for 7.4% of all cardiac malformations. There is a strong association between AVSD and Trisomy 21. If left untreated the malformation will lead to progressive heart failure, cyanosis, and premature death.

Aims: The aims of this thesis were: **I** to compare the accuracy of 2D and 3D echocardiography in assessing morphological and functional valve features, using surgical description as reference and, compare reasons for disagreement. **II.** to evaluate long-term outcomes after primary repair of complete AVSD and identify risk factors for long-term survival and reoperation. **III.** To evaluate the impact of concomitant complex cardiac anatomy in a cohort of nonsymdromic patients with complete AVSD and compare surgical outcomes. **IV.** To evaluate the total burden of reoperations after previous repair of AVSD including long-term survival and to identify risk factors for reoperation.

Methods and Results: 20 consecutive patients with AVSD were prospectively included in Study **I**. The accuracy in 2D was 79% and, in 3D 83%. 3D was significantly better in assessing Rastelli type and inferior leaflet into the right ventricle.The main reasons for disagreement were inability for the technique to visualize the feature. **II.** 304 consecutive patients underwent surgical correction for complete AVSD between 1993 to 2018. Outcome for 55 young infants (mean age 1.6±0.6 months) vs 249 older infants (mean age 5.1±5.2 months) were compared. Overall mortality was 1.0%. Overall survival at 20 years was 95.1%±1.3%) and freedom of LAVV related reoperation was 92.6%±1.7%). with no differences between young and older infants. **III.** Between 1993 and 2018 62 nonsyndromic patients underwent complete AVSD repair. 16/62 patients had concomitant complex cardiac anatomy. Survival was studied using Kaplan-Meier estimates and competing-risk analysis estimated the risk of reoperation with death as the competing event. Actuarial survival was 100% vs 66.7% at 10 years in noncomplex vs complex group (P<.01). No difference in reoperation rate was found (P=.30). Competing risk analysis showed no difference in reoperation between groups (P=.28). **IV.** All patients with surgical correction of AVSD underwent follow-up 2020. Of 477 patients who underwent initial repair, 53 patients (11.1%) underwent a total of 83 reoperations. Perioperative mortality at reoperation was 2/53 (3.8%) with no late deaths during follow-up. In patients requiring a LAVV-related reoperation, a re-repair was performed in 90% (26/29). Estimated overall survival was 96.2%±2.6% (95%CI 91.2–100) vs 96.7%±0.9% (95%CI 94.9-98.5) in the Any reoperation group vs the No reoperation group, respectively.

Conclusions: I: 2D and 3D had similar agreement rates but 3D was more accurate in assessing some features. Combining the 2 methods in clinical practice may increase accuracy.**II.**Our results support complete repair before 3 months of age, if clinically necessary, and avoid palliative measures. **III.** Nonsyndromic patients without complex cardiac lesions have good long-term outcomes, whereas nonsyndromic patients with concomitant complex cardiac anatomy still are a high risk population. **IV.** The risk of reoperation after repair of AVSD was low and not different from patients not needing a reoperation. A LAVV-related re-repair was possible in most cases with a good long-term durability

Key words Atrioventricular septal defect, Surgery, Echocardiography, Trisomy 21, Survival, Reoperation

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To my wonderful Birgitta, without whom I would be nothing

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This thesis is based on the following publications, which is referred to in the text by their Roman numerals (I-IV)

I Hakacova N, Higgins T, Malm T, Wierup P, Maynard C, **Ramgren Johansson J**

Comprehensive echocardiographic imaging of atrioventricular valves in children with atrioventricular septal defect: Accuracy of 2D and 3D imaging and reasons for disagreement

Anatol J Cardiol 2019;21:214-21

II **Ramgren JJ**, Nozohoor S, Zindovic I, Gustafsson R, Hakacova N, Sjögren J

Long-term outcome after early repair of complete atrioventricular septal defect in young infants

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III **Ramgren JJ**, Zindovic I, Nozohoor S, Gustafsson R, Hakacova N, Sjögren J

Impact of concomitant complex cardiac anatomy in nonsyndromic patients with complete atrioventricular septal defect

J Thorac Cardiovasc Surg 2022 Apr;163(4).1437-1444

IV **Ramgren JJ**, Nozohoor S, Zindovic I, Gustafsson R, Hakacova N, Sjögren J

Reoperations after repair for atrioventricular septal defects: >25 years experience at a single center

Semin Thorac Cardiovasc Surg 2022 Jun 20:S1043-0679(22)00140-x. DOI 10.1053/j.semvasc.2022.06.008 Online ahead of print

Populärvetenskaplig sammanfattning (Summary in Swedish)

Atrioventrikulär septumdefekt (AVSD) är ett medfött hjärtfel som drabbar hjärtats skiljeväggar och inflödesklaffar. Hjärtmissbildningen är relativt vanlig och utgör drygt 7% av alla medfödda hjärtfel. Den är anatomiskt uppdelad i tre varianter där den kompletta formen har hål nedtill mellan de båda förmaken och ett hål upptill i kammarskiljeväggen. Det finns en gemensam stor inflödesklaff till de båda kamrarna. I den partiella formen finns ett hål nedtill i förmaksskiljeväggen medan kammarskiljeväggen är intakt. Klaffen är gemensam men med öppningar till respektive kammare med en klyvning i det främre klaffseglet på vänster sida. I den intermediära formen finns ett kvarstående anatomiskt hål i kammarskiljeväggen som är helt eller delvis täckt av klaffmaterial. Det finns en nära association mellan AVSD och Trisomi 21, även kallat Downs syndrom (DS). Tre fjärdedelar av barnen som föds med den kompletta formen av AVSD har också DS medan knappt hälften av barnen som föds med DS har komplett AVSD. Vid de partiella och intermediära formerna av AVSD förekommer DS hos drygt 40% av barnen. Tidigare forskning har indikerat en mera komplex klaffmissbildning hos barn med normala kromosomer.

Efter födelsen utvecklas ett tilltagande blodflöde och kvarstående högt tryck till lungorna via hålen i förmaks- och kammarskiljeväggarna som kan leda till ökande hjärtsvikt och ökande läckage i den gemensamma AV-klaffen. Om hjärtfelet lämnas obehandlat utvecklas allvarlig hjärtsvikt, skador på lungkärlen och tills sist en förtidig död.

Behandlingen är kirurgisk operation med slutning av hålen i förmaks- och kammarväggarna och samtidigt en reparation och uppdelning av den gemensamma AV-klaffen till två fungerande klaffar. Tidigare forskning har talat för att optimal operationstidpunkt är vid 3–6 månaders ålder om det är kliniskt möjligt att vänta. Alternativen för barn som tidigt utvecklar svår hjärtsvikt trots full behandling är försök till avhjälpande behandling där man stryper lungpulsådern tillfälligt med ett band eller tidig korrektion av hjärtfelet. Sedan 1993 har vår strävan varit att undvika avhjälpande åtgärder och i stället reparera hjärtfelet tidigt, före 3 månaders ålder, hos dessa barn.

Inför operation är kartläggningen av hjärtfelet och den gemensamma AV-klaffen och dess funktion helt beroende av ultraljudsundersökning (Ekokardiografi).

Denna avhandling utgörs av fyra delarbeten vars syfte var; att undersöka träffsäkerheten av 2 dimensionell och 3 dimensionell ekokardiografi jämfört med intraoperativ kirurgisk bedömning, samt orsaker till oenighet mellan metoderna hos barn med AVSD; att undersöka långtidsresultaten efter korrektion av komplett AVSD och betydelsen av tidig operation före 3 månaders ålder vid svår hjärtsvikt;

att undersöka betydelsen av samtidiga komplexa hjärtmissbildningar hos barn med komplett AVSD och normala kromosomer; samt att undersöka långtidsresultaten efter reoperation efter tidigare korrektion av AVSD

I delarbete I undersöktes 20 patienter som genomgick planerad operation för olika typer av AVSD. Före operation utfördes tvådimensionell (2D) och tredimensionell (3D) ultraljudsundersökning av hjärtat och klaffapparaten. Under operationen noterades klaffkarakteristika av operatören som jämförelse. Delarbete II och III var retrospektiva undersökningar baserade på 304 patienter som opererats för komplett AVSD. I delarbete II jämförde vi långtidsöverlevnad och behov av reoperation hos barn som opererats före 3 månaders ålder med barn som opererats efter 3 månader ålder hos alla patienter. I delarbete III undersökte vi en subgrupp av 62 patienter med komplett AVSD och normala kromosomer för att utröna betydelsen av samtidiga andra komplexa hjärtfel avseende långtidsöverlevnad och reoperationsbehov. I delarbete IV genomfördes en retrospektiv undersökning baserad på 477 patienter som genomgått operation för AVSD. Vi jämförde långtidsöverlevnad hos barn som behövt reoperation med barn som inte behövt reoperation och analyserade långtidsrisken för både klafforsakad reoperation och alla typer av reoperation.

I delarbete I fann vi att 3D ekokardiografi bättre kunde visualisera några klaff funktioner än 2D. Tekniska begränsningar är den vanligaste orsaken till oenighet mellan metoderna. Bättre kunskap om specifika begränsningar hos metoderna talar för att kombinera de två metoderna i klinisk praxis.

I delarbete II kunde vi inte påvisa någon signifikant skillnad mellan barn som opererats före 3 månaders ålder jämfört med barn som opererats efter 3 månaders ålder avseende långtidsöverlevnad och behov av reoperation. Tidig och sen dödlighet var mycket låg liksom reoperationsbehovet.

I delarbete III visade vi att barn med komplett AVSD, normala kromosomer och avsaknad av samtidiga komplexa hjärtfel har mycket låg dödlighet och en risk för reoperation som är jämförbar med barn med komplett AVSD och trisomi 21 medan gruppen med samtidiga komplexa hjärtfel utgör en högriskgrupp för, framför allt, ökad dödlighet

I delarbete IV fann vi att reoperation var relativt vanligt men dödligheten var låg och långtidsöverlevnaden skilde sig inte statistiskt från de barn som inte behövt genomgå reoperation. Re-reoperation av den vänstersidiga AV-klaffen var vanligast och framgångsrik i hög utsträckning och med god hållbarhet. Reoperation av vänstersidig utflödes förträngning var näst vanligast och kan ibland vara en kirurgisk utmaning.

Sammanfattningsvis har vi visat att 2D och 3D ekokardiografi undersökning bör kombineras vid undersökning inför operation av AVSD. Tidig operation av barn med komplett AVSD och hjärtsvikt medför ingen ökad risk jämfört med operation

efter 3 månader. Barn med komplett AVSD, normala kromosomer och samtidiga komplexa andra hjärtmissbildningar är en högriskgrupp för ökad dödlighet efter operation. Långtidsöverlevnaden hos barn som genomgått reoperation efter reparation av AVSD är hög och skiljer sig inte statistiskt från barn som inte behövt reoperation.

Abbreviations

AVSD	Atrioventricular septal defect
cAVSD	Complete atrioventricular septal defect
pAVSD	Partial atrioventricular septal defect
tAVSD	Transitional atrioventricular septal defect
SB	Superior bridging leaflet
IB	Inferior bridging leaflet
LAVV	Left atrioventricular valve
DS	Down Syndrome
NS	Nonsyndromic
CHD	Congenital heart disease
PPHN	Pulmonary hypertension in the newborn
PAH	Pulmonary arterial hypertension
POVD	Pulmonary obstructive vascular disease
PVR	Pulmonary vascular resistance
RACHS-1	Risk adjustment for congenital heart surgery score
BDG	Bidirectional Glenn shunt
SP	Single patch
DP (2-P)	Double-Patch (2-Patch)
MSP	Modified single patch
VSD	Ventricular septal defect
LVOTO	Left ventricular outflow tract obstruction
uAVSD	Unbalanced atrioventricular septal defect
AVVI	Atrioventricular valve index
BVR	Biventricular repair
TOF	Tetralogy of Fallot
DORV	Double outlet right ventricle
RVOTO	Right ventricular outflow obstruction
SR	Staged repair
PR	Primary repair
IQR	Interquartile range
CI	Confidence interval
OR	Odds ratio
HR	Hazard ratio
DOLAVV	Double orifice LAVV
RAVV	Right atrioventricular valve
CHS	Congenital heart surgery

1 Introduction

1.1 Atrioventricular septal defect

1.1.1 What´s in a name?

Several terms have been used to describe a complex group of malformed hearts characterized by a deficiency of myocardial tissue at the aspect of atrioventricular junction. Embryologically based terms as “endocardial cushion defects” and “persistent common atrioventricular canal” have been frequently used over the years but found lacking in fully describing the malformation. Instead, a nonembryological term “Atrioventricular septal defect” was proposed by Becker and Anderson in 1982 (1). The pathognomonic features being a deficiency in the atrioventricular septum, with a common atrioventricular junction guarded by a common atrioventricular valve different from the normal heart. This was beautifully demonstrated by Anderson and Becker, working with heart specimens presenting with “partial”, “intermediate”, or “complete” forms of atrioventricular septal defect. After removing all valvular tissue from the atrioventricular junction, it was no longer possible to distinguish between individual hearts, one from another. All hearts showed a common atrioventricular junction completely different from the normal heart (2).

1.1.2 Atrioventricular septal defect (AVSD) with a common atrioventricular junction

Atrioventricular septal defect (AVSD) is a complex spectrum of malformations affecting the atrioventricular septum and the formation of the atrioventricular inlet valves with the basic characteristic being a common atrioventricular junction (1, 3, 4). The malformation is classified in complete, intermediate, and partial, forms. In the complete form (cAVSD) we find a common atrioventricular junction, a common atrioventricular valvar orifice, and a deficiency in the septal aspects of the atrioventricular junction allowing for shunting at both ventricular and atrial level. In the partial form (pAVSD) there is only shunting at the atrial level through an ostium primum defect, a common atrioventricular junction but with two separate valvar orifices. In the intermediate or transitional form (tAVSD) the anatomical

defect in the ventricular inlet septum has been partially or completely closed by reactive valvular tissue. A form exists with only a ventricular component of septal deficiency and upwardly displaced leaflets with ventricular shunting only. This very rare form seems to be at the mild end of the AVSD spectrum with less cardiac deformities.(5).

The common atrioventricular junction leads to an unwedging of the aorta that will be more anteriorly placed than with a normal atrioventricular junction. Consequently, the inlet-outlet proportions are altered with a longer outlet. This may lead to narrowing and elongation of the outflow tract to the aorta. The atrial septum may fail to meet the ventricular septum and thus create the atrioventricular septal defect with the ventricular septum having a scooped-out appearance (4).

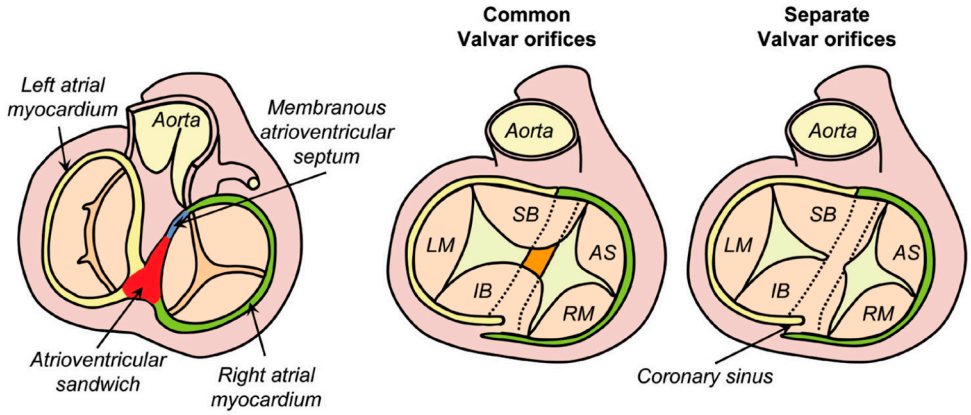

Figure 1.1 Diagram showing the normal atrioventricular junction (left) and the common atrioventricular junction with a common valvar orifice (middle) and 2 separate orifices (right). AS = anterosuperior, IB = inferior bridging, LM = left mural, SB = superior bridging, RM = right mural.
Reproduced with permission from Adachi, Uemura and Ho (Surgical anatomy of atrioventricular septal defect *Asian Cardiovasc Thorac Ann 2008;16:497-502*)

1.1.3 Characteristics of the common atrioventricular valve

The valve guarding the atrioventricular junction normally has 5 leaflets, two leaflets that bridge over the atrioventricular septal defect and are inserted and supported within the right and left ventricle, called superior bridging (SB) and inferior bridging (IB) leaflets. The left mural leaflet is solely related to the left ventricle guarding the left lateral aspect of the left atrioventricular valve. The space between the superior and inferior bridging leaflets constitutes a zone of apposition (ZoA) between the two bridging leaflets (3). Regardless of if there are one or two valvar orifices, the atrioventricular valve will keep its 5-leaflet configuration.

1.1.4 The Rastelli classification

In 1966 Giancarlo Rastelli, working as research associate at the Mayo clinic, reviewed 30 autopsy specimens of complete persisting common atrioventricular canal defects prompted by the various problems encountered in surgery. This led him to identify three specific types, related to the configuration and attachments of the superior bridging leaflet of the common atrioventricular valve (6). The Rastelli classification is based on the configuration of the superior bridging leaflet only in hearts with complete AVSD. Intermediate or partial forms of AVSD were not included in the initial study. In 20 of the 30 examined hearts, no or minor associated cardiac anomalies were found. In 10 hearts major associated cardiac anomalies were found.

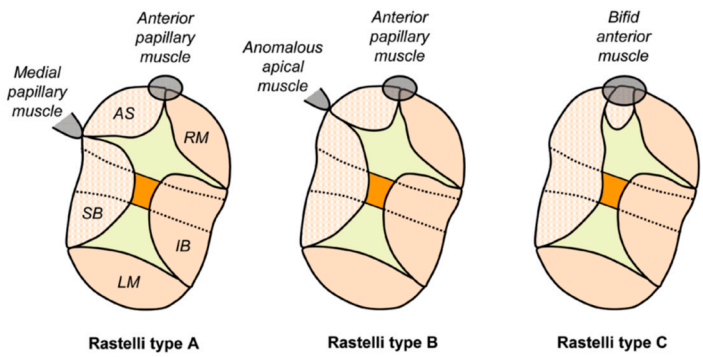

Figure 1.1
AS = anterosuperior, IB=inferior bridging, LM=left mural, SB=superior bridging, RM=right mural Reproduced with permission from Adachi and Uemura (4). (Surgical anatomy of atrioventricular septal defect *Asian Cardiovasc Thorac Ann 2008;16:497-502*)

Type A, divided superior bridging leaflet over septum with chordae to the septum (70%) **Type B**, divided superior bridging leaflet attached to anomalous papillary muscle close to the septum in the right ventricle (15%). **Type C**, undivided superior bridging leaflet unattached to the septum (15%).

90% of the 10 hearts with associated major cardiac anomalies were found to have type C anatomy of the superior bridging leaflet (6).

In angiocardiography studies, it was possible to show that in type A anatomy the left ventricular outflow tract had an elongated and narrowed appearance, that was not seen in types B and C. Interestingly, the angiographic appearance of the outflow tract in partial atrioventricular septal defect was similar to that of complete AVSD with type A anatomy (7).

Maybe the most important early consequence of the Rastelli classification was the finding that the most common Rastelli type A was the least likely to have major associated cardiac anomalies and had an anatomy well suited to the surgical

techniques that were developed at the Mayo clinic. Between 1964 to 1968 they could report a 3-fold reduction in mortality after corrective surgery (8).

1.1.5 Genetics in atrioventricular septal defect

Atrioventricular septal defect is relatively common congenital heart defect accounting for 7,4% of all cardiac malformations (9). Down Syndrome (DS) is the most common autosomal chromosome anomaly, with a birth prevalence of 1-2 per 1000 live births (10, 11). There is a well-known strong association between Complete AVSD and Down Syndrome (60-86%) (12) whereas the frequency of congenital heart disease (CHD) in children with Down Syndrome has been reported between 25-47,5% (11, 13). Partial AVSD has a lower association with Down syndrome 22.6% and 20.9% as reported by Buratto et al and Mery et al in 2 large, recent studies. (14, 15). Non-syndromic atrioventricular septal defect has a relatively low birth prevalence of 0,97-1.32 per 10000 live births. (9).

1.2 Echocardiographic visualization of the atrioventricular septal defect

1.2.1 Early experience with ultrasoundcardiography in Lund

Figure 1.2
Professor Nils-Rune Lundström 1928 – 2022. Paediatric cardiology, Children´s Hospital, Lund University. Reproduced by permission from G. Björkhem.

Inge Edler, working at the Medical Clinic in Lund and Helmuth Hertz from the department of Physics investigated the use of ultrasonic sound, to visualize the

movement of the heart walls, and published their results in 1954 (16). Working with cardiology in infants and children, Nils-Rune Lundström realized the advantages of a non-invasive method. At the first congress on Ultrasonic Diagnostics in Medicine in June 1969 in Vienna, Lundström and Edler presented their work on reflected ultrasound in the diagnosis of congenital heart disease(17). Several publications from the paediatric cardiology department in Lund, in the field of congenital heart disease and echocardiography, soon followed (18-21).

1.2.2 2D and 3D echocardiography and atrioventricular septal defect

The development of echocardiography, rendering 2D images of the cardiac structures in motion noninvasively, was a great technological innovation in the diagnosis of cardiac disease (22). However, in 2D echocardiography, the need of subjective geometric assumption limits accuracy and increase the variability, due to the complex nature of the AV-valve. To visualize all cardiac components and AV-valve features in AVSD still requires reconstruction of a virtual image in the mind of an experienced echocardiographer (23). 3D echocardiography has become an important tool for pre-surgical planning. In complex congenital heart disease (24) 3D "en face" projections of the atrioventricular common AV-valve viewed in "surgical view" can be helpful in visualizing anterior and inferior leaflets and their attachments to the crest of the septum. (25). However, 3D is still hampered by slower frame rates and lower image resolution (22). Gain settings during acquisition and postprocessing is important, especially in small children with thin valves, to reduce "noice" that may impede visualization, but at the same time to avoid "holes" or other artefacts from inadequate gain (24).

In most patients with AVSD the diagnosis can adequately be made by 2D echocardiography. For surgical planning, a combination of 2D and 3D echocardiography is optimal (22).

1.3 Surgical treatment of atrioventricular septal defect

1.3.1 Surgical methods

The first successful intracardiac repair of complete AVSD was performed by C. Walton Lillehei in 1955 under direct vision and controlled cross-circulation. (26). Despite early success, perioperative mortality was high. Since then, there has been significant improvement in early and late results and evolution of the surgical strategies (27-30).

The surgical aims are to close the atrial and ventricular septal defects and at the same time reconstruct the common atrioventricular valve into two separately functioning, competent valves. Over the years three surgical methods have evolved with somewhat different techniques how to reconstruct the atrioventricular valve and close the septal defects (31-33).

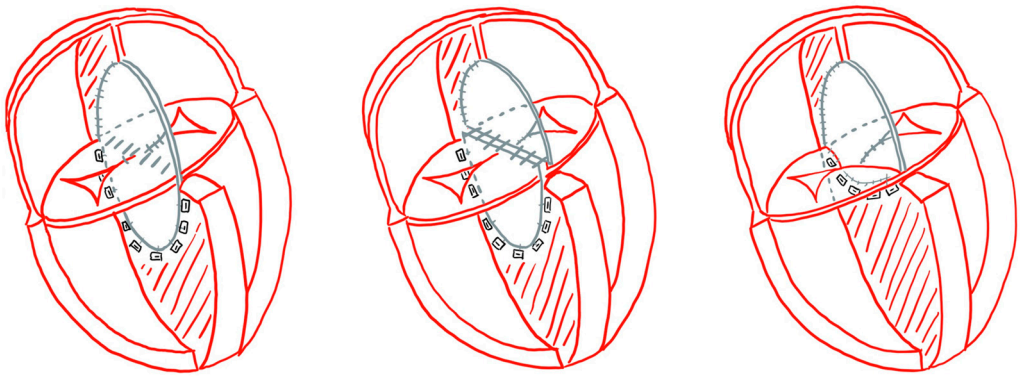

Figure 1.2
To the left is the **single-patch technique**, in the middle is the **double-patch technique**, and to the right is the **modified single patch technique** illustrated. Reproduced with courtesy from Nina Hakacova and Lea Christierson

1.3.2 Single Patch Technique

The repair technique was described by Maloney in 1962. The atrioventricular septal defect was closed by a single Dacron patch. The superior and inferior bridging leaflets are divided over the septum to accommodate the single patch which first sutured to the ventricular septum. The divided bridging leaflets are reattached to the patch with interrupted sutures (31) and atrial septal defect is closed with the same patch.

1.3.3 Double Patch Technique

The double-Patch technique was introduced by Trusler and Mills in 1975. The ventricular septal defect (VSD) was closed separately with a Dacron patch, sutures are placed through the upper end of the patch and then passed through the valve leaflets and through the lower edge of a pericardial patch which will close the atrial defect (32).

1.3.4 Modified Single Patch Technique

The modified single patch technique was reported, independently by Wilcox and Nunn, in 1997 and 1999 respectively. The ventricular septal defect was closed by

multiple interrupted pledgeted, direct sutures to the right side of septal crest, passed through the bridging leaflets and then passed through the lower edge of a pericardial patch used to close atrial defect (33-35).

1.3.5 Closing the Zone of Apposition

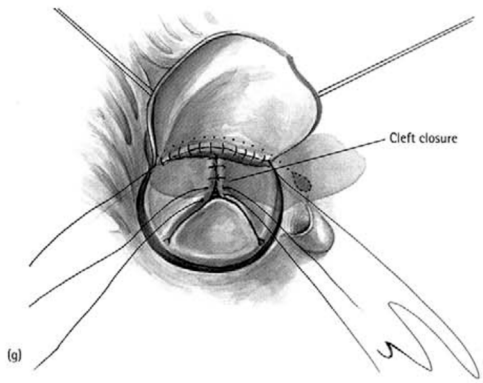

Figure 1.3
Closure of the Zone of Apposition by interrupted figure-of eight stiches. Reproduced from Jonas and Mora with permission from SAGE Publishing. (36).

The left common atrioventricular junction is guarded by a three-leaflet valve: the left anterior and inferior bridging leaflets and the left mural leaflet. The configuration of the left AV-valve is different from the normal mitral valve due to the unwedging of the aorta with a smaller mural leaflet. The area between the two bridging leaflets was initially thought of as a "cleft" but Piccoli et al could show in anatomical studies 1979 that the cleft was a true commissure and closing it would not produce a normal mitral valve. (37). The three-leaflet concept was introduced, and non-closure of the cleft was advocated by Alain Carpentier (38) in 1983. Anderson and co-workers introduced the concept of a common atrioventricular valve and the area between the anterior and inferior bridging leaflet being the Zone of Apposition (ZoA) with morphological features that different from an isolated mitral cleft (1, 39). However, over time the need to address the ZoA at surgery to avoid severe regurgitation of the left AV valve became evident. Wetter et al published in 2000 their results of 159 patients operated with repair of complete AVSD with two-patch technique. Their institutional policy was initially the trileaflet technique leaving the ZoA open, which was then changed to a bileaflet repair and closure of the Zoa. This gave them the opportunity to compare the outcomes of two groups with different surgical approaches. 63 patients with the ZoA left open to 96

patients who had closure of the ZoA at surgery. They could show highly significant improvements in long term survival and freedom from reoperation in patients who had ZoA closure (40). Today closure of the ZoA, if anatomically possible, is recommended in most centres. (12, 41-43). However, Buratto and coworkers from Royal Children´s Hospital in Melbourne have challenged this dogma in a recent article published in 2022 (44). In a large series of 455 patients who were repaired for cAVSD between 1990 to 2019 were reviewed to determine the effect of cleft closure. Of the 6 surgeons performing more than 25 cAVSD repairs over the study period, 4 surgeons routinely closed the cleft while 2 surgeons preferentially left the cleft open. During surgery manoeuvres were made to create a large coaptation area in the cleft. No difference in rate of left atrioventricular valve (LAVV) reoperation by surgeon was found. They found no significant difference in freedom from reoperation at 10 years (86.8% in the cleft open group vs 80.2% in the cleft closure group). Overall survival at 10 years was 91.2% with no significant difference in estimated long-term survival. However, there was a significantly higher rate of preoperative moderate or greater LAVV regurgitation in the cleft closure group, while, in the cleft open group, they found that a deficient lateral (mural) leaflet was more common, indicating a higher risk of valve stenosis if the cleft would have been closed. In 25 patients a second bypass run was needed, unfortunately data regarding their findings is omitted. Propensity score matching created 106 well-matched pairs divided in two groups, “cleft closed” and “cleft open”. In the matched groups there was no significant difference in survival (*P*=.71), freedom from reoperation (*P*=.26), or freedom from LAVV reoperation (*P*=.13). Reoperation rates for LAVVR remain high, >25% at 20 years (45).

How to manage the zone of apposition still must be said to be scientifically unclear, even though closure of the ZoA, if possible, is preferred in most centres (12, 29, 40-43, 46).

1.3.6 Down Syndrome and pulmonary hypertension in complete AVSD – Timing of surgery

Infants and children with DS develop pulmonary hypertension with a prevalence of 28% (47). It may result from CHD, developmental lung disease as well as airway obstruction. Pulmonary hypertension in the newborn (PPHN) is a common diagnosis that can persist beyond the neonatal period (48). Patients with complete AVSD develop symptoms in infancy with heart failure or failure to thrive with unrestricted pulmonary blood flow, and high pulmonary arterial pressure. Patients with DS have a higher risk of developing persistent pulmonary arterial hypertension (PAH). Early work by Clapp and co-workers showed that persistent pulmonary hypertension and pulmonary obstructive vascular disease (POVD) can develop already in the first year in children with DS. (49). Yamaki and associates reported a more severe form of pulmonary vascular disease in cAVSD and DS (50). A

significantly higher pulmonary vascular resistance (PVR) in DS was found by Rizzoli et al. However, they could show that the increased operative risk was related to higher pulmonary vascular resistance as well as incremental risk factors as a common AV-valve, operative age, and LAVV incompetence. Down syndrome was not an early or late risk factor of mortality (early *P*=.71 and late *P*=.87). The reoperation rate for valvular incompetence were higher in patients without Down syndrome, 9.5% (12/127) vs 4.3% (4/94) (*P*=.07). The authors conclude that babies with Down syndrome are at risk of having the most severe form atrioventricular canal defect, *i.e.,* cAVSD, but probably are more favourable for repair with a lower incidence of reoperation for LAVV regurgitation. Earlier surgical correction is warranted to neutralize the risk of pulmonary vascular obstructive disease (51). Today, early correction, before 6 months of age, preferably 3 to 4 months, is advocated by most centres, to prevent irreversible pulmonary vascular disease (12, 46).

1.3.7 Protective effect of Down Syndrome in surgical repair of atrioventricular septal defect

Life expectancy for children with DS have increased to 60 years in the current era. However still mortality in infants with DS is 5 to 8 times higher than in children without DS. This is thought to be related to a higher incidence of CHD in children with DS. Evans and co-workers (52) have studied a large population-based study of more than 50000 children that were operated for congenital heart defects. Patients were risk stratified according to the risk adjustment for congenital heart surgery score (RACHS-1). 4231(8.2%) patients had DS. Children with DS were found to be more likely to survive to hospital discharge than children without DS. Multivariate logistic regression showed lower odds of death with an odds ratio = 0.60 CI95% 0.47-0.76, thus showing a protective effect of DS on in-hospital mortality. In contrast, DS patients have a higher incidence of airway obstruction, risk of prolonged intubation time as well as increased pulmonary vascular reactivity. As expected, they found a significantly higher in-hospital mortality in DS patients with shunt dependant pulmonary circulation or single ventricle palliation with bidirectional Glenn shunt (BDG) (52). A protective effect on hospital mortality of DS was also found by Dhillon et al (13). DS patients had a lower mortality after AVSD repair than nonsyndromic (NS) patients, but a higher mortality after operations of BDG and Tetralogy of Fallot/Pulmonary atresia (TOF/PA). Over time there was a trend towards lower mortality in NS patients reaching the mortality rate of DS patients. Other authors could not confirm a protective effect on actuarial survival but could show a protective effect on freedom of reoperation in DS patients (42, 43). This might be due to a lower incidence of complex valve anatomy such as double orifice, single papillary muscle and dysplastic LAVV as well as right ventricular dominance and left-sided obstructions in DS. (12). Formigari and

coworkers included in their study of 206 patients, not only cAVSD patients suitable for biventricular repair, but also patients eligible for initial palliative procedures including Norwood palliation (53). Unbalanced ventricles were the only independent risk factor regarding survival at multivariate analysis. Patients with unbalanced ventricles were significantly more frequent in NS patients. NS patients also had higher prevalence of pulmonary banding and cumulative mortality after palliative procedures was higher after surgical palliation. Freedom from reoperation after biventricular repair or definitive univentricular palliation was significantly lower in NS patients, (HR 0.28 CI95% 0.08-0.80). The authors concludes that DS is a protective factor in all cardiac surgical procedures, including complex palliative procedures in patients with cAVSD.

1.3.8 Long-term outcomes after repair of complete atrioventricular septal defect

Survival for patients with complete AVSD has significantly improved over the decades since the early 1970s (29, 54, 55). In a large, population-based study from Sweden (54) 801 children with AVSD were identified. Of these, 502 patients with isolated complete AVSD were included, between 1973 and 1997, in the study. The prevalence of atrioventricular septal defect was 0.31 per 1000 live born. The prevalence of Down syndrome in Sweden over the same time period was 1.29 per 1000 liveborn. The rate of operations increased from 39% in 1973-77 to 97% in 1993-97. The mean age at operation in patients with DS decreased from 39.9 months in the early period to 4.2 months in 1993-97 ($P<.0001$), while in children with normal karyotype it decreased from 19.2 months to 7.6 months ($P<.05$) Early postoperative mortality decreased, during the same time periods, from 28.1% to 1%. ($P<.0001$). The cumulative 5-year postoperative mortality decreased from 35.5% in 1973-77 to 8,5% in 1993-97 ($P<.005$). The cumulative postoperative mortality for all isolated cAVSD at the endpoint of the study 2001 was 27.5%. There was no significant difference in cumulative mortality between patients with DS and nonsyndromic patients ($P=.4$).

Ginde and coworkers (55) investigated a total of 198 patients who underwent complete surgical repair for isolated cAVSD between 1974 and 2000. Surgery was performed with classic 1-patch or the 2-patch technique, along with closure of the cleft. Mean age at time of repair was 1.36 ±1.9 years with a median of 8.1 months. The mean age decreased from 1.96 years in the early era (1974-1990) to 9.9 months in the late era (1991-2000). Early operative death was defined as 30-day mortality or before hospital discharge, resulting in an overall early mortality of 10.1%. The early mortality decreased from 18,2% to 2.9% in the late era. There were 15 late deaths, giving an estimated overall survival of 85% and 82% at 10 and 20 years, respectively. By multivariable analysis, only the need for reoperation was a significant risk factor for late mortality. Early era had a trend towards statistical

significance (*P*=.07). A total of 26 patients needed reoperation, whereof 6 patients required an early reoperation. The overall estimated freedom from reoperation was 88%, 83% and 78% at 10, 20 and 30 years, respectively. By multivariable analysis classic 1-patch technique was a significant risk factor for reoperation (HR 3.71; 95%CI 1.56-8.78). No risk factors for LAVVR or LVOTO were found.

In a large, population-based, single center study from Finland, (29) 388 consecutive patients with repair of cAVSD between 1962 and 2014 were analysed regarding mortality and reoperation rates on a decade-by-decade basis. 73.3% had DS. Associated cardiac anomalies included VSD (3.4%), Coarctation of the aorta (3.9%), PDA (17.5%) DORV (0,5%), Pulmonary valve stenosis (82.3%), TAPVR (0.3%) and TOF (3.9%). The 2-patch technique was used since 1980s. There were 42 operative deaths and 25 late deaths. Actuarial survival for all patients (n=388) was 85.8% (±1.8%), 84.3% (±1.9%) and 82.8% (±2.0%) in 1 year, 5 years and 15 years, respectively. Comparing actuarial survival by decade of operation using the Kaplan-Meier method showed a statistically significant decrease in mortality every decade (*P*<.001). A total of 23 late deaths occurred during follow-up and no significant differences were found between decades. 29 patients underwent 31 LAVV-related reoperations. In addition, 15 patients underwent 15 other reoperations. Actuarial freedom of LAVV-related reoperation was 94.8% (±1.2%), at 1 year, 92.9% (±1.4%) at 5 years and 90.9% (±1.6%) at 15 years with no significant difference in reoperation rates through the decades (*P*=.621). Only later decade of operation was a statistically significant protective factor against reoperation and death with a per-decade OR of 0.52 (95%CI 0.39-0.68, *P*<.001)

1.3.9 Double patch versus modified single patch – Is there a superior technique?

In the current surgical era, the double patch (DP) and the modified single patch (MSP) has become the most used techniques for cAVSD repair. The use of two separate patches enables closure of the atrioventricular septal defect without dividing the bridging leaflets and became the most utilized repair technique in repair of cAVSD (12, 42, 43, 56). The modified single patch technique was popularized by G Nunn (35). There is no need for a VSD patch nor division of the bridging leaflets. The VSD is closed by direct suturing of the valve down to the right side of the septal crest using interrupted sutures. The atrial septal defect is closed by an autologous pericardial patch. There has been concerns regarding obstruction of the left ventricular outflow tract (LVOTO), especially when the VSD is large, as well as the long-term patency of the LAVV. Therefore, the method was used selectively but soon Nunn and colleagues started to apply the technique to all patients with cAVSD. They showed significantly shorter cardiopulmonary bypass and aortic cross clamp times compared to DP repair. Initial results reported by Backer et al indicated a lower incidence of late reoperation and a lower rate of heart block

compared to DP (57). Fong and associates have evaluated the long-term outcomes of MSP compared to DP in several publications (58-62). In a collaboration between all four congenital heart surgery centres, they have reviewed their results of biventricular repair of cAVSD in Australia from 1990 to 2015. A total of 819 patients were operated, 252 patients were operated with MSP and 567 patients with DP. Propensity score matching rendered 223 matched pairs. Primary study endpoints were long-term survival and freedom from reoperation after initial cAVSD repair. There was no significant difference in unmatched or matched cohorts in early mortality (MSP vs DP); 2.4% vs 2.8% and 3.1% vs 2.2%. Event free survival at 15 years was 76% and 74% respectively. They found no significant difference between repair techniques in reoperation for LAVV regurgitation or left ventricular outflow tract obstruction or need for permanent pacemaker. Data showed that residual LAVV regurgitation still was a problem with around 10% of patients who need a LAAV related reoperation. In another study by Fong and coworkers, investigating a cohort of 829 patients after repair of cAVSD (61), they found that Moderate left atrioventricular valve regurgitation predicts reoperation and pulmonary artery band (PAB) predicts long term mortality whereas age<3 months and weight <3kg were not associated with increased risks of mortality or reoperation. This indicates that PAB should be avoided in favour of early repair. DS was found to be protective against reoperation.

In a commentary: “This case is closed” in JTCVS 2020, Carl L Backer concluded that both surgical techniques can yield excellent long-term results. (63). However, long-term data after the MSP repair technique still is lacking compared to the more extensively studied DP repair. Reoperation rates were relatively high, around 16% in the study, although no difference was found between repair techniques. Early data from Nunn and colleagues(35) indicated initially no need of LVOTO reoperation after MSP repair but Fong and colleagues (60), in 2020 found similar rates of LVOTO reoperation in the two techniques. Therefore, further investigations are still warranted before “the case can be closed”.

1.3.10 Unbalanced atrioventricular septal defect

Of all children born with complete AVSD, 7-10% (64) have an unbalanced AVSD (uAVSD), with anatomically related features of ventricular hypoplasia and malalignment of the atrioventricular junction over the two ventricles. Malalignment and ventricular hypoplasia can be toward the left or the right side with right- or left-sided dominance. (R-uAVSD, L-uAVSD) The malalignment of the atrioventricular junction may lead to an abnormal inflow pattern directed mostly to the larger ventricle and further preclude a biventricular repair (BVR). In right-sided dominance, complex left sided AV-valve anatomy (65), and left ventricular outflow obstruction as well as distal aortic arch hypoplasia and coarctation are common. (66). uAVSD is commonly associated with heterotaxy syndrome.

L-uAVSD is much less common with few reports in the literature. Severe right ventricle and right-sided AV valve hypoplasia and malalignment restricting inflow to the right ventricle have an outcome similar to tricuspid atresia and a single ventricle palliation. In less severe forms of L-uAVSD a biventricular repair can be achieved with a one and half ventricle repair with a bidirectional Glenn shunt. To help maintain cardiac output in biventricular repair leaving an atrial septal defect helps maintaining cardiac output (67).

Surgical options in uAVSD

In severe R-uAVSD with hypoplastic left ventricle/left AV-valve and large VSD, a single ventricle palliation is uniformly advocated. (64, 67). In milder forms of unbalance a biventricular repair may be an option. However, diagnostic tools to guide surgical decision making has been lacking. To standardize the degree of observed AV junction malalignment the atrioventricular valve index (AVVI) was introduced by Cohen and co-workers (67). Echocardiographic measurement of the left and right AV valve areas is made and the AVVI is calculated by dividing the smaller valve area with the larger valve area. All balanced AVSD had AVVI higher than 0.67. An AVVI < 0.30 precludes biventricular repair. The new modified AVVI, calculated by dividing the left AV valve area with the total AV valve area was proposed by Baffa et al in 2008. (68). The Unbalanced AVSD Working Group of the Congenital Heart Surgeons Society (CHSS) (69) collected data from 356 patients seen at four CHSS centres, from January 2000 to December 2006. Modified AVVI was used, and patients were classified as unbalanced if AVVI≤0.4 (Right dominant) or ≥0.6 (left dominant). Most patients had a balanced AVSD with 0.4<AVVI<0.6 and underwent BVR. They could identify a range of mAVVI (0.19-0.39) where surgical strategies vary and a disproportionate increase in mortality. AVVI effectively characterize transition towards unbalanced AVSD which correlate to anatomic substrate and help select surgical strategy (69). Arunamata and collegues found, in a cohort of 46 patients with right dominant uAVSD, that the RV/LV inflow angle, measured on echocardiography, in systole, was found significantly smaller in patients undergoing single ventricle palliation. An inflow angle of ≤ 114° and an AVVI of ≤ 0.70 measured as the ratio of the left atrioventricular valve area divided by the right atrioventricular area, yielded a sensitivity of 100% and 88%, respectively, for single ventricle palliation (70). Managing unbalanced AVSD remains one of the biggest challenges in paediatric cardiac surgery. Reproducible echocardiographic measurements may help support biventricular repair in selected patients.

1.3.11 Surgical repair of complete atrioventricular septal defect with Tetralogy of Fallot

Complete AVSD can be associated with complex cardiac malformations such as Tetralogy of Fallot (TOF) and double outlet right ventricle (DORV)(71, 72).

Complete AVSD with TOF is a rare malformation found in 5% to 10% of patients with complete AVSD. In 1.7% of patients scheduled for surgical repair of TOF, concomitant cAVSD was found(73).

Staged repair (SR) versus Primary repair (PR)

cAVSD-TOF is a surgically challenging malformation. The combined lesion constitutes less than 1% of all congenital lesions. Down syndrome is common in patients with cAVSD-TOF, 60% to 80%. (72, 74-76). The anatomic features are, comparable to isolated complete AVSD, but the deficiency in the interventricular septum reaches anteriorly and upward, below the aorta, with a varying degree of override of the aortic valve. An aortic override of less than 50% constitutes TOF while an override of more than 50% constitutes DORV of Fallot type. DORV with origin of both great arteries from the morphological right ventricle with a muscular subaortic infundibulum is a rare entity separated from tetralogy of Fallot (77). The anterior bridging leaflet is significantly bridging the septum, typically, without chordal attachments to the septum (Rastelli type C). The Rastelli type C anatomy was found by Shuhaiber et al in 56 of 61 patients operated for cAVSD-TOF (72). Ong and collegues describe detaching the anterior and superior bridging leaflets which facilitates closure of the subaortic extension of ventricular septal defect without LVOTO (71). Right ventricular outflow obstruction (RVOTO) may be present to varying degree as in isolated TOF, combined with annular hypoplasia and pulmonary valvular stenosis or even pulmonary atresia. The typical goose-neck deformity of left ventricular outflow tract rarely cause significant obstruction in cAVSD-TOF.(78).

Surgical options

The development of progressive cyanosis and/or cyanotic spells are the most common indications for intervention in these patients. Implantation of a shunt will alleviate the cyanosis but may lead to hyper perfusion and increased left ventricular end diastolic volume and increased atrioventricular valve insufficiency (79, 80).

Vitanova et al used SR in patients with cyanosis (<80%), very young age, or low weight who required urgent operation. (75). 22 patients had SR vs 25 patients with PR. SR patients were younger and had more frequently cyanosis than patients having PR. There was no significant difference after repair, regarding 10-year survival and no risk factors for death could be identified. There was no significant difference in 10-year freedom of reoperation for atrioventricular valve regurgitation. At least moderate LAVV regurgitation was the only risk factor for reoperation

(p=0.01). The authors concluded that staged repair was not inferior to primary repair regarding mortality or reoperation rate. Critically ill or small infants with severe cyanosis should be considered for staged repair. (75).

In a large series of patients with cAVSD-TOF, including 61 patients over a period of 29 years (72). Trisomy 21 was present in 80% of patients. The surgical approach evolved from palliation with a systemic-to-pulmonary shunt to primary anatomic repair. 36 patients had primary repair of both lesions at a median age of 9 months (1 month to 16 years). Age at definitive repair for all patients was 1,2 years (0 – 36.9 years). Surgical correction included cAVSD repair with single- or double-patch technique with closure of the zone of apposition if possible. Infundibular resection of RVOTO was mainly done through an infundibular incision and the valve was measured with hegar dilators. Transannular repair was performed if the pulmonary valve diameter was less than -2 Z score. In 8 patients, a transatrial and transpulmonary approach was used, 4 patients required homograft conduit implantation. Overall early mortality was 7% with an estimated 5-year survival after definitive repair of 82% Overall 30% of survivors needed reoperation. Estimated freedom from reoperation at 5 years was 80%. In patients, receiving a valved conduit, time to reoperation was significantly shorter. Brancaccio and collegues have shown that type of RVOTO relief nor choice to use a RV-to PA conduit influence survival. (81). However, avoiding a valved conduit had a significantly higher freedom of reoperation in patients, at 10 years 62.2% in the non-conduit group vs 14% in the conduit group.

McElhinney and Reddy from UCSF published 1998 their experience with early primary repair CAVSD-TOF (82). Eight patients with a median age of 4.6 months at primary repair were operated with a single patch technique. All had Rastelli type C with a large anterior bridging leaflet, a large, inlet and outlet VSD with an anteriorly malaligned muscular outlet septum and subpulmonary obstruction. To minimize the risk of left ventricular outflow obstruction the anterior bridging leaflet is divided obliquely following the maligned outlet septum. Relief of right ventricular outflow obstruction included infundibular muscular resection, pulmonary valvotomy, infundibular or transannular patching or implantation of a valved conduit. Median cardiopulmonary bypass and cross clamp times were relatively long, 213 minutes and 159 minutes respectively. Follow-up time with a median of 45 months showed no 30-day mortality. One patient died 7 months postop due to respiratory infections. Early to mid-infancy complete repair of cAVSD-TOF is supported, in part, according to the authors (82) by data from Michielon and colleagues showing that early correction of cAVSD at 4 months had significantly less LAVV regurgitation before and after repair of cAVSD compared to correction at 5-12 months or > one year. Postoperative none or trivial regurgitation in 96% (4 months) vs 85% (5-12 months) vs 60% (> one year) (83).

Najm and coworkers explored management protocols for cAVSD-TOF at Hospital for Sick Children in Toronto. 38 children were managed between 1981 to 1997. 21

patients were palliated with a systemic-to-pulmonary shunt with 2 deaths before complete repair. 31 patients underwent complete repair, 14 with initial palliation. There were 2 early deaths after repair and one late death in the palliated group. Patients with palliation underwent repair at an older age, required longer ventilatory- and inotropic support and stayed longer in intensive care and hospital ward. The reoperation rate was 35%, more than half of the reoperations were due to RVOTO and pulmonary artery obstruction. Overall primary repair was found superior to initial palliation cAVSD-TOF (80).

Hoohenkerk and coworkers in Leiden, reported 28 years of experience with transatrial-transpulmonary repair of CAVSD-TOF without the use of conduits in 20 consecutive patients (74). Five patients were initially palliated with a systemic-to-pulmonary shunt. Definitive repair included a transatrial, double-patch repair of cAVSD and relief of infundibular stenosis and pulmonary valvotomy if needed. A short transannular incision was made in all patients. No conduits were used. Early mortality was low, but 6 patients (30%) needed 8 reoperations. One patient needed a mitral valve replacement due to a dysplastic LAVV. 2 patients needed residual VSD closure, and 2 patients needed RVOT relief. and one patient pulmonary artery patching. Freedom from reoperation at 25 years was 71%.

1.3.12 Isolated versus complex complete atrioventricular septal defect

Mery and colleagues presented their large experience in repair of isolated and complex complete atrioventricular septal defect in 2018. Their aim was to present outcomes and risk factors of survival and reoperation for all cAVSD patients including associated cardiac or extracardiac malformations. The cohort was divided into two groups. Isolated cAVSD (350 patients) including only minor associated lesions versus Complex cAVSD (56 patients) with concomitant TOF (61%), DORV (13%), Total anomalous pulmonary drainage (TAPVD) (5%) and aortic arch obstruction (21%) (84). cAVSD repair was predominantly performed at 4 to 6 months (Isolated 5 months vs Complex 8 months P=0.01). DP was the preferred repair technique for the cAVSD. The zone of apposition was closed primarily if LAVV stenosis could be avoided. 70% to 80% of predicted normal diameter was accepted. In patients with TOF a transatrial approach with mini-transannular patch or implantation RV to PA conduit, if necessary, was used. 10 patients had a transannular patch, and 10 patients had conduit implantation.

Patients in the isolated group were younger and had DS more commonly (P<0.01). Complete closure of the cleft was possible in 75%. In 25 patients (6%) it was left unrepaired, mainly due to a deficiency in left lateral leaflet tissue (18 patients).

Perioperative mortality was 2% in the isolated group vs 4% in the complex group. Multivariable analysis showed operation in recent era was protective for mortality (HR: 0.3). Preoperative ventilator support, (HR: 5.5), prior aortic arch intervention

(HR: 3.9), deficient left lateral leaflet (HR: 3.8), and increased cardiopulmonary bypass time (HR: 1.1) were risk factors for mortality.

Ten-year incidence of reoperation was 9% (CI95% 6% - 13%) vs 20% (CI95% 7% - 32%) in isolated and complex groups, respectively. Overall, 40 patients underwent 50 reoperations. The most common reoperation was LAVV repair in 75%, whereas in the complex group conduit replacement was the most common procedure. In conclusion the study shows that similarly excellent results can be achieved even in complex CAVSD. However, reoperation rates remain a concern.

1.3.13 Reoperations after repair of AVSD

The results of complete repair of AVSD of all types have improved significantly over the years (14, 29, 59). However, reoperation, due to LAVV regurgitation, has remained a concern with reoperation rates between 5% to 19% at 10 years (14, 85-90).

In a large study by Pontailler and colleagues (87) they reviewed 412 patients who underwent complete repair of different types of AVSD and identified 47 patients requiring reoperation for LAVV dysfunction, with a reoperation rate of 11.4%. The study group also included 13 additional patients who had their initial AVSD repair at a primary institution. A total of 60 patients needed reoperation for LAVV dysfunction, 52 (87%) with isolated LAVVR, 2 (3%) isolated stenosis and 6 (10%) with both stenosis and regurgitation. 24/60 (40%) needed reoperation within the month after primary repair. At first reoperation, 54 repairs (90%) and 6 replacements (10%) were performed. Half of the subsequent reoperations for LAVVR ended up in valve replacement, in total 17 LAVV was replaced.

In multivariate analysis, double-orifice LAVV (OR=5.04, 95%CI: 1.39-18.27, *P*=.0014), unbalanced ventricles with small LV (OR=4.06, 95%CI: 1.58-10.44, *P*=.004), prior palliative surgery (OR=3.5, 95%CI: 1.14-10.8, *P*=.029) and LAVVR grade >2 at discharge (OR=21.96, 95%CI: 8.91-54.09, *P*<.001 were independent risk factors of LAVV reoperation.

Overall mortality after primary repair of AVSD was 15/412 (3.6%) In the study group reoperated for LAVV dysfunction, 8 patients died (13%). Independent risk factors for death were unbalanced ventricles with small right ventricle (OR=52.61, 95%CI: 10.04-275.81, *P*<.001), prior palliative surgery (OR=5.63, 95%CI: 1.22-26.08, *P*=.027) and reoperation for LAVV dysfunction (OR=16.27, 95%CI: 3.89-68.09, *P*<.001). Valve-related death was the most common cause of death, 6/15.

The outcomes presented in this study are mainly influenced by postoperative LAVV function with poorer survival after LAVV reoperation and further valve replacement. However, valve preservation was obtained in 72% with and estimated overall survival of 93% at 10 years after reoperation.

In two studies from 2012 and 2015 the Leiden group has investigated long-term results after reoperation for LAVVR (86) and a 37-year experience with reoperation after primary repair of AVSD of all causes to identify predictors of poor outcome (91).

In the first study (86)Hoohenkerk and colleagues identified 45/312 (14.4%) who underwent reoperation for severe LAVVR between 1976 and 2006. 28 patients (62%) had cAVSD, 10 (22%) pAVSD and 7 (16%) tAVSD. DS was present in 44%. Associated cardiovascular anomalies was found in 15 patients (33%), including TOF (13%), Double-orifice LAVV (DOLAVV) (16%) and coarctation of the aorta (4%). LAVV was dysplastic in 42%. LAVV regurgitation at primary repair was severe in 51%. Cleft closure was performed in 60% at primary repair.

Mean interval between initial repair and reoperation was 1.83 years (range, 0.02 to 21.05 years). 14 of 45 patients (31%) were reoperated in the first year, 5 of whom within the first 30 days. Associated cardiovascular anomalies, LAVV dysplasia and preoperative severe LAVVR were risk factors of reoperation. Primary cleft closure was associated with less risk of reoperation. LAVV dysplasia was also a predictor of subsequent reoperation. The multivariable Cox regression showed that associated cardiovascular anomalies (hazard ratio [HR], 3.40; 95%CI 1.78-6.50; *P*<.001), LAVV dysplasia (HR, 8.99; 95%CI 4.87-16.61; *P*<.001) and cleft closure (HR, 0.49; 95%CI 0.27-0.92; *P*=.027) were independent predictors of reoperation.

In hospital mortality was 6.7% and a late mortality rate of 4.4%. Estimated overall survival was 88.1% at 15 years after reoperation. The estimated survival after valve replacement was significantly lower than after valve repair, P=.01. Using a competing risk model, the estimated incidence of non-reoperation death in the total cohort was 8% at 15 years after primary repair. The estimated incidence of death after reoperation for LAVVR was 2% at 15 years initial repair. The 15-year estimates of incidence of reoperation and reoperation-free survival were 21% and 71% respectively.

To conclude, they found the incidence of reoperation for LAVVR was14,4%. The 15-year reoperation rate for LAVV regurgitation was 21%. Nonclosure of the cleft was a risk factor for LAVVR reoperation. LAVV replacement had a significantly lower estimated overall survival.

In the second study, Sojak and coworkers (91) reviewed a large cohort of 457 consecutive patients with all types of AVSD with focus on patients who underwent reoperation at the department cardiothoracic surgery in Leiden over 37-year period.79 patients were initially included. 10 patients were lost to follow-up, 69 patients with complete data were enrolled in the current study. The objective was to evaluate patients undergoing reoperation and to identify predictors of poor outcome.

40.6% had pAVSD,21.7% had tAVSD and 37.7% had cAVSD. DS was present in 40,6%. The frequency of LAVV dysplasia and DOLAVV was 21.7% and 4.3%

respectively. Two of 3 patients with DOLAVV also had pseudo-parachute LAVV. The median age at first reoperation was 62.4 (range 1.6-845) months and the median age to first reoperation was 22.3 (range 0.2-845) months. The most common indications for first reoperation were LAVV pathology (65.6%) and residual septal defect (19.4%). LVOTO relief (4.3%), right AVV (RAVV) pathology (4.3%), cardiac arrhythmia requiring pacemaker (PM) implantation (3.2%), RVOTO (2.2%) and endocarditis (1.1%).

Overall, 69 patients underwent 113 reoperations. At first reoperation 47 patients were reoperated with LAVV valvuloplasty, and 14 patients underwent LAVV replacement, one additional patient had LAVV replacement due to endocarditis. At last follow-up 65.9% of 41 survivors of LAVVP were prosthesis-free.

In hospital mortality was 14.5%. Seven patients died after LAVV surgery; 2 out of 3 patients died after LVOTO relief with Ross-Konno procedure and 1 patient died after RAVVP. Univariable and multivariable binary regression identified presence of DOLAVV as the only independent risk factor of in-hospital mortality, OR 14.5; 95%CI 1.2-178.7; *P*=.037. Long-term survival after LAVV pathology were significantly lower in patients needing LAVVR.

In contrast, Malhotra and colleagues (92) reported, in 2008, their results of 31 patients with previous repair (mean age 5.0 months) of AVSD who were reoperated (median age 12.6 months) due to LAVV pathology. They could not show any significant difference in estimated long-term survival nor freedom of reoperation between LAVV repair vs LAVV replacement. (*P*=.82 and *P*=.62 respectively). However, a significantly higher incidence of pacemaker implantation (65% vs 13%, *P*=.005) was found. They also noted development of severe left ventricular dysfunction and cardiomyopathy in 3 of 14 patients receiving a mechanical valve replacement.

Reoperation rates between 11.2% to 17.2% are reported in the studies from Leiden and Paris. In the study by Malhotra and colleagues from Denver some patients had initial repair performed at another hospital but reported data indicates a lower reoperation rate at 7.1% in patients having both initial repair and reoperation performed at the hospital in Denver. In patients reoperated for LAVV-related pathology, a second reoperation were required in 33.3% to 39.1% of the cases. To summarize, the issue of reoperations after primary repair of AVSD, especially LAVV-related reoperation, remains to be further investigated.

2 Aims of this research

2.1 Background for study initiation

2.1.1 Study I

Preoperative precise visualization of anatomical and functional abnormalities of AV-valve in atrioventricular septal defect is important for preoperative surgical preparation and impaired visualization may impair outcomes. (93) Echocardiography is currently the only imaging modality that can visualize AV-valves in real time. In 2D echocardiography, the need of subjective geometric assumption limits accuracy and increase the variability, due to the complex nature of the AV-valve (94). 3D echocardiography may miss smaller anatomic structures due to lower resolution (94), but has shown potential to describe different anatomical structures in the heart (24, 95-97). There are limited data on the accuracy of 3D in imaging of the AV-valves in patients with AVSD. (25). Therefore, we decided to perform a prospective study in 20 consecutive patients with AVSD and evaluate a total of 520 AV-valve features with both 2D and 3D, with surgical description as reference.

2.1.2 Study II

Surgical repair of complete atrioventricular septal defect has progressively been undertaken earlier in life to avoid pulmonary hypertension and premature death. Elective repair of cAVSD at 3 to 6 months of age has become the contemporary standard management in many pediatric cardiac surgery centers (60, 98). The rationale for performing elective repair of the infant at 3 to 6 months of age and avoid corrective surgery in young infants less than 3 months old is related to concerns about the surgical complexity and the fragility of the AV-valve tissue (99-101). Unfortunately, a considerable number of patients with cAVSD develop pharmacologically refractory congestive heart failure within the first months of life. In this group of patients, early surgical intervention must be considered. Some authors advocate the use of palliative interventions with pulmonary banding followed by delayed repair (102). Others have suggested that corrective surgery for cAVSD in young infants has similar outcomes compared with older infants (103,

104). Our treatment strategy has been early cAVSD repair in patients failing medical treatment. However, the optimal management for this complex population is still unclear. Therefore, we wanted to investigate if any significant differences regarding long-term survival or freedom from LAVV-related reoperation could be found in patients requiring early primary correction compared to elective repair.

2.1.3 Study III

To accurately predict the prognosis and optimize results after surgical repair of complete atrioventricular septal defect, it is crucial to identify patients with an increased risk of poor outcome. Nonsyndromic patients with cACSD are clinically known to have inferior outcomes when compared to patients with cAVSD with trisomy 21 (12, 13, 43, 53, 105). This may, in part, be explained by the presence of concomitant complex cardiac anatomic lesions, which is more common in nonsyndromic patients (79, 84). Mery and colleagues (84) recently reported that patients with cAVSD and concomitant complex anatomic lesions had increased rates of mortality and reoperations when compared with noncomplex patients. However, there is no contemporary research that has investigated long-term outcomes in a selected population of nonsyndromic patients with cAVSD. It is valuable to study these different populations to improve the understanding cAVSD because the published data on this topic is limited. Therefore, we wanted, in a nonsyndromic cohort, investigate the impact of concomitant complex cardiac anatomy and compare the outcomes after surgical repair of cAVSD.

2.1.4 Study IV

Results of primary repair of atrioventricular septal defect of all types have improved over the last decades (60, 105, 106). Improved anatomic understanding, coupled with enhanced surgical technique and perioperative care, have yielded good early and late outcomes, and because of the high survival rate, more patients have become potential candidates for reoperation. The majority of reoperations are performed due to severe LAVV regurgitation with a recurrence rate of 5% 19% at 10 years (14, 85-87, 107). A significant number of reoperations, however, are performed due to residual shunts or LVOTO, which in some cases can be very complex and have a substantial impact on clinical outcome. Previous studies of reoperations in AVSD patients have focused on LAVVR and the majority are based on referrals from other institutions. (108, 109). Following the centralization and regionalization of paediatric cardiac surgery our department became responsible for a population of 5 million with a geographical referral pattern and all initial repairs and subsequent reoperations are performed at our institution with no referrals from other institutions. Therefore, we wanted to evaluate the total burden of reoperations in a consecutive cohort undergoing primary repair for AVSD at a large-volume centre

2.2 Specific study aims

2.2.1 Study I

The aim of Study I was to compare the accuracy of 2D and 3D echocardiography in assessing morphological and functional valve features in AVSD using surgical operative descriptions as reference, and to compare the reasons for disagreement.

2.2.2 Study II

The aim of Study II was to evaluate data after repair of complete atrioventricular septal defect and assess survival and identify risk factors of left atrioventricular valve-related reoperations with focus on primary corrections in the first months of life.

2.2.3 Study III

In study III we studied a cohort of patients with non-syndromic complete atrioventricular septal defect with and without concomitant complex cardiac anatomy and compared the surgical outcomes after repair.

2.2.4 Study IV

Study IV aimed to evaluate the total burden of reoperations after previous repair of atrioventricular septal defect including long-term survival and to identify risk factors for reoperation.

3 Material and methods

3.1 Patients and study design

3.1.1 Study I

This was a prospective, non-randomized, non-blinded, single centre study. From 2013 to 2015, 20 children were consecutively enrolled at the time of routine transthoracic echocardiography (TTE) at the Paediatric Cardiology ward, Children´s Hospital Lund, Skånes University Hospital, Sweden. Inclusion criteria were diagnosis of AVSD, age 0 to 18 years and 2D and 3D echocardiography available at admission. Exclusion criteria were previous AVSD surgery. All surgeries were performed at the Paediatric Cardiac Surgery unit, Department of Paediatric surgery and Neonatology, Children´s Hospital, Skåne University Hospital, Lund Sweden.

In each patient 26 valve features were assessed. Abnormal valve features were defined as the feature that had impaired morphology or function. For 2D TTE imaging a commercially available ultrasound system (Philips Medical Systems, Andover, MA, USA) with 7 MHz and 5MHz probe was used. 3D imaging was acquired using Philips iE33 (Philips Medical Systems, Andover, MA, USA), using the X7-1 probe in all patients. In one patient X5-1 was also used. The QLab software (Philips Medical Systems) was used for offline analysis.

The valve was assessed by the surgeon on the arrested, non-beating heart. Testing for regurgitation was done by floating the valve with cold saline. Anatomical features of the valve and subvalvular apparatus were assessed perioperatively and a drawing was made after the surgery.

Primary endpoints were accuracy of 2D, and 3D compared to surgical descriptions, respectively, and comparison of different reasons for disagreement in each modality.

3.1.2 Study II

Paediatric cardiac surgery in Sweden (about 10 million inhabitants) is regulated by the Swedish National Board of Health and Welfare. Paediatric cardiac surgery was centralized and regionalized in late 1992 to two centres of similar size, (Lund and

Gothenburg). All treatments are available to all patients in need of surgery and all patients are distributed evenly between the two centres according to a geographical referral pattern.

In a retrospective, single centre study, a total of 304 patients who underwent repair of complete atrioventricular septal defect between April 1993 to October 2018 at the Paediatric Cardiac Surgery Unit in Lund were included in the study. Data was collected from the Paediatric Cardiac Surgery Sections computerized surgical patient database containing preoperative, perioperative, and postoperative variables, prospectively registered, related to all paediatric cardiac operations performed at our centre. All operative notes were reviewed. When necessary, additional data were obtained by reviewing clinical charts or contacting referring physicians. The diagnosis of complete AVSD was defined as the presence of a common atrioventricular valve with common atrioventricular junction with a primum atrial defect and an inlet VSD. The balance of the defect was assigned with a combination of preoperative echocardiographic notes and the surgeons notes of "unbalanced" in the operative notes. Patients with unbalanced AVSD operated with a single ventricle treatment algorithm (8 patients during the study period) were excluded.

The results for young infants, less than 3 months of age were compared with children older than 3 months. The primary endpoints were survival and need for LAVV related reoperation. Early mortality was defined as 30-day mortality and late mortality as any mortality occurring after the first 30 days after surgery. Early reoperation was defined as reoperation less than 30 days after initial AVSD repair, and late reoperation was defined as reoperation more than 30 days after the initial AVSD repair. Survival data were obtained from the Swedish National Board of Health and Welfare (Socialstyrelsen, Sweden). A LAVV-related reoperation was defined as the need for a reoperation for regurgitation or stenosis in the LAVV with or without additional symptoms such as heart failure, failure to thrive or pulmonary hypertension.

3.1.3 Study III

This was a single institution, retrospective, observational study where we studied a cohort of patients with nonsyndromic complete atrioventricular septal defect with and without concomitant complex cardiac anatomy. We retrospectively screened all patients who underwent CAVSD repair between April 1993 to October 2018 in Lund. 239 patients with trisomy 21 and 3 patients with other genetic syndromes were excluded leaving 62 nonsyndromic patients for inclusion in the study cohort.

Perioperative data has been prospectively registered in our departmental database since 1993, any additional data necessary for this study was obtained by retrospective review of patients charts and operative notes.

The definition of concomitant complex cardiac anatomy included TOF, DORV, Total anomalous pulmonary venous return, concomitant aortic arch repair, multiple VSD´s, staged repair of coarctation of the aorta and a persisting left superior vena cava.

Late survival data are obtained from the Swedish Causes of Death Register governed by the Swedish Board of Health and Welfare with more than 99% coverage. 2 patients in the study population were referred from abroad; 1 patient was a private referral from Greece and was postoperatively transferred to her home country and late follow-up could not be performed; the second patient was a referral organized through the United Nations High Commissioner for refugees after the civil war in former Yugoslavia in the 1990s and was transferred back to her home country and late follow-up was not possible. Subsequently, 60 patients were included in the long-term survival and reoperation analysis.

Primary endpoints measures were survival and need for reoperation after surgical repair of cAVSD in nonsyndromic patients with concomitant complex cardiac anatomy compared with those without.

3.1.4 Study IV

Study IV was single centre, retrospective, observational study using data from our, previously described institutional database. We performed a retrospective database search between April 1993 and October 2020 for all consecutive patients undergoing surgical correction of AVSD of all types at our department. Our review identified patients who underwent AVSD redo surgery for inclusion in our study population. The cohort who did not need reoperation for LAVVR allowed for identification of risk factors for reoperation and evaluation of overall survival after primary AVSD repair in a competing risk scenario.

All types of AVSD such as partial, transitional and complete were included. The diagnosis of pAVSD was defined as a primum atrial septal defect and a cleft in the LAVV according to the Society of Thoracic Guidelines. The diagnosis of tAVSD was defined as having a common AV valve with two-valve orifices with a primum ASD and a small ventricular component. The diagnosis of cAVSD is a common AV-valve with a common valvar orifice with a primum atrial defect and an inlet VSD.

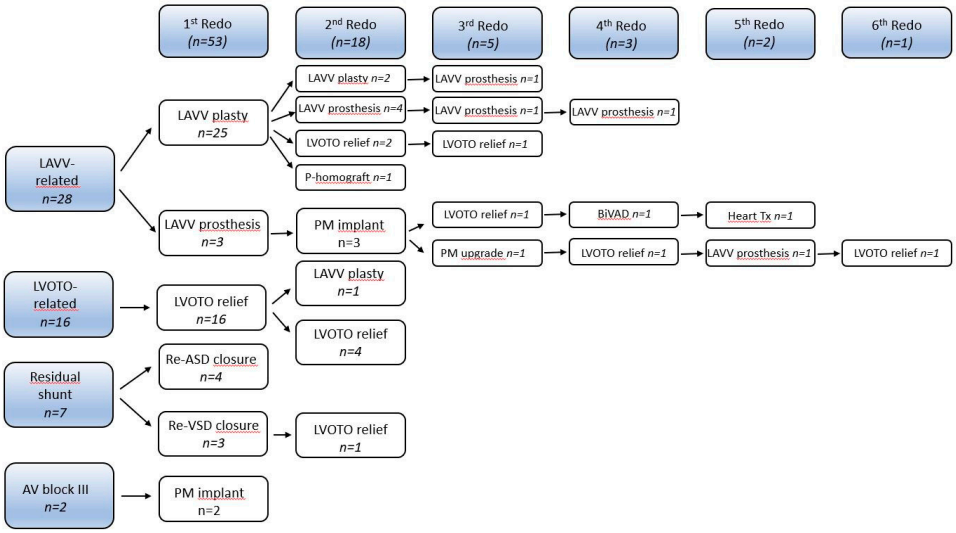

Figure 3.2
All-cause reoperations in AVSD population (1993- 2020)

The primary endpoint was long-term survival following reoperation. Secondary endpoints were perioperative mortality at reoperation, freedom from any cause reoperation and freedom from LAVV-related re-repair and procedural success at first re-repair.

3.2 Ethical aspects

Study I; The study was conducted in compliance with the declaration of Helsinki, and the research protocol was approved by the locally appointed Ethics Committee. (Ref 2013/601, October 9, 2013) Informed consent was obtained from the legally authorized representative of all patients.

Study II – VI; All studies were performed according to the principles of the Helsinki Declaration of Human Rights and were approved by the Ethics Committee for Clinical Research and the Skane University Hospital Review Board at Lund University, Sweden. (Ref 2018/926; December 4, 2018). The need for patient consent was waived.

3.3 Surgical technique

In study I, the echocardiographic investigations were all performed before surgery. The surgical assessment of specific valve features was performed during the surgical repair of the AVSD, and the findings were postoperatively noted together with a drawing.

In study II, during the study period, 8 surgeons performed surgical repair on patients with cAVSD at our department, but most early repairs were performed by 2 surgeons. The 2-patch repair was the standard technique of choice, but intraoperative individualization of the repair was according to surgeons' preference. Median sternotomy, cardiopulmonary bypass and cold intermittent antegrade and retrograde blood cardioplegic arrest was uniformly used. We use frequent saline testing to assess the anatomy and symmetry of the common AV valve during valve repair. Special attention is directed towards the left sided valve and the development of the anterior and inferior bridging leaflets and chordal arrangements, presence of incomplete commissural development or deficiency of left mural leaflet, extra clefts including double orifice, number, and arrangement of papillary muscles. The VSD is closed with a polytetrafluoroethylene (PTFE) patch. Care is taken to place as much valve tissue as possible on the left side. To close the zone of apposition without consumption of valve tissue, we used 7-0 monofilament propylene sutures placed as figure-of-8 stiches and placing the stitches in such a fashion to maintain as much coaptation height as possible when the LAVV cleft is closed. During the valve repair we try to avoid creating unnecessary tension to the valve leaflets, preserve maximum amount of valve tissue, avoid cutting secondary chords and respect the natural symmetry of the valve. The primum atrial septal defect was closed with an untreated, autologous pericardial patch. Generally, the coronary sinus was maintained on the right side of the heart and in the majority of the patients the cleft in the LAVV was completely closed.

In study III, we studied a subgroup of 62 nonsyndromic patients with and without concomitant complex cardiac anatomy. Our surgical technique regarding repair of cAVSD has been presented in detail in study II. In patients with concomitant TOF and DORV of Fallot type our preference has been a transatrial transpulmonary approach with infundibular muscle resection and pulmonary valve commissurotomy. If not sufficient, an infundibular or transannular patch is added. We have tried to avoid conduit implantation, due to increased risk of early reoperation. It has been possible to close the cleft completely in 81% and maintain the coronary sinus on the right side of the heart.

In study IV, we studied a cohort of 477 patients with pAVSD, tAVSD and cAVSD with focus on the total burden of reoperations. Our surgical technique regarding repair of cAVSD has been presented in detail in study II. In patients with pAVSD the primum atrial defect was closed with an autologous pericardial patch and the

cleft was closed as much as possible to allow optimal leaflet mobility and avoid valvular stenosis. In tAVSD, the VSD, if still patent, was directly closed by suturing the bridging leaflets down to the septal rim with pledgeted sutures also incorporating the base of an autologous pericardial patch that closes the primum atrial defect.

An LAVV-related reoperation was deemed necessary in the presence of an echocardiographically significant stenosis (mean gradient >10 mm HG) or LAVV regurgitation (more than moderate) with and without additional symptoms including heart failure, failure to thrive, or pulmonary hypertension. Regurgitation was graded mild, moderate, and severe based on echocardiographic findings. LVOTO was relieved by membrane resection and/or myectomy. The Konno procedure was not performed on any patient. Residual septal defects were closed with a patch or direct suture. Pulmonary regurgitation was managed with pulmonary homograft implantation. Permanent pacemakers were implanted transvenously or epicardially based on the patient´s weight and age.

3.4 Statistical analysis

3.4.1 Study I

Continuous data was reported as mean ±standard deviation if normally distributed or as median and interquartile ranges (IQRs) in skewed distributions. Categorical data was reported as proportions, and the chi-square test was used to compare differences between groups. When the expected frequency was <5, Fisher´s exact test was used. An inter-observer correlation was made using the Pearson R correlation. A probability of <0.05 was considered significant. Statistical analysis was performed using the statistical package for the Social Sciences Version 10.1.0 for Windows.

3.4.2 Study II

Continuous variables were presented as mean±standard deviation and as median and interquartile range if the distribution was skewed. The Student t test was used to compare normally distributed continuous variables or using the Mann-Whitney *U* test if variables were not normally distributed. Categorical data was reported as proportions, and the chi-square test was used to compare differences between groups. When the expected frequency was <5, Fisher´s exact test was used. The Kaplan-Meier estimate was used to assess actuarial survival and freedom from reoperation after surgical repair. The log-rank test was used for comparison between groups. Decade-by-decade trends for performing early repair for cAVSD were analysed using 1-way analysis of variance. Univariable and multivariable Cox

regression analyses were performed to determine independent predictors of long-term mortality and late reoperation. The inclusion criterion for the full model was $P \leq .200$, and the limit for stepwise backward elimination was $P < .100$. Cox regression results were expressed as hazard ratio (HR) with 95% confidence interval (CI). Statistical analysis relied on SPSS statistical software version 24 (SPSS Inc, Chicago, IL.)

3.4.3 Study III

Continuous variables were presented as mean±standard deviation and proportions were presented as numbers and percentages. Baseline and surgical variables were evaluated using univariable logistic regression. Kaplan-Meier estimates of survival were used to analyse survival. Group comparison between the complex group and the noncomplex group were performed using the log-rank test. We analysed the risk of reoperation with competing-risk analysis, in which death was the competing event. Gray´s test was used to test the equality of the cumulative incidence curves between groups. Statistical analysis relied on standard statistical software (SPSS, IBM corp released 2017, IBM SPSS statistics for Mac, version 26. Armonk, NY). The Kaplan-Meier and the competing risk curves were plotted using R version 4.0.3 including cmprsk package.

3.4.4 Study IV

Continuous variables were reported as mean±standard deviation. Median and interquartile range were presented if data were skewed. Student *t* test was used to compare normally distributed variables, if not, Mann-Whitney *U* test was used. Categorical variables were described as numbers and percentages and compared using chi-square test. Fisher´s exact test was used if the expected frequency was less than 5. Kaplan-Meier estimate was used to assess actuarial survival and freedom from reoperation after surgical repair. The log-rank test was used for between group comparison. The risk of reoperation was analysed with competing risk analysis, where death was the competing event. Uni- and multivariable Cox regression analyses were performed to determine independent predictors of any reoperation and LAVV-related reoperation. The inclusion criterion for the full model was $P \leq .200$, and the limit for stepwise backward elimination was $P < .100$. Results of the Cox regression were expressed as hazard ratio (HR) with 95% confidence interval (CI). A P value of < 0.05 was considered statistically significant. Statistical analysis relied on SPSS statistical software version 24 (SPSS Inc, Chicago, IL).

4 Results

4.1 Study I

4.1.1 Study population and patient characteristics

20 patients planned for elective repair of AVSD were consecutively enrolled in the study at the time of routine transthoracic echocardiography at the paediatric cardiology ward, Children's Hospital, Lund, Skånes University Hospital, Sweden.

11 patients with cAVSD and 9 patients with pAVSD/tAVSD with a mean age of 8 months (range 3-72 months), and a mean weight of 5,6 kg (range 3.5-21 kg). 9 patients had trisomy 21 (45%) and 1 patient had Noonan syndrome (5%). 25% of patients had associated minor cardiac anomalies such as persisting arterial duct (2), ostium secundum atrial septal defect (2) and pulmonary valve stenosis (1).

Twenty-one main features, (in total 26 features), of the AV-valve were described in each patient.

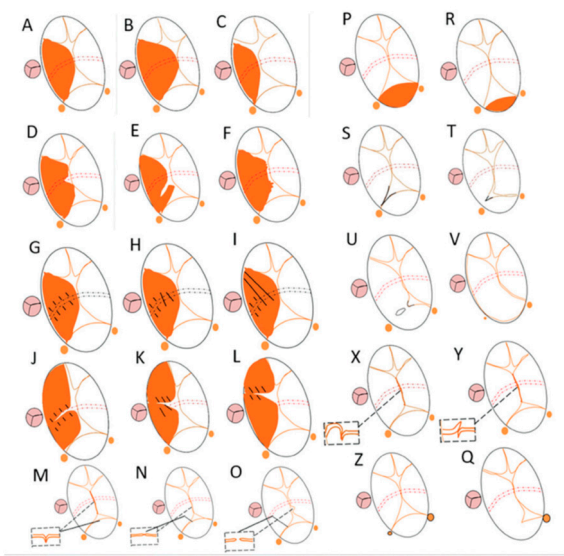

Figure I.1 Anatomical and functional characteristics of the AV valve complex features, including leaflets, commisures, chordae, and/or papillary muscles

4.1.2 Baseline characteristics

In total 520 AV-valve features were described in 20 patients. Abnormalities were found in 57 (11%) of these AV-valve features. Most often in abnormalities of the superior commissure (Double orifice or short in 45% of patients) and coaptation abnormalities between the bridging leaflets (Diastasis or short coaptation in 45% of patients) were found. Left sided AV-valve regurgitation was present in 85% of patients (mild 75%, moderate 25%, severe 0%).

4.1.3 Technical details

For 2D imaging, a probe S8-3 was used in all patients. The frame rate of the 2D images was 79±17 mHz (mean±SD). For 3D imaging a probe X7-1 was used in all patients, in one patient, in addition to the X7-1 probe, a X5-1 probe was used. The frame rate of the 3D images was 32±2 mHz. Heart rate during investigations were 138±8bpm, with normal distribution. No sedation or anesthesia was given during echocardiographic investigation.

4.1.4 2D imaging of AV-valve complex

2D ultrasound agreed with the surgical description in 413/520 (79%) AV-valve features. Most often, the disagreement was related to the assessment of the Rastelli type (disagreement in 40% of patients) and the assessment of the superior commissure: inadequate recognition of the double orifice type of commissure (5% of patients) or under/overestimation of the commissure in 30% of the patients.

4.1.5 3D imaging of the AV-valve complex

3D ultrasound agreed with the surgical description in 432/520 (83%) AV valve features. Disagreement was most often related to the evaluation of the zone of apposition: presence of diastasis/smaller area (disagreement in 30% of patients).

4.1.6 Comparison of the accuracy between 2D and 3D echocardiography

2D and 3D echocardiography had similar accuracy in almost all AV valve features except in assessment of Rastelli type and the extension of the inferior leaflet into the RV, (P=0.038 and P=0.011, respectively.) In almost 48% of cases where 2D was accurate, the 3D was inaccurate and vice versa. A significant reason for misdiagnosis of both 2D and 3D was that the technique could not visualize that particular valve feature. Judgement of the observer or inadequate image quality was

not a significant reason for disagreement. There was no significant difference in image quality of any specific valve feature (*P*=0.632). 27% in 2D and 30% in 3D of valve features were visualized with low quality. 3D studies were evaluated by two experienced observers. Their opinions were highly correlated (r=0.640; *P*=0.002).

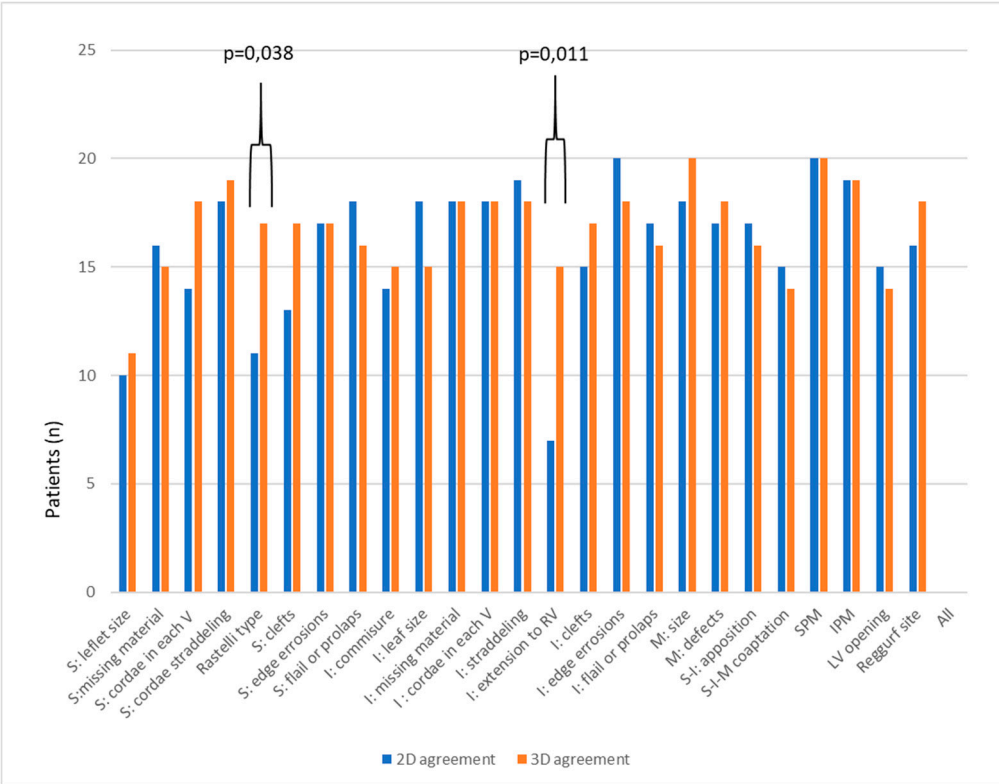

Figure I.1 Comparison of accuracy in the assessment of the AV-valve complex features ot 2D (blue columns) and 3D (red columns).
S – superior; I – inferior; M – mural; V – ventricle; RV – right ventricle; LV – left ventricle; SPM – superior papillary muscle; IPM – inferior papillary muscle.

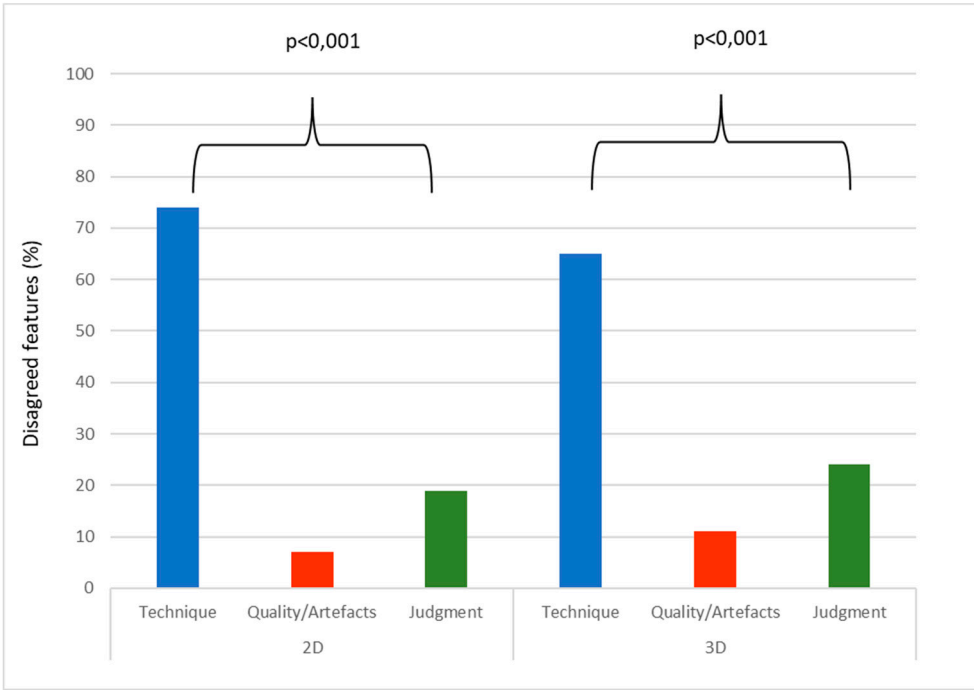

Figure I.2 Comparison of different reasons for disagreement in each modality.

4.2 Study II

4.2.1 Study population and patient follow-up

Study II included 304 consecutive patients who underwent surgical correction of complete AVSD between April 1993 to October 2018. Mean follow-up was 13.2±7.8 years (median 14.0 years; interquartile range, 7.0-20.0 years). The follow-up was performed in January 2019 and was 99% (300/304) complete. 3 patients emigrated during the follow-up period, and 1 patient was untraceable due to an incomplete recorded Social Security number. These 4 patients were excluded from evaluation for late survival and reoperation.

4.2.2 Patient characteristics

The baseline characteristics of the Study population (n=304) are presented in Table II.1. Patients are stratified by early repair (< 3 months; n=55) versus standard repair (≥ 3 months; n=249). The mean age at the time of repair was 4.5 ± 4.9 months

(median, 3.0 months; interquartile range [IQR], 3 4 months. The median age at time of repair did not change significantly over the three decades: 1993 to 1999, 4.0 months (mean 4.6 ±4.0 months; IQR 3-4 months); 2000 to 2009, 3.0 months (mean 3.9 months±2.9 months; IQR, 3-4 months; and 2010 to 2018, 3.0 months (mean 5.3±7.5 months; IQR, 3-4.5 months) (*P*=.11). 239 patients had Trisomy 21.

Patients in group 1 (n=55) were younger at primary repair (1.6 months vs 5.1 months, *P*=<.001), had lower weight (3.9 kg vs 5.4 kg, *P*=.001), had a higher presence of concomitant CoA (7.3% vs 2.0%, *P*=.04), were more likely to have associated noncardiac anomalies (15% vs 6%, *P*=.04) and were more often prematurely born (≤ 36 wk.) (18% vs 8%, *P*=.03), (table II.1).

Preoperative echocardiographic and intra operative variables are presented in table II.2. Patients operated before 3 months had significantly higher presence of unbalanced AV-valve/ventricles (9.1% vs 2.4%, *P*=.03), had a severe preoperative AV-valve regurgitation (16.4% vs 5.2%, *P*=.01). Surgically related variables showed that complete cleft closure was achieved less often in the early repair group (84% vs 88%, *P*=.03), and cardiopulmonary bypass time was significantly longer (152±47 min vs 136±48 min, *P*=.03)

Table II.1 Patient characteristics stratified by early repair < 3 months vs standard repair >3 months

Variables	Total (n=304)	Repair < 3 mo (n=55)	Repair ≥ 3 mo (n=249)	*P* value
Age at repair (mo)	4.5 ± 4.9	1.6 ± 0.6	5.1 ± 5.2	<.001
Weight at repair (years)	5.2 ± 1.5	3.9 ± 0.6	5.4 ± 1.5	<.001
Female gender	163 (53.6)	29 (52.7)	134 (53.8)	.88
Trisomy 21	239 (79)	39 (71)	200 (80)	.12
Associated cardiac anomalies (all)	46 (15.1)	10 (18.2)	36 (14.5)	.49
Additional VSD	12 (3.9)	2 (3.6)	10 (4.0)	.63
CoA	9 (3.0)	4 (7.3)	5 (2.0)	.04
Persisting LSVC	9 (3.0)	2 (3.6)	7 (2.8)	.74
Tetralogy of Fallot	7 (2.3)	0 (0)	7 (2.8)	.36
Pulmonary atresia	6 (2.0)	1 (1.8))	5 (2.0)	.70
Genetic syndrome other than trisomy 21	3 (1)	0 (0)	3 (1.2)	.55
Associated non-cardiac malformation	22 (7.2)	8 (14.5)	14 (5.6)	.04
Premature (≤36 wk)	31 (10,2)	10 (18.2)	21 (8.4)	.03

Table II.2 Echocardiographic and intraoperative variables stratified by early repair (< 3 months) versus standard repair (≥ 3 months)

Variables	Total n = 304	Repair (< 3 mo) n = 55	Repair (>3 mo) n = 249	*P* value
Cardiac and valve anatomy				
LAVV double orifice	12 (3.9)	2 (3.6)	10 (4.0)	.63
LAVV incomplete commisures	39 (12.9)	8 (14.8)	31 (12.5)	.65
LAVV extra cleft	26 (8.6)	4 (7.3)	22 (8.9)	.47
Anterior bridging leaflet divided over septum	92 (30.3)	12 (21.8)	80 (32.1)	.13
Anterior bridging leaflet free floating	51 (16.8)	8 (14.5)	43 (17.3)	.63
LV single papillary muscle head	18 (5.9)	6 (10.9)	12 (4.8)	.11
Nonrestrictive VSD	257 (84.5)	50 (90.9)	207 (83.1)	.15
Unbalanced AV valve/ventricles	11 (3.6)	5 (9.1)	6 (2.4)	.03
Preoperative severe AV valve regurgitation/heart failure	22 (7.2)	9 (16.4)	13 (5.2)	.008
Surgical repair				
CBP time (min)	139 ± 48.3	152 ± 46.7	136 ± 48.3	.03
Aortic crossclamp time (min)	90.2 ± 25.8	93.6 ± 22.5	89.5 ± 26.6	.28
2-patch technique	280 (92.1)	50 (90.9)	230 (92.4)	.78
Cleft closure complete	264 (86.8)	46 (83.6)	218 (87.6)	.03
Coronary sinus in right atrium	286 (96.6)	53 (98.1)	233 (96.3)	.43

4.2.3 Early and Late mortality

The 30-day mortality was 1.0% (3/304) and was distributed as 0 patients among young infants and 3 patients among the 249 older infants. (P= 1.0). There was a total of 11 late deaths during follow-up, whereof 5 patients had a cardiac cause of death. None of the late deaths were related to cardiac reoperations. Two of the late deaths occurred before hospital discharge, giving an in-hospital mortality of 1.6%. Overall actuarial survival (n = 300) was 95.1% (± 1.3%) at 10, 20 and 25 years.

In the univariable analysis, risk factors for mortality included an associated cardiac malformation (*P* = .006), an additional VSD (*P*=.043), CoA (*P*<.001), a persistent LSVC (*P*=.020), and an unbalanced AV valve/ventricles (*P*=.045). Predictors of overall mortality after multivariable analysis is shown in Table II.3

There was no significant difference in survival estimates between patients having early repair (<3 months) vs standard repair (≥3 months). (Figure II.1)

Table II.3 Multivariable Cox regression analysis for predictors of overall mortality after surgical repair for complete atrioventricular septal defect

	HR (95% CI	*P* value
Additional VSD	5.2 (1.1 – 26)	.04
CoA	14.7 (3.9 – 56)	<.001
Persisting LSVC	6.1 (1.2 – 29)	.03
Genetic syndrome other than Trisomy 21	12.8 (1.6 – 103)	.02

4.2.4 Reoperations

19 patients (6.3%) required 26 LAVV-related reoperations after initial repair of complete AVSD. During follow-up, 4 patients had a second LAVV-related reoperation, and 3 patients needed a third reoperation, whereof one had a mechanical valve replacement. Four of the 19 patients needed reoperation within 30 days. 3 of whom survived to hospital discharge. The other 15 patients had a late LAVV related reoperation. In addition, 10 patients (3.3%) had other reoperations during follow-up: 4 patients were reoperated for subvalvular aortic stenosis; 2 patients had permanent pacemaker implantation; 2 patients required closure of recurrent VSD plus an additional repair of a perforated aortic cusp in one of the patients. 1 patient needed closure of an ASD and 1 patient was reoperated due to endocarditis and RVOTO.

4.2.5 Risk factors for LAVV-related reoperation

Univariable analysis showed that; Low weight at repair (*P=.032*), Any associated cardiac malformation (P=.044), Persistent LSVC (P=.020), Concomitant tetralogy of Fallot (*P*=.035), Anterior bridging leaflet divided over septum (*P*=.048), and Presence of an unbalanced AV valve/ventricles (*P*=.001) were significant risk factors for LAVV-related reoperation. On the contrary, Presence of Trisomy 21 was protective for LAVV-related reoperation (*P*=.005). Multivariable Cox regression analysis for predictors for LAVV-related reoperation after surgical repair for complete AVSD is presented in table II.4

Table II.4 Multivariable Cox regression analysis for predictors for left atrioventricular valve-related reoperation after surgical repair for complete atrioventricular septal defect

	HR (95%CI)	*P* value
Persisting LSVC	5.9 (1.3 – 27)	.02
Unbalanced AV valve/ventricles	8.0 (2.6 – 29)	.001
Preoperative severe AV valve regurgitation/heart failure	4.6 (1.5 – 15)	.007

Actuarial freedom of LAVV-related reoperation was 92.6% (±1.7%) at 20 years and actuarial freedom of any reoperation was 89.4% (±1.9%) at 20 years. There was no significant difference in rate of LAVV-related reoperation: 84.7% (±6.9%) versus 93.9% (±1.7%) (P=.084) nor Any reoperation: 84.8% (±5.0%) versus 90.5% (±2.0%) (*P=.11)* between patients undergoing early repair (<3 months) vs standard repair (≥3 months) at 20-year follow-up. (Figure II.2 and Figure II.3).

Figure II.1 Kaplan-Meier estimates of overall survival after early surgical repair for cAVSD in younger infants (<3 months) versus repair in older infants (≥3 months) (P=.079). Shaded area represents 95% CIs

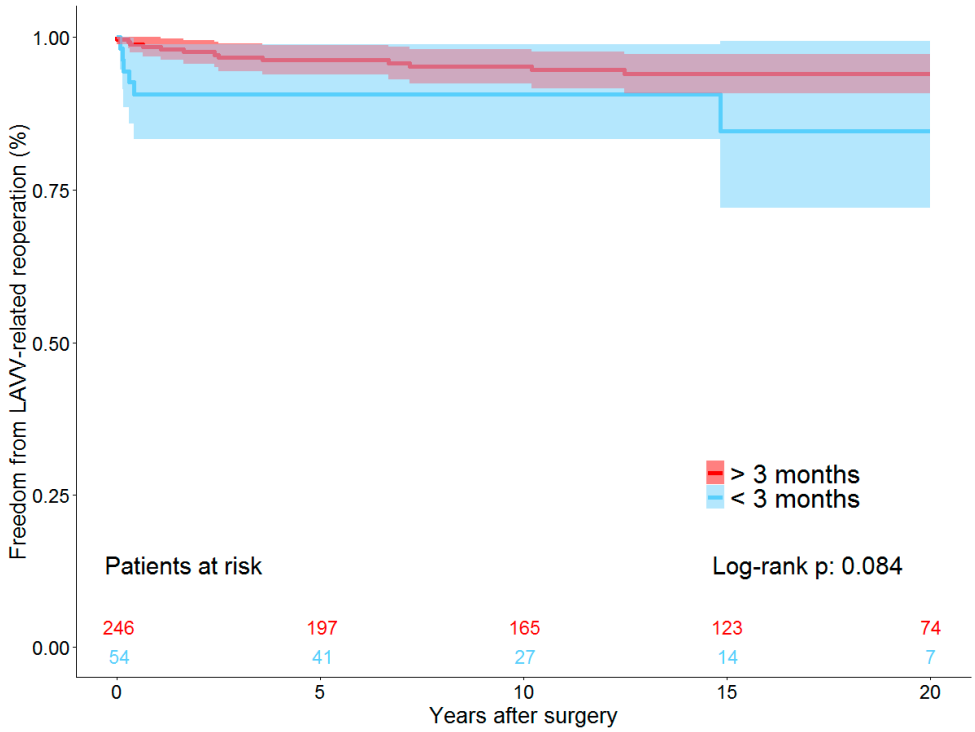

Figure II.2 Kaplan-Meier estimates of actuarial freedom from LAVV-related reoperation after early surgical repair for cAVSD in younger infants (<3 months) versus repair in older infants (≥3 months) (P=.084). Shaded area represents 95% CIs

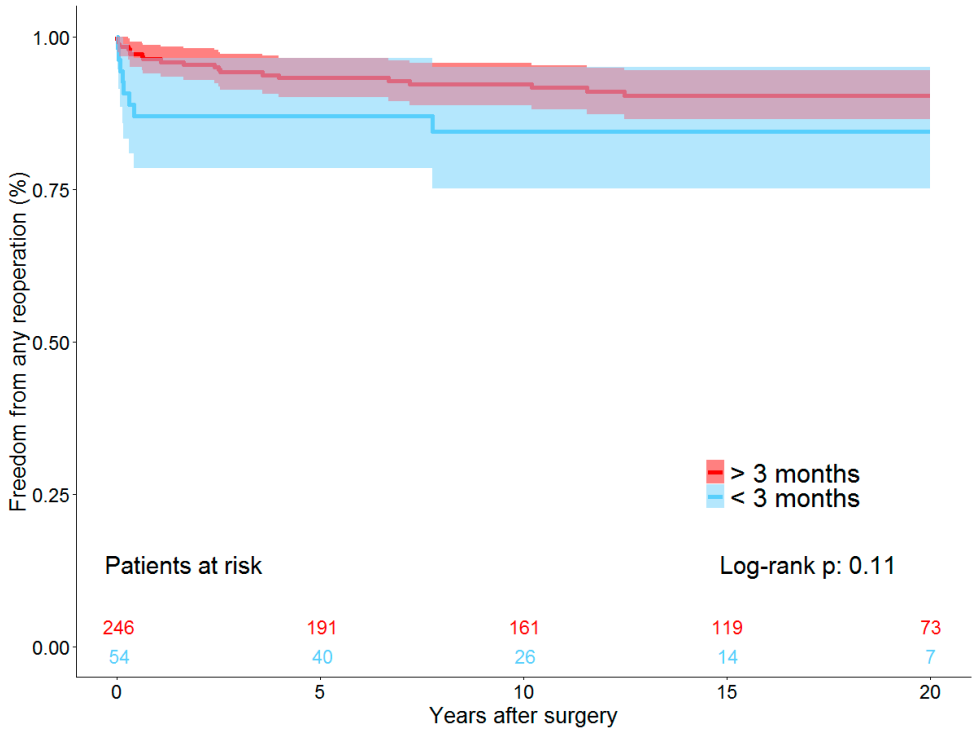

Figure II.3 Kaplan-Meier estimates of actuarial freedom from any reoperation after early surgical repair for cAVSD in younger infants (<3 months)versus repair in older infants (≥3 months) (P=.11). Shaded areas represents 95% CIs

4.3 Study III

4.3.1 Study population and patient follow-up

In study III we included a subgroup of 62 consecutive nonsyndromic patients who underwent surgical repair of complete AVSD between April 1993 and October 2018 at Skane University Hospital, Lund, Sweden. A total of 239 patients with trisomy 21 and 3 patients with other genetic syndromes were excluded. Follow-up was performed in January 2019 with a mean follow-up was 12.7 ± 7.9 years (median ,13.0; IQR 6.5-20.2). 2 patients were referred from abroad and late follow-up was not possible. Subsequently, 60 patients were included in the long-term survival and reoperation analysis.

The definition of concomitant complex cardiac anatomy has been described in chapter **3.1.3**

4.3.2 Patient characteristics

16 patients had complex cAVSD (26%) and 46 patients (74%) had noncomplex cAVSD. Patients in the complex cAVSD group more often presented associated noncardiac malformations compared with the noncomplex cAVSD group (31% vs 9%, OR 4.77, 95%CI 1.1-20.8; *P*=.01). Baseline characteristics are presented in Table III.1, and echocardiographic and intraoperative variables presented in Table III.2, stratified in complex vs noncomplex complete AVSD.

The anatomy of the LAVV did not differ between study groups except that a free-floating anterior bridging leaflet was significantly more common in the complex group, 31% vs 7% (OR, 6.52; 95%CI, 1.35-31.54; *P*=.02). We also found that durations of cardiopulmonary bypass (180 ± 60 minutes vs 117 ± 128 minutes) (OR, 1.04; 95%CI, 1.02-1.07; *P*<.01) and aortic crossclamping (106 ± 26 minutes vs 80 ± 23 minutes) (OR, 1.04; 95%CI, 1.02-1.07; *P*<.01) were significantly longer in the complex group. Deficient left mural leaflet was not found to be more common in complex cAVSD (*P*=.45) (Table III.2). However, incomplete cleft closure at valvuloplasty (8/13; 62%) was more frequent in patients with deficient left mural leaflet (OR, 0.06; 95%CI, 0.01-0.25; *P*<.001). Deficient left mural leaflet (OR, 0.08; 95%CI, 0.15-4.30; *P*=.58) or fragile/dysplastic LAVV leaflet (OR, 1.40; 95%CI, 0,25-7.86); *P*=.51) had no significant association with later reintervention, respectively.

Table III.1 Baseline characteristics of complex complete atrioventricular septal defect versus noncomplex complete atrioventricular septal defect

Values were expressed as number and percentage, or as mean ± standard deviation. OR, Odds ratio; CI, confidence intervall; DORV, double outlet right ventricle; NA, not available; TAPVR, total anomalous pulmonary venous return; VSD, ventricular septal defect; LSVC, left superior vena cava; TOF, tetralogy of Fallot; PS, pulmonary valve stenosis.

Characteristics	Complex n=16	Noncomplex n=46	OR (95%CI)	*P*
Age at repair (mo)	6.5 ± 7.4	5.0 ±3.5	1.06 (0.95-1.19)	.44
Weight at repair (kg)	5.8 ± 2.8	5.5 ± 1.6	1.07 (0.81-1.41)	.63
Female gender	10 (63)	28 (61)	1.07 (0.33-3.46)	.91
Associated cardiac malformations				
DORV	2 (13)	0 (0)	NA	NA
TAPVR	1 (6)	0 (0)	NA	NA
Additional VSD	7 (44)	0 (0)	NA	NA
Coarctation of the aorta	2 (13)	0 (0)	NA	NA
LSVC	6 (38)	0 (0)	NA	NA
TOF	3 (19)	0 (0)	NA	NA
PS/pulmonary atresia	2 (13)	0 (0)	NA	NA
Associated noncardiac malformations	5 (31)	4 (9)	4.77 (1.09-20.82)	.01
Premature (≤36 wk)	0(0)	3 (7)	NA	NA

Table III.2 Echocardiographic and intraoperative variables of complex complete atrioventricular septal defect versus noncomplex complete atrioventricular septal defect

Characteristics	Complex n=16	Non-complex n=46	OR (95%CI)	*P*
Intraoperative cardiac and AV-valve anatomy				
LAVV				
Double orifice	2 (13)	5 (11)	1.17 (0.20-6.73)	1.00
Closed commissures	6 (38)	6 (13)	3.90 (1.03-14.71)	.06
Extra cleft	1 (6)	5 (11)	0.55 (0.06-5.07)	1.00
Anterior bridging leaflet				
Divided over septum	3 (19)	10 (22)	0.83 (0.20-3-50)	1.00
Free floating	5 (31)	3 (7)	6.52 (1.35-31.54)	.02
Deficiency of left mural leaflet	4 (25)	9 (20)	1.37 (0.36-5.26)	.45
LV single papillary muscle head				
Fragile/dysplastic leaflet	2 (13)	3 (7)	2.05 (0.31-13.53)	.60
	4 (25)	5 (11)	2.73 (0.63-11.81)	.17
Echocardiographic findings				
Nonrestrictive VSD	13 (81)	30 (65)	2.31 (0.573-9.32)	.23
Unbal. AV valve/ventricle	1 (6)	4 (9)	0.70 (0.72-6.77)	1.00
Preop severe AV valve regurgitation/heartfailure	1 (6)	6 (13)	0.44 (0.05-4.01	.67
Surgical repair				
CBP time (min)	180 ± 60	117 ± 28	1.04 (1.02-1.07)	<.01
Aortic crossclamp (min)	106 ± 26	80 ± 23	1.04 (1.02-1.07)	<.01
2-patch technique	15 (94)	35 (76)	4.71 (0.56-39.85)	.16
Coronary sinus in RA	14 (93)	44 (96)	0.64 (0.05-7.56)	.72
Complete cleft closure	11 (69)	39 (85)	0.40 (0.11-1.49)	.27

4.3.3 Mortality

Perioperative mortality (30-day plus in-hospital mortality) was 3.2% (2/62). The first patient required intensive preoperative care including resuscitation on multiple occasions. 17 days after primary repair, the patient died of a circulatory collapse. The second patient had a staged repair of coarctation in the neonatal period. At primary repair, concomitant multiple VSDs and fragile valve leaflets lead to a replasty at postoperative day 30. The patient eventually died at postoperative day 68, while still in the hospital. Two additional late deaths occurred, 1 patient died at home on postoperative day 57, and 1 patient died 6 years after the cAVSD repair. Actuarial survival was significantly better in the noncomplex group when compared with the complex group: 100% vs 77.8% ± 9.8% at 5 years, and 100% vs 66.7% ± 14.9% at 10 years, respectively (*P*=<.01) (Figure III.1)

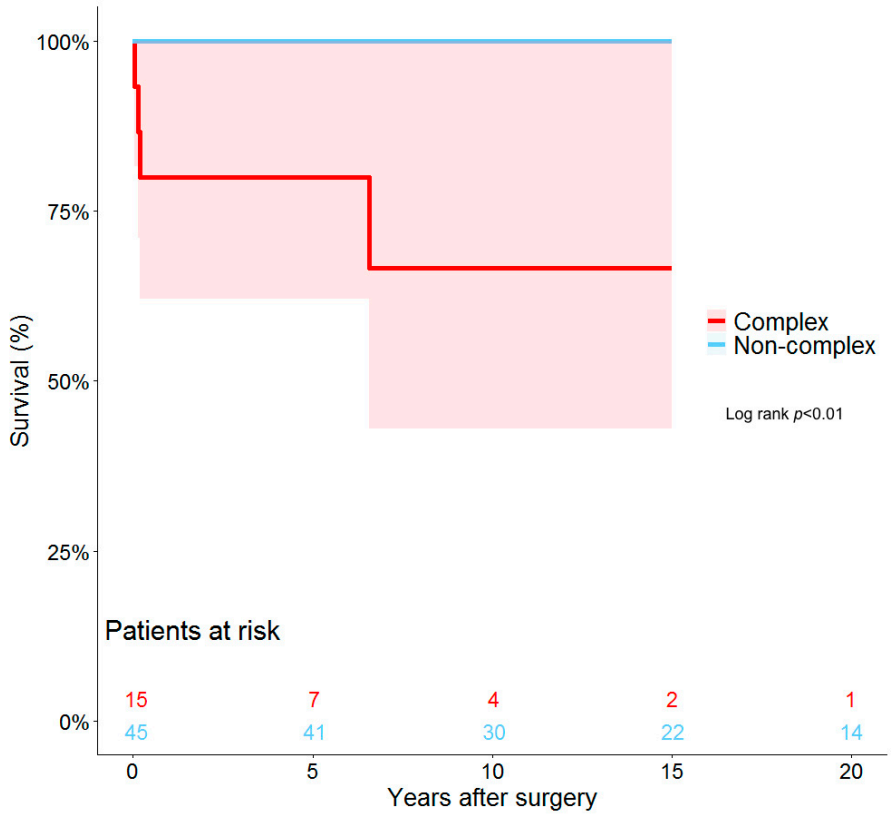

Figure III.1 Actuarial survival after surgical repair in complex cAVSD versus noncomplex cAVSD in a nonsyndromic population (P<.01). Shaded area represents 95%CI

4.3.4 Reoperations

Overall, 11 patients underwent a total of 18 reoperations. All reoperations are presented in Figure III.2

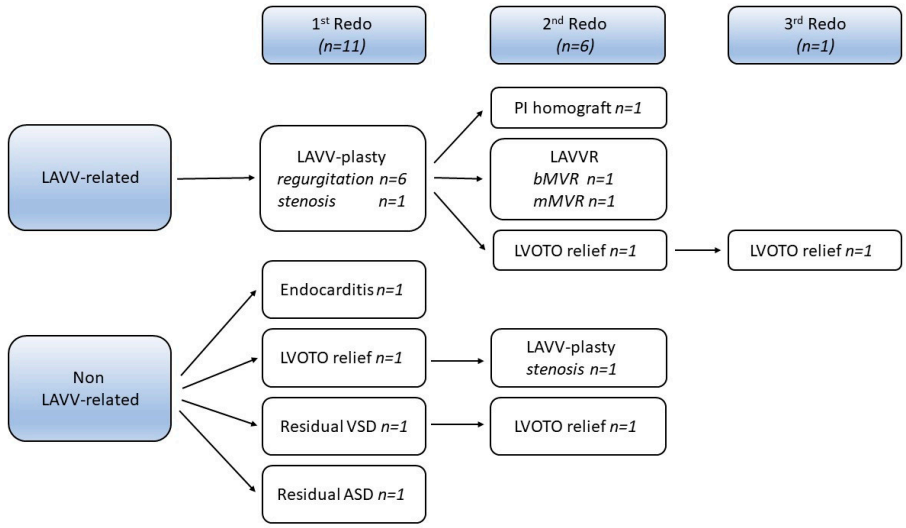

Figure III.2 Patient flowchart for all reoperations

LAVV, Left atrioventricular valve; PI, pulmonary insufficiency; LAVVR, left atrioventricular valve regurgitation; bMVR, biological mitral valve replacement; mMVR, mechanical mitral valve replacement; LVOTO, left ventricular outflow tract obstruction; VSD, ventricular septal defect; ASD, atrial septal defect

The median time to first reoperation was 3.7 months (IQR, 0.6-20) after primary repair. Six of the 11 reoperated patients required a replasty of the LAVV at first redo procedure due to significant regurgitation. In 1 patient, LAVV stenosis with a mean gradient of 17 mmHg was the primary indication for reoperation. A second reoperation was required in 6 patients (3 in the complex group and 3 in the noncomplex group) at 31.2 months (IQR, 8.2-149.8) after primary repair. There was no significant difference in reoperation rate between the complex group (4/16; 25%) and the noncomplex group (7/46; 15%) (OR, 1.86, 95%CI, 0.46-7.45; *P*=.30). Overall mortality after reoperation was 9.1% (1/11), with an incidence of reoperation at 1 and 10 years postoperatively in the complex vs the noncomplex group of 20.0% (95%CI, 0-41.1) vs 13.3% (95%CI, 0-31.2) and 29.5% (95%CI, 3.0-56.0) vs 27.6% (95%CI, 0-60.0), respectively.

Cumulative incidence function of reoperation by complexity status analyzed with death as a competing risk demonstrated no statistically significant difference between groups (*P*=.28) (Figure III.3)

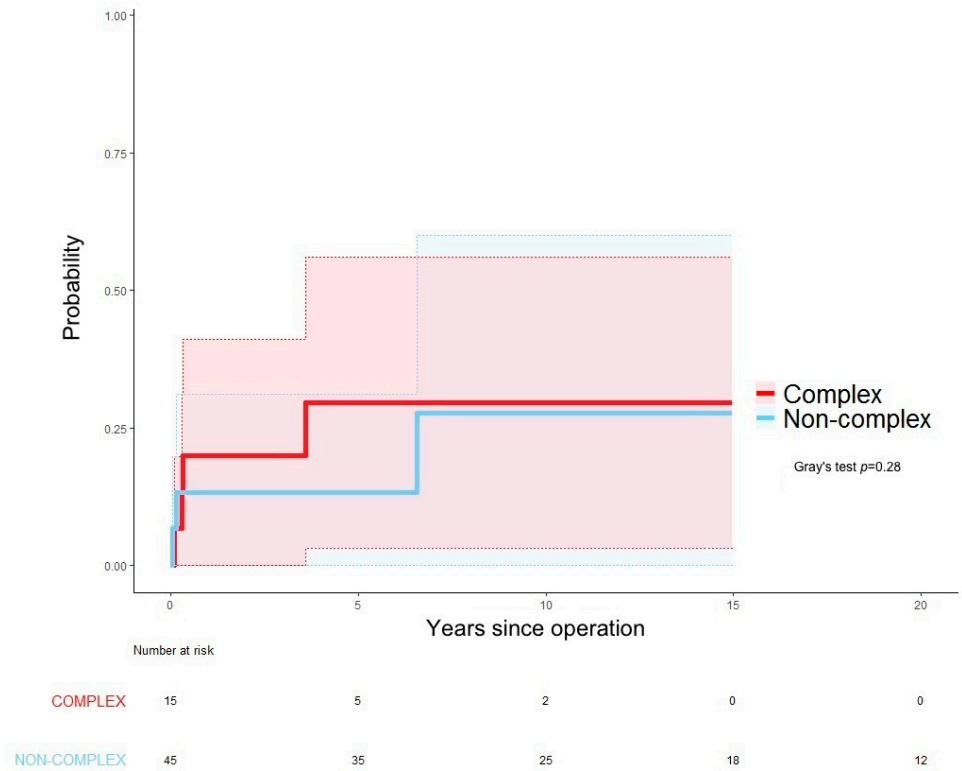

Figure III.3 Cumulative incidence function of reoperation by complexity status analyzed with death as a competing risk. Gray´s test was used to test equality of the cumulative incidence curves between groups

4.4 Study IV

4.4.1 Study population and patient follow-up

In study IV we included 477 consecutive patients who underwent initial surgical repair of AVSD of all types, between April 1993 and October 2020. We identified 53 patients needing reoperation who were included in our study population. The cohort of patients who did not need reoperation allowed for identification of risk factors for reoperation and evaluation of overall survival after primary repair in a competing risk scenario.

6 patients were lost to follow-up (5 of whom had moved abroad, and one was untraceable). Subsequently, 471 patients were included in the survival analysis. In

addition, during 1993-2020 a total of 8 patients were allocated to a palliative single ventricle pathway and were not included.

We identified 53 patients (11.1%) who underwent a total of 82 reoperations (Figure IV.1). All 53 reoperated patients had initial repair performed at our institution and no reoperated patient was lost to follow-up. The baseline characteristics of the study population undergoing reoperations are presented in Table IV.1.

4.4.2 Results

The median age at the time of first reoperation was 1.9 years; (IQR 0.4-6.0 years); pAVSD age was 5.1 years (IQR 1.0-22.6 years), tAVSD age was 2.4 years (IQR 0.8-5.5 years), and cAVSD age was 1.9 years (IQR 0.35-5.6 years). The median interval between initial surgical repair and first reoperation independent of type of AVSD was 1.1 years (IQR 0.2-3.9 years). For pAVSD, the interval was 1.9 years (IQR 0.2-16.1 years); for tAVSD 1.1 years (IQR 0.2-3.9 years); and for cAVSD 0.9 years (IQR 0.3-3.9 years).

In patients undergoing reoperation there were significantly more patients with TOF 6% vs 1.2% (*P*=.050), incomplete commissures 23% vs 11% (*P*=.013), LV single papillary muscle head 11% vs 3% (*P*=.013), unbalanced AV-valves/ventricles 13% vs 3% (*P*=.002), incomplete cleft closure 23% vs 11% (*P*=.035) and severe LAVVR 9% vs 0% (*P*<.001). (Table IV.1)

4.4.3 Mortality and long-term survival

Perioperative mortality in reoperated patients was 3.8% (2/53). There were no late deaths after hospital discharge in the study group. Overall survival stratified for Any reoperation versus No reoperation during follow-up was 96.2 ± 2.6% (95%CI 91.2-100) vs 96.7 ± 0.9 (95%CI 94.9-98.5) at 20 years, respectively, (*P*=.80). (Figure IV.2)

Table IV.1Patients undergoing reoperation after primary repair for AVSD
*per years increment; **per kilo increment

Characteristic	Reoperation n=53	No reoperation n=418	*P* value
AVSD subtypes			
pAVSD	4 (8)	74 (18)	
tAVSD	17 (32)	71 (17)	
cAVSD	32 (60)	272 (65)	.012
Age at primary repair* (y)	1.0 ± 2.3	1.6 ± 3.2	.081
Weight at primary repair** (kg)	7.5 ±7.3	9.3 ± 10.7	.121
Female gender	27 (51)	227 (54)	.644
Trisomy 21	21 (40)	253 (61)	.004
Associated cardiac malformations (any)	18 (34)	104 (25)	.155
Coarctation	2 (3.8)	11 (3)	.648
Tetralogy of Fallot	3 (6)	5 (1.2)	.050
Prior cardiac/palliative surgery	4 (8)	17 (4)	.248
Double orifice LAVV	2 (4)	15 (4)	.946
Incomplete commissures	12 (23)	45 (11)	.013
Extra cleft	7 (13)	38 (9)	.340
LV single papillary muscle head	6 (11)	13 (3)	.013
Unbalanced AV-valves/ventricle	7 (13)	11 (3)	.002
Cleft closure at primary repair			
Complete	41 (77)	367 (89)	
Incomplete	12 (23)	46 (11)	.035
Residual mitral regurgitation			
None/mild	39 (74)	389 (93)	
Moderate	9 (17)	29 (7)	
Severe	5 (9)	0	<.001

4.4.4 Reoperations after primary repair for AVSD

Main indications for all first reoperations are listed in Table IV.2.

The cumulative incidence function of Any reoperation (with death as competing risk) was 13.0% (95%CI 9.4-16.5) at twenty years) (Figure IV.3).

Independent risk factors for Any reoperation were concomitant TOF (HR, 6.13 95%CI 1.86-20.2; *P*=.003), Unbalanced AV-valves/ventricles (HR, 5.24 95%CI 2.30-11.9; *P*<.001), moderate LAVVR (HR, 2.88 95%CI 1.37-6.05; *P*=.005), severe LAVVR (HR, 40.7 95%CI 14.9-111; *P*<.001). Trisomy 21 was protective of any reoperation (HR, 0.51 95%CI 0.29-0.90; *P*=.019) (Table IV.3).

Left atrioventricular valve pathology was the main indication for first reoperation in 28 patients (53%). In addition, one patient with LAVV pathology was assessed for re-repair after previous LVOTO relief and included in the re-repair cohort. In total, a LAVV re-repair was performed in 90% (26/29) of patients evaluated first time for LAVV pathology Perioperative findings of the LAVV at first repair are presented in Table IV.5. All LAVV repair procedures used at first re-repair are presented in Table IV.6 (Supplemental). Six patients undergoing LAVV re-repair required a second reoperation for LAVVR pathology. At follow-up, 19 of 24 operative survivors (79%) treated with re-repair for LAVV pathology, were still prosthesis-free.

The cumulative incidence function of reoperation for LAVVR (with death as competing risk was 6.9% (95%CI 4.2-9.6) at 20 years (Figure IV.3).

Independent risk factors for LAVV-related reoperation are presented in Table IV.4 (Supplementary material). Replacement with a prosthesis in the LAVV was performed in 3 patients at first reoperation. All 3 needed a permanent pacemaker implantation at a second reoperation. A total of 8 patients eventually had their LAVV replaced with a prosthetic valve.

LVOTO was the second most common indication for first reoperation (16/53) after initial repair. LVOTO was relieved by membrane resection or myectomy or both. Of the total number of reoperation procedures during follow-up, 27 reoperation procedures were related to LVOTO pathology.

Table IV.2 Indications for first reoperation after primary repair for AVSD
*Six patients were lost to follow-up (2 with pAVSD and 4 with cAVSD)
Values presented as number and percentages (%)

Indication for reoperation	pAVSD	tAVSD	cAVSD	Total
Number of primary repairs	78 (16.6)	88 (18.7)	305 (64.8)	471 (100)*
LAVV pathology	2 (2.6)	9 (10.2)	17 (5.6)	28 (5.9)
LVOTO	1 (1.3)	6 (6.8)	9 (3.0)	16 (3.4)
Residual shunt	1 (1.3)	2 (2.3)	4 (1.3)	7 (1.5)
Pacemakerimplantation	0 (0)	0 (0)	2 (0.7)	2 (0.4)
Total	**4 (5.1)**	**17 (19.3)**	**32 (10.5)**	**53 (11.1)**

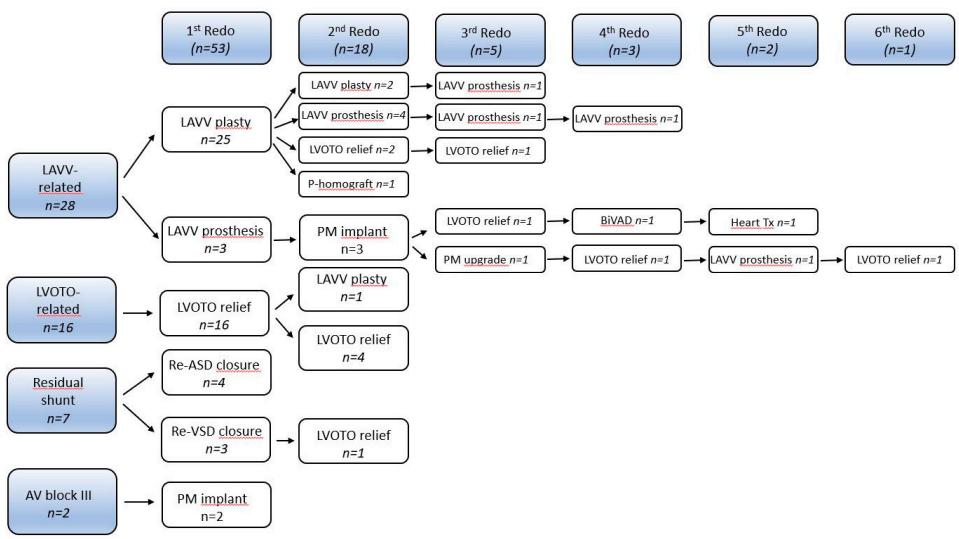

Figure IV.1 All-cause reoperations in AVSD population (1993-2020)

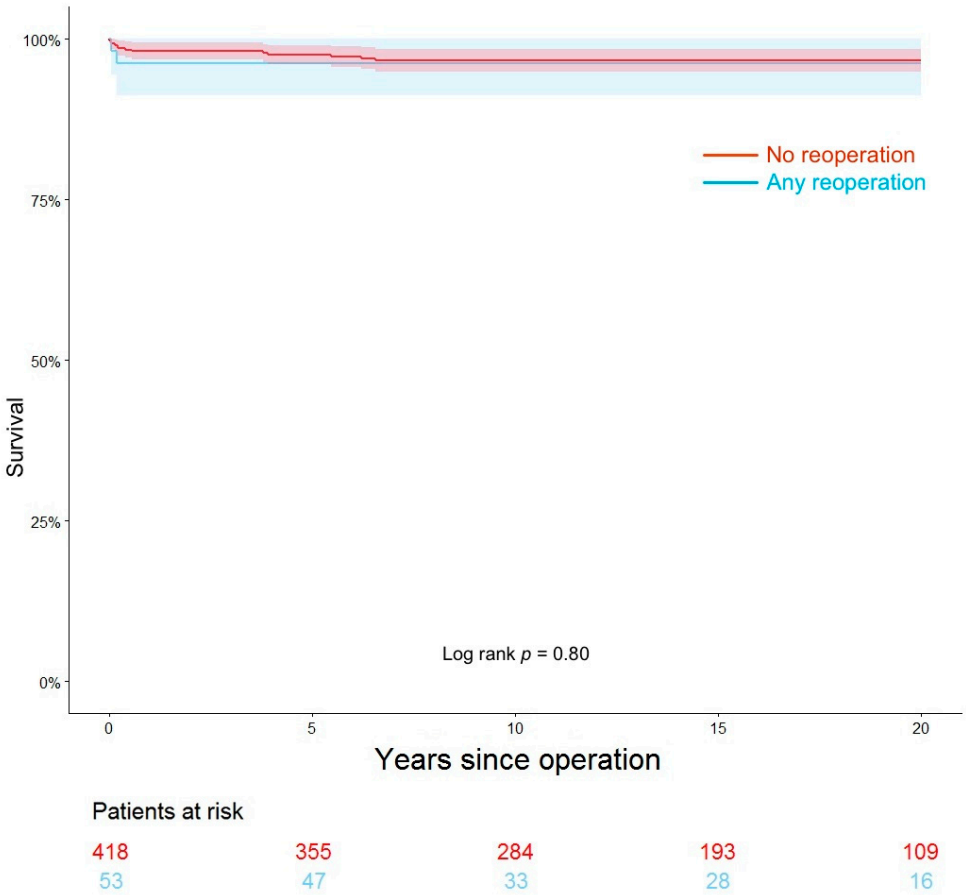

Figure IV.2 Estimated overall survival for patients undergoing Any reoperation vs. No reoperation during follow-up after primary AVSD repair (n = 471). Shaded areas represent 95% CI

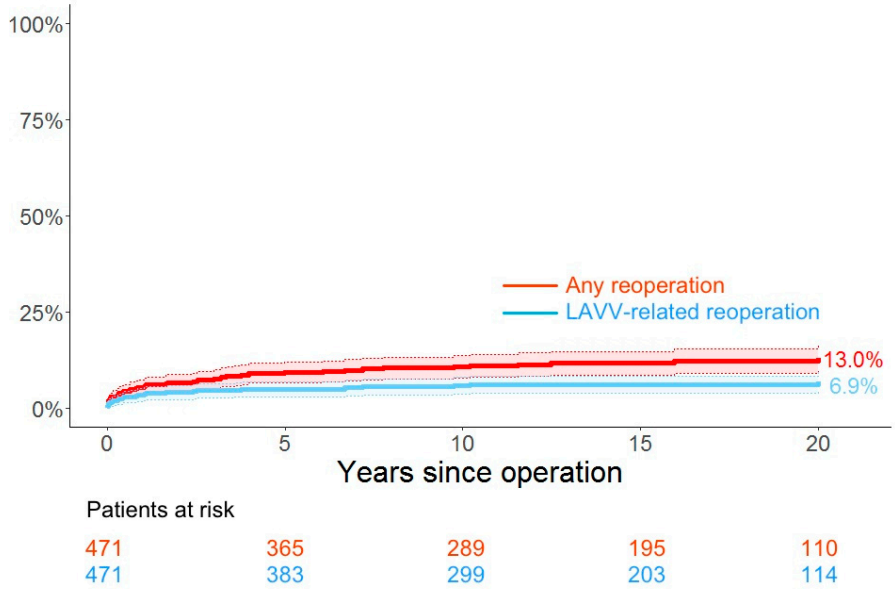

Figure IV.3 Cumulative incidence function of Any reoperation and Reoperation for LAVVR with death as a competing risk (n=471). Shaded areas represent 95% CIs

Table IV.3 Univariable and multivariable analysis of risk factors for any reoperation after repair of AVSD

Characteristic	Univariable HR (95%CI)	*P* value	Multivariable HR (95%CI)	*P* value
AVSD subtypes				
pAVSD	1			
tAVSD	5.11 (1.72-15.4)	.003		
cAVSD	1.96 (0.69-5.55)	.206		
Age at primary repair (y)	0.99 (0,98-1.01)	.276		
Weight at primary repair (kg)	0.98 (0.94-1.02)	.367		
Female gender	0.93 (0.54-1.60)	.797		
Trisomy 21	0.39 (0.22-0.67)	.001	0.51 (0.29-0.90)	.019
Associated cardiac malformations	1.78 (1.00-3.14)	.049		
Coarctation	1.79 (0.44-7.36)	.421		
Tetralogy of Fallot	5.15 (1.59-16.7)	.006	6.13 (1.86-20.2)	.003
Prior cardiac/palliative surgery	2.06 (0.74-5.70)	.166		
Double orifice LAVV	1.05 (0.25-4.31)	.950		
Incomplete commissures	3.00 (1.56-5.77)	.001		
Extra cleft	1.63 (0.73-3.62	.230		
LV single papillary muscle head	3.29 (1.40-7.69)	.006		
Unbalanced AV valve/ventricles	5.24 (2.36-11.6)	<.001	5.24 (2.30-11.9)	<.001
Incomplete cleft closure	2.43 (1.28-4.63)	.007		
Residual mitral regurg.				
None/mild	1			
Moderate	3.65 (1.76-7.59)	.001	2.88 (1.37-6.05)	.005
Severe	69.4 (24.5-197)	<.001	40.7 (14.9-111)	<.001

Table IV.4 Supplementary. Univariable and multivariable analysis of risk factors for reoperation for LAVVR after primary repair of AVSD

Characteristics	Univariable HR (95%CL)	*P* value	Multivariable HR (95%CL)	*P* value
pAVSD	1			
tAVSD	4.45 (0.96-20.6)	.057		
cAVSD	2.2 (0.51-9.52)	.291		
Age at primary repair (y)	0.99 (0.97-1.01)	.213		
Weight at primary repair (kg)	0.94 (0.86-1.03)	.176		
Female gender	1.13 (0.54-2.40)	.743		
Trisomy 21	0.32 (0.14-0.70)	.005	0.46 (0.19-0.98)	.046
Associated cardiac malformations	1.71 (0.79-3.71)	.173		
Coarctation	3.40 (0.81-14.3)	.095		
Tetralogy of Fallot	5.22 (1.23-22.1)	.025	9.08 (2.02-40.9)	.004
Prior surgery/palliative surgery	3.03 (0.92-10.0)	.070		
Double orifice LAVV	0.97 (0.13-7.17)	.979		
Incomplete commissures	1.36 (0.47-3.93)	.568		
Extra cleft	1.62 (0.56-4.68)	.371		
LV single papillary muscle head	2.99 (0.90-9.89)	.073		
Unbalanced AV valve/ventricles	7.07(2.69-18.62)	<.001	6.73 (2.38-19.1)	<.001
Incomplete cleft closure	2.15 (0.87-5.32)	.096		
Residual mitral regurg.				
None/mild	1			
Moderate	4.65 (1.83-11.8)	.001	3.98 (1.50-10.5)	.005
Severe	73.8 (25.6-213)	<.001	87.6(28.7-267)	<.001

Table IV.5 Perioperative findings in LAVV at re-repair
*More than one pathologic finding may have been present in any given patient

Pathology*	n	%
Repair dehiscence	15	58
Residual cleft	7	27
Dysplastic leaflet tissue	7	27
Stenosis after prior repair	4	15
Abnormal leaflet pliability	3	12
Leaflet perforation	3	12
Leaflet prolapse/tethering	2	7
Double orifice	2	7
Deficient mural leaflet	1	4
Additional cleft (previously unrepaired	1	4
Septation patch dehiscence	1	4
Myxomatous leaflet tissue	1	4
Chordal rupture	1	4

Table IV.6 Supplementary. Intraoperative repair techniques at first re-repair for LAVVR
*More than one repair technique may have been performed in any given patient

Repair technique*	n	%
Cleft/Zone of apposition repair	19	73
Re-closure	19	73
Primary closure	0	0
Papillary muscle splitting	6	23
Leaflet perforation repair	2	8
Commissurplasty LAVV	1	4
Partial posterior annuloplasty	1	4
Posterior leaflet expansion	1	4
Chordal readaptation	1	4
Double orifice closure	1	4

5 Discussion

Atrioventricular septal defect (AVSD) is a complex malformation affecting the atrioventricular septum and the formation of the atrioventricular inlet valves with the basic characteristic being a common atrioventricular junction with either a common valve orifice or two valve orifices. The surgical understanding of this complex lesion was promoted by two important events, the publication by Becker and Anderson in 1982, proposing a new nomenclature to precise and accurate describe hearts with AVSD (1) and the introduction of cross-sectional echocardiography (2). Combining morphological sections of the heart with echocardiographic visualization further advanced the understanding of AVSD (110, 111).

In **study I** we evaluated the accuracy of both 2D and 3D imaging in 26 specified features of the AV-valve complex in children with AVSD, using the surgical description as reference method. In a previous study, Van den Bosch and co-workers(25) showed, using surgical description as gold standard, that 3D echocardiography was highly accurate in assessing the Rastelli classification and depicting the morphology of the inferior bridging leaflet by its attachment to the crest of the ventricular septum. However, in this relatively small sample, other features of the AV-valve were not assessed. Precise visualization of the whole AV-valve complex is a key determinant of appropriate preoperative preparation, and its underestimation may lead to impaired patient outcomes (93). Therefore, in our study we evaluated 520 valve features in 20 patients. Abnormalities were found in 57 (11%) out of 520 AV-valve features. 2D and 3D were accurate in 79% vs 83%. We also showed that, in most cases where it was not possible to visualize the feature by 2D, it was possible by 3D, and vice versa. This information is of key importance when combining the two methods in clinical practice (23).

Centralization of paediatric cardiac surgery in Sweden

In late 1992 Sweden´s paediatric cardiac surgery centers were centralized to two centers of similar size with regionalized care and a geographical referral pattern (112). Sweden's centralization strategy has not only allowed for a sufficient patient volume but also facilitated recruitment of highly trained staff at all levels of support with significant improvements in surgical results (112). The importance of centralization and regionalization is supported by several authors. Welke and colleagues (113) published in 2020 a theoretical model for delivery of congenital

heart surgery in the United States. They found that a threshold of >300 CHS operations per year was optimal and the only one supported by data (114). Further, they estimated a median hospital volume of 451 operations with a median travel distance of 35.1 miles, following the concept that the number of CHS hospitals in the United States could be reduced while simultaneously shortening patient travel distances (113). Sakai-Bizmark and co-workers studied the effect of regionalization in 33,288 patients undergoing paediatric cardiac surgery at 180 hospitals. Their report, based on statewide inpatient data from 11 states that collectively represent 46% of the US population, the authors concluded that regionalization reduced mortality and cost, indicating fewer complications, but paradoxically increased length of stay (115).

In **study II**, we showed excellent long-term survival and durability of the LAVV repair. Furthermore, we could not demonstrate any significant difference in long-term survival or LAVV related reoperation nor any reoperation after repair of cAVSD in young infants (<3 months old) when compared with older infants even though early repair is considered more challenging, and previous reports have advocated palliative procedures in complex patients. (102, 116, 117). Since the beginning of the 1990s our department has used 3 to 4 months of age as our standard preference for correction of cAVSD. Our study shows that median age at time of repair did not change significantly over the study period which agrees with a recent study from Finland (29). In patients who are stable on medical treatment surgical correction seems to be optimal at 3 to 4 months of age. However, in patients who develops early pharmacological refractory congestive heart failure, correction in the very first months of life is necessary and preferable to palliative procedures. (118). In the present study approximately 20% of the patients underwent repair as young infants due to deteriorating clinical status, which is similar to rates reported by Suzuki and co-workers (119). Our present findings indicate a greater disease burden in the young infants with a significantly higher presence of risk factors such as prematurely born children and low weight infants. Furthermore, unbalanced AV valves/ventricles and severe preoperative AV regurgitation were more frequent in young infants undergoing LAVV repair (Table II.1 and Table II.2) Finally we found that infants less than 3 months of age less often had complete cleft closure which may be explained by our surgical strategy to avoid LAVV stenosis. However, our findings differ from the results in a recent study of patients undergoing primary correction aged less than 3 months, in whom no significant difference in cleft closure was found. (104). In our study, we could not demonstrate any difference in long-term survival or LAVV related reoperation in young infants when compared with older infants. However, there was a trend, 90.2% versus 96.1%, toward impaired long-term survival in young infants, but this finding was not statistically significant (P= .079). The current literature presents contradicting results with some studies indicating an increased risk of longer hospital stay (120) or mortality (30, 105), whereas other studies demonstrate similar results in both age groups (29, 55,

102-104). The early repair group, in our study, presented more often with coarctations of the aorta and noncardiac malformations compared with patients undergoing elective repair as older infants. Our treatment strategy in patients with cAVSD and coarctation of the aorta is to perform the surgery for aortic arch obstruction in the neonatal period and delay the cAVSD repair out of the neonatal period with pharmacological therapy and avoiding concomitant pulmonary artery banding.(118). A similar strategy, performing pulmonary artery banding at the time of coarctation surgery have been shown to generate superior survival compared to performing cAVSD repair with concomitant aortic arch repair in the neonatal period (121). There were only 3 patients undergoing cAVSD repair in the neonatal period in our study population, one of these patients needed a concomitant aortic arch repair.

Freedom from LAVV reoperation after cAVSD repair was 92.6% at 20 years in our present study which is similar to other recent studies (29, 104). Independent predictors of LAVV related reoperation were a persistent LSVC, presence of unbalanced AV valve/ventricles and, severe AV valve regurgitation preoperatively. Most of these risk factors will cause valve repair to be more technically challenging. However, our present data did not show a difference in need for reoperation between the age groups. Our results follow the findings of other studies (104, 122).

Nonsyndromic patients with cAVSD are often regarded as a high-risk population for surgical repair. However, in **study III**, our present data suggest that the subset of nonsyndromic patients with no concomitant complex cardiac anatomy may be repaired with good long-term survival and an acceptable risk of reoperation. On the other hand, the corresponding group with concomitant complex cardiac anatomy show significantly higher mortality rates and still proves to be a high-risk population. In our opinion, the complexity of the concomitant cardiac lesions is the crucial determinant of patient prognosis and not the karyotype itself.

The current study is supported by contemporary data from Dhillon and co-workers (13) demonstrating an improved trend in hospital mortality for nonsyndromic patients in the last decade. Our current study showed 12% perioperative mortality in the complex group but no mortality in the noncomplex group. In a recent publication, Mery and colleagues (84)[Mery et al 2018] reported perioperative mortality of 4% in complex cAVSD (patients with concomitant TOF, DORV, TAPVR, or aortic arch repair) compared with 2% in noncomplex cAVSD. Previous authors have presented similar results including early mortality rates of 4% to 8% (71, 72, 74, 75, 77) in patients with concomitant TOF or DORV, with the exception of Hoohenkerk and colleagues, who found no early mortality in a cohort of 20 patients with a combination of cAVSD and TOF.

We believe the differences in perioperative mortality may be explained in part by the differences in the variables used for inclusion in the complex group. In the present study, we focused on variables representing cardiac anatomic complexity

and adopted Mery and colleagues´(84) previously used criteria for complex cAVSD, which included concomitant TOF, DORV, TAPVR, and concomitant arch repair. (84). In addition, we included further anatomic lesions such as multiple VSDs, staged repair of CoA, and a persisting LSVC. The increased surgical complexity caused by most of these variables seems intuitive, whereas a persisting LSVC may seem more benign at first impression. However, there may be a potential relationship between a persistent LSVC and abnormalities during fetal development in the secondary heart field. (123). Postema and co-workers (124) demonstrated an association between a persistent LSVC and cardiac and extracardiac anomalies and suggested that the combination of LSVC with heart defects like TOF and AVSD might then be a part of a continuum of abnormalities in the secondary heart field. This variable may also be of importance due to the direct effect of the dilated coronary sinus, both as potential restriction of LAVV-annular growth and a deviation of inflow towards the right side of the heart.

Previous studies evaluating outcome after cAVSD repair in patients with concomitant complex cardiac lesions have presented a mixed cohort of patients with trisomy 21 and nonsyndromic patients making outcome data difficult to compare. In the study by Mery and colleagues, trisomy 21 was present in 87% of isolated cAVSD but also in 63% of patients with complex cAVSD. Hypothetically, the protective effect of Trisomy 21 might influence outcome.

We could not identify any significant difference in the probability for reoperation when performing a competing-risk analysis between the complex and the noncomplex group. Our intraoperative AV valve findings (Table III.2) showed similar findings between the complex and the noncomplex groups except for free-floating anterior bridging leaflet being, as expected, more frequent in the complex group. In contrast to Suzuki and colleagues,(119) we could not identify any significant correlation between deficient left mural leaflet and reoperation. We found a trend towards higher reoperation rate in the complex group /25%) when compared with the noncomplex group (15%) but it did not reach statistical significance (P=.30). Mery and colleagues reported a 10 year incidence of reoperation of 20% in the complex group (84), whereas others have described even higher reoperation rates ranging from 25% to 55% in the most complex subgroup (71, 74, 75). Several authors have reported superior long-term prognosis in patients with cAVSD with Trisomy 21. (12, 53, 71). In our nonsyndromic cohort the first reoperation was at a median of 2.7 months after initial repair, 7 of 11 reoperations being LAVV-related procedures, which is similar to data from Pontailler and colleagues.(87) Other centers have reported median intervals of 1.1 to 2.5 years for reoperation, primarily caused by LAVV-related operations.(12, 53, 55, 86). In contrast, Mery and colleagues (84) reported a median time to first reintervention of 3 years after primary repair with the majority of reoperations being conduit replacements. Likewise, a previous report from Shuhaiber and colleagues (72) demonstrated conduit replacements as a common indication for reoperation with a

significantly shorter time to reoperation in patients with a conduit. In our sample, 21% of complex patients had TOF and11% had DORV of Fallot type, all of whom could be repaired initially without the use of a conduit compared with the report by Mery and colleagues, in whom 61% of those with complex cAVSD had concomitant TOF and 13% had DORV.

In **study IV** we evaluated the total burden of reoperations in a consecutive cohort undergoing primary repair for AVSD. Our data showed that reoperation was relatively common (11.1%), but the mortality was low. We could not find any significant difference compared to patients who did not undergo reoperation. Re-repair was possible in most cases with very good long-term durability. Valve replacements often required subsequent surgical procedures, especially pacemaker implantations.

Most studies evaluating reoperations after AVSD repair have focused on LAVV pathology. (86, 87, 92). The procedures related to other causes than LAVV may be significant, both in number and surgical complexity. and have an impact on long-term survival. Sojak and colleagues (91) evaluated all reoperations after initial repair in a mixed AVSD cohort. In their study 34% of the procedures at first reoperation were not LAVV-related. In comparison, we found that 47% of the procedures were related to other causes than LAVV during follow-up (median 14.1 years).

In our present study we found a mortality of 3.8% (2/53) at reoperation which is similar to some studies (86, 92, 125). These two patients were both of cAVSD subtype and had early reoperation (postoperative day 3 and day 30 respectively) in line with previous studies suggesting that early reoperation for LAVV dysfunction is associated with poor outcome (87). Unbalanced AV/ventricles, concomitant Tetralogy of Fallot, moderate and severe LAVV regurgitation were identified as independent risk factors of LAVV-related reoperation, as well as for Any reoperation. (Table IV.3 and Table IV.4). These findings are clinically intuitive and similar to previous reports (86, 87, 91).

The cumulative incidence function of Any reoperation, using death as competing risk, was 13% and 6.9% for LAVV-related reoperation at 20 years. The overall need of reoperation after initial repair for AVSD was 11% which is similar to previous studies. (14, 60, 87, 91, 105, 106).There were no late deaths in our reoperated cohort, and we could not demonstrate any difference in long-term survival at 20 year follow up between patients having a reoperation (96.2%)or not (96.7%); *P*=0,8. Our results are similar or better than previous reports (86, 87, 91). Repair of a previously repaired valve due to LAVVR can be technically demanding. Still, our repair rate was 90% which is higher than some reports (46, 91) but similar to a series presented by Pontailler and colleagues (87). Dehiscence of previous repair, a residual cleft or dysplastic leaflet tissue were the most common findings at re-repair. To close the cleft at initial repair is commonly acknowledged as important to avoid future

reoperations (40, 86, 125). The most common re-repair technique in our study was re-closure of the cleft, sometimes with papillary muscle splitting made to increase the mobility of the leaflets. In order to close the cleft as often as possible without consumption of valve tissue, we have used interrupted 7-0 monofilament polypropylene sutures placed as figure-of-8 stiches and taking care to maintain as much coaptation height as possible when the LAVV cleft is closed.(46).

The time to reoperation in our cohort was shorter than described by Stulak and colleagues.(109). Previous studies have argued that early repair of the LAVV may prevent dysplastic changes that render it unrepairable (91). We believe that repeated, routine echocardiography during follow-up has helped identify patients at an early stage, that previously may have been missed due to lack of clinical findings. In our clinical experience, advanced secondary changes in the valve leaflets after longstanding LAVV regurgitation are now less common. Our present data support this since only 38% of subsequent procedures after the first reoperation were LAVV-related, which lower than previous studies (91). At the last follow-up, 19 of 24 operative survivors (79%) treated with re-repair for LAVV pathology were still prosthesis free, which is better than the results in previous reports (87, 91).

Of the total number of reoperations (n = 82) there were 27 procedures (33%) performed in 21 patients related to LVOTO pathology. (Figure IV,1). Myers and co-workers presented 35 LVOTO-reliefs at first reoperation with a recurrence rate of 20% (7/35) which is similar to our study showing a recurrence rate of 25% (4/16) (126). The Konno procedure was not performed in any patient, which is similar to the series by Devlin and coworkers (106), but in contrast to other studies (91, 126, 127). In a report from Sojak and colleagues, mortality after the Konno procedure was noticeable as in the study by Myers and coworkers (91, 126). Although these series include complex patients, this indicates that some reoperations for LVOTO should be addressed with special attention. Our data suggests it may be preferable to perform a less radical measure when feasible and instead accept a possible recurrence in the future since the reoperation procedures *per se* seem to carry a low mortality risk when performed in a large volume center. We believe that the Konno procedure should be considered only in selected cases, and when indicated, patients should be referred to large-volume centers due to the complexity of the procedure.

5.1 Study limitations

In **study I** patients were evaluated by the same operator, often first with 2D and then with 3D, so the methods were not blinded to each other. Both modalities were however biased at the same time, which does not favor one of them only. Moreover, reassessment of the images was done by the surgeon after the procedure, so the subjective interpretations and influences from another modality that might have played a role before the surgery were eliminated. The surgical assessment was considered as a reference for all features, although there are features that were better visualized with echocardiography (such as the grade and location of the insufficiency). The number of patients in the study was limited to 20; however, it is not the actual number of patients, but rather 26 AV-valve features in each patient that were studied, which makes a total number of examined AV-valve features 520.

Study II was a retrospective study with the inherent limitations in this type of study design. Furthermore, the estimates of late survival and reoperation are, despite a relative largely population with long follow-up, based on few events. Finally, although this is an all comers-inclusion series with pediatric cardiac surgery referrals representing half of the Swedish population, it is still a single-center study and it is not always possible to generalize data from single-center studies to the surgical community.

Study III has all the inherent shortcomings of a retrospective study, and because the study design excluded all patients with trisomy 21, it also has a somewhat limited sample size. Furthermore, given the relatively small sample, there may be an inability to account for confounders despite the use of advanced statistical techniques. Overall, the complex group is a heterogeneous group that includes a variety of pathologies that probably convey different implications. However, being 1 of only 2 Swedish centers for pediatric cardiac surgery gives us a referral area of approximately 5 million inhabitants, which previously has provided us with one of the largest reported cohorts of patients with cAVSD. Although cAVSD is a relatively common congenital heart defect, all studies on its subcategories are at risk of being underpowered.

Limitations of **study IV** include its retrospective nature, the relatively small number of events, and its single center study design. Since populations studying reoperations are rather small by nature and some events have low rates the findings following some complex statistical analyses, even though correctly performed, may have to be interpreted cautiously.

6 Conclusions

6.1 Study I

In study I we found that 2D and 3D echocardiography had similar agreement rates with surgical description. 3D echocardiography was more accurate in the assessment of some features compared to 2D echocardiography. In most cases where it was not possible to visualize the particular feature by 3D, it was possible to do so by 2D, and vice versa. We conclude that specific knowledge of specific reasons for inaccuracies in assessing the AV-valve complex with 2D and 3D echocardiography can guide the use of two techniques when combining them in clinical practice.

6.2 Study II

In study II we could show excellent long-term survival and durability of the left atrioventricular repair with no significant difference in long-term survival or reoperation after repair of cAVSD in young infants (<3 months) when compared to older infants (≥3 months). Our results support repair of complete atrioventricular septal defect before 3 months of age, when clinically necessary, and avoid a 2-staged palliative approach.

6.3 Study III

In study III our data show that nonsyndromic patients without complex cardiac anatomy have good long-term survival and an acceptable risk of reoperation, comparable to outcomes for patients with complete atrioventricular septal defect with trisomy 21. However, the corresponding group of nonsyndromic patients with concomitant complex lesions still are a high-risk population, especially regarding mortality.

6.4 Study IV

In study IV we showed that the risk of perioperative mortality in AVSD patients undergoing reoperation was low and long-term survival was very good and not significantly different when compared to patients who did not need reoperation. Re-repair for left atrioventricular valve regurgitation was possible in most cases and showed long-term durability. Reoperations after primary AVSD repair are generally complex and demanding but when performed at a large-volume centre they can result in a low perioperative mortality and very good long-term outcome.

7 Future perspectives

The present thesis has shown excellent long-term results after repair of AVSD. The development of better perioperative and postoperative care, as well as centralized and regionalized paediatric cardiac surgery, has played a significant role in achieving these results.

However, AV-valve regurgitation after repair and subsequent need of reoperation remains a problem, especially in young infants. Even though in study II, the difference between young infants less than 3 months old versus older infants regarding long-term survival or LAVV-related reoperation was not statistically significant, there was a trend toward need of LAVV reoperations in younger infants (*P*=.084). Future development of new AV-valve repair techniques applicable in the growing child is therefore important.

In Lund, we are currently working on an AV-valve reconstruction technique with leaflet expansion, of the mural leaflet, with untreated autologous pericardium and a sub-partial annuloplasty, in the growing child to try to avoid AV-valve replacements further on.

In terms of development of diagnostic methods, we need better understanding of AV-valve flow dynamics in cAVSD to achieve a durable AV-valve repair. Dehiscence of the zone of apposition after previous repair was the most common finding at re-repair in our cohort (128). This indicates that the suture line alone cannot withstand the force of valve closure. To better understand how to close the zone of apposition and at the same time unload the sutures, especially in young infants, is of interest for further development of AV-valve repair techniques.

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This thesis is based on studies of long-term results after surgical treatment of atrioventricular septal defect. It is focusing on accuracy between 2D and 3D echocardiography in assessment of AV-valve features and long-term outcomes after early correction in the first months of life of complete atrioventricular septal defect. We also wanted to evaluate the long-term impact of concomitant complex cardiac anatomy in nonsyndromic patients as well as the total burden of reoperations after repair of atrioventricular septal defect.

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