Atrioventricular septal defect (AVSD)

A study of 219 patients who underwent surgery for AVSD at Rikshospitalet from 1979 to 1999

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Abstract

Background: The present study evaluates 219 consecutive patients that underwent surgical repair for AVSD in a long term follow-up.

Methods: The patients had a surgical correction for AVSD at Rikshospitalet from January 1979 to December 1999. The follow-up was closed in January 2009. AVSD with additional defects and syndromes were included.

Results: Forty-two patients died during the observational period. Early mortality was 12.8% and late mortality was 6.4%. Early mortality declined from 40% to 5.7%. Median age at primary repair declined from 13.5 months to 5.5 months. A total of 133 patients (60.7%) presented with Down syndrome, 78 (35.6%) was without Down syndrome, 8 (3.6%) had other syndromes. Both the mortality rate and the need of reoperation were lower in the patients with Down syndrome. A total of 139 patients (63.5%) had complete AVSD, 33 (15%) partial AVSD, 28 (12.8%) intermediate AVSD, 3 AVSD and Teratology of Fallot, 19 (8.7%) AVSD in addition to another defect. No significant difference among the techniques related to reoperational rate (p=0.367). The cleft closure rate was 80.36% (176 patients), and it was left open in 39 (17.8%). In patients without Down syndrome it was of high significance to close the zone of apposition (p=0.001). Reoperation was necessary in 29 patients (13.25%), MI was an indication in 14 (48.3%).

Conclusions: Repair of AVSD has improved significantly during the last 30 years. Median age at primary repair declined from 13.5 months to 5.5 months. We found no significant difference in the frequency of reoperation with different techniques. Closure of the zone of apposition seems to be of significant importance in non Down patients only.

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The study is based partly on the database Datacor. This archival database has provided a valuable resource and it reflects a 30 years management of patients with AVSD. Professor Harald Lindberg and other coworkers deserve a great deal of credit for this archival work. A special mention is to be given to Susan Gibbs who formed the precursor for the database in 1971.

We would like to thank the pediatric cardiologists at Rikshospitalet and in the peripheral outpatient clinics. Their patient records and the database Berthe provided excellent follow up data. Our thanks also go to our father Øyvind Skraastad for contributing with knowledge of the anesthetic management in the patients with AVSD. The anesthesiologist Kari Wagner deserves a special mention for her extensive postoperative note completing the postoperative complications in the AVSD patients.

These clinical advances observed are of fundamental importance for the patients with AVSD. The future will give us similar inspiring achievements in all parts of medicine. This is an important starting point for our work as medical doctors.

Contents

Introduction

Atrioventricular septal defect (AVSD) is a congenital heart defect with different subgroups that vary in severity and complexity. AVSD is also known as the Atrioventricular Canal defect and previous it was called an endocardial cushion defect (22, 39). The defect is a result of developmental anomalies in the Atrioventricular canal (AV canal), which leads to varying degrees of left-to-right shunting between atria, ventricles and AV valve incompetence (14, 23).

AVSD occurs in about 7% of all congenital heart diseases (CHD) and in 3.5 per 10,000 live births (3, 19, 75). It is well known that AVSD is associated with genetic and chromosomal abnormalities, and the most frequently seen is Down syndrome (50%-74%) (73). Isolated AVSD occurs in only one fifth of the patients (11). The etiology of AVSD is characterized by genetic complexity and heterogeneity (1).

The first reported surgical intervention was performed on partial atrioventricular septal defect (Partial AVSD) in 1955 by Lillehei el at (40). Although surgical repair and treatment of AVSD has improved significantly during the last decades, left atrioventricular valve dysfunction (LAVV dysfunction) and left ventricular outlet obstruction (LVOTO) still remain a challenge and influence the reoperation rate and short and long-term survival. In literature the mortality rates range from 8.7 to 21.7% and reoperation rates from 6.4 to 16.6 % (39, 41, 42, 43, 44).

Early surgical correction is obligate in order to avoid the development of pulmonary vascular obstructive disease (PVOD), which earlier resulted in higher immediate postoperative mortality, long-term morbidity and mortality (43, 45).

The purpose of this study is to describe the AVSD, both theoretically (Part I) and by presenting a clinical follow up study (Part II). In Part one we focus on the various aspects of AVSD to contribute to a more fully understanding of the development and treatment of the defect. This part deals with the embryology of the normal heart and AVSD, the genetics and etiology, its morphology, pathophysiology and clinical features. We also describe perioperative medical treatment, surgical palliation and different surgical techniques.

As the second part we performed a retrospective study of surgical experience with 219 consecutive patients with AVSD who underwent surgical correction at the National Hospital of Norway, Rikshospitalet from January 1979 to December 1999. A longterm follow up was performed, and the closing date of the study was January 2009 which gives an evaluation up to 30 years of experience with surgical correction for AVSD.

In this follow up of patients we have focused on the mortality and short and long term outcome. The immediate surgical complications including reoperations have been recorded.

We also wanted to examine whether Down syndrome influenced the prognosis for surgical repair. And throughout the study there is given a special attention to the difference between patients with Down syndrome, patients without Down syndrome and other syndromes. Another interesting aspect was whether or not age at primary repair did influence long term survival or the frequency of reoperations. Different surgical approaches to the treatment of AVSD were evaluated. We also investigated whether the zone of apposition (ZoA) also named cleft always is to be closed.

Part I - AVSD

Embryology

In this section the embryological aspects which are of importance in order to understand the morphological complexity of AVSD will be given a short review. A brief comparison of the differences in the extracellular matrix between patients with and without Down syndrome is also discussed.

From the middle of the third week of gestation, the cardiogenic region develops in the cervical part of the fetus. The cells are derived from the mesodermal layer of the trilaminar embryonic disc. This cardiogenic precursor cells form a horseshoe shaped tube with endothelium on the inside surrounded by myoblasts (27, 28, 29). The final position of the heart in the thorax is a result of the rapid growth of the cephalic part of the central nervous system, the fetus grows and folds cephalic and laterally. This causes the heart tubes to fuse at day 21-22 and to form a continues tube. The newly formed heart tube consists of five regions from cephal to caudal position respectively; the bulbous cordis (truncus arteriosus and the conus arteriosus), the primitive ventricle, the common atrium, truncus arteriosus and sinus venosus. The AV canal connects the common atrium and the common ventricle, and blood is pumped from the sinus venosus towards the truncus arteriosus. The heart tube elongates and bends and by day 28 the cardiac loop is complete (29, 31, 32).

Formation of septa in the primitive atrium, the AV canal, the ventricle and outflow tract occurs between the fourth and seventh week of gestation. By the end of the fifth week the two endocardial cushions, one inferior and one superior and the two lateral atrioventricular cushions project into the lumen, and fuse to make a complete division of the AV canal (28, 29, 30, 32).

Extracellular matrix is a component in the endocardial cushions. Extracellular matrix lies between the inner endothelium and outer myocard, and it has a complex mixture of different components such as collagens, fibronectin and fibrillin. Both endothelial and mesenchymal cells in this area differentiate to produce the extracellular matrix which forms valves and septa (3, 10, 29).

In the developing heart the septum primum, which consists of the endocard, starts growing from the roof into the lumen towards the endocardial cushions in the AV canal. The septum

does not completely divide the lumen, and it leaves an opening called the ostium primum, which is closed as the septum primum fuses with the endocardial cushion. In AVSD, failure of fusion of the endocardial cushion and septum primum leaves an interatrial communication, the ostium primum (29).

Further the septum secundum, which is a thick muscular septum, arises from the roof on the right side of the septum primum. Septum secundum leaves a passage between the two atria, the foramen ovale, which maintains the right-to- left-shunt in the fetus. The septum primum fuses with septum secundum after birth, and if this fails the condition called patent foramen ovale occurs (29).

The formation of a dual chambered ventricle is established by three different septa. This is the conotruncal septum, the muscular part of interventricular septum, which is formed from the medial walls in the expanding ventricles, and the inferior endocardial cushion in the AV canal. The interventricular septum does not divide the cavity completely, leaving an interventricular foramen. Completion of the conotruncal septum and further expansion of the inferior endocardial cushion towards the muscular interventricular septum, closes the interventricular communication. The closing tissue forms the membranous portion of the interventricular septum and is mostly composed of the endocardial cushion (29, 32). In AVSD the ventricular component results from a defect in this membranous part of the septum (30, 50).

In summary failure of fusion of the endocardial cushions is the underlying developmental defect leading to AVSD (3). AVSD were for this reason formerly known as the endocardial cushion defect (29).

Development of the normal heart valves requires interactions among different regulatory patways. The early heart valve progenitors are localized in the endocardial cushions in the AV canal and the outflow tract of the primitive heart tube. A remodeling of the extracellular matrix in the endocardial cushions takes place and the valves develop to become thin fibrous leaflets (3, 9). The mature heart valves consist of elastin rich exctracellular matric components, proteoglycan and collagen. This dense connective tissue is covered by endocardium. The heart valves continue to mature and it is proposed that there is a continus remoldeling of the valve tissue into juvenile stages (9, 8).

The aortic and pulmonal valves arise from the cushions in the outflow tract, and the bicuspid and tricuspid atrioventricular valves (AV valves) develop from the endocardial cushions in the AV canal. Morphological and structural differences among the mural and septal AV valve leaflets exists (8).

To the left in the atrioventricular region (AV region), the mitral valve develops with two leaflets, and the tricuspid valve consisting of three leaflets to the right. More detailed the septal leaflets develop from the fused inferior and superior endocardial cushions, and the mural leaflets are derived from the mesenchymal cushions, which lies laterally in the AV canal (8).

Extracellular matrix components in Down syndrome and non Down syndrome

Resent research have shown differences in the components of the extracellular matrix in the Down syndrome patients compared to normal tissue. Extracellular matrix is as previously detailed a component in the endocardial cushion which further is a major contribute to the heart valves. Fibroblasts from Down syndrome patients have an increased adhesive capacity for collagen VI. What makes this relevant for AVSD, is that collagen VI is an HSA 21 gene (Trisomy of human chromosome 21) and is expressed in the extracellular matrix during development of the AV canal. Collagen VI is also over expressed in the extracellular matrix in Down syndrome. The exact genetic contribution to these changes has not yet been detected, but the results from the article suggest that there are some HSA21 proteins that change the extracellular matrix, and that will affect the normal development of the endocardial cushions (9, 15). Other series suggest different genetic abnormalities in extracellular matrix and heart valve development in Down patients, but this will not be further described (7).

Genetics and etiology

The comprehension of the complete pathogenesis and genetics are not fully understood, but studies over the past decade improve the understanding of the heterogeneous mechanism of its causation (3). The discovery of AVSD in association with other complex CHD, several different syndromes and chromosomal anomalies, as an autosomal dominant defect exhibiting incomplete penetrance, or as a sporadic occurring malformation are findings that emphasize the suggestion of heterogenousity (13). Isolated AVSD is only seen in one fifth of the patients (11).

In this section, we would like to focus on some candidate genes, what characterizes the syndromic and chromosomal features according to genetics, the sporadic occurring and the possibility to inherit AVSD. The possible etiological differences between the subtypes of AVSD will also be given a short review.

Candidate genes

Two AVSD loci on two different chromosomes have been identified (2). These regions are thought to contain susceptibility gene for non-syndromic AVSD (6).

Sheffield et al. found AVSD 1 locus on chromosome 1p21-p31 in 1997 in a large family study, and the susceptibility gene demonstrated the inheritance of an autosomal dominant trait with low penetrance. In 2006 the matricellular protein CCN1 located on chromosome 1p22-p31, which is the exact AVSD 1 susceptibility region, was implicated to be a candidate gene in developing AVSD. The CCN1 protein has a regulatory function in cardiac development, and deficiency results in accelerated apoptosis in the endocardial cushion tissue and altered development of the ventricular septum and the AV valves. Complete lack of the protein gave rise to complete AVSD (55%) and VSD (45%). The trait was complete penetrance. Haploinsufficiency in CCN1 also displayed AVSD in various degrees. Deficiency in this matrix signaling protein can lead to autosomal dominant AVSD (6).

The second AVSD locus, AVSD 2 was identified through analyses of people with 3 P-Syndrome. This syndrome occurs due to a deletion of 3p25, and one third of the patients with this syndrome present with AVSD. The candidate gene found in the second AVSD locus is CRELD 1, a cell adhesion molecule on chromosome 3p25 (2). CRELD1 was the first recognized candidate gene in AVSD and it is expressed during development of the endocardial cushions (1). This knowledge provided new insight in the pathogenesis of the sporadic occurring AVSD, and a possible overlap with the syndromic AVSD (2).

CRELD 1 mutations occur in about 3% of euploid individuals with AVSD, most frequently associated with partial AVSD. Among children with partial AVSD a total of 4.5% have a CRELD 1 mutation. An article published in the American Journal of morphological genetics in 2006 hypothesized that the mutations in CRELD1 found in the euploid individuals may be a contributing factor in developing AVSD in Trisomy 21.

They also discovered that the severity of the heart defect was greater in the patients with Down syndrome who had complete AVSD compared to the euploid individuals with an

isolated partial AVSD. This suggests the possibility that Trisomy 21 might exacerbate the effect of the CRELD 1 mutation. Both groups had the same mutation I CRELD1. Among individuals with Down syndrome and AVSD, a total of 5.1 % have a mutation in CRELD 1 (1).

There are five known mutations in CRELD1 associated with AVSD. Two of these mutations are found in individuals with Down syndrome and AVSD (1). The mutations alone are not sufficient to cause the defect, which indicates the polygenetics (14). CRELD1 mutations increase the general risk for developing AVSD, with other risk factors such as Trisomy 21. These mutations may be inherited as autosomal dominant with incomplete penetrance or occur de novo (1).

Chromosomal abnormalities and syndromes

AVSD are most commonly found in people with chromosomal anomalies, most frequent in Down syndrome. Studies present different percentages, 60 to 66% (3, 14) and 50 to 74% (73). The incidence of CHD in children with Down syndrome is 40%, and out of these about 60% have an isolated AVSD, mostly complete (4, 11).

Down syndrome critical region (DSCR) on the long arm on chromosome 21 is thought to be responsible for most of the anomalies in Down syndrome (46, 47, 48). Given the high frequency of AVSD in this population, and due to the known DSCR, this population provides a valuable resource for the identification of contributing genes in developing AVSD (1, 7). In relation to this DSCR, there has been identified one heart defect critical region from 21q22.13 to 21qter by Korenberg et al in 1992 (1). And a narrowed Down syndrome congenital heart disease region was published by Barlow et al in 2001. This study also proposed a candidate gene, Down syndrome cell adhesion molecule (DSCAM), which is expressed during AV valve development (5). Interference with this molecule leads to disturbed migration of mesenchymal cells from the AV cushions (3).

Other important chromosomal anomalies associated with AVSD includes 3p25 deletion (35%), 8p2 deletion (40%), trisomy 13 (36%), trisomy 18 (12 to 55%). Of importance is also Turner syndrome (45 X0) and 22q11.2-deletion syndrome (Velo-Cardio-Facial-Syndrome) (3). In these chromosome anomalies, AVSD often presents as a complete form (14), and are often associated with other cardiovascular malformations as well (3).

A variety of syndromes are associated with AVSD, and they can be divided into autosomal dominant and autosomal recessive. It has been estimated that 22% of AVSD without Down syndrome or heterotaxy have a Mendelian genetic syndrome (3). Genes mapped to AVSD in these different syndromes have not yet been detected (14).

The most important autosomal dominant syndromes are Noonan syndrome with a frequency of AVSD on 15 %, and the Holt-Oram syndrome with a frequency of 4%.

Important autosomal recessive conditions associated with AVSD are Smith-Lemli-Opizt syndrome (26%) and different forms of Oriofacial-digital syndrome (33 to 59%).

Future genetic analyses of different known syndromes and chromosomal anomalies associated with AVSD will improve the understanding of the molecular basis of AVSD (3, 14).

Developmental defects

Failure in developing normal left-right axis asymmetry results in Heterotaxy (24). The incidence of AVSD among people with Heterotaxy syndromes has been estimated to 6.9 % (25). An example of a defect in the left axis formation is Ivermark syndrome, which is characterized by asplenia, AVSD and other malformations. Research has detected genes mapping for situs anomalies and these genes are thought to influence the formation of AV valves and septum (3).

Isolated AVSD

Isolated AVSD refers to the defect without other intra or extracardiac malformations. Only one fifth of the AVSD occur as an isolated cardiac defect. This makes AVSD unique among cardiac malformations, because almost 75 % of the AVSD`s occur in association with a chromosome defect (11). Among the cases of isolated AVSD, 5 to 10% has an affected first degree family member. As previously described, this can be a result of alternations in AVSD locus one or two, they can be inherited separately as autosomal dominant with incomplete penetrance or occur de novo. The frequency of AVSD among children with normal karyotype is estimated to be 1 /10000 live births (1).

Comparing the different morphological types of isolated AVSD demonstrates various etiologies among complete, intermediate and partial. Complete AVSD as an isolated phenomenon was found in 12.2 % in a research, and it was associated to preconceptual maternal diabetes or antitussive use (11, 14). Isolated cases of partial AVSD, occurred in 55% in the same study, and were associated with a family history and paternal exposures to

ionizing radiation. The intermediate form had a frequency of 15.6% in isolated AVSD and almost the same risk factors as complete AVSD (11).

Possible etiologic differences between the subtypes of AVSD

The Baltimore- Washington infant study on live-born cases and controls (1981 to 1989) has provided useful information regarding the various subtypes of AVSD according to genetic and environmental risk factors (11, 14, 26). Complete AVSD and primum AVSD are more likely to occur when there is a family history of congenital heart disease. Extracardiac anomalies are associated with the complete and intermediate form compared to primum AVSD which occur as an isolated finding in 55% (14).

Down syndrome has been found in one third of the primum AVSD compared to a much higher frequency in especially the complete form (79.3%) (4, 11).

Morphological aspects of atrioventricular septal defect

The different types of AVSD represent a spectrum of anatomical malformations of the heart.

There are a number of different ways to describe AVSD morphologically. In general, the defect is sub classed into complete, intermediate and partial AVSD (54). The nomenclature is mainly based on the presence of an atrial septal defect (ASD), absence or presence of an inlet ventricular septal defect (VSD) and AV valve abnormalities. The left AV valve in AVSD has a trifoliate appearance compared to the normal bicuspid left AV valve. The three cusps are described as left superior leaflet (LSL), left inferior leaflet (LIL) and left lateral leaflet (LLL) on the basis of their location (52). An Italian cardiac surgeon, Giancarlo Rastelli, introduced a classification system in order to divide the different variations of the complete AVSDs. This classification system is mainly based on the attachment of the superior bridging leaflet, and is referred to as modified Rastelli types A, B and C, which have implications for surgical repair (54).

The morphological classification in this study is based on dividing patients into partial, intermediate and complete AVSD. In this section a description of the Rastelli classification system is included, due to get a more precise understanding of the morphological aspects of the AVSD.

Complete and intermediate AVSD

Complete AVSD is characterized by a common AV valve orifice, an interatrial and an interventricular communication to a lesser or greater extent. The left AV valve has a trifoliate appearance with LIL and LSL resembling the normal anterior (septal) mitral cusp with a cleft (52). This cleft is actually a commisure, and whether it is called a cleft or a zone of appostion is determined by common usage and universal approval (68). The left lateral leaflet, is much smaller than LIL and LSL, and has a triangular shape (52).

The interventricular shunt seen in complete AVSD is mainly located beneath the LSL, and to a lesser and more variable extent under the LIL (52).

The degree of abnormality is a continuous spectrum of gradations between the partial and the complete AVSD. The term intermediate is somewhere between these two extremes with one valve orifice an interatrial communication and a small interventricular communication (52). Although there is one common atrioventricular valve annulus, the superior and the inferior bridging leaflets of the valve remains fused at the top of the ventricular or rarely the atrial septum, forming distinct features of the left and right AV valve components (22, 54).

Partial AVSD

Partial AVSD is the simplest type and is mainly characterized by a deficiency in the atrial septum, forming an ostium primium atrial septal defect (primum ASD) with two separate atrioventricular valve annuli.

The septal defect may include only a deficiency in the atrial septum, or there may be an isolated inlet VSD. Deficiency in the inlet ventricular septum leads to absence of the normal offset of the left and right atrioventricular valves, which results in the attachment of the valves at the same level. Transtional AVSD is the term used when the partial AVSD has a small inlet VSD (54, 22). A patent foramen ovale is often seen in correlation to partial AVSD (52).

The two valve orifices are a result of the presence of a connecting tongue of tissue between the superior and the inferior bridging leaflet (54). The left superior leaflet (LSL) and the left inferior leaflet (LIL) are connected to a variable extent anteriorly, near the crest of the ventricular septum (52, 54).

The Rastelli type A, B and C

As mentioned above, the left AV valve in complete AVSD has a trifoliate appearance with completely separated LSL and LIL. The Rastelli classification systematizes the features of

complete AVSD based on the degree of bridging of the LSL across the crest of the ventricular septum. The LSL may be entirely on the left ventricular side of the septum, or may, to a variable degree extend onto the right ventricular side. Rastelli divided the bridging degree and the attachment of the LSL into three classes, type A, B and C. To make the classification of complete AVSD more precise, the degree of bridging has later been classified from 0 to 5.

In Rastelli type A (bridging degree grade 0 or 1), the medial end of the superior bridging leaflet is attached to the crest of the interventricular septum by multiple chords (52). The leaflet itself may extend slightly into the right ventricle attached to the medial papillary muscle (54). There is a slightly or missing bridging of the LSL, and the chordal attachment is to the ventricular crest (52).

In Rastelli B (bridging degree grade 2 or 3), the left superior bridging leaflet extends further medially into the right ventricle and is attached to an anomalous papillary muscle arising from the septomarginal trabeculation (52, 54). The attachement to the papillary muscles in the right ventricle gives rise to both moderate and mild degree of bridging. In the state of mild bridging, the chorda from the LSL are attached to a medial papillary muscle in the right ventricle. When moderate bridging occurs, the chordal attachement of the LSL is to an accessory apical papillary muscle in the right ventricle (52).

In the Rastelli type C (bridging degree grade 4 or 5), the superior bridging leaflet extend completely into the right ventricle (54). The chorda of the LSL attaches to an accsessory anterolateral papillary muscle.

In the situation of a Rastelli B or C, the LSL extends into the right ventricle without any attachement to the ventricular crest, which gives rise to a free-floating LSL.

In complete AVSD, the LIL shows a variable degree of bridging into the right ventricle, but do not show the same pattern of bridging as the LSL does (52).

Different cardiac defects have been linked to the Rastelli classification of the LSL in complete AVSD. In relation to Rastelli type A, the aorta and the pulmonary artery tend to be positioned more to the left compared to Rastelly type C defects. Subaortic obstruction and coarctation of the aorta (CoA) is commonly seen in the Rastelli type A defects (54). The increased occurrence of LVOTO in Rastelli type A defects is a result of the direct adhesions of the superior bridging leaflet to the septal crest, which creates a funnel shape in the outlet of the left ventricle. Hearts with free-floating leaflets, commonly seen in Rastelli type B and C, are

less likely to have ventricular outflow obstruction (56). Teratology of Fallot (TOF) occurs more frequently in Rastelly type C defects (54).

The term unbalanced AVSD refers to the situation where the common AV valve is positioned either more to the left or to the right, creating limited filling of the contralateral ventricle. The consequence is a hypoplastic contralateral ventricle (54).

Left ventricular outflow tract obstruction (LVOTO)

Three important morphological features have been detected in the association with LVOTO. The normal wedged position of the aortic valve between the mitral and tricuspid annuli is absent, and the aortic valve is elevated and deviated anteriorly (54).

In normal configured hearts the distance between the aortic valve and the left ventricular apex roughly equals the distance between the mitral valve orifice and the apex (52). In contrast to the normal heart, the distance between the aortic valve orifice and the cardiac apex is increased, which creates a longer left ventricular outflow tract. This elongation together with the anteriolry deviated aortic valve are referred to as the "Gooseneck deformity" (22).

Further, extensive areas of fibrous membranes and ridges between the aortic valve and the LSL, accessory left AV valve tissue or bulging of the anterolateral muscle bundle into the left outflow tract creates a tendency of narrowing of the left outflow tract (52, 87).

The three main features as detailed above can give rise to the left ventricular outflow tract obstruction, but the problem is a greater postoperative than prior to any intervention (52).

The papillary muscles

Among other malformations related to AVSD, the left ventricular papillary muscles may show an abnormal arrangement (54). Typical abnormal arrangement includes the presence of a third papillary muscle, and in some cases there may be only one papillary muscle. In the situation of one single papillary muscle, producing a "parachute" type of valve, the surgical challenges related to repair increases. In some cases the papillary muscles may be directed towards an already narrowed and elongated left ventricular outflow tract resulting in subaortic obstruction. Although the posterior papillary muscle is placed more laterally than normal, the chordal attachments of the leftward components of the common AV valve in the left ventricle are usually normal (52).

The conducting system

The defect in the AV septum creates an abnormal localization of both the coronary sinus ostium and the conduction system.

The coronary sinus ostium is located more inferiorly, and if the interatrial communication is great, it can even be located in the left atrium. The atrioventricular node (AV node) is positioned inferior and posterior of the coronary sinus, the His bundle is shorter than normal and positioned posteriorly, the left bundle branch is localized posteriorly, the left division of the left bundle branch has fewer fibers than normal and its length is increased, the left posterior division is shorter than normal and the right bundle branch is longer than normal. Electrophysiological findings show an early activation of the posterobasal part of the heart, as a result of posterior displacement of the left bundle branch and a shortening of the posterior division. The superior anterior wall shows delayed activation due to hypoplasia and increased length of the left anterior part of the left bundle branch. The right bundle branch is abnormally long, which gives rise to a delayed activation of the right ventricle. These anatomical findings and the morphological deviation of the conduction system are of importance in the situation of a surgical repair of the defect and the abnormalities seen on the ECG (52, 50).

Pathophysiology

Hemodynamic components

There are basically three major hemodynamic components of interest in AVSD. Interatrial shunting, interventricular shunting and AV valve regurgitation. The hemodynamic aspects of AVSD differ among the various subtypes of the defect and with other associated cardiac anomalies (23, 35).

A left-to-right shunt through the VSD results in an increased blood flow through the pulmonary vascular system (16, 23, 35, 70). When the left to right shunt is large, the right ventricular and pulmonary artery pressure approach or equal systemic pressure. Pulmonary vascular resistance rises rapidly and is elevated after 6 to 12 months or sometimes earlier. It is one of the most significant variables to measure according to timing of surgical repair (53).

Finally the physiological aspects of complete AVSD are the sum of the nonrestrictive interatrial and interventricular communications and the degree of left and right AV valve leakage (23).

Hemodynamic consequences

There is a difference in developing the increased pressure in the pulmonary vascular bed regarding the different types of AVSD. In AVSD primum the left to right shunt occurs in a low-pressure system, and for this reason the PVOD is developed later in childhood compared to the complete form of AVSD. PVOD is a severe hemodynamic consequence of AVSD (35, 36, 77).

Normally the vascular bed in the lungs is a low-pressure system with pulmonary artery pressure around 12-16 mmHg. Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary artery pressures at rest > or =25 mm Hg or exercise PA pressures > 30 mmHg (69, 37). PAH is classified into 5 subgroups and the second subgroup is pulmonary hypertension (PH) with left heart disease. A patient with AVSD and a large nonrestrictive VSD will have PH, and may or may not have PVOD. Different terms have been used when describing the changes in the pulmonary vascular bed. PVOD is the correct term used when the vascular disease in the lungs is a result of a heart defect, which is true in AVSD (18, 77).

Histopathological changes in the pulmonary vascular bed in PVOD is characterized by vasoconstriction, vascular proliferation and remodeling in the vascular walls. Pulmonary endothelial cells, smooth muscle cells and fibroblast function contribute to the pathological changes in the vascular bed. In response to increased pulmonary blood flow, the pulmonary vascular bed undergoes remodeling. The changes in the vessels lead to an increase in the mean pulmonary artery pressure and pulmonary vascular resistance (18, 69). The pulmonary vascular disease is classified by Heath Edwards into 6 different stages. It is divided on the basis of medial hypertrophy and cellular intima reaction, intimal fibrosis, vascular dilatation and vascular lesions such as cavernous and angiomatid lesions. Grade 6, the most severe degree has necrotizing and dilatated lesions in the pulmonal vessels (53).

If left untreated, AVSD can lead Eisenmenger syndrome or reaction. Eisenmenger syndrome is defined as pulmonary hypertension due to longstanding CHD. The two main features of the CHD that can cause Eisenmenger syndrome are high flow and high pressures. As the pulmonary vascular resistance approaches and equals the systemic arterial resistance, the left-to- right shunting decreases and is reversed. The right-to-left shunting results in a higher amount of desaturated blood to the systemic circulation, and the patient becomes visible cyanotic (35, 39, 69).

Down syndrome and pulmonary vascular obstructive disease

Of interest is that children with Down syndrome and left-to-right shunt show a more rapid progression towards PVOD compared to patients without Down syndrome. The reason for the increased risk remains unclear. Further investigations needs to be performed to discover the vulnerability that the Down children have for developing PVOD. What is known about the Down population is that they have an underdeveloped midfacial region and upper airways abnormalities which makes them more prone to recurrent upper airways infection and obstruction. Lung abnormalities such as thinned media of the pulmonary arterioles and a reduction in the number of alveoli (35%) are acquired postnatally due to the developmental abnormalities. These factors considered together are high-risk factors for pulmonary vascular disease (18, 63).

A study published in the European Journal of Pediatrics in 2009 showed that the mean pulmonary artery pressure and pulmonary vascular resistance were significantly higher in Down syndrome group compared to the non Downs patients. The population without Down syndrome had a higher pulmonary blood flow (18).

Clinical features and diagnostics

Making an early diagnosis in newborns with AVSD is crucial to the outcome. Detecting AVSD in the prenatal or neonatal period may allow surgical management to be planned before the onset of irreversible PVOD compromises the chances of successful corrective surgery. Delaying the diagnosis until heart failure or PVOD is established may adversely affect growth and neurodevelopement which may further result in lower cognitive, behavioral, and educational performance. (22, 49, 67)

Two-dimensional and / or Doppler echocardiography, with a high specificity and sensitivity, is considered as the universal way of detecting AVSDs during the prenatal and neonatal period and in young infants (49). Other methods such as electrocardiography, x-ray and cardiac catheterization can help to determine the final diagnosis (22, 55).

Auscultation, symptoms and physical findings

Pathological findings in auscultation and clinical examination are related to the degree of the left-to-right shunt and presence of left AV valve regurgitation.

Patients with partial AVSD often present with symptoms of heart failure in the first decade of life, but can be asymptomatic beyond this age (52). In comparison, complete AVSD is more

severe and the onset of symptoms presents earlier, with progressive heart failure usually in the first year of life and in many cases during the first months (53). The time of onset varies along with the size of the interatrial communication, the interventricular communication and the presence and degree of left AV valve regurgitation.

The clinical presentation of partial AVSD is more or less identical to an isolated ASD. But the presence of an apical systolic murmur as a sign of mild AV valve regurgitation is pathogonomic for partial AVSD (52).

The degree of shunting is measured by comparing pulmonary and systemic blood flow (Q_P / Q_S). In general, a Q_P / Q_S less than 1.5 and up to 1.8 is in most cases asymptomathic. In the situation of a shunt greater than 1.8 to 2, clinical signs are diagnostic of a large shunt is seen in most patients. A large interatrial shunt gives rise to an overactive left parasternal systolic lift.

Typical auscultatory findings are a fixed splitting of the second heart sound throughout the respiratory cycle, systolic and diastolic murmur over the left precordium and near the apex caused by the interventricular communication and a possible AV valve regurgitation, a mid-diastolic tricuspid flow murmur present in borderline situations only on inspiration (22, 51, 52).

In association with progressive heart failure, tachypnoe, poor peripheral perfusion, cardiomegaly, increased ventricular activity and failure to thrive are some of the characteristic seen in the patients. Untreated, almost all the patients that present with a large interventricular communication have per definition PH, and will develop PVOD and eventually Eisenmenger complex early in life, and the patient becomes cyanotic (53, 55).

Electrocardiogram

As earlier described the conduction system differs from the normal heart. The abnormalities of the conduction system are the underlying cause of the characteristic electrocardiographical findings. Three main features are described in the literature, PR interval prolongation, QRS axis deviation and an abnormal ventricular activation (22, 52, 55). The presence of counterclockwise frontal plane loop anterior and to the right strongly suggests the diagnosis AVSD. Other features seen on the ECG are such as left and right ventricular hypertrophy (52).

The PR interval prolongation (first degree heart block) is seen in approximately 50% of the patients, due to delayed interatrial and atrioventricular nodal conduction.

Superior left axis deviation is seen in ECG and varies from moderate to extreme. The QRS axis is either superior to the left or superior to the right, and in extreme cases reach minus 180 degrees. Studies have shown that patients with Down syndrome and AVSD have a greater incidence of extreme left axis deviation. Superior left axis deviation seen together with counterclockwise loop is the results of congenital absence of the anterior division of the left bundle branch (17, 55, 88, 89). In patients with AVSD and Down syndrome both the occurrence of non surgical and late surgical AV block has been observed. The Down patients could be more prone to this phenomenon because they have a reduced amount of extracaridac mesenchyme at the venous pole which in the end results in that the AV node cannot receive the anterior sinonodal input (12).

X-ray

The chest radiography shows pictures that vary along with the degree of shunting and left AV valve regurgitation. The chest radiography reflects a large Q_P / Q_S through enlargement of the right atrium and ventricle, and the right atrium becomes especially large if left AV valve regurgitation co exists with the defect. The cardiomegaly seen in complete AVSD is often more prominent, and can obscure nearly the whole lung fields as a result of a higher degree of left-to-right shunting, and a typical bulge of the upper right atrial shadow together with left and right ventricular dilatation are typical findings on chest x-rays. Pulmonary vessels drawings shows enlargement of the pulmonary trunk in the upper left portion of the cardiac silhouette included increased marking of the pulmonary vasculature far out in the periphery. X-rays can also show an abnormally small transverse aortic arch (22, 51, 55).

In cases of heart failure, x-ray may show interstitial pulmonary edema and areas of pulmonary consolidation and atelectasis due to a possibly secondary compression of smaller airways as a result of abnormally enlarged central pulmonary vessels (51).

Patients surviving the stage of heart failure develop increased pulmonary vascular resistance and in this situation the x-ray show a heart that is less enlarged, with enlarged central pulmonary arteries and clear lung fields (52).

Cardiac catheterization

Cardiac catheterization is in most instances only performed when there is a clinical concern about the possibility of significantly elevated pulmonary vascular resistance. This is usually seen in patients with late presentation of AVSD, who are more than six to eight months old (56) A study from Rikshospitalet, Norway in 1993 demonstrated that patients with AVSD and Down syndrome had a higher pulmonary vascular resistance compared to patients without Down syndrome (78). Indication for preoperative cardiac catheterization includes evaluation of the pulmonary artery pressure and pulmonary vascular resistance, delineation of branch pulmonary artery anatomy and assessment of ventricular size for biventricular repair in the situation of unbalanced AVSD (56). Cardiac catheterization can provide answers in relation to size of the shunting, pulmonary and systemic pressures, resistances and flows. Basic data obtained at cardiac catheterization to measure the degree of shunting includes oxygen content and saturation of the blood in the right atrial, pulmonary arterial, aortic or peripheral arterial blood, and if possible, the left atrial blood. Pulmonary (Q_P) and systemic (Q_S) blood flows and Q_P / Q_S are calculated with pulmonary vascular resistance (R_P). Pulmonary vascular resistance in absolute units times body surface area is of importance when predicting operability (53, 79).In the situation of elevated R_p a further evaluation of the responsiveness of the pulmonary vasculture is needed. This is achieved in the catheterization lab by using 100% oxygen, nitric oxide or nitroprusside (53, 93, 94). This can be supplied by a test of cardiac performance during isoproterenol infusion or during exercise (53, 79).

Echocardiography

Echocardiography is considered the best method in assessing AVSD. Echocardiography together with flow imaging and Doppler interrogation establishes the type of atrioventricular septal defect and assesses the hemodynamic consequences. The method is non-invasive and the diagnosis can also be made during fetal life. Cross sectional echocardiographic studies characterize the pathognomonic morphologic features of AVSD together with the relationship between septal structures and the atrioventricular junction. Estimating ventricular size and left ventricular outflow tract gooseneck deformity are other features that can also be defined by echocardiography (22, 67, 89).

There are five important morphological goals in echocardiographic assessments of AVSD. The hallmark in diagnosing AVSD is the absence of the normal crux of the heart and AV valve offset. Echocardiography should assess the relationship between the atrioventricular junction and the underlying ventricles. To establish whether the defect is balanced or

unbalanced, ventricular size is of importance. The fourth goal is the degree of AV valve regurgitation, both width of the regurgitant jet and extent of flow into the corresponding atria. The last morphological feature of importance is to detect associated cardiac lesions (22, 66).

Color flow imaging and Doppler interrogation is used to establish the levels and degree of shunting between the atria and the ventricles, the presence or absence of AV valve regurgitation and the competence of the right and left components of the AV valve (22).

A research made by the University of Alabama suggests that three-dimensional transthoracic echocardiography (3DTTE) may be a useful supplement to 2DTTE in assessment of AVSD. Using 3DTTE in diagnosing AVSD results in a more comprehensive evaluation of the defect, valves and cardiac chambers compared to 2DTTE. The ability to make multiple cutting planes facilitates different perspectives and angulations. This possibility gives rise to a more accurate assessment of the number and size of all five individual leaflets of the common AV valve, defects in the leaflet tissue, assessment of the extension of the superior bridging leaflet into the right ventricle, and chordal and papillary muscle attachments compared to the images produced by using 2DTTE (54).

Treatment

Preoperative medical management

The definite treatment of AVSD is surgical correction. As detailed above cardiac failure develops when the shunt is large and in case of significant mitral valve leakage. The patient presents symptoms and signs of a volume burden on the heart, in addition to the secondary effect on the lung function. This leads to increased cardiac and respiratory work. These children present respiratory symptoms, as tachypnoe and failure to thrive. Very often undiagnosed or untreated infants will have respiratory infections. The cardiac failure needs to be treated before surgery in order to stabilize the preoperative condition of the infant. Traditional medical treatment of cardiac failure will counteract these negative hemodynamic and neuroendocrine components in the defect. Medications used are diuretics, ACE-inhibitors, digitalis and betablockers. An effective treated cardiac failure will improve significantly the outcome of the surgery for AVSD (35, 92).

In pediatric cardiac failure nutritional supplements could be needed due to that calorie consumption is increased and the eating ability decreased. It is important to prevent failure to thrive because energy state may interfere with total mortality after cardiac surgery. An important measure is to enrich the milk with high-energy supplements and to give parts or all the food through a naso-gastric tube or through a percutaneous endoscopic gatrostomy (PEG) (35).

Surgical palliation of the AVSD

Pulmonary artery banding (PAB) is a palliative surgical treatment. A supravalvular pulmonal stenosis is established by a constrictive band around the first part of the arteria pulmonalis. The constriction is adjusted preoperatively by measuring the pressure gradient across the banding. This procedure reduces the shunt volume, normalizes the pressure in the distal pulmonary vascular bed and therby prevents the development of PVOD.

In a few cases the ventricular septal defect cannot be corrected surgically, because additional defects will be found in the muscular part of the septum. In this situation the cardiac output is predominantly leaving the heart through the pulmonary artery even after a surgical closure of the membranous septal defect. PAB could then be a beneficial surgical palliation (35, 70).

The general opinion about PAB is that it is no longer recommended as a palliative surgical procedure unless other assocciated anomalies make primary repair a high risk operation (61). Another series suggest that PAB still is an option in very young infants, or in infants with low birth weight, due to the technical concerns about valve tissue (58).

Surgical repair of AVSD

AVSD has been successfully repaired since the beginnings of cardiac surgery (57). Due to better anatomic understanding of the lesion and better operative and postoperative care, the results have improved since Lillehei and colleagues reported the first successful repair in 1955 (60). Despite the significant decrease in perioperative and postoperative mortality, a significant incidence of early and late AV valve dysfunction, postoperative conduction abnormalities and significant incidence of late LVOTO are still reported (57, 58).

Various methods of repair have been successfully applied since 1955, and today modified single-patch technique (also referred to as Nunn technique), one-patch technique and two-patch technique are the commonly used approaches in repairing the defects (39, 45, 57, 58, 59). The three different methods targets the same five important areas; closing the interatrial communication, and if present, closing the interventricular communication, avoiding damage on the atroventricular bundle and the bundle of His and maintain, create functional, non-regurgitant and non-stenotic AV valves and avoid late LVOTO. In an attempt to avoid left AV valve regurgitation, the LSL and LIL may be sutured together, left as a tricuspid structure or attached to the patch (52).

There are still different opinions whether one-patch, modified single-patch or two-patch technique are producing the lowest postoperative mortality and morbidity, and so far no single technique is proven to be superior to another, on the basis of long term follow-ups to conclude on this matter (45, 56, 57, 58, 59, 60). Although there are some disagreements related to surgical approach, early intervention of complete AVSD has become the treatment of choice. Early intervention prevents cardiac failure, the potential for pulmonary vascular obstructive disease and the propensity to incurrent respiratory infections (45, 57). Surgical repair of complete AVSD by 3 to 6 month is widely accepted among surgeons in order to avoid pulmonary vascular obstructive disease (57, 58, 60). Masamichi Ono and colleagues showed that patients who only received conservative therapy early in life demonstrated significant pulmonary hypertension and high pulmonary resistance at a mean age of 15.2 months compared with the patients who underwent early surgical repair (45). On the basis of

histologic specimens from patients with and without Down syndrome, Yamaki and associates reported a more severe form of PVOD in patients with Down syndrome, with significant differences in the amount of initial lesions and medial thickness of the small pulmonary arteries (63). On the basis of this finding and the fact that at least 50% of the patients with AVSD also present with Down syndrome, early repair of the defects is strongly suggested (39, 43, 44, 58).

Surgical and technical preparations

At the onset of surgery, a midline sternotomy is made to open the chest cavity. In the situation where autologous untreated pericardial patch is used in the process of repairing, a large piece of the patient's pericardium is removed (52). The repair is performed with bicaval and aortic cannulation for cardiopulmonary bypass (CPB) and cold antegrade cardioplegia as myocardial protection (58, 60). Mild to moderate hypothermia (24°C to 34°C) is utilized in all procedures (41, 45, 57, 58, 60). Mean bypass time varies from 103 minutes to 122 minutes, using respectively modified single-patch technique and two-patch technique (45, 57).

The right atrium is then opened, and the malformation is examined. A longitudinal incision is made in the atrium from the tip of the right atrial appendage parallel to the right coronary artery and extended between the right ventricle and the inferior vena cava (41). The morphological features, opening and closing patterns and any regurgitation of the LSL and the LIL are noted, both through examination and injection of cold saline solution.

To ascertain the severity of residual AV valve dysfunction and a potential leakage through the patched VSD or ASD a routine intraoperative transoesophageal echocardiography evaluation is performed. Further valve repair is attempted in the situation of more than moderate left AV valve dysfunction (41, 58, 60).

Today, several different options exist regarding placement of the coronary sinus on the left atrial side or the right atrial side of the patch. There have been successful results demonstrated with both techniques, which leaves the choice down to personal preference (41). A morphological feature of importance is the displacement of the AV node posteriorly and inferiorly away from the regular triangle of Koch, which is at the apex were it is normally positioned. This displacement makes the coronary sinus more proximal to the atrioventricular junction, and this localization determines whether or not there is enough room to place the interatrial patch to leave the coronary sinus draining to the right atrium without damaging the AV node (56). An important advantage in leaving the draining of the coronary sinus to the

right atrial side is elimination of additional mixing of saturated and desaturated blood. In situations where a left-sided superior vena cava drains into the coronary sinus there are no other options than placing the coronary sinus draining into the right atrium to avoid a right-left shunt of blood (41, 64). On the contrary, the coronary sinus should be localized on the left atrial side in case of correcting coronary sinus type-total anomalous pulmonary venous drainage (41).

Two-Patch Technique

In this procedure two different patches are used to close the communications between the atrias and the ventricles (52). The ventricular component is closed separately from the atrial component thus avoiding division of the bridging leaflets (56). Different patch materials are used in the closing of the ostium primum defect, such as autologous untreated pericardial patch, glutaraldehyde-treated autologous pericardium patch or bovine pericardium patch are mainly used. Dacron patch, glutaraldehyde-treated autologous pericardium patch, untreated autologous pericardium, bovine pericardium and polytetrafluorethylene patch are used in the closing of the ventricular component (41, 57, 58, 59, 61). Different suggestions related to the patch material have recently been discussed, and an article in Cardiovascular Pathology strongly suggests the use of glutaraldehyde treated pericardium as the best choice. The reason for this statement is that preservation in glutaraldehyde promotes cross-linking of collagen and decreases its antigenicity, although it remains possible that a host response to foreign tissue would occur after implantation (41). The presence of synthetic patch material in the left ventricular outlet, where a two-patch technique is used, may further encourage fibrotic obstruction in the naturally narrow (gooseneck deformity) left ventricular outlet. It may contribute to increased rigidity in the posterior wall of the left ventricular outlet, and promote turbulence in the left ventricular outlet during systolic contraction (57).

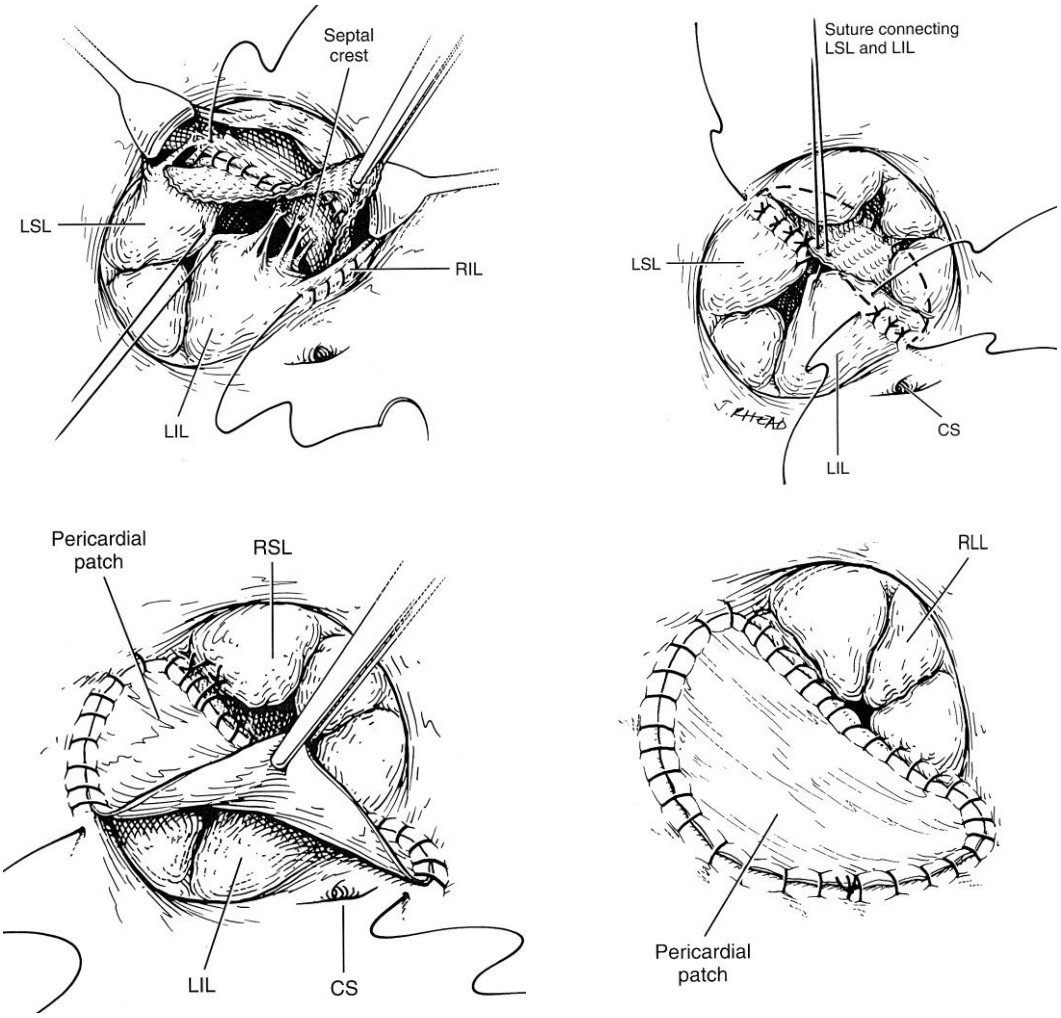


Figure 1. Two-patch technique (52)

The first step in repairing the defect is to visualize the size of the interventricular and the interatrial communication. In order to visualize the size of the malformation, a fine polypropylene suture is left loose between the anterior opposing parts of the LSL and LIL. After the suture is made, the leaflets can be retracted to visualize the degree of the interatrial and the interventricular communication. The ventricular patch is sutured with continuous suture to the right side of the ventricular crest. Chordae of the RIL and RSL, and LIL and LSL stay respectively on the right and the left side of the ventricular patch. Any chordae that interfere with the suturing are cut. The reason for this is that the anterior edges of the leaflets are sutured to the ventricular patch. The suture line of the ventricular patch is completed anteriorly and the anterior edges of LIL and LSL are anchored to the ventricular septal patch. In order to avoid left AV valve regurgitation, the left-side valve apparatus at the patch has to be appropriately narrow. The risk of either left outflow tract obstruction or left AV valve regurgitation increases respectively when the stitches are placed too far down on the patch or too high (52). Complete closure of the ZoA in the left AV valve is done in most cases, using

continous 5/0 braided suture in two layers (57), or more recently separate stitches with monofilament (91).

The last step in the repair is to use the former removed pericardial piece or any other material detailed earlier in order to close of the atrial septal defect component. The suture line incorporates the top of the ventricular patch, the left AV valve and the inferior and superior rim of the atrial defect, including a possible foramen ovale if present (52).

The competence of the left AV valve is tested before the complete closing the interatrial communication, and small annuloplasty sutures between the LSL and LLL and between LIL and LLL are made if the injection of saline solution indicates a regurgitant left AV valve (52).

Single patch technique

In this procedure, a single patch is used in the closing of both the interatrial and interventricular communication. The patch material is almost always pericardium. In comparison to the two-patch technique, described above, and the modified single-patch technique, discussed below, the LSL, LIL, RSL and RIL are all anchored to the patch.

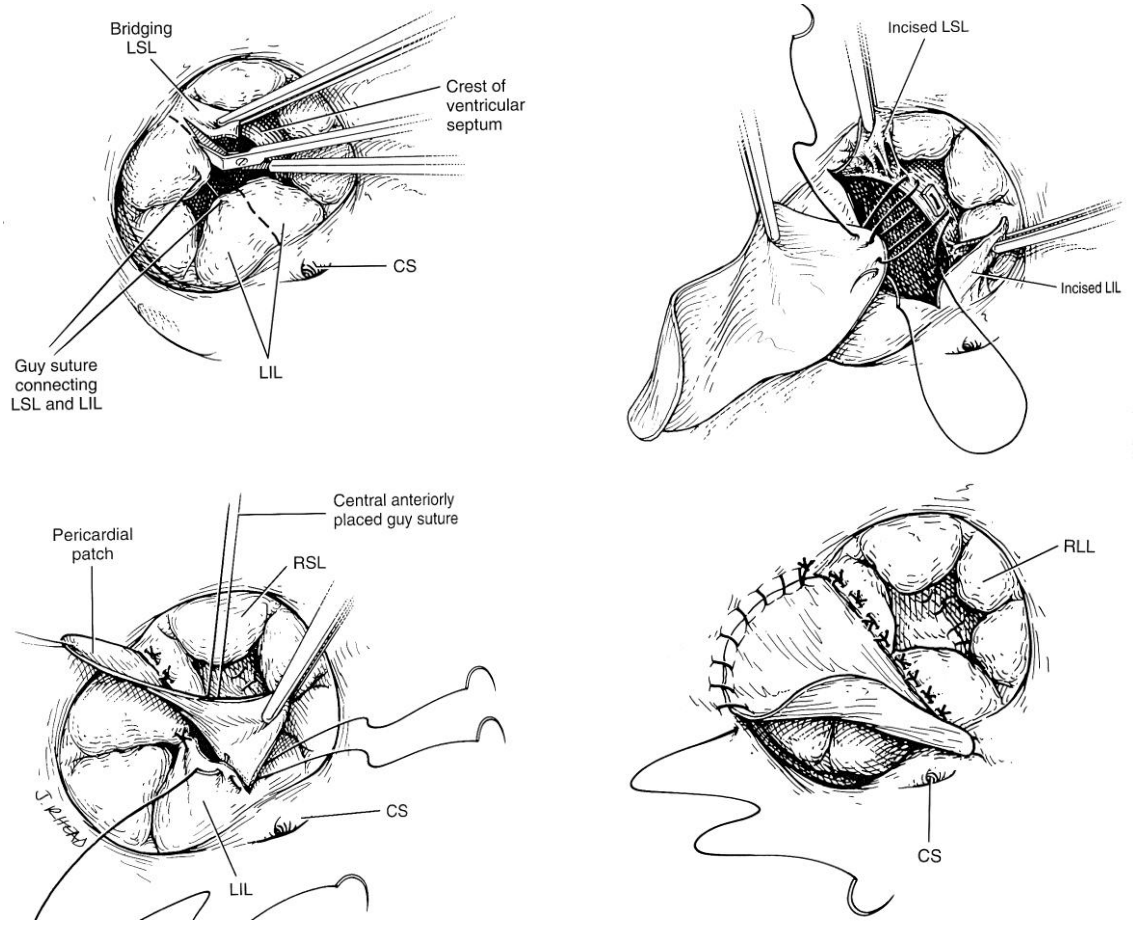


Figure 2. Single patch technique (52)

The most anterior portions of the LSL and LIL apposing edges are identified, and a suture is placed to retain that apposing relationship and left loose. In order to expose the interventricular communication and to accommodate the waist of the patch, bridging leaflets superiorly and in some instances inferiorly are incised laterally to the valve annulus. After this incision has been made, the ventricular portion of the patch is attached to the right side of the crest using continuous or interrupted synthetic monofilament mattress sutures and continued upward anteriorly (52). In order to avoid the conduction fibers, the suture line posteriorly is localized behind to rim of the defect. Double-pledgeted horizontal mattress sutures are used in the anchoring of the left and right AV valve leaflets to the waist of the patch. Pericardium pledgets are most widely used, and often a single strip on the left-sided aspect. In contempt to narrow the annulus and contribute to AV valve competency, the strip is made somehow shorter than the anteroposterior width of the annulus. In order to avoid post operative or long-term complications such as left AV valve regurgitation and LVOTO, the gap between the LSL and LIL is closed with fine interrupted sutures at its opposing edges to the previously placed marking suture. If necessary, annuloplasty sutures are placed on the lateral commissures (52). Finally the upper part of the patch is sutured to the margin of the atrial septum defect (45).

The Nunn technique or modified single-patch technique

In modified single-patch technique, one patch is used to close the interatrial communication combined with direct suture of the interventricular component. The VSD is closed with direct suture, either multiple interrupted mattress sutures or not-pledgeted, interrupted, horizontal mattress sutures placed on the right side of the interventricular septal crest (56, 57). The suture is then passed through the bridging leaflets of the common valve, through one edge of the patch used in closing the atrial septum defect. Sutures are placed on the right side of the ventricular crest in order to avoid potential conduction tissue (60). The next step is to tie down in order to obliterate the VSD. The length of the ASD patch is chosen to be shorter than the septal crest, so that suture tying results in a support of the suture line and a central annuloplasty of the common orifice. This ensures that adequate leaflet tissue is available for valve leaflet coaptation (57, 60).

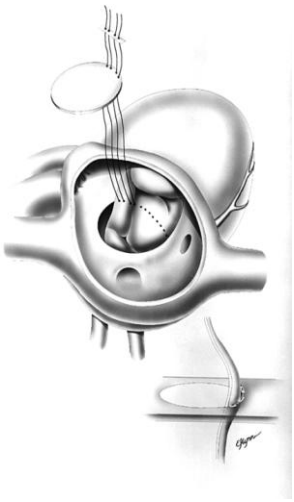


Figure 3. Modified single-patch technique (60)

Avoiding the division of the leaflets is one of the advantages in using modified single patch technique. In this way leaflet loss in suture lines is minimalized, and placement of the sutures directly from the spetal crest through the leaflets avoids entrapment of chordae associated with bridging leaflets, thus making as much leaflet tissue available as possible for coaptation. This is particulary important in the early repair of the defects, where the leaflet tissue are more fragile (57).

No-patch technique

In recent years, a fourth technique has been described in the surgical repair of AVSDs, the no-patch technique.

After right atritomy is performed, the VSD component is closed directly using U shaped interrupted pledgeted sutures. The pledgets are left on the right side of the ventricular crest. In order to close the VSD, stiches are then passed through the corresponding bridging leaflets and directly tied (65). After closing the VSD and the cleft in the left AV valve, the ostium primium defect is closed by bringing the border of the defect along with the AV valves (64). Running suture is started at the superior edge of the defect joining the crest of the defect to the newly created AV valves partitioning. This suture line is placed one millimeter to the right of the previous sutures closing the VSD, and the suture is then passed through the crest of the defect. The superior suture line is completed with a second suture line, started at the inferior part of the defect, where the inferior part of the crest of the ostium primum joins the posterior leaflets with superficial bites on the inferior AV valve leaflet running slightly obliquely until the level of the ventricular septum is reached (65).

A study published in Interactive Cardiovascular Thoracic Surgery claims that this technique gives rise to several advantages compared to both the single- and two-patch technique. A better valve competence is achieved by not using a VSD patch, because the level of the left AV valve implantation at the crest of the septum is lowered producing an increased area of coaptation. The technique is also less time consuming, which gives rise to decreased ischemic and total pump time (65). No-patch technique leads to a small reduction of the size of the atrium, compared to patch technique, which produces an increased size. The authors claim that this reduction may help prevent the occurrence of post operative arrythmias (64).

Questions yet to be answered are whether this technique applies too much tension on the tissues and subsequent tear with possible risk of valvular disruption (65).

Anesthetic management

The anesthetic management of these patients will be based on a strategy that decreases the pulmonary hyper flow during induction of anesthesia and to minimize the risk of precipitating and aggravating the cardiac failure before and during surgery. Since addition of oxygen during induction leads to pulmonary vasodilatation, anesthesiologists prefer to give as little extra oxygen as possible. Correct handling of the airways and a rapid preparation of these patients before surgery is of outmost importance. An experienced pediatric anesthesiologist will be able to perform a safe and fast peripheral vascular access, tracheal intubation, and later on establish arterial and central venous lines that will be necessary for the rest of the procedure. The appropriate depth of anesthesia will be of importance to avoid the clinical hazards of inducing pulmonary hypertension or manifest cardiac failure. This is more important than what kind of drugs or methods of anesthesia during induction or maintenance of anesthesia.

These clinical guidelines shared by all members of the professional team will also be important in the postoperative care of this patients finding the right time for extubation of the patient, the optimal level of sedation and pain treatment and the appropriate level of monitoring the patients in the intensive care unit (ICU) (33, 35, 71, 92).

Part II Clinical follow-up study

Methods

This is a retrospective study of 219 consecutive patients who fulfilled the criteria for AVSD, and underwent surgical correction at Rikshospitalet, Norway, from January 1979 to December 1999. The closing date of the study was January 2009. The purpose of this research is to evaluate 30 years of experience with AVSD, according to surgical techniques and short and long-term follow-up.

This study is based on patients' records, and contains no personally identifiable data. Pre-and postoperative data were collected from databases. One of our databases, DataCor, was established in 1989 by the national hospital in Norway, Rikshospitalet. The database contains information about patients who have undergone cardiac surgery, and it contains records back from 1971. The follow-up data was collected from a cardiologic database, Berthe, patient's records and DataCor.

The parameters analyzed were diagnosis, bi-diagnosis, former palliation, surgical techniques, complications, reoperations and follow-up. More details can be found in the appendix.

Patients

All patients included in this study were diagnosed with AVSD and surgically treated for AVSD. The age of the patients at surgery and the time when surgery was performed were registered.

The patients were divided into different groups according to diagnosis and bi diagnosis. Patients were organized into one of the six following group based on diagnosis: Complete AVSD, partial, intermediate, AVSD and teratology of Fallot (TOF), AVSD and absent pulmonary valve syndrome (ABS PV) and the last group was AVSD and other defects.

Since AVSD is a defect associated with genetic abnormalities, especially Down syndrome, we categorized the group bi-diagnosis into Down syndrome (DS), Non-down syndrome (NDS) and other syndromes (OS).

Surgical techniques

Corrective operation was performed through a midline sternotomy and total cardiopulmonary bypass using antegrade cold crystalline cardioplegia, St. Thomas solution, through aortic and bicaval cannulae with cooling to rectal temperature on 28°C. Aortic crossclamp time and cardiopulmonary bypass time were unfortunately not available our in database for this time period.

Five different surgical techniques were used in the repair of the defects. One-patch technique, two-patch technique and modified single-patch technique / the Nunn technique. Another thechinque that was used was a direct suture of the VSD when the ZoA was persisting in the membranous portion of the septum and a patch closing of the atrial component. The last category was other surgical techniques for more complex and additional defects.

Before the year 2000, Gore-Tex has exclusively been used as patch-material in order to close both the atrial- and ventricular defects. In the early eighties closing the VSD and ASD were performed using Dacron-patch, but an incident of severe hemolysis resulted in changing of patch material. After the year 2000 pericardial patch is the material of choice in closing the ASD, and gore-tex-patch is still used in repairing the ventricular component.

A prospective closure of the zone of apposition was also registered in our group of patients.

Complications

In order to obtain a review of postoperative complications after primary surgery and reoperation six main categories were chosen: Reoperation, arrhythmias, low cardiac output, renal failure, CNS complications and infections. To each headline additional subgroups was specified (appendix). Indications for acute reoperation were early postoperative bleeding, late tamponade and dehiscence. Temporary pacemaker, permanent pacemaker, medical treatment and cooling therapy constituted the group of arrhythmias. The group low cardiac output was defined by receiving epinephrine (> 0.05 microgr/kg&min), dopamine (>5 microgr/kg/min) and other inotropic agents. Postoperative renal failure with a creatinin level above 150 μmol/l was classified according whether the patient received peritoneal dialysis, hemodialysis or medication only. CNS complications were defined as convulsions, temporary paresis, permanent paresis and positive CTscan or MRI. The last registered group was postoperative infections, which implied superficial and deep sternal wound infections, pneumonia and sepsis.

Reoperation

Indications for reoperation were mitral regurgitation (MI) which in our study equals left AV valve regurgitation (LAVV), postoperative persistent VSD, ASD and sub aortic stenosis (SAS). Surgical techniques used in reoperations were resuturing the ZoA, mitralvalve plasty, mitral ring, mechanical or biological valve, patch on VSD and ASD and resection of sub aortic stenosis.

Follow-up

The patients were followed up in the main unit or in peripheral outpatient clinics by a pediatric cardiologist. Functional class was recorded regarding Warners-Somerville ability index grade 1 to 4 (90). Further was type of heart rhythm, grade of mitral regurgitation and medication were registered.

Statistical analysis

Statistic analysis was performed with the statistic package SPSS PC version 16.0. The statistical analysis was carried out by using the Pearson's chi-square test, Log rank test, Breslow and Tarone-Ware test. Kaplan-Meier survival probabilities and were calculated in relation to freedom from death or reoperation. A p-value less than 0.05 was considered as statistical significance and p less than 0.01 as highly significant.

Results

Patients, diagnose and bidiagnose

219 consecutive patients underwent corrective surgery for AVSD in the unit from 1979 – 1999. Follow-up was possible in 215 patients, whereas 4 patients were lost to follow up. In our population 117 (53%) of the patients were girls and 102 (47%) were boys. Sex according to diagnosis showed that 72 boys and 67 girls presented with complete AVSD, 12 boys and 21girls had partial AVSD, and 10 boys and 18 girls had the diagnosis intermediate AVSD. Three boys had TOF and AVSD. A total of 5 boys and 11 girls had AVSD and other defects.

Table 1. Male and female distribution of diagnosis

DIAGNOSIS	MALE	FEMALE
CAVSD	72	67
PAVSD	12	21
IAVSD	10	18
AVSD + TOF	3	0
XAVSD	5	11
TOTAL	102	117

According to diagnosis, complete AVSD was present in 139 (63.5 %) patients, 33 (15%) patients had partial AVSD, 28 (12.8%) patients had intermediate AVSD, 3 (1.4%) had AVSD included TOF, none was registered with AVSD or ABS PV, and a total of 16 (7.3%) patients had AVSD in addition to another defect.

Table 2. Diagnosis and bidiagnosis

DIAGNOSIS	NON DOWN	DOWN	SYNDROME	TOTAL
CAVSD	36	100	3	139
PAVSD	20	9	4	33
IAVSD	12	15	1	28
AVSD + TOF	1	2	0	3
XAVSD	9	7	0	16
TOTAL	78	133	8	219

In the group AVSD and other defects a total of 7 patients represented with coarctation of aorta (CoA), and out of these 4 patients had only CoA. The 3 remaining patients with CoA had CoA and cerebral palsy, CoA, aortic arch hypoplasia and parachute mitral valve, CoA and aortic arch hypoplasia, and CoA and persistent ductus artreriosus. A total of 8 patients had the following diagnosis in addition to AVSD; left isomerism, double outlet right ventricle (DORV), dextrocardi (DC), situs inversus (SI) and total anomalous venous drainage (TAPVD), heterotaxi, sub aortic stenosis (SAS). One patient had muscular VSD, another presented with parachute mitral valve, and the last patient had a parachute mitral valve and interrupted aortic arch (IAA). Data about one patient was missing.

In the group bi diagnosis, 133 (60.7%) patients had DS, 78 (35.6%) patients had NDS and 8 (3.6%) patients had other OS. In the population "other syndromes" the Carpenter syndrome, Lennox-Gastaus syndrome, Fetal Alcohol Syndrome, Noonan syndrome and 2 patients with Holt Oram syndrome were present. In two out of the eight patients in the group, data about specific syndromes were missing.

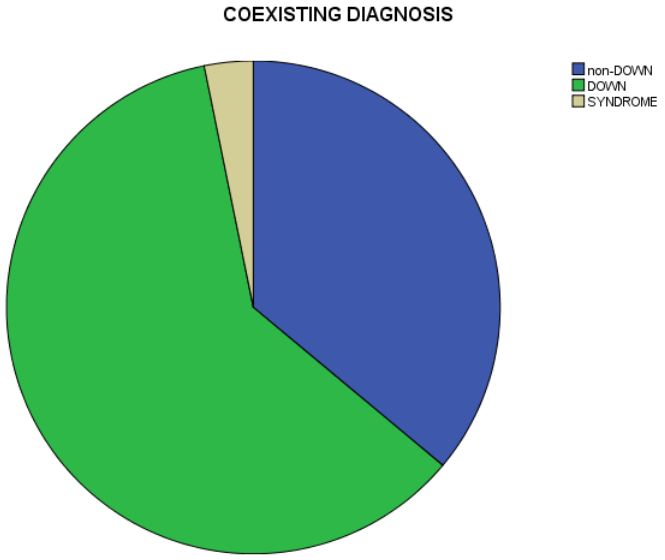


Figure 4. AVSD and coexisting diagnosis

Former palliation such as pulmonary artery banding (PAB), and shunting was performed in totally 26 (11.8%) patients, respectively 24 patients with PAB and 2 with Blalock-Taussig shunt. According to time period 2 patients had a PAB in the period 1979 to 1984, 10 patients had PAB from 1985 to 1989, 11 patients had PAB from 1990 to 1994 and only one patients with PAB from 1990 to 1995. One patient received a shunt in 1993 and one in 1995. In the patients who required PAB, 17 patients had CAVSD, one patient presented with partial

AVSD, and 6 patients with AVSD and other diagnose; CoA and hypoplastic aortic arch, three with CoA, one with left isomerism, and one patient with unknown other diagnose. One of the patients with shunt had AVSD and TOF and the other presented with partial AVSD.

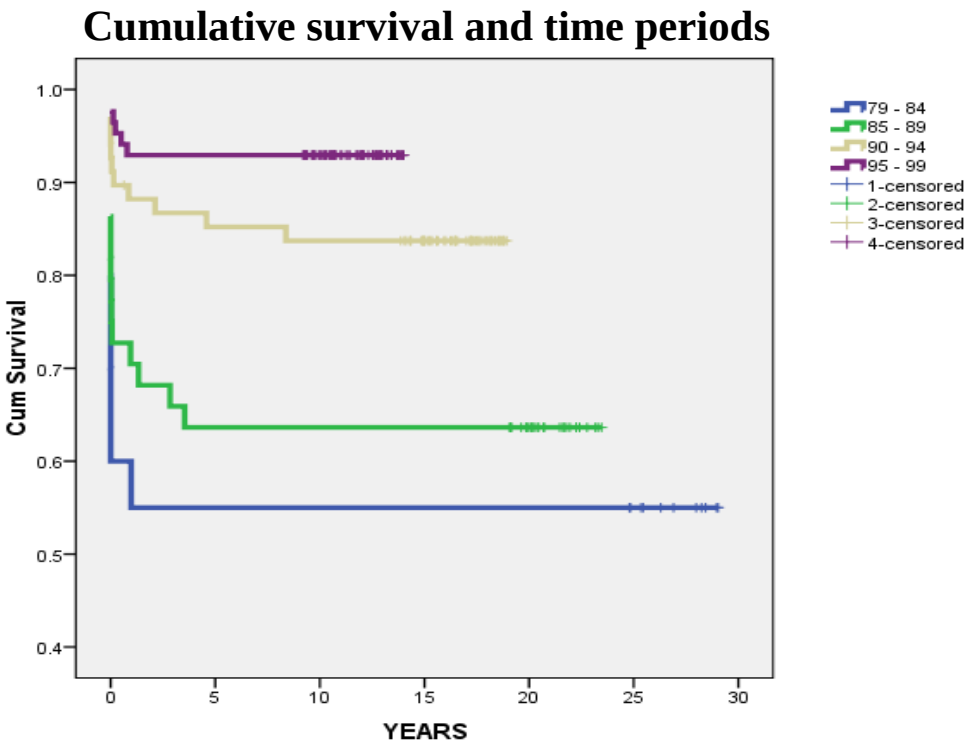
Mortality

In our study a total of 42 patients died during follow up period (1979-2009). The overall mortality rate was 19.18%. There were 28 early deaths (<30 days after primary surgery). The early mortality rate was 12.78. Early mortality rate shows a decline from 40% to 1.1% from the time period 1979 to 1984 and 1995 to 1999. A total of 8 patients experienced in - hospital mortality after being surgical corrected between 1979 to 1984, 12 patients from 1985 to 1989, 7 patients from 1990 to 1994 and only one patient with early mortality after surgical correction from 1995 to 1999.

Late death occurred in 14 patients with a late mortality rate at 6.39% (14/219=0.06392). Late mortality according to different time periods for primary surgery showed that one patient who was surgical corrected in 1979-1984 experienced late mortality, 4 patients with late death when operated in 1985-1989, 6 patients died in the group primary surgery from 1990-1994 and 3 patients died after have undergone primary surgery from 1995 to 1999.

Table 3. Time periods and early mortality

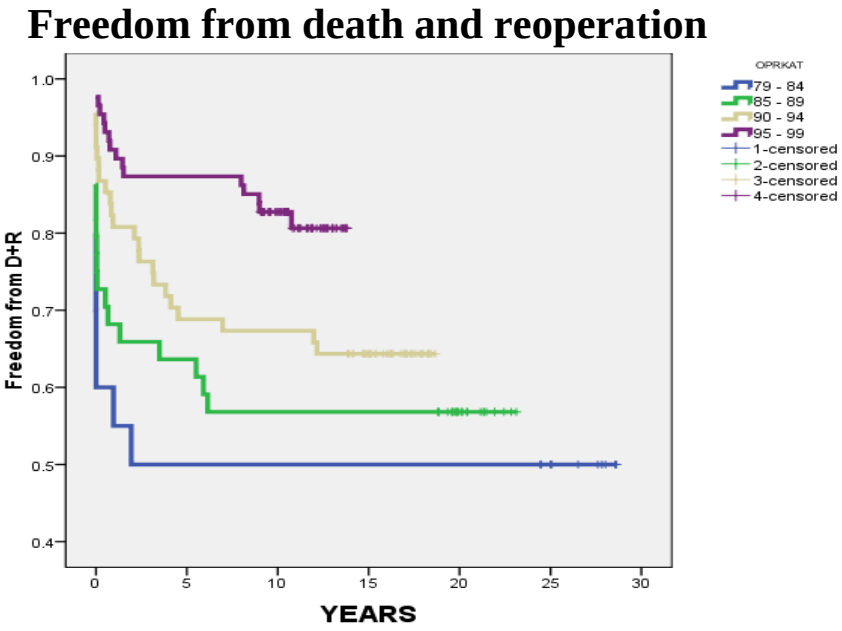
PERIODE	TOTAL NUMBER OF SURGICAL CORRECTED PATIENTS	% EARLY MORTALITY	AGE, ALL
1979-1984	20	40	2.36
1985-1989	44	27	1.45
1990-1994	68	10.3	1.18
1995-1999	87	5,7	1.01



Overall Comparisons			
	Chi-Square	**df**	**Sig.**
Log Rank (Mantel-Cox)	28,298	3	,000
Breslow (Generalized Wilcoxon)	29,118	3	,000

Figure 5. Cumulative survival and time periods

The patients were divided into groups according to when they had their primary surgery. See table 3. An overall comparison of the four groups using Log rank and Breslow showed a highly significant difference comparing the groups with a p value 0.000. This is in consistence with the high early mortality rate previously detailed in the early periods of the study.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	15.300	3	.002
Breslow (Generalized Wilcoxon)	18.615	3	.000

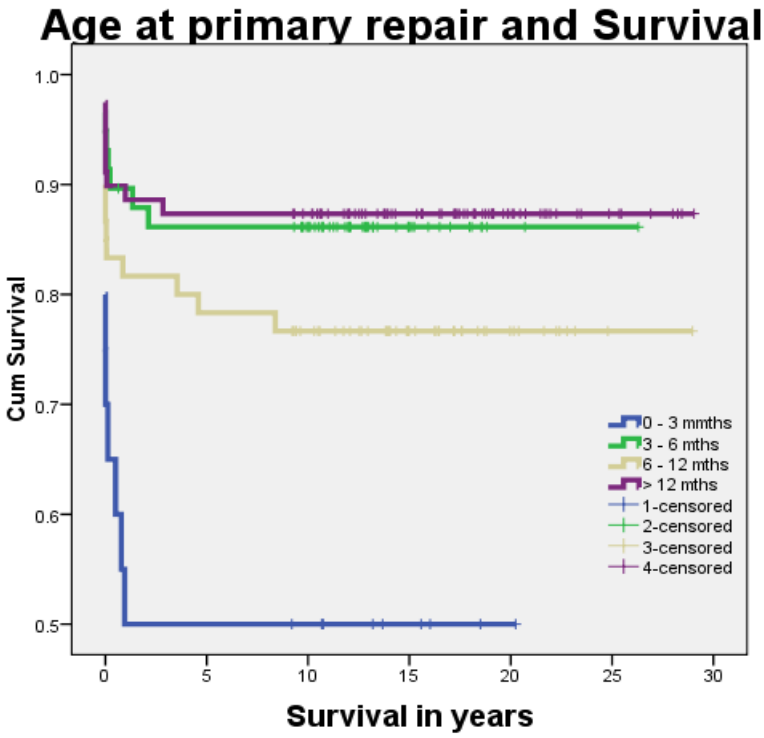
Test of equality of survival distributions for the different levels of OPRKAT.

Figure 6. Results from different time periods: Freedom from death and reoperation

Freedom from death and reoperation in the different time periods were further examined. Chi-Square test, Log Rank and Breslow showed a highly significant difference due to the different time periods with a p value of 0,002 and 0,000 respectively. This is similar to the results of cumulative survival of the same time periods.

Age at primary repair

Age at primary repair ranged from 5 – 2751 days, with a median of 254 days (8.3 months). Our material was further divided into four time periods, 1979 – 84, 1985 – 89, 1990 – 94 and 1995 – 99. In the period 1979 to 1984, median age at the time of primary repair was 411 days (13.5 months). Median age for primary repair in the period 1990 – 1989 was 357 days (11. 7 months), 240 (7.9 months) days in the period 1990 – 1994 and 168 (5.5 months) days in the period 1995 – 1999.



Overall Comparisons

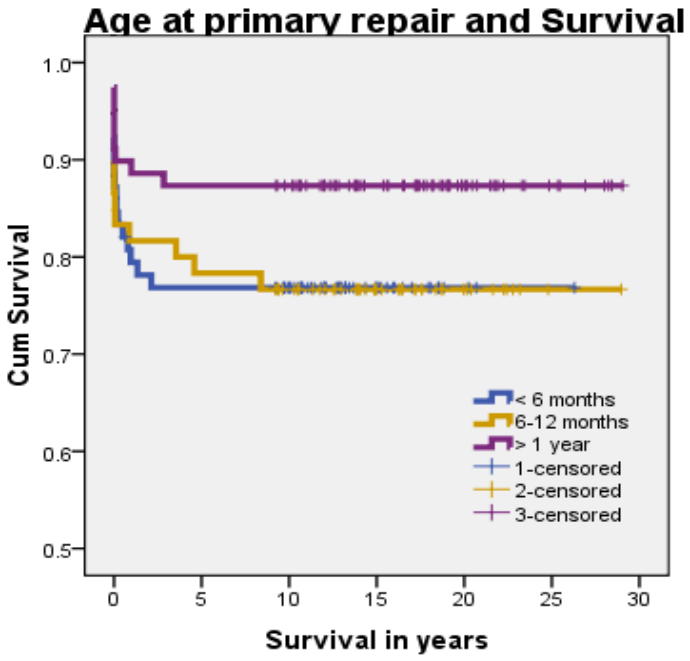
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	18.648	3	.000

Test of equality of survival distributions for the different levels of ALDERKAT.

Figure 7. Age at primary repair and survival

Patients were divided into four age categories related to age at primary repair. We chose the groups: under 3 months, 3 – 6 months, 6 – 12 months and over 1 year old. Totally 20 patients (9.2%) underwent primary repair before the age of 3 months, 58 (26.7 %) were from 3 – 6 months, 60 (27.7 %) were 6 – 12 months old and 79 (36.4%) were older than one year at the time of primary repair. Age was missing in two patients in the material. The group age less than three months at primary repair stands out compared with the other three categories, with a survival rate at 50%. Among these 10 patients less than 3 months 4 patients have Down syndrome, one presented with Noonan syndrome, another with the Holt Oram syndrome, the remaining 4 were without Down syndrome. One of the Down patients presented with CoA, another with parachute mitralvalve. One of the patients without Down syndrome had a parachute mitral valve and IAA, and this patient presented with preoperative collaps. The cause of death from the autopsy reports were pulmonary hypertensive crises in 6 patients, the

rest 4 causes of death were missing. Age category 2 – 4 has a survival rate ranging from 76.7% to 87. 3 %. An overall survival for the four groups was 80. 6 %. An overall comparison of the four groups, using Log Rank and Chi-square tests, showed highly significant difference comparing age category 1 with category 2, 3, and four, with a p-value on 0.000.



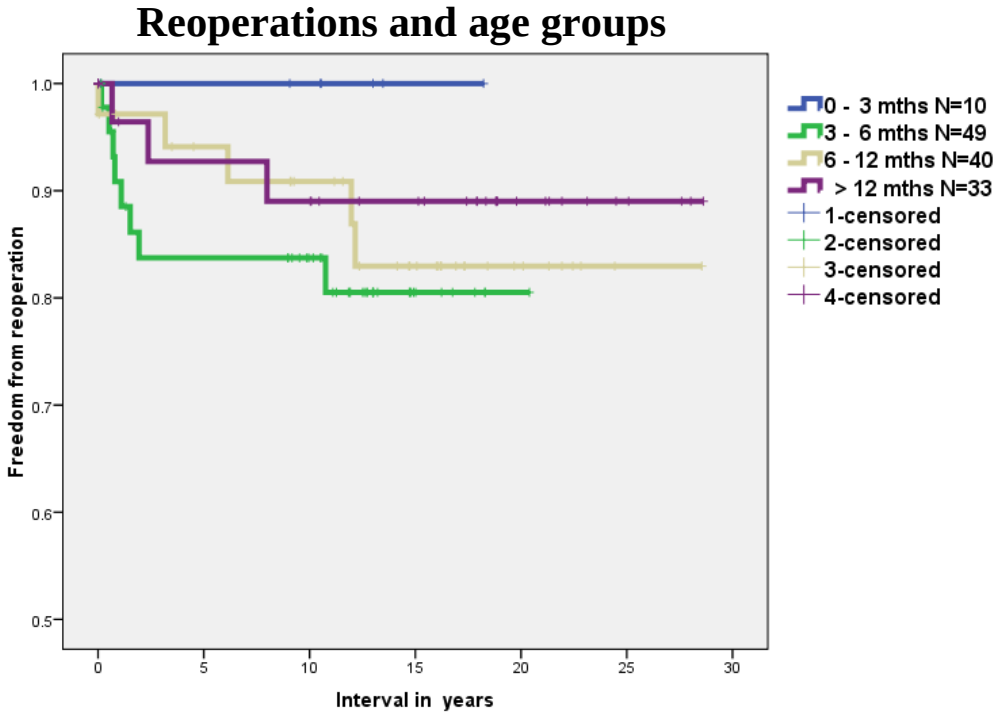
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.511	2	.173
Breslow (Generalized Wilcoxon)	3.530	2	.171

Test of equality of survival distributions for the different levels of ALDERKAT.

Figure 8. Age at primary repair and survival

In order to make the groups more comparable according to total number of patients, the age group under 3 months (n=20) were added to the group 3 to 6 months (n=58), the rest of the groups were as previously described. An overall comparison between the groups based on the different division of the material using Log Rank and Breslow showed no significant difference combining age group < 6 months (n=78) with 6 -12 months (n=60) and >1 year (n=79), with a p value with Log rank 0,173 and a p value with Breslow 0,171.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	2.073	3	.557
Breslow (Generalized Wilcoxon)	2.210	3	.530

Test of equality of survival distributions for the different levels of ALDERKAT.

Figure 9. Age groups and freedom from reoperation in CAVSD

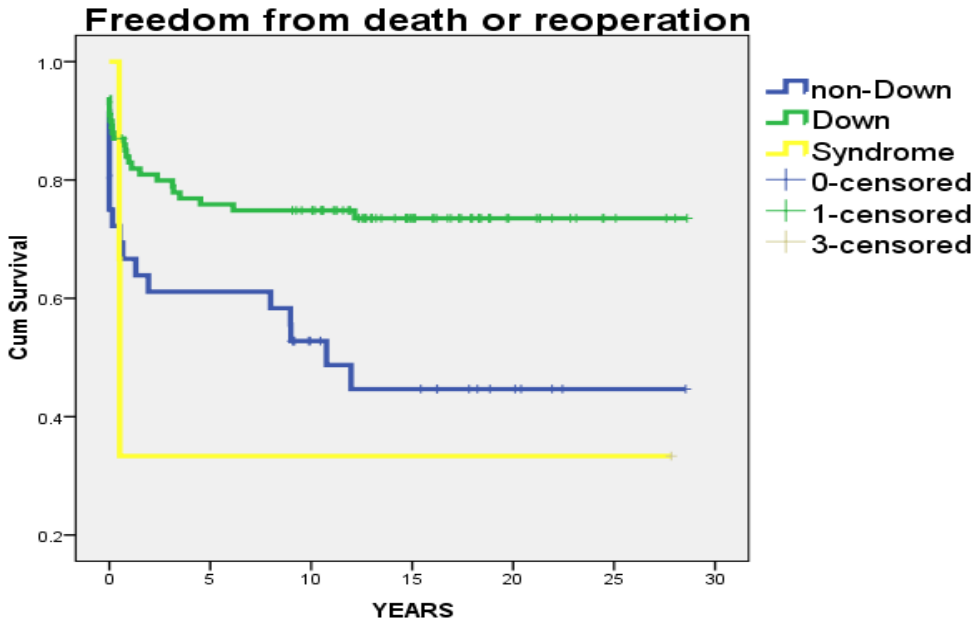
A total of 139 patients were surgical corrected for CAVSD. The total number in each age category is presented in figure 7. Data about 7 patients were missing. A total of 29 patients were reoperated. Out of these there were 18 patients with CAVSD. According to the different age groups one patients had the primary surgery fro CAVSD before the age of 3 months, 9 patients were surgical corrected from 3 to 6 months, 6 patients had their primary surgery from 6 to 12 months and 2 patients were surgical corrected for CAVSD after 12 months. An overall comparison of age groups and freedom from reoperation in CAVSD showed no significant using Log Rank with a p value of 0.557 and Breslow with a p value of 0.530.

Diagnosis, bidiagnosis, freedom from death or reoperation

Complete AVSD

As mentioned earlier, 139 (63.5%) of the patients presented with complete AVSD. This group was further divided into non Down syndrome (NDS), Down syndrome (DS) and other syndromes (OS). Among the 139 patients, 36 (25.9%) were categorized as NDS, 100 (71.9 %) had DS and 3 (2.2%) had OS. Freedom from reoperation was registered in 29 (80. 6%) in the

NDS group, compared to 90 patients (90%) within the DS group and 2 patients (66.7%) among the patients with OS. Four patients in the NDS group needed one reoperation (11%), 8 among the DS patients needed one reoperation (8%) and no reoperation was needed in the OS group. The need of a second reoperation was necessary in 2 patients in the NDS group, 2 within the DS group and one in the group with OS. A third reoperation was performed on one NDS patient.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	10.811	2	.004

Test of equality of survival distributions for the different levels of BI_DIAG.

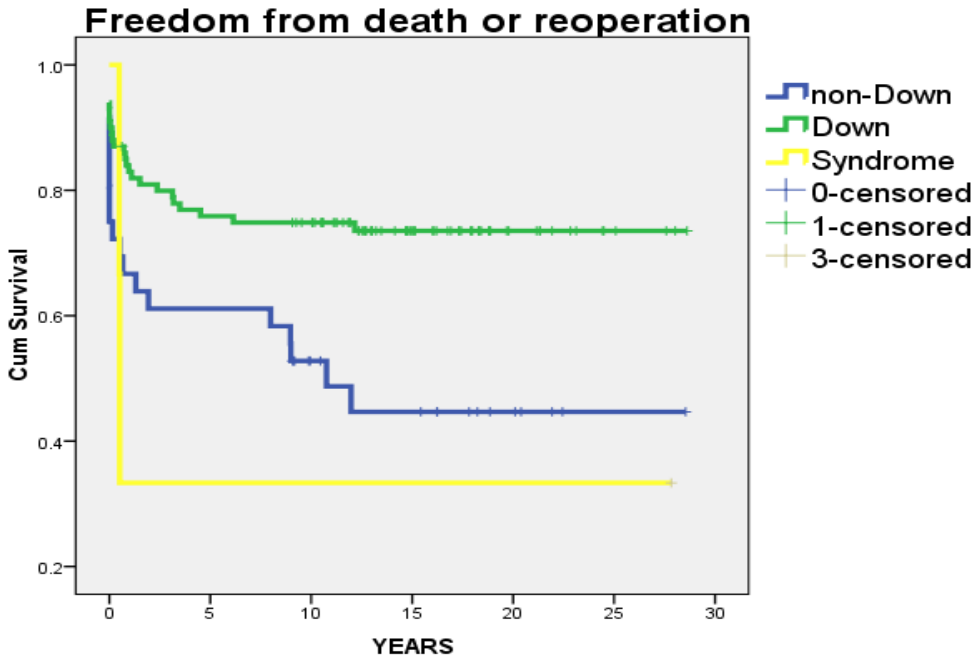
Figure 10. Freedom from death or reoperation

Freedom from death or reoperation was estimated comparing the three groups. An overall comparison, showed a significant better outcome among the Down syndrome patients with CAVSD, with a p-value of 0.04. The patients with other syndrome had worse outcome than the Down patients and the patients without Down syndrome.

Partial AVSD

A total of 33 patients were diagnosed with partial AVSD. Among these, 20 patients were in the NDS group, 9 had DS and 4 patients had OS. Reoperation was unnecessary in 28 of the patients, and 17 of these were in the NDS group, 8 had DS and 3 had OS. One reoperation

was performed in 5 patients. Out of these 3 patients were categorized as NDS, 1 had DS and 1 had OS.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.452	2	.798

Test of equality of survival distributions for the different levels of BI_DIAG.

Figure 11. Freedom from death or reoperation

An overall comparison of freedom from death or reoperation, using Log Rank and Chi square tests, showed no significant difference between the three groups, with a p-value of 0,798. Although there was no demonstrated significance, there is an observed tendency that the outcome for the Down syndrome patients is better than the non Down patients and the patients with other syndromes. The outcome for the patients with other syndrome is worse.

Intermediate AVSD

A total of 28 patients presented with intermediate AVSD. Out of these, 12 patients had NDS, 15 had DS and 1 was in the group OS. Freedom from reoperation was registered totally 24 of the patients, 10 in the NDS group, 13 in the DS group and 1 in the OS group. One reoperation was performed in totally 3 patients, where 2 patients had NDS and 1 patient had DS.

Table 4. Intermediate AVSD, bidiagnosis and reoperations

	No-redo	**One redo**	**Two redo's**	**Three redo's**	**Total**
Non Down	10	2	0	0	12
Down	13	1	1	0	15
Syndrome	1	0	0	0	1
Total	**24**	**3**	**1**	**0**	**28**

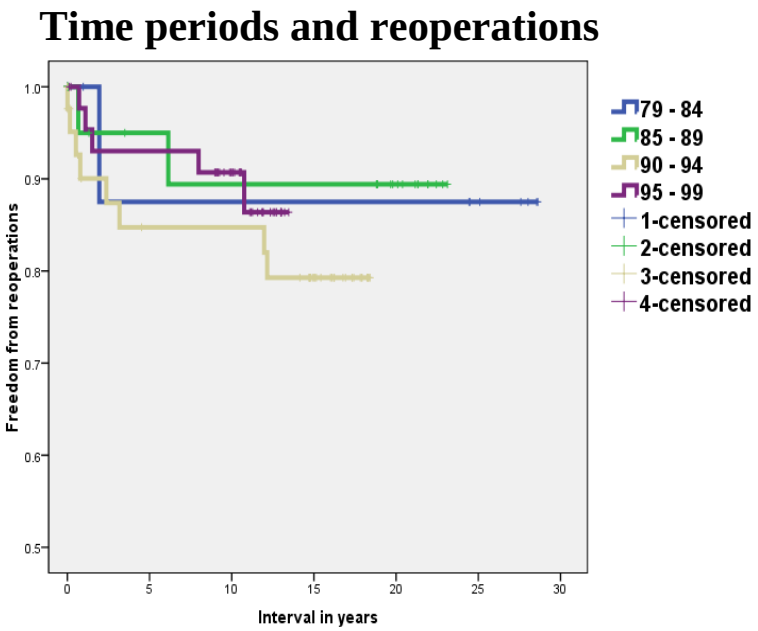
AVSD and other defects

In our material patients were in the group with AVSD and other defects. The NDS group contained 9 patients (56.2%) and 2 patients in this group needed one reoperation. Down syndrome was present in totally 7 patients (43.8%), and no one required reoperation.

Table 5. XAVSD, bidiagnosis and reoperations

	No-redo	**One redo**	**Two redo's**	**Three redo's**	**Total**
Non Down	7	2	0	0	9
Down	7	0	0	0	7
Syndrome	0	0	0	0	0
Total	**14**	**2**	**0**	**0**	**16**

Time periods and reoperation:



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.470	3	.689
Breslow (Generalized Wilcoxon)	1.469	3	.689

Test of equality of survival distributions for the different levels of OPRKAT.

Figure 12. Time periods and freedom from reoperations

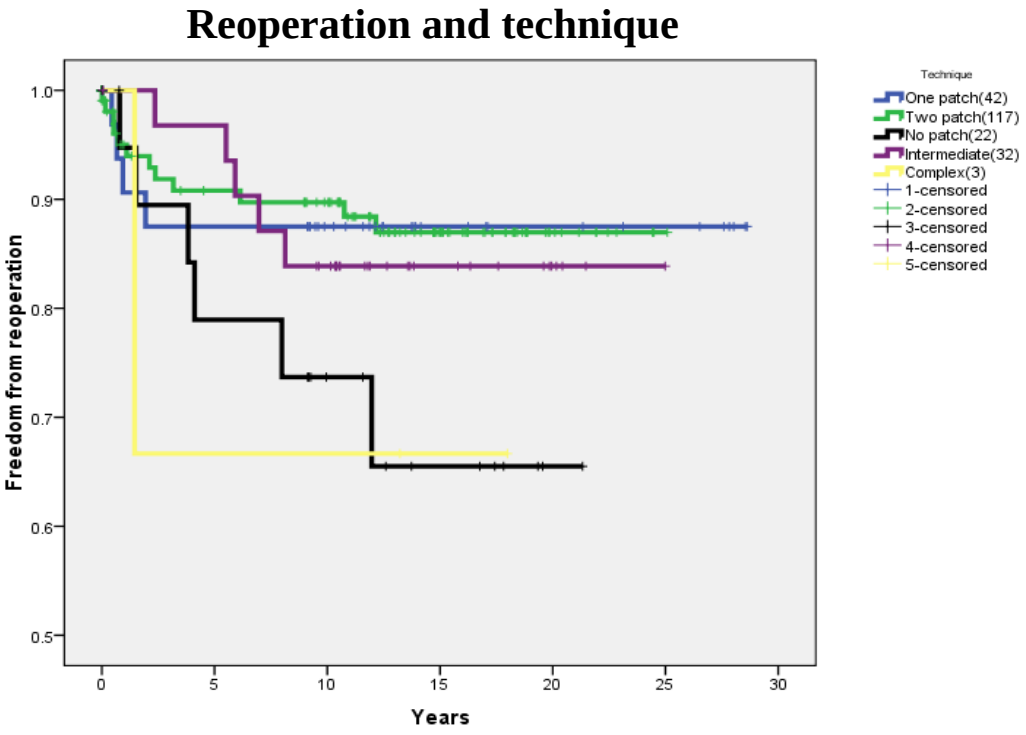
Results from the different time periods and freedom from reoperations showed no significant difference using Chi-Square, Log Rank, Breslow with a p value of 0,689. Of importance is that the early mortality rate in the early time period was high, leaving this group of survivors biased neither to die nor to need a reoperation.

Techniques and reoperation

A total of 7 different surgeons performed the corrections in the study period. An overall comparison using Chi square and Kaplan Meier survival curves showed no significant difference in outcome regarding the surgeons.

Five different surgical techniques were used in the repair of the defects. Totally 42 (19.2 %) patients underwent one-patch technique as primary repair. Two-patch technique was performed on 117 patients (53.4%). Modified single-patch technique / the Nunn technique was used in the repair of 22 patients (10%). In 32 patients (14.6%) direct suture of the VSD component and ZoA together with a patch closing of the atrial component was performed. In

3 patients (1.4%), other surgical techniques were performed (complex). These techniques involved direct suture of the ASD and plasty of the pulmonary artery. Information about surgical techniques was unavailable in 3 patients (0.01369).



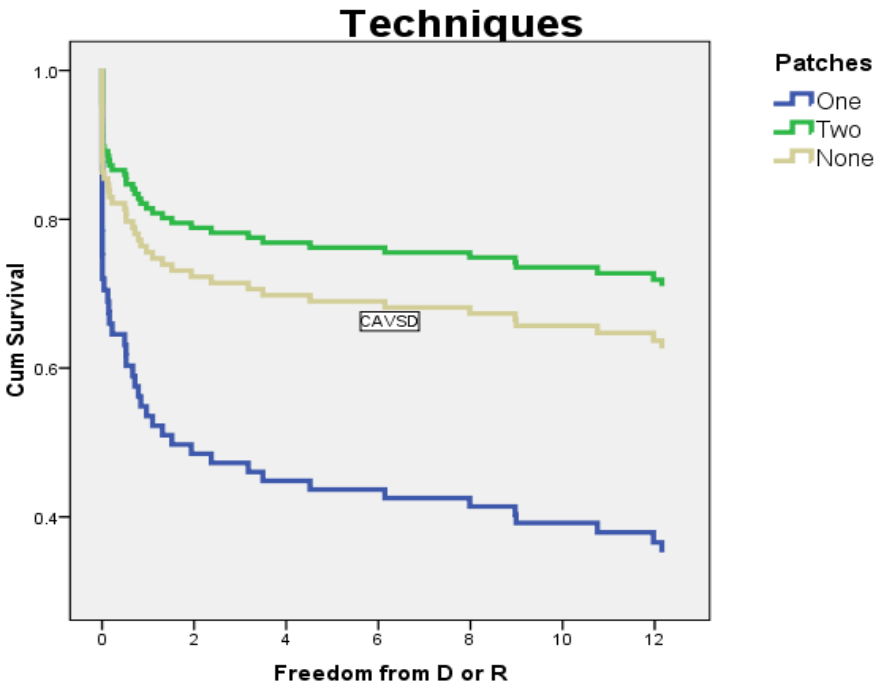
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.147	4	.273
Breslow (Generalized Wilcoxon)	4.298	4	.367
Tarone-Ware	4.707	4	.319

Test of equality of survival distributions for the different levels of TEKNIKK.

Figure 13. Reoperation and technique

An overall comparison of freedom from reoperation in the five different surgical techniques was estimated using Log Rank, Breslow, Tarone-Ware and Chi-Square, showed no significant difference among the techniques related to reoperational rate with a p-value on 0.273, 0.367 and 0.319. Although no significance was demonstrated, there is an observed tendency that the No-patch technique and the "complex" technique had a worse outcome.



Omnibus Tests of Model Coefficients[a,b]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
415.952	10.046	2	.007	7.570	2	.023	7.570	2	.023

a. Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 423,522

b. Beginning Block Number 1. Method = Enter

Figure 14. Freedom from death and reoperation and technique

Further comparison of freedom from death and reoperations using one-, two- and no-patch technique as primary repair of patients presenting with CAVSD, using Log likelihood function and Chi-square tests, showed a significant difference between the three surgical techniques with a p-value on 0,007 and 0,023. The one-patch technique in CAVSD was significantly worse compared to the other techniques.

Reoperation was necessary in totally 29 patients (13.2 %) out of the 219 patients who underwent surgical repair of AVSD. Mitral regurgitation as an indication for reoperation was present in a total of 14 patients (48.3%). ASD was present in totally 3 patients (10.3%), whereas combinations of either mitral regurgitation, VSD or ASD were an indication for reoperation in 12 patients (41.4%). Among the bidiagnosis groups, 14 patients within the group non Down syndrome (18 %), whereas 13 patients diagnosed with Down syndrome

(9.8%) needed reoperation and reoperation was necessary in 2 patients (25 %) within the group other syndromes. The techniques used in the reoperations are present in table 7.

Table 6. Indications for first reoperation

Indications registered at the first reoperation	**Down**	**NDS**	**OS**	**Total**
Mitral regurgitation	5	9	0	14
Ventricular septal defect	0	0	0	0
Atrial septal defect	2	1	0	3
Combination: (MI+VSD, MI+ASD,SAS, others)	6	4	2	12
Total	**13**	**14**	**2**	**29**

Table 7. First reoperation and technique

Techniques registered at the first reoperation.	**Down**	**NDS**	**OS**	**Total**
Resuture of the zone of apposition	3	6	0	9
Plasty	0	2	0	2
Plasty + ring	2	1	0	3
Mechanical valve	0	1	0	1
Biological valve	0	0	0	0
ASD + Patch	1	0	0	1
Mitral regurgitation + ASD	3	2	1	6
Mitral regurgitation + VSD	1	1	1	3
Resection of SAS	1	0	0	1
Other technique	0	1	0	1
ASD suture	2	0	0	2
Total	**13**	**14**	**2**	**29**

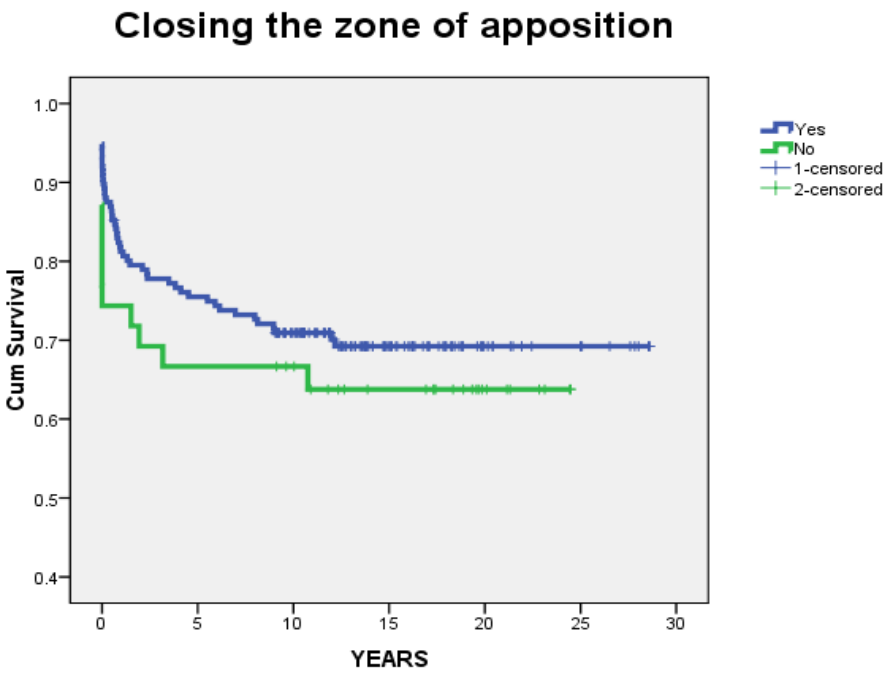
A second reoperation was performed in 7 patients with the following indications; MI and VSD, a total of 5 patients had a second reoperation due to mitralvalve regurgitation alone and out of these 3 had plastic and a ring, and 2 had only plastic. One patient had a second redo because of SAS and a resection was performed.

Only one patient underwent a third reoperation. This patient had CAVSD and was without Down syndrome and was initially operated with one patch technique in 1985. Eight months later the patient underwent the first reoperation due to mitral regurgitation and a resuture of the cleft was performed. Another 2 years after the first reoperation a second reoperation was performed because of mitral regurgitation, and the procedure was mitral valve plastic. The same day the patient experienced cardiogenic shock and a third redo was performed due to acute mitral regurgitation. This patient died 2 weeks later.

Closing the zone of apposition

Complete closure of the zone of apposition was performed in totally 176 patients (0.8036) and was left open in 39 patients (0.178). Information about cleft closure was unavailable in 4 patients (0.01826). Among the 6 patients presenting with parachute mitral valve, the zone of apposition was closed in 3 and it was left open in the remaining 3 patients. Only one patient in our study had double orifice mitral valve and the cleft was left unsutured.

Evaluation of closing the zone of apposition was divided into five different categories: A general comparison, closing the ZoA in patients with complete AVSD, closing the ZoA in patients with Down syndrome, closing the ZoA in patients without Down syndrome and closing the ZoA versus reoperation rate.



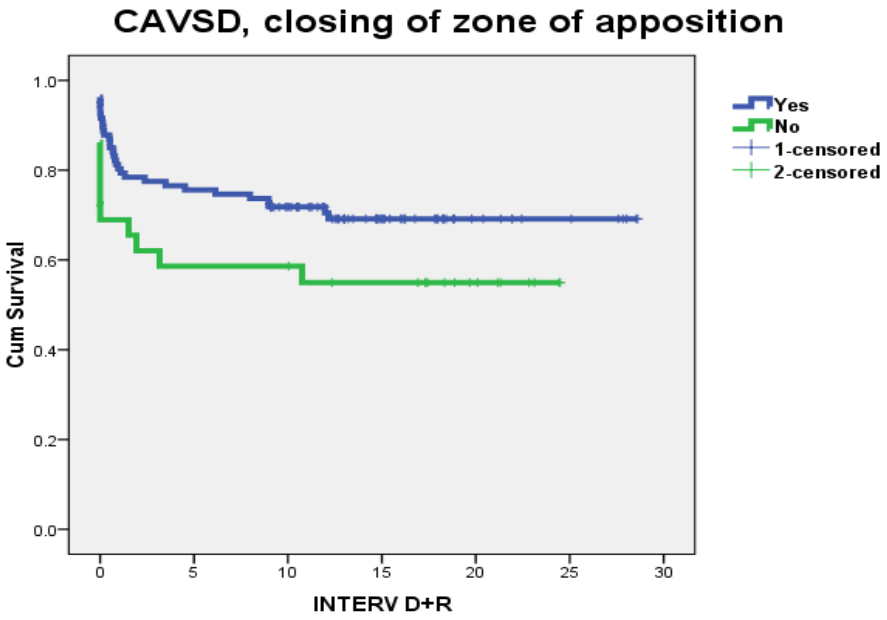
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.810	1	.368
Breslow (Generalized Wilcoxon)	1.373	1	.241

Test of equality of survival distributions for the different levels of SPLITT.

Figure 15. Closing the zone of apposition, an overall comparison

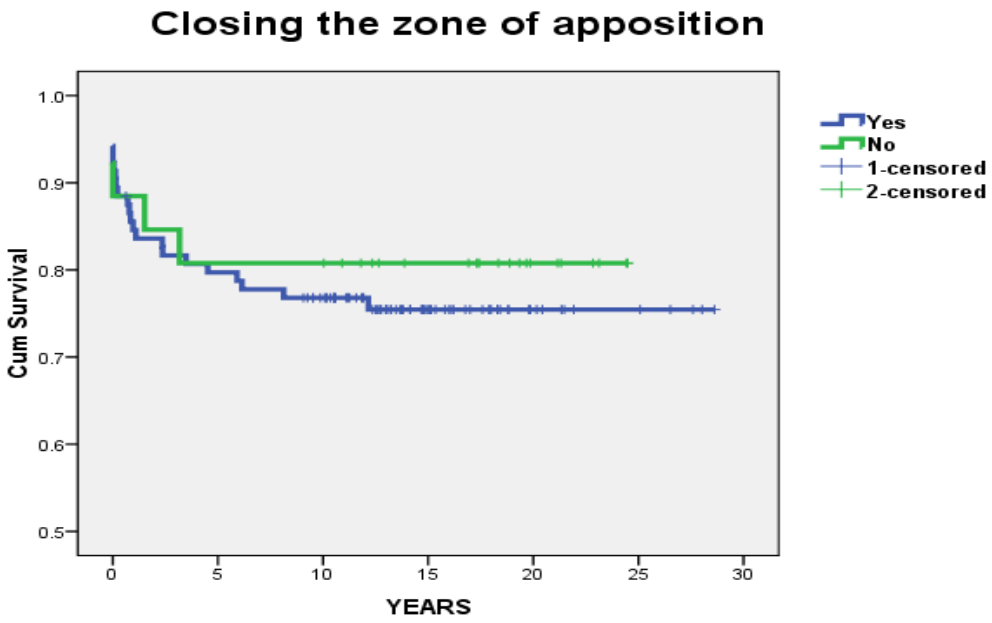
An overall comparison between the two groups using Log Rank, Breslow and Chi-Square tests, showed no significant difference in survival between the two groups, with a p-value on 0.368 and 0.241. But there is an observed tendency that closing the ZoA leads to higher survival than leaving the cleft open.



	Chi-Square	Df	Sig.
Log Rank (Mantel-Cox)	3.000	1	.083
Breslow (Generalized Wilcoxon)	4.049	1	.044

Figure 16. Closing the zone of appostion in CAVSD

Further evaluation of closing the zone of apposition in patients with complete AVSD, showed a borderline significant difference in survival rates with a p-value on 0.083 and 0.044 using respectively Log Rank and Breslow.



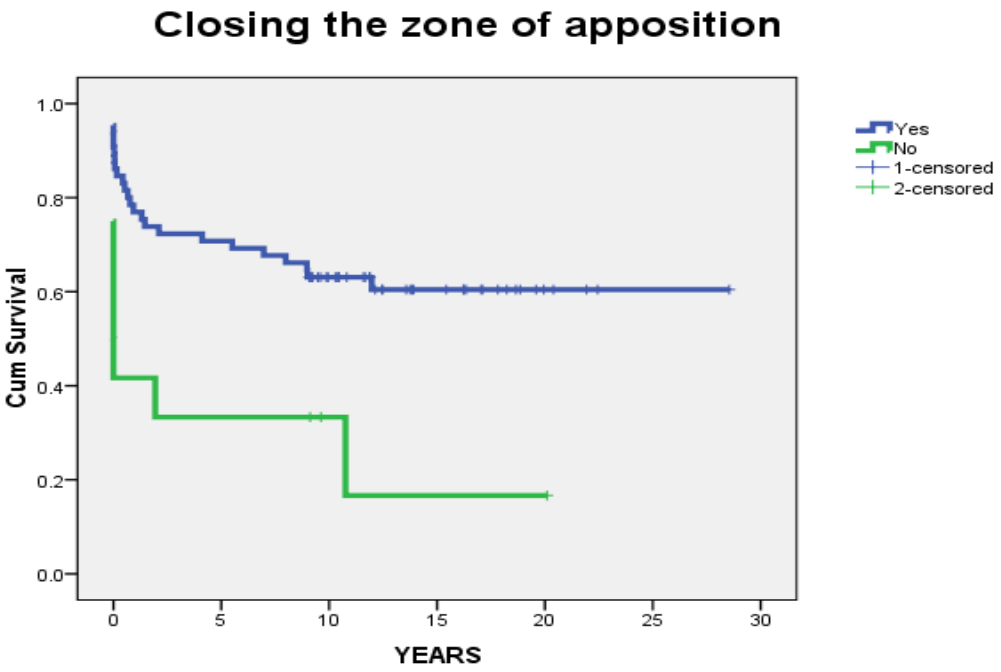
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.242	1	.623
Breslow (Generalized Wilcoxon)	.158	1	.691

Test of equality of survival distributions for the different levels of SPLITT.

Figur 17. Closing the zone of apposition in Down patients

An overall comparison of closing the zone of apposition in patients with Down syndrome showed no significant difference between the two groups with p-values on 0,623 using Log Rank and 0,691 using Breslow.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	10.519	1	.001
Breslow (Generalized Wilcoxon)	11.784	1	.001

Test of equality of survival distributions for the different levels of SPLITT.

Figur 18. Closing the zone of apposition in non-Down patients

An overall comparison of closing the zone of apposition in patients without Down syndrome, using Chi-Square, Log Rank and Breslow tests, showed a highly significant difference between the two groups with a p-value on 0.001.

Closing the ZoA was performed in 176 patients and the ZoA was left open in 39 patients. The overall reoperation rate in our group of patients was 13.2% (29 patients). Twenty-five of these patients had a significant mitral insufficiency alone or together with either residual ASD or VSD. The reoperation rate did not differ among the two groups, closing the ZoA or let it be open, 13.6% and 10.3% respectively. This indicates that cleft closure do not influence the reoperation rate because of MI.

Postoperative care

Data related to length of stay (LOS) at the intensive care unit between 1979 to 1999 showed a tendency (non-significant) towards shorter LOS, ICU-stay and time on a ventilator through the periods. The median time on ventilator was 24 hrs in the early period versus 18 hours from 1995-99.

Complications

124 patients (56.6 %) had no complications after primary repair and 82 patients (37.4 %) presented with complications. Information about postoperative complications was unavailable in 13 patients (5.9%).

Among the patients with complications early reoperation was needed in 10 patients. Among these patients 5 needed reoperation as a consequence of bleeding, there was one late tamponade, dehiscence occurred in one patient and there were other reasons in the 3 remaining patients. Arrhythmias were detected in 31 patients, and temporary pacemaker was needed in 24 patients, one patient needed permanent pacemaker, anti-arrhythmic drugs were needed in 5 patients and one patient needed postoperative cooling. Postoperative low cardiac output was defined as the requirement of more than 0.05 microgr/kg/min adrenaline or 5 microgr/kg/min dopamine. A total of 32 patients fulfilled the criteria of low cardiac output, where 27 patients needed more than 0.05 microgr/kg/min of adrenaline and over 5 microgr/kg/min dopamine was necessary in 5 patients. Postoperative renal failure was defined as creatinine over 150 μmol/l. PD (peritoneal dialysis) was necessary in 2 patients. Central nervous system complications were present in totally 4 patients, whereas 2 of these patients presented with postoperative convulsions and 2 patients had positive CTscan or MRI. Infections where detected in 3 patients postoperatively. One patient had a superficial wound infection, one presented with a deeper wound infection and one patient got sepsis.

Follow-up

Follow-up data was primarily based on data according to rhythm, functional class Warners-Somerville ability index (1-4), degree of mitral regurgitation (0-4), the need of medications and status as alive or dead after surgery. Follow-up was possible in a total of 215 (98.2%) patients, whereas 4 patients were lost to follow up. Median follow up time recorded was 4738 days (12. 98 years), ranging from 0 days to 10599 days (29. 04 years). Closing date for this study was 19.01.09.

During follow-up cardiac rhythm (ECG) was registered in totally 164 patients (75%). 42 patients died during follow up. The remaining 13 patients had no data on cardiac rhythm.

A vast majority of the patients had a sinus rhythm (158/164). Four patients had permanent pacemaker. All patients with pacemakers had Down syndrome. One received the permanent pacemaker after the first surgical repair one patient needed the permanent pacemaker after first reoperation. The two remaining patients received the pacemaker during the follow-up period.

Table 8. Rythm at follow up

Rythm	Down	Non-Down	Syndromes	Total
Unknown	0	1	1	2
Sinus	100	54	4	158
SV	0	2	0	2
PM	4	0	0	4

Functional performance was based on Warners-Somerville ability index. This was registered in totally 211 patients. Out of these patients 201 were in class 1 and only one patient was in functional class 3. Data was missing in totally 8 patients.

Table 9. Functional class. Warners-Somerville ability index

Functional class	Down	Non-Down	Syndromes	Total
1	121	74	6	201
2	5	3	1	9
3	1	0	0	1
4	0	0	0	0

The degree of mitral regurgitation was classified into five different groups, where degree 0 was defined as unsignificant and degree 4 is defined as severe regurgitation. Data about degree of mitral regurgitation was available in totally 170 patients (77.6%). Information about according to mitral regurgitation was missing in 49 patients (22.4%), whereas 42 of these patients were dead, 27 due to early death and 15 due to late death. A total of 50 patients had MI grade 0.93 patients had MI grade 1. 26 patients were in the group MI grade 2. Only one patient with DS had MI grade 3 at follow up. No one had MI grade 4.

Table 10. Mitral regurgitation

Degree of MI	Down	Non-Down	Syndromes	Total
0	33	15	2	50
1	60	32	1	93
2	13	11	2	26
3	1	0	0	1
4	0	0	0	0

The need of medical treatment and number of medications was available in totally 170 patients (77.6%). Data was unavailable in 49 patients (22.4%), whereas 42 of these patients were dead, 27 early deaths and 15 late deaths. A total of 161 patients used no medications at follow-up, 8 patients in our series used one medication. No one used 2 medications, and one patient with Down syndrome used 3 medications. A vast majority of the medication was levaxine due to hypothyreosis.

Table 11. Medication

Number	Down	Non-Down	Syndrome	Total
0	102	54	5	161
1	4	4	0	8
2	0	0	0	0
3	1	0	0	1

Discussion

Mortality

Our study of 219 consecutive patients reflects a 30 years experience in the surgical management of infants and children with AVSD in Rikshospitalet. These represent a great majority of all patients in Norway that underwent surgery for AVSD. A small portion of patients with AVSD (15 to 20%) were treated at Haukeland University Hospital up to 2003. These patients are not included in the present study.

The overall mortality rate in our study was 19% and 42 patients died during the observational period. In-hospital mortality was 12 % (28 patients) and 14 patients died later during follow-up. In the beginning of the study period (1979-1984), the surgical repair of AVSD was associated with a very high early mortality rate (40%). From 1995-1999 early mortality decreased to 5.7%. These findings are consistent with reports from others (23, 39, 44, 45, 58,) and underline that the prognosis for surgical repair of AVSD has fundamentally improved. Evaluation of the early mortality in patients with AVSD the last 10 years in our clinic shows a further decline to 0.5% (91). This change represents a substantial achievement in reducing the risk of surgery and perioperative mortality in this group of patients. Similar advances can be observed in treatment of other CHD, leaving substantial mortality to patients with critical aortic stenosis and complex cardiac lesions combined with malformations other vital organs (72).

The reasons for that are obvious – a better selection of patients through a systematic approach to preoperative diagnosis is an important issue. The surgical performance based on the volume quality relationship of the surgeon is essential. This includes a better understanding of the morphology of the defect and a corresponding improvement of surgical techniques. The team approach to each patient including all kinds of personnel; the cardiac surgeon, the pediatric cardiologist, the pediatric anesthesiologist and the nurse intensivist leads to a common specific strategy to minimize perioperative risks. The focus on avoiding pulmonary hypertensive events and management of postoperative cardiac failure is essential. Thus, by three decades the surgical repair of AVSD has changed from a high-risk two-staged procedure including palliative pulmonary artery banding and a later definitive procedure to a complete one-stage surgical repair, most often performed before the age of 4-6 months.

When comparing the results and especially the mortality rate of our study with other studies, we need to describe a specific limitation of our inclusion of patients. In the present study no patients were excluded since they all underwent surgery at Rikshospitalet. However, in evaluating the mortality rate in the present study compared to other studies we of course also need the specific preoperative inclusion criteria. In our study no such data was registered on the in the whole group of AVSD patients referred to the hospital, including those who were not accepted for surgery. The level of acceptance for surgery immediately influences the mortality rate in a group of surgical patients.

Different types of AVSD and additional defects

We have chosen to include the all the different types of AVSD with associated anomalies. This is important from an epidemiologic point of view since this approach adds knowledge to the vide variation of patients, the coexisting cardiac and non- cardiac malformations and comorbidity found in different patients with AVSD. A majority of other studies presenting the results of surgical repair on AVSD have focused on either partial or complete AVSD and have excluded major associated anomalies, such as Teratology of Fallot, double outlet right ventricle, transposition, total anomalous pulmonary venous drainage, single papillary muscle, unbalanced ventricles, and other syndromes except from Down syndrome. The present study included all patients that underwent biventricular correction regardless of their comorbidity.

However, when the study turns from description of patients into an evaluation of the quality, risk analysis and the prognosis of different treatments, it is of great importance to have comparable groups of patients of a certain size. We have chosen to include other syndromes, and in our study the rate of other syndromes is low (3.6%), apparently too low for analysis. However this group stands out with worse outcome compared to the Down- and non Down syndrome group.

The sub grouping of patients is necessary for the significance of the comparisons and lead to a high level of precision regarding interpretation of data and conclusions. The special challenge within the field of AVSD is the group of patients without Down syndrome since many of these patients have a wide variety of lesions (16, 45, 73). Our findings show a significantly better survival in the group of patients with Down syndrome compared to the non Down patients. Sixty percent of the patients in our study had Down syndrome. The reports from others indicate a number of patients with Down syndrome ranging between 50 to 74% (73).

The reported prevalence of AVSD with normal caryotype range from 10 to 40% which is in consistence with our study (35.6%) (22).

When comparing 100 patients with Down syndrome and CAVSD with 36 patients without Down syndrome and CAVSD the mortality rate was significantly higher among the patients without Down syndrome. This is in accordance with other reports (20, 45, 73), but the implications of this finding have later on been challenged by many workers. Miller and coworkers present an epidemiologic follow up study of infants with AVSD showing a similar overall survival probability among patients with or without Down syndrome (73). These workers focus on the different pattern of associated major non-cardiac malformations in these two groups of patients. The major difference is that the patients without Down syndrome had a higher incidence of coexisting laterality defects (heterotaxy). In their study the infants with heterotaxy and AVSD had 6-fold higher mortality rate than patients without heterotaxy. The influence of coexisting malformations on the survival rate may influence the interpretations of the prognosis of surgical repair in the non Down group. In their study Down syndrome per se was not a positive predictor of survival (73). Abnormal development of the left-right axis such as heterotaxy is associated with CHD, especially AVSD and malformations of the spleen (3). Among these, asplenism may be a potential hazard to perioperative survival in the child. But a causality between these findings remains to be elucidated.

In our study we had only one patient with heterotaxy and AVSD. This patient belongs to the non Down group, but at such a low incidence of heterotaxy we cannot interpret our data regarding the role of coexisting non-cardiac malformations as independent risk factors for surgical mortality.

The group without Down syndrome also has a higher frequency of cardiac malformations than the patients with Down syndrome. The different kinds of malformations in the left ventricular outflow tract are considered to be a significant cause of the higher mortality rate (80). A higher prevalence of malformations in the left ventricular outflow tract among patients without Down syndrome is also reported (43, 80). In the present study we had only one patient with SAS and Down syndrome.

Thus, the heterogeneity of the different AVSD patients is considered more and more important for the evaluation of prognostic factors including mortality rate. The patient with Down syndrome and AVSD is different in many respects from a patient without Down

syndrome with AVSD. These other clinical features seem to be more important for the overall outcome after surgery than the Trisomy 21 itself.

The frequency of different subtypes of AVSD will also differ among the patients of Down syndrome compared to the patients without Down syndrome. In the present study 75.2% of the Down patients presented with CAVSD, partial AVSD was 6.7%, 11.3% had intermediate, 1.5% had AVSD and TOF, and AVSD and other defects was present in 5.3%. The frequency of CAVSD and Down syndrome is consistent with other reports, whereas the frequency of the other subtypes will vary. In the present study 46.2 % of the non Down patients had CAVSD, 25.6% had PAVSD, 15.4% had IAVSD, 1.3% had AVSD and TOF, and AVSD and other defects was present in 11.5%. Boening et al (11, 39) have shown that presence of CAVSD represents a higher risk of mortality. As long as the relative frequency of different subtypes of AVSD is varying in the two groups of patients , and the risk of mortality varies with different subtypes, this may influence the analysis of results regarding surgical risk within the Down and non Down patients.

Age of primary repair

Age of primary repair is one of the factors that possibly could influence the prognosis. In the present study age at primary repair had no significant influence on the mortality rate. The age of the primary surgical procedure has declined through the observation period of the study. In the period from 1975-1979 the median age at primary repair was 13.5 months whereas the median age of the patients from 1995-1999 was 5.5 months.

The surgery for AVSD has changed significantly through the three decades. In the late seventies many patients were repaired by a two staged procedure with a palliative PAB preceding the definitive repair. PAB has been performed in 26 patients in the present study. But a PAB is not exclusively indicating a preceding palliation in a two-staged surgical repair since this can also be a part of a correction when AVSD is part of a more complex defect (58, 61).

By time, single early reparative surgical procedure was considered to be beneficial for the patient with AVSD. If the PAB should be omitted as a preceding procedure, an early repair had to be performed. The reason for that was the increasing risk of developing pulmonary vascular obstructive disease by time after birth. This is especially important in the patients

with Down syndrome, because these patients are more vulnerable to a rapid change of the pulmonary vascular bed than patients without Down syndrome (18).

Even though there is general agreement on early repair within the first 6 months of life, there are different opinions regarding the optimal age within infancy. In the pediatric cardiac program in the Department of Cardiothoracic surgery at Rikshospitalet the recommended time for primary definitive correction of AVSD is at the age of 3 to 6 months. This is supported by other coworkers (43, 57, 58).

Other surgeons prefer surgery to be performed earlier (43, 81). In a study presenting long-term follow up of 100 consecutive patients undergoing definitive early repair of complete AVSD from 1999-2009 the median age at surgery was 3.8 months and they experienced no early or late mortality (81). Singh and coworkers showed that the surgical risk was similar in patients below three months of age compared to a group of patients older than three months (85). These findings indicate that it is possible to perform a large scale surgical program in early infancy at a very low perioperative surgical risk.

However, the benefits of early surgical repair and low incidence of PVOD must be weighed against the possible risk factors by operating infants younger than 3 months. Low age means fragility of the valve tissue, and a great matter of concern is whether or not early repair can avoid left AV valve regurgitation. A study performed with surgical correction younger than 3 months and weight less than 4 kg presented an independent risk factor for reoperation with the indication left AV valve regurgitation (43). Another report emphasize that patients requiring surgery before the age of 3 months had a much higher incidence of left AV valve regurgitation (58). It has also been suggested that early repair may prevent the progression of AV valve regurgitation associated with the cardiac enlargement in a delayed surgery. But the same authors mention the concern of the fragility of the valve tissue in early repair and possible need for reoperation (45).

In an attempt to conclude, the advances in the cardiac surgery in newborns and early infancy have made it possible to perform safe surgery in newborns and early infancy without an increased risk for perioperative mortality. For the patients of AVSD there will be a sufficient time frame in infancy for low perioperative risk, necessary preoperative medical treatment of the volume-induced cardiac failure and avoidance of pulmonary hypertension in patients with AVSD.

Surgical technique

The choice of different surgical techniques depends on the morphology of the AVSD and the individual preference of the surgeon. In the present study there was no significant difference in surgical outcome between the 7 different surgeons. The surgical technique by itself seems to influence the mortality rate when the one-patch, two-patch or no-patch techniques are applied. The present study indicates that the use of the one-patch technique in CAVSD produces significantly more risk of death compared to the other two techniques. This finding is not in consistence with other reports (57, 59). Jeong et al demonstrated no differences in surgical outcome in CAVSD between the modified single patch technique, one patch technique and the two patch technique (59). Similar results are reported by Nunn, but he also suggests that there could be a survival advantage of the modified single patch technique for CAVSD compared to the two- patch technique (57). He found that the modified single patch technique could be carried out with low reoperational rate for left AV valve leakage, no need to close residual VSD and a low incidence of LVOTO (57). Another study by Backer and coworkers compared the modified single patch technique with the two-patch technique and found no difference in early and late mortality and need of reoperation due to LVOTO, left AV valve dysfunction or residual VSD. A limitation was a relatively short follow-up (6 years) (62).

Wheter the modified single pacth technique is superior to the two-patch technique is widely debated and the issues include postoperative LVOTO, reoperation for residual VSD and preserved AV valve function (57, 59, 62). The two- patch technique with the synthetic material in the left ventricular outlet could cause LVOTO by promoting fibrotic obstruction (57). In the modified single patch technique the AV valve is pulled down to the ventricular crest and thereby also has a potential in causing a narrowed left ventricular outflow tract (62). Supporters of the modified single patch technique promote the simplicity of the technique by avoiding the VSD patch and report no incidence of residual VSD (57, 62). A limitiation of the modified single patch technique is that it is not suitable in all patients with CAVSD if the VSD is too large and if there are additional defects such as TOF (59).

Today the techniques preferred in our institution is the two- patch technique and the modified single patch technique. The two- patch technique is used when the VSD is large, and the modified single patch technique is carried out when the VSD is less significant. Both these techniques can be performed with adequate surgical outcome (57, 59, 81). The two- patch

technique is a safe and reproducible surgical method (81). This technique avoids the dividing and reattachment of the leaflets (56, 58). In the small infants the valve tissue can be more fragile and this technique will preserve more valve tissue (58).

In the present study we found that there was no significant difference in the frequency of need of reoperation by using the different techniques, and this is similar to what other reports have shown (nr 6, 82, 84).

The zone of apposition

Closing the zone of apposition was increasingly accepted from the beginning of the 1990s, and surgical improvement was reported (39, 76). In our institution the procedure was adopted from the beginning of the study period (1979) and there has been a tendency in a more aggressively approach towards closing the ZoA. In the present study the closure rate was 80.36%. The ZoA was left open in 17.8%. Whether it was completely closed or left open was the surgeon's preference.

An overall comparison between cleft closure and leaving the cleft open, showed no significant difference in freedom from death and reoperation. However, we found that closing the ZoA was of significant importance in the non Down patients. A possible explanation to observation is that the AV valves in these patients have more pronounced malformations than the valves in the Down patients. Once the leakage is successfully closed by surgery this probably contributes significantly to improved survival. The valves in the Down patients have more abundant tissue which allows easier reconstruction (43). On the other hand closing the ZoA in the Down patients showed no significant different between closing or leaving the cleft open. Since a majority of the included patients have Down syndrome, the overall comparison will reflect the finding in the group of patients with Down syndrome.

It seems to be a general agreement among surgeons that closing the ZoA should be performed when the morphology of the left AV valve allows it without producing stenosis (76). Leaving the ZoA unsutured results in significant postoperative left AV valve incompetence (42). Closing the ZoA in CAVSD reduces the risk of left AV valve regurgitation and thereby decreasing the reoperation rate and cleft closure may lead to better survival (58, 76, 84).

Reoperation

In performing a long-term follow-up study the rate of reoperation is an important issue. In the present study 29 patients (13%) underwent reoperation. Among the reoperated, 25 of them had either mitral regurgitation alone or combined with residual leakage of either the ASD or the VSD. Mitral regurgitation is the major cause of reoperations. The need of reoperation is based on the findings from echocardiography. A retrograde flow into the pulmonary veins is an important sign of significant mitral leakage. This makes surgical intervention necessary. We had no surgical mortality after first reoperation, but significant leakage persisted in another 6 patients. They had a second reoperation; all these patients had mitral regurgitation alone. Only one required a third reoperation and that patient died during this reoperation.

This shows clearly that the residual leakage can be eliminated by surgery, whereas mitral regurgitation will persist as a problem in a fraction of the patients even after the first reoperations. Different surgical approaches were used, mitral valve plasty, mitral ring or mitral valve replacement. The treatment of mitral valve leakage by the first reoperation is successful in more than 80% of the patients and another surgical correction will reduce or eliminate the mitral valve regurgitation in the rest of the patients. However, a longer-term follow-up will probably identify patients that sooner or later need mitral valve repair.

When comparing our results with the corresponding results from other workers, our patients have all different subtypes of AVSD whereas most other studies present the results of only one subgroup of AVSD. Our results are similar to other studies according to mitral regurgitation as an indication for the first and second reoperation (39, 40, 43, 58, 68, 81). Only one patient required reoperation for SAS. A similar finding has been reported by Boening and coworkers with one reoperation for LVOTO among 121 patients with AVSD (39). This is not consistent with other reports regarding LVOTO after AVSD repairs. Literature report a higher incidence of postoperative LVOT obstruction requiring reoperations (2.7% to 5.6%) (58, 81, 82, 83). A possible contributing factor in the present study is the low rate of PAVSD (15%) compared to other findings of a 25% rate (68). The rate of LVOTO has been found to be higher in PAVSD and Rastell type A (86). The reported incidence of LVOTO in PAVSD is 3 to 7% (40). Another possible suggestion in our study is the surgical management of the anterior part of the VSD. They have been using a “comma shaped” patch over VSD (91), which is emphasized by Van Arsdell and coworkers. By using a large anterior

component to the VSD patch, the outflow tract is enlarged and the possibility for causing SAS is decreased (87).

We found a higher rate of reoperation in the group of patients without Down syndrome. The abundant leaflet valve tissue in patients with Down syndrome may be beneficial for a successful repair of the mitral dysfunction in AVSD. This is similar to the findings of others (43, 45, 80).

In our group of patients the frequency of need of reoperation is independent of the time when surgery was performed. However, during the first years of our follow-up study the early mortality was very high and it is probably misleading to compare the rate of reoperation from different time periods of our study since the mortality rate is different.

The present study shows that the rate of reoperation is independent of the age at primary repair. This indicates that lowering the age of the patient in trying to find the optimal time for a primary definitive repair, has not increased the risk of reoperations. This is in accordance with the findings from other workers (82). Another finding which has been previous reported (58, 84) is that different surgical techniques for closure of AVSD will not significantly influence the rate of reoperation (58, 84).

Rhythm disturbances and cardiac failure

The surgical repair of AVSD may harm the conduction system and produce total AV block postoperatively. In our study 4 patients needed a permanent pacemaker, one after the first surgical repair, one after the first reoperation and the two remaining received the pacemaker during the follow-up time. All these patients had Down syndrome. This is a low rate, but of course this complication represents a challenge for the patient in a life-long treatment. Until now we have no tools or surgical techniques eliminating this risk, and total AV block is a predictable part of the risk in a large scale surgical program. Dodge-Kathami and coworkers report a post operative incidence of complete heart block requiring permanent pacemaker at 3.7% (43). It has also been reported that the Down patients with AVSD have a higher frequency of pre- and postoperative AV block (12).

The incidence of cardiac failure and need of drugs for cardiac symptoms are low in our study. One patient had significant cardiac failure and needed medical treatment for this condition.

Limitations

The advantage of this retrospective study is that it includes patients from the last 30 years and thereby represents the innovative development of the surgical repair of cardiac defects in children. Our study also has a follow-up completeness of 98.2% which seems to be sufficiently high for reasonable analysis. In the beginning of the study there was a considerable preoperative mortality and at the end almost all defects are treated successfully with a high functional capacity of the children afterwards. In that way our study is like a walking through most of the history of pediatric cardiac surgery.

This movement by time is also a fundamental change in all kinds of perioperative care within the fields of pediatric cardiology, anesthesiology, and intensive care. Of course all these advances influence the results, and in that perspective a retrospective long-term study will have some limitations regarding what is the most crucial step forward and when it took place. These questions can hardly be answered, and our fundamental improvement is a continuum of advances in all fields mentioned.

The interpretations of the results must also be done with caution regarding the great heterogeneity of the patients. As long as every kind of patients who had surgical repair for AVSD was included, there is a great variety of comorbidity which may affect the results. This makes critical evaluation and comparisons between groups difficult.

When the study is retrospective, you will not be able to influence the data and parameters that were collected at the time the patient was treated. What is considered relevant data changes by time and you often have a restricted number of observations from the first study period compared to what is available in the last period of inclusion.

This study lack multivariate analysis of risk factors, which means that the correction for concomitant variation of different parameters is not available for evaluation. In that way the present study is rather a descriptive, observational study than an advanced analysis of different hypotheses regarding causes and effects. However, the statistics used is recommended for non parametric data and the Log Rank test, Breslow and Tarone Ware test together are preferable in that they differ in weighting the factors they use.

Conclusions

- The results of surgical repair of AVSD have improved significantly during the last three decades, from a high mortality rate to almost zero the last ten years.

- Primary definitive repair can be performed in early infancy without significant mortality.
- The observation that the group of patients without Down syndrome has a higher mortality rate is confirmed in our study, but his is probably due to concomitant cardiac and non- cardiac malformations in this group or
- The need of reoperation is 14%.
- The risk of reoperation is almost entirely associated with mitral regurgitation.
- The incidence of reoperation is higher in the group of patients without Down syndrome
- The risk of reoperation or mortality cannot be linked to different surgical techniques
- The long term follow-up shows stable outcomes with a low rate of AV block and significant cardiac failure. The need of a permanent pacemaker is approximately 2%.

Appendix: AVSD material

Op. Dato:			Kirurg:ST=1;HL=2;OG=3;ES=4;AF=5;EØ=6;SB=7;KS=8,Andre=9					
Diagnose:	Komplett AVSD	1						
	Primum ASD	2						
	Intermediate (VSD)	3						
	AVSD + TOF	4						
	AVSD + ABS, PV	5						
	AVSD + annet	6						
Bidiagnoser;	Non-Down	0						
	Down	1						
	Syndrom, annet	3	spesifiser					
Tidligere palliasjon:								
	Ingen	0						
	BAP	1						
	Shunt	2						
	Annen	3	spesifiser					
Teknikk:	En-patch	1						
	To-patch	2						
	Nunn	3						
	Dir sutur VSD+patch	4						
	Annen	5	spesifiser					
Sutur av splitt	Ja	1						
	Nei	2			Sutur:	Ukjent	10	
						Monofil	11	
						Flettet	12	
Komplikasjoner:				Ingen	0			
Reoperasjon		1		Blødning	11			
				Sentamponade	12			
				Sternumløsning	13			
				Annet	14	spesifiser		
Arrythmi		2		Temp PM	21			
				Perm PM	22			
				Medik. terapi	23			
				Kjøling	24			
Low Cardiac Output		3		Adrenalin>0,05	31			
				Dopamin >5	32			
				Annen inotropi	33	spesifiser		
Nyresvikt (kreat > 150)		4		Ingen/medik	41			
				PD	42			
				HD	43			
CNS		5		Kramper	51			
				Forb. parese	52			
				Varig parese	53			
				Pos rtg/MR	54			
Infeksjoner		6		Overfl sår	61			
				Dyp sår	62			
				Pneumoni	63			
				Sepsis	64			
				Annet	65	spesifiser		
Follow-up:	Dato:		Funksjonklasse 1-4			MI	0-4	Medik: antall
	Rytme: Ukjent	0	Sinus	1	Suprav. 2	PM	3	
Status:	**Levende:**	**1-3**	**Død:**	**0**	**Lost to fwup:**	**9**	**Dødsdato**:	
Reop: Dato:		Indikasjon:MI=1;VSD=2;ASD=3;Kombinasjon=4(spesifiser)						
	Teknikk: Mitral:	Resutur splitt=11, Plastikk=12, Plastikk+ring=13, Mek. klaff=14, Biol. klaff=15						
	VSD:	Sutur=21, Patch=22						
	ASD:	Sutur=31, Patch=32						
	Komb.	MI+VSD=41, MI+ASD=42, ASD+VSD=43, annen=44(spesifiser), SAS=45						
LOS;dager:	ICU,dager	RESP_T:timer						

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