DILEMMAS IN ATRIOVENTRICULAR SEPTAL DEFECT REPAIR

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DILEMMAS IN ATRIOVENTRICULAR SEPTAL DEFECT REPAIR

Dilemma's in atrioventriculair septum defect correctie
(met een samenvatting in het Nederlands)

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If I have all knowledge, but do not have love, I am nothing.
Love never fails.
(1 Cor 13:2,8 – NIV)

Contents

GENERAL INTRODUCTION

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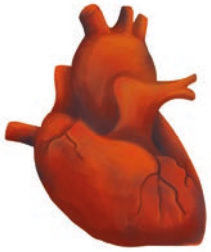
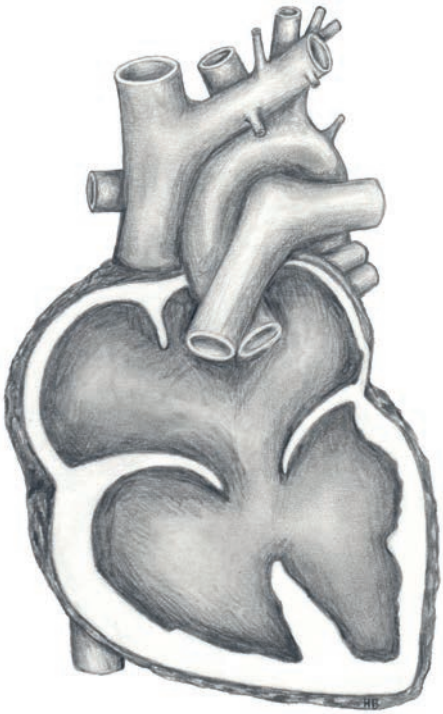


Introduction

Atrioventricular septal defects

Atrioventricular septal defects (AVSD) account for 3.4 % of all congenital heart defects and over half of the heart defects seen in children with trisomy 21 (1,2). This defect encompass a wide spectrum of anatomic findings and can be subdivided into partial, intermediate, and complete types, with the presence of a common atrioventricular junction being the pathognomonic feature (3). Partial AVSD (PAVSD) has an atrial septal defect (ASD) just above the atrioventricular (AV) valves along with a trifoliate left AV valve (LAVV) leading to varying degrees of LAVV regurgitation. Complete AVSD (CAVSD) consists of a ventricular septal defect (VSD) just below the plane of the AV valves, an ASD immediately superior to the plane of the AV valves, and instead of two AV valve orifices, a single or common AV valve orifice (Figure 1) (2). The Rastelli classification describes three types of CAVSDs based on the morphology of the superior (anterior) bridging leaflet, its degree of bridging, and its chordal attachments (4). Intermediate AVSD is "intermediate" between the partial and complete lesions: there are two distinct left and right AV valve orifices, an ASD adjacent to the AV valves, and a ventricular septal defect below the AV valves (5).

Figure 1. Complete atrioventricular septal defect – made by Hannah Blaauw



The hemodynamics in patients with a PAVSD are similar to patients with a large ASD, with increased right ventricular stroke volume. However, PAVSD patients may develop progressive cardiomegaly and congestive heart failure that is more significant than in patients with a secundum ASD without LAVV insufficiency.
In patients with a CAVSD, the large left-to right shunt causes right ventricular and pulmonary artery pressures to approach systemic pressure. These patients have significant pulmonary hypertension from birth which is unrelenting until they have complete intracardiac repair. The pulmonary hypertension and congestive heart failure is worsened by the presence of AV valve insufficiency, which increases the ventricular volume overload. Rapid elevation of pulmonary vascular resistance and progression of pulmonary vascular obstructive disease may evolve and require early repair (2). Most centers currently recommend complete repair at the age of 3-6 months (6).

The first successful repair of a CAVSD was reported by Lillehei and colleagues in 1955, using cross-circulation and direct suture of the atrial rim of the septal defect to the crest of the ventricular septum (7).

Single patch repair

In 1962, James Maloney and Frank Gerbode independently described a single-patch technique suspending the AV valve tissue to a single patch that closed both the ASD and VSD (8,9). The common AV valve is cut, and the patch is inserted in such a fashion that the lower portion of the patch closes the VSD, the AV valves are suspended to the patch, and the upper portion of the patch closes the atrial component.

Double patch repair

The double-patch technique was first described by George Trusler in 1975. He used separate patches of prosthetic material and pericardium to close the ventricular and atrial component (10).

Modified single patch repair

Most recently, Ben Wilcox and Graham Nunn have reported a technique of repair using direct closure of the VSD and thus avoiding the use of a patch for the ventricular component of the defect (11,12).

Suture closing of the LAVV zone of apposition was standard in all three repair techniques.

Patients with heart failure in the first 3 months of life, complex anatomy, or unbalanced ventricles may not be suitable for immediate biventricular repair, and pulmonary artery banding may be used to protect the pulmonary circulation. By using this technique, the decision to perform complete repair or single ventricle palliation may be deferred until the child grows (13-17).

Surgical outcomes

The first cohort of patients with surgical correction of CAVSD had a high mortality of 45% and a high incidence of complications such as complete AV block, residual AV valve regurgitation, and subaortic stenosis (18). A major breakthrough, resulting in a significant reduction of the incidence of postoperative heart block, occurred in 1958 when Maurice Lev described the location of the bundle of His in patients with CAVSD (19). Better understandings of the anatomy and refinements in surgical techniques have led to a dramatic improvement in patient outcome over the past three decades. In the current era, overall mortality rate after CAVSD repair went down to 2.9 % (20). However, despite improved survival, several single-center studies report that up to 14% of the patients require some form of reintervention to address LAVV regurgitation within 10 to 15 years (21-25). Furthermore, reintervention for left ventricular outflow tract (LVOT) obstruction is needed in up to 3.5% of patients (21,22,24,25). The need for unplanned cardiac reintervention in patients with congenital heart disease is strongly associated with increased mortality (26).

Although several preoperative, intraoperative, and postoperative factors may influence outcome after congenital heart operations, the adequacy of the surgical repair is likely the most important factor. Until recently there were no quality monitoring tools available in congenital cardiac surgery.
Technical performance score (TPS), a tool developed to determine technical adequacy of congenital cardiac repairs, has been shown to be an important predictor of both early and midterm outcomes across a wide range of congenital cardiac procedures (27). This raises questions as to a possible association between TPS and pre- and post-discharge outcomes in patients with CAVSD. Does the presence of residual lesions before discharge, as measured by TPS, accurately identify patients requiring post-discharge reinterventions? Which subcomponents of TPS best predict post-discharge reinterventions? These are the questions to be addressed in order to analyze the emerging clinical problem of reinterventions in the AVSD population.

Left atrioventricular valve

LAVV regurgitation is the most common indication for reintervention after repair. The cause of LAVV regurgitation can be attributed to abnormal morphology of the LAVV encompassing abnormal leaflets, atypical clefts, and abnormal subvalvular apparatus that result in leaflet prolapse and/or restriction. At primary repair, every effort should be made to address these abnormalities and ensure adequate tension-free coaptation of the LAVV leaflets (28).

Saving the LAVV by surgical repair is first choice when reintervention is indicated but results have turned out not to be durable in all patients. They therefore may end up requiring a valve replacement. With increasing numbers of patients surviving AVSD repair, valve replacement can be anticipated to be necessary more often. The influence of AVSD subtype on outcomes after repair (e.g. LAVV replacement) is not yet known and justifies further study.

Preoperative LAVV morphology and function remain the most important markers for successful

repair and thus predictors of post-discharge reintervention on the AV valve. Some types of dysplastic valves carry a higher risk for replacement which may even be required in infants.
An important limiting factor in LAVV replacement in infants has been the availability of appropriately sized prosthetic valves. Furthermore, early reoperation for replacement to compensate for somatic growth will be necessary when a suitably sized prosthesis is used (29-31).
A 15-mm prosthetic heart valve has been tested clinically and was subsequently FDA approved in March 2018 (Abbott's Masters HP 15-mm) (32). This particular prosthesis was already clinically available for off-label use in The Netherlands since 1998 (St. Jude Medical (SJM), St Paul, MN, USA) allowing the opportunity to report a nationwide long-term experience with up to 20 years follow-up with this particular valve in mitral position in infants and neonates. Understanding clinical outcome in patients who have undergone MVR with a small mechanical prosthesis can serve as a benchmark to determine utility and benefits of bioprosthetic options, such as the stented bovine jugular vein conduits, that have recently been introduced as an alternative (33).

Improving outcomes of AV valve repair in AVSD patients may be a key to better survival. Previous studies have shown the risk for LAVV reoperation being irrespective of repair technique (single or double patch) (34,35). While several materials are available for VSD closure in CAVSD repair, including autologous pericardium, preserved xenopericardium, and various prosthetic materials (eg, polyethylene terepthalate [Dacron, DuPont, Wilmington, Delaware] and polytetrafluoroethylene [Gore Tex, W. L. Gore & Associates, Inc, Flagstaff, Arizona], CorMatrix [Aziyo Biologics, Silver Springs, Maryland]), superiority of one material over another has yet to be defined (36).
Using fresh untreated autologous pericardium when closing the atrial and ventricular portion of the septal defect may preserve the natural dynamics of the AV valve. Using this patch material may have the potential to grow and adapt to complex 3D movement patterns in the center of the heart and may preserve LAVV function and prevent reinterventions.

Unbalanced atrioventricular septal defects

Unbalanced CAVSD represent 10-15% of all AVSD and are characterized by underdevelopment of one of the ventricles and varying degrees of malalignment of the common AV valve over the hypoplastic ventricle and associated hypoplasia of the outflow valve related to decreased flow (37-39). Type and severity of symptoms depend on which ventricle is affected and may be a variant of the presentation of hypoplastic left heart syndrome (typically with signs of low cardiac output as the ductus arteriosus closes) when the left ventricle is severely affected. When the right ventricle is affected, decreased blood flow to the lung and right-to-left shunting may cause cyanosis. The core challenge of unbalanced AVSD, as is now widely understood, is to accurately predict the risk of achieving (and maintaining) a biventricular end state as compared to the risk (early and late) associated with univentricular palliation, and thereby properly assign surgical strategy to the patient in question. This prediction is straightforward at the extremes of the anatomic spectrum (severely unbalanced or nearly balanced) but is difficult when unbalance is potentially significant but of moderate degree. Management strategy for unbalanced CAVSDs includes single-ventricle palliation and primary or staged biventricular repair. More recently, biventricular conversion from single-ventricle palliation and staged biventricular recruit-

ment have also been advocated particularly in patients with trisomy 21 and heterotaxy who tolerate single-ventricle palliation poorly (40-42). Studies comparing outcomes in patients with unbalanced CAVSDs, grouped according to management strategy, are needed. This raises the question whether hypoplastic left-sided heart structures in patients with AVSD and left-sided hypoplasia grow and will become adequate after biventricular repair.

Outline of the thesis:

The aim of this thesis is to report upon clinical outcomes of AVSD repair and of LAVV replacement in neonates, infants and adults and to report upon clinical outcomes of repair of hypoplastic left heart complex. In **Chapter 2** the association between a technical performance score and outcomes after complete AVSD repair is determined. **Chapter 3** provides an analysis on which subcomponents of the technical performance score best predict post-discharge reinterventions. An analysis of our national cohort of AVSD patients who underwent LAVV replacement is presented in **Chapter 4** in order to compare patient characteristics and outcomes among 2 AVSD subtypes. In **Chapter 5** our nationwide experience with up to 20 years follow-up with a 15-mm mechanical prosthesis in mitral position in infants and neonates is presented. A collaborative study together with Boston Children's Hospital is presented in **Chapter 6**, focusing on clinical outcomes after implantation of 15-17 mm mechanical prostheses in mitral position. **Chapter 7** provides a retrospective review of AVSD patients who underwent VSD and ASD closure with fresh untreated autologous pericardium, with particular attention to AV valve function. **Chapter 8** reports on the outcomes of CAVSD double patch repair comparing fresh untreated autologous pericardium with other patch material for VSD closure. In **Chapter 9** mid-term outcomes in patients with unbalanced CAVSDs were assessed according to management strategy (single-ventricle palliation versus biventricular repair or conversion). In **Chapter 10** the effect of biventricular repair on dimensions of left-sided heart structures was assessed and clinical results of patients with hypoplastic left heart complex were evaluated. Finally, **Chapter 11** provides a summary of all studies presented in this thesis with discussion of future perspectives.

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TECHNICAL PERFORMANCE SCORE: PREDICTOR OF OUTCOMES IN COMPLETE ATRIOVENTRICULAR SEPTAL DEFECT REPAIR

2

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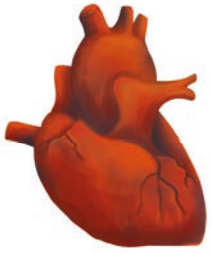


Abstract

Purpose:
Technical Performance Score (TPS) has been associated with both early and late outcomes across a wide range of congenital cardiac procedures. We wished to validate TPS as predictor of outcomes for complete atrioventricular septal defect (CAVSD) repair.

Methods:
Single center retrospective review of patients following balanced CAVSD repair between 1/1/2000 and 3/1/2016. We assigned TPS (class 1-no residua, class 2- minor residua, class 3-major residua or reintervention pre-discharge for residua) based on summation of sub-component scores from discharge echocardiograms. Outcomes of interest were in-hospital complications, postoperative days on ventilator, and post-discharge reintervention.

Results:
Among 350 patients, median age was 3.2 (IQR: 2.4, 4.2) months. Fifty-four (16%) had class 1 TPS, 218 (62%) Class 2, 63 (18%) Class 3, and 15 (4%) unscorable. There were 36 (10%) complications and median postoperative days on ventilator was 2 (IQR 1, 3) days. There were 34 (10%) post-discharge reinterventions. Median follow-up was 2.6 (IQR: 0.09, 7.9) years. On multivariable modeling, class 3 TPS was associated with complications (OR, 5.45; 95 % CI, 1.06-28.1; p= 0.04), prolonged postoperative ventilator days (HR, 0.54; 95% CI, 0.37-0.80; p=0.002) and post-discharge reintervention (HR, 5.61; 95% CI, 1.28-24.5; p=0.02) after adjusting for covariates such as age, weight, genetic abnormality, concomitant procedure, prematurity and second bypass run.

Conclusions:
At our center, CAVSD repair was associated with low morbidity. TPS may identify those with complications, prolonged days on ventilator, and require post-discharge reinterventions and thus provides feedback on areas of improvement and allows identification of patients who warrant closer follow-up.

Introduction

Complete atrioventricular septal defects (CAVSD) account for approximately 3.4 % of all congenital heart defects and over half of the cardiac defects seen in children with trisomy 21 [1,2]. The first successful repair of CAVSD was reported by Lillehei and colleagues in 1955, with 45 % mortality [3,4]. Better understandings of the anatomy and refinements in surgical techniques have led to a dramatic improvement in patient outcome over the last three decades. In the current era, overall mortality is around 2.9 % [5]. However, despite improved survival, several single-center studies report that up to 10% of the patients require some form of reintervention within 10 to 15 years, to address left atrioventricular valve (LAVV) regurgitation and left ventricular outflow tract (LVOT) obstruction [6-11].
While several preoperative, intraoperative and postoperative factors may influence outcome after congenital heart surgery, the adequacy of the surgical repair is likely the most significant factor. Technical Performance Score (TPS), a tool developed to determine technical adequacy of congenital cardiac repairs, has been shown to be an important predictor of both early and midterm outcomes across a wide range of congenital cardiac procedures [12]. TPS has been shown to be strongly associated with not only pre-discharge outcomes such as mortality, adverse events and resource utilization, but also with post-discharge mortality and unplanned reintervention [13]. Additionally, an optimal TPS can compensate for unfavorable preoperative physiologic status and adverse events during surgery [14].

We wished to validate the association between TPS and pre-discharge outcomes, such as complications and postoperative days on ventilator, and post-discharge outcomes, such as need for reintervention in patients with balanced CAVSD.

Material and Methods

Patient population

A retrospective review of patients who underwent repair of balanced CAVSD between January 1, 2000, and March 1, 2016, was performed with IRB approval. Demographic, clinical, surgical, echocardiographic and follow-up data were obtained. The primary complete repair of CAVSD was considered as the index surgery. Patients with associated major intracardiac anomalies (e.g. arch obstructions, double outlet right ventricle) were excluded. Patients with partial AVSD, intermediate AVSD, tetralogy of Fallot with CAVSD, or severely unbalanced forms of CAVSD were excluded. Mild imbalance was not considered as exclusion criteria. Preoperative echocardiographic reports were used to determine balance; with mild imbalance representing (a) minimal override of the common AV valve i.e., 50-to 60% of the common AV valve committed to one of the ventricular chambers, with equal sized ventricles or (b) equal commitment of AV valve to both ventricles and the hypoplastic ventricle being near apex forming.

Technical performance

Intraoperative and postoperative technical performance was scored as previously reported from our center [12]. Intraoperative TPS was assigned according to the intraoperative echocardiographic qualitative and quantitative findings and status of conduction at time of operating room exit. Discharge TPS was assigned according to pre-discharge/pre-reintervention echocardiographic qualitative and quantitative findings and clinical status at discharge from index surgery. The CAVSD repair was divided into its subcomponents. Each subcomponent is assigned a score of class 1 (optimal, trivial or no residua), class 2 (adequate, minor residua) or class 3 (inadequate, major residua or pre-discharge reintervention for residua), based on specific echocardiographic criteria (Appendix 1). The overall score for the procedure is based on the summation of the subcomponent scores and is class 1 if all subcomponents received a class 1 score, class 2 if one or more of the subcomponents were class 2 but none were class 3, and class 3 if any of the subcomponents were class 3. Any unplanned surgical or catheter based reintervention for residua in the anatomic area repaired during CASVD surgery or the need for permanent pacemaker placement resulted in a class 3 (inadequate) score.

Primary Predictor

As the quantitative measures (vena contracta, ASD, VSD dimensions) were missing in 78% of intraoperative echocardiograms and 57% of discharge echocardiograms, TPS based on qualitative measures was selected. Furthermore as 118 (34%) of subjects did not have intraoperative echocardiograms, discharge qualitative TPS was chosen as primary predictor.
Other covariates included in analysis are listed in table 1.

Outcomes of interest

The outcome variables that were analyzed were the following:

- Primary: post-discharge reintervention
- Secondary: in-hospital complications, postoperative days on ventilator, postoperative intensive care unit (ICU) length of stay and postoperative hospital length of stay.

Post-discharge reinterventions were defined as surgical or catheter based reinterventions on areas repaired at CAVSD surgery including placement of permanent pacemaker. Complications were defined as pre-discharge (1) death or heart transplant; (2) need for extracorporeal membrane oxygenator (ECMO) support; (3) re-exploration for bleeding; (4) re-exploration for low cardiac output syndrome (LCOS); (5) diaphragm plication; (6) vocal cord paralysis/paresis; (7) delayed sternal closure; (8) mediastinitis requiring debridement; (9) postoperative ventilator support >7 days. Pre-discharge surgical or catheter based reinterventions on the anatomic area of repair and placement of permanent pacemakers were not considered as complications, because they are components of the TPS. Postoperative days on the ventilator was defined as total number of days on the ventilator after index surgery and included all reintubation days. Postoperative ICU length of stay was defined as total postoperative days in the ICU including days re-admitted to the ICU during hospitalization for index surgery.

Statistical Analysis

Patient and procedural characteristics were summarized as frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Unadjusted relationships between TPS and patient outcomes were assessed using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Time to post-discharge reintervention was estimated using the Kaplan-Meier method. Logistic regression analysis was used to evaluate the relationship between TPS and the outcome pre-discharge complications, adjusting for clinically relevant predictor variables. Cox proportional hazards models were used for the outcomes postoperative days on ventilator and post-discharge reintervention. For days on ventilator, patients who died prior to extubation were censored on the date of death. For reintervention, follow-up began on the day of hospital discharge; only patients discharged alive without heart transplantation were included. For each outcome, forward selection was used to develop a multivariable model of baseline patient factors associated with that outcome; $p<0.05$ was required for retention in the final model. Qualitative TPS was then added to these models. Odds ratios and hazard ratios were estimated with 95% confidence intervals. Statistical analysis was performed with SAS® version 9.4, SAS Institute Inc., Cary, NC, USA.

Results

There were 350 patients included in the analysis. Patient and procedural characteristics are represented in Table 1. There were 211 (60%) females, 67 (19%) were premature, and 305 (87%) patients had some form of genetic anomaly (trisomy 21 in 294 (84%), heterotaxy in 5 (1%) and other in 6 (2%)). The median age at surgery was 3.2 (IQR: 2.4, 4.2) months. Median postoperative days on ventilator was 2 (IQR: 1, 3) and median postoperative ICU length of stay (LOS) was 3 (IQR: 2, 5) days. Median postoperative hospital length of stay was 7 (IQR: 6, 12) days. Fifty-four (16%) had class 1 TPS, 218 (62%) Class 2, 63 (18%) Class 3, and 15 (4%) unscorable. There were 15 deaths (4%) (6 (1.7%) pre-discharge and 9 (3%) post-discharge), 36 (10%) complications (including pre-discharge mortality) and 34 (10%) post-discharge reinterventions.

Table 1. Patient and procedural characteristics (n=350)

Characteristic	Value [number (percentage) or median (IQR)]
Median age at surgery in months	3.2 (2.4, 4.2)
Neonate	14 (4%)
Weight, kg	4.3 (3.7,5.0)
Female	211 (60%)
Prematurity	67 (19%)
Any genetic syndrome	305 (87%)
Trisomy 21	294 (84%)
Heterotaxy	5 (1%)
Other genetic syndrome	6 (2%)

Characteristic	Value [number (percentage) or median (IQR)]	
Balance, by preoperative echo		
Well-balanced	322 (92%)	
Mildly right dominant	16 (5%)	
Mildly left dominant	12 (3%)	
Preoperative common atrioventricular valve regurgitation		
None	49 (14%)	
Mild	189 (54%)	
Moderate	30 (9%)	
Severe	4 (1%)	
Not reported	78 (22%)	
Surgical procedure		
Single patch	57 (16%)	
Double patch	255 (73%)	
Australian technique	38 (11%)	
Concomitant procedure*	33 (9%)	
Second bypass run	17 (5%)	
Intraoperative TPS	Qualitative	Quantitative
Class 1 – Optimal	78 (22%)	19 (6%)
Class 2 – Adequate	141 (40%)	54 (15%)
Class 3 – Inadequate	13 (4%)	5 (1%)
Not reported	118 (34%)	272 (78%)
Discharge TPS	Qualitative	Quantitative
Class 1 – Optimal	54 (16%)	52 (15%)
Class 2 – Adequate	218 (62%)	75 (21%)
Class 3 – Inadequate ^	63 (18%)	24 (7%)
Not reported	15 (4%)	199 (57%)
Complications#	36 (10%)	
Death/transplant pre-discharge	6 (2%)	
Post-discharge reintervention	34 (10%)	
Death/transplant post-discharge	9 (3%)	
Median follow up in years	2.6 (0.09, 7.9)	
Median postoperative days on ventilator	2 (1, 3)	
Median postoperative ICU length of stay in days	3 (2, 5)	

**Included: left ventricular outflow tract tissue resection, pulmonary artery band takedown, repair of coarctation of the aorta, other. Not included: patent ductus arteriosus ligation.*
^ 10/66 (15%) of TPS class 3 had pre-discharge reintervention for residual lesions.
 # Pre-discharge death/transplant; extracorporeal membrane oxygenator support; re-exploration for bleeding; re-exploration for low cardiac output; diaphragm plication for paralysis or paresis of the diaphragm; paralysis or paresis of the vocal cord; delayed sternal closure; mediastinitis requiring exploration and debridement; postoperative ventilator support longer than 7 days.
ICU: intensive care unit; TPS: technical performance score.

Univariable and multivariable analysis of the association between discharge qualitative TPS and outcomes of interest are depicted in Tables 2, 3 and 4. On multivariable modeling, class 3 TPS was associated with complications (OR, 5.45; 95 % CI, 1.06-28.1; p= 0.04), prolonged postoperative days on ventilator (HR, 0.54; 95% CI, 0.37-0.80; p=0.002) and post-discharge reintervention (HR, 5.61; 95% CI, 1.28-24.5; p=0.02), after adjusting for other covariates. On multivariable modeling, class 3 TPS was also associated with prolonged postoperative ICU length of stay (HR, 0.53; 95% CI, 0.36, 0.78; p=0.001) and postoperative hospital length of stay (HR, 0.49;

95% CI, 0.34, 0.72; p<0.001). Supplemental Table 5 breaks down the distribution of TPS for CAVSD sub-components. Supplemental table 6 represents intra-operative revisions, pre-discharge and post-discharge reinterventions on AVSDI, left ventricular outflow tract and/or placement of permanent pacemaker. 10 patients had a pre-discharge reintervention. Among the 8 patients who survived discharge, 4 (50%) patients had post-discharge reinterventions. Detailed information about reinterventions are depicted in supplemental tables 6, 7 and 8, and figure 1. Of the 344 subjects discharged alive, post-discharge reintervention rates were as follow; Class 1: 3.5%, Class 2: 6.1% and Class 3: 28.3%. Twenty five (7.3%) patients needed a post-discharge reintervention on the left atrioventricular valve, with 9 (2.6%) patients having > 1 post-discharge reintervention on the left AV valve. There were 16 (4.7%) post-discharge reinterventions on the LVOT. Figure 2 represent the Kaplan–Meier survival analysis curve for post-discharge reinterventions based on discharge technical performance scores, with Class 3 TPS having a significantly higher post-discharge reintervention rate (log rank p<0.001) compared to Class 1.

Table 2. Univariable and Multivariable Analysis: Complications

Variables	Unadjusted Odds Ratio (95% CI)	p value	Adjusted Odds Ratio (95% CI)	p value
Age at Surgery ≤ 60 days	2.56 (1.18, 5.57)	0.02		
Neonate	10.6 (3.47, 32.3)	<0.001		
Prematurity	4.13 (2.00, 8.50)	<0.001		
Trisomy 21	0.33 (0.15, 0.70)	0.004		
Any Prior Procedure ^	8.91 (3.56, 22.3)	<0.001		
Concomitant Procedure*	8.31 (3.67, 18.8)	<0.001	10.3 (3.99, 26.8)	<0.001
Weight < 3.5 kg	4.50 (2.16, 9.40)	<0.001	4.91 (2.07, 11.7)	<0.001
Second Bypass Run	4.06 (1.34, 12.3)	0.01	7.27 (2.03, 26.0)	0.002
Preoperative CAVV regurgitation				
None/trivial	1.00			
Mild	1.52 (0.43, 5.40)	0.52		
Moderate/severe	6.39 (1.61, 25.4)	0.009		
Not reported	1.28 (0.30, 5.36)	0.74		
Balance, by preoperative echo				
Well-balanced	1.00			
Right dominant	3.25 (0.99, 10.7)	0.05		
Left dominant	1.95 (0.41, 9.30)	0.40		
Discharge TPS				
Class 1 – Optimal	1.00		1.00	
Class 2 – Adequate	2.34 (0.53, 10.4)	0.26	2.40 (0.50, 11.6)	0.28
Class 3 – Inadequate	8.13 (1.77, 37.4)	0.007	5.45 (1.06, 28.1)	0.04

C statistic 0.807 for multivariable model.
Only variables with p≤0.2 are shown in the unadjusted analyses above.
^ Included: pulmonary artery band (n=16) and coarctation repair (n=10).
**Included: left ventricular outflow tract tissue resection, pulmonary artery band takedown, repair of coarctation of the aorta, other. Not included: patent ductus arteriosus ligation.*
CAVV: common atrioventricular valve; CI: confidence interval; TPS: technical performance score.

Table 3. Univariable and Multivariable Analysis: postoperative days on ventilator

Variables	Unadjusted Hazard Ratio (95% CI)	p value	Adjusted Hazard Ratio (95% CI)	p value
Age at surgery ≤ 60 days	0.69 (0.51, 0.92)	0.01		
Neonate	0.50 (0.29, 0.86)	0.01		
Trisomy 21	1.45 (1.08, 1.96)	0.01		
Any prior procedure ^	0.53 (0.34, 0.83)	0.006		
Weight < 3.5 kg	0.56 (0.42, 0.76)	<0.001	0.59 (0.43, 0.81)	0.001
Concomitant procedure*	0.49 (0.33, 0.72)	<0.001	0.51 (0.34, 0.77)	0.002
Prematurity	0.67 (0.50, 0.88)	0.004	0.65 (0.48, 0.88)	0.005
Second bypass run	0.59 (0.36, 0.98)	0.04	0.44 (0.26, 0.76)	0.003
Balance, by preoperative echo				
Well-balanced	1.00			
Right dominant	0.75 (0.45, 1.24)	0.26		
Left dominant	0.62 (0.35, 1.10)	0.10		
Discharge TPS				
Class 1 – Optimal	1.00		1.00	
Class 2 – Adequate	0.81 (0.60, 1.10)	0.18	0.79 (0.59, 1.07)	0.14
Class 3 – Inadequate	0.48 (0.33, 0.71)	<0.001	0.54 (0.37, 0.80)	0.002

C statistic 0.673 for multivariable model.
Only predictors with p≤0.2 are shown in the unadjusted analysis above.
Hazard ratio < 1 corresponds to a longer time on ventilator. Trisomy 21 had a protective effect.
^ Included: pulmonary artery band (n=16) and coarctation repair (n=10).
**Included: left ventricular outflow tract tissue resection, pulmonary artery band takedown, repair of coarctation of the aorta, other. Not included: patent ductus arteriosus ligation.*
CI: confidence interval; TPS: technical performance score.

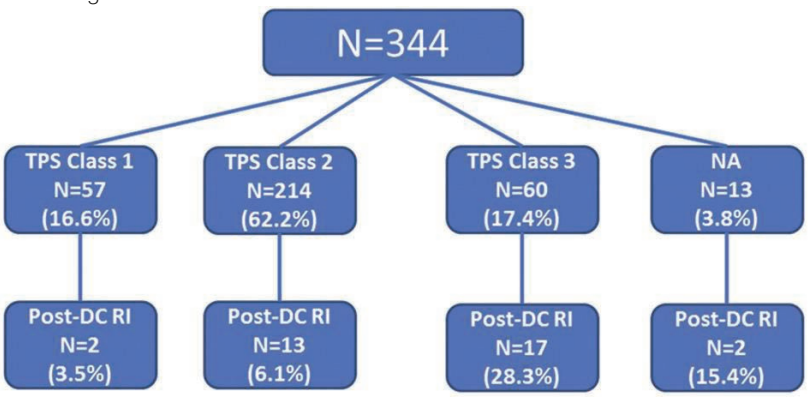
Table 4. Univariable and Multivariable Analysis: post-discharge reintervention

Variables	Unadjusted Hazard Ratio (95% CI)	p value	Adjusted Hazard ratio (95% CI)	p value
Surgical procedure				
Single patch	1.00			
Double patch	2.36 (0.71, 7.85)	0.16		
Australian	3.47 (0.90, 13.4)	0.07		
Any prior procedure ^	2.85 (0.99, 8.13)	0.05		
Trisomy 21	0.25 (0.13, 0.51)	<0.001	0.30 (0.14, 0.63)	0.002
Concomitant procedure*	3.71 (1.61, 8.57)	0.002	2.11 (0.88, 5.05)	0.09
Balance, by preoperative echo				
Well-balanced	1.00			
Right dominant	4.79 (1.83, 12.5)	0.001		
Left dominant	1.62 (0.38, 6.86)	0.51		

Variables	Unadjusted Hazard Ratio (95% CI)	p value	Adjusted Hazard ratio (95% CI)	p value
Discharge TPS				
Class 1 – Optimal	1.00		1.00	
Class 2 – Adequate	1.31 (0.30, 5.83)	0.72	1.21 (0.27, 5.41)	0.79
Class 3 – Inadequate	7.25 (1.67, 31.4)	0.008	5.60 (1.28, 24.5)	0.02

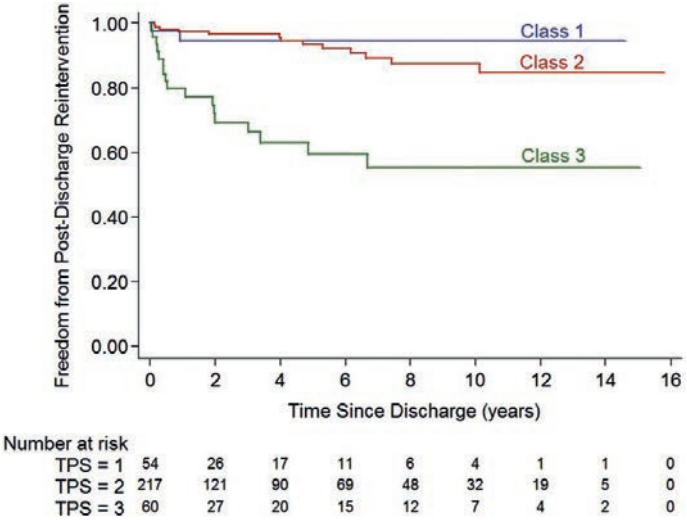
C statistic 0.793 for multivariable model.
Only variables with p≤0.2 are shown in the unadjusted analysis above. Trisomy 21 had a protective effect.
^ Included: pulmonary artery band (n=16) and coarctation repair (n=10).
**Included: left ventricular outflow tract tissue resection, pulmonary artery band takedown, repair of coarctation of the aorta, other. Not included: patent ductus arteriosus ligation.*
CI: confidence interval; TPS: technical performance score.

Figure 1: Post-discharge reintervention in the anatomic area repaired at CAVSD surgery in patients who survived to discharge.



In this cohort (n=350), there were 6 pre-discharge deaths. One of them had TPS Class 2, and 5 of them had TPS Class 3.

Figure 2: Kaplan Meier estimation of time to post-discharge reintervention based on TPS. Class 1 TPS is represented in blue, Class 2 TPS in green and Class 3 TPS in red. The number at risk at each time point is provided in the table below the graph.



Discussion

The last decades have seen a dramatic decrease in mortality following repair of balanced CAVSD [5]. However, despite decrease in mortality, need for reinterventions remains a major problem, with reoperation rates varying between 10-15% [9,15,16]. Requiring a reintervention after discharge from CAVSD repair has been shown to be an important risk factor for late mortality and may lead to intraoperative or postoperative adverse events during reintervention hospitalization, ultimately resulting in poor patient outcomes and higher cost [6,17].

In the present study we evaluated TPS after adjusting for patient factors related to outcome. We demonstrated the ability of TPS to predict in-hospital outcomes such as complications and postoperative days on ventilator and post-discharge reinterventions in patients who underwent CAVSD repair. We included other clinically relevant preoperative and intraoperative variables however, postoperative variables were not included in our analysis because of the high co-linearity between the TPS and these variables.

In our series intraoperative revision of residua was effective. Among the 14 patients who had intraoperative revisions, 3 were able to achieve a Class1 TPS at discharge, 7 a class 2 TPS and only 4 patients had class 3 TPS related to major residua, one of whom died post discharge and one required subsequent intervention.

In our study, there were 34 (10%) post-discharge reinterventions with majority related to the left AV valve (25 (7.3%)) or the LVOT (9 (2.6%)). This is consistent with other studies that report a reoperation rate of 10-15% [9,15,16]. Concomitant procedure and TPS Class 3 were significant risk factors for post-discharge reinterventions on multivariable analysis. Reported risk factors for reinterventions are age younger than 3 months at repair [15], age older than 6 months at repair [18], weight less than 4 kg [15], associated cardiovascular anomalies [9], abnormal left AV valve morphology [9,16], aortic arch obstruction [16], preoperative severe left sided AV valve regurgitation [16], non or partial left AV valve cleft closure [19] and moderate or greater left AV valve regurgitation at discharge [18]. Our study differs from these in that our patient population only included well balanced CAVSD without major intracardiac abnormalities. In our study as in the study of Xie and colleagues. younger age was not associated with higher complication rates during hospital stay [18]. Our study as in other studies also demonstrated that trisomy 21 had a protective effect (compared with patients without trisomy 21) on post-discharge reinterventions [20-24].

In our study, there were 36 (10%) complications and this is similar to reports from the Society of Thoracic Surgeons Congenital Heart Surgery Database [25]. In comparing complications with other studies, in our study, pre-discharge surgical or catheter based reinterventions on the anatomic area of repair and placement of permanent pacemakers were not considered as complications, because they are components of the TPS. Nevertheless, almost all patients

(36/38 - 95%) who underwent reintervention pre-discharge or placement of PPM had other complications. Specific in-hospital outcomes, such as discharge mortality 6 (2%), placement of permanent pacemaker 6 (2%), median postoperative length of hospital stay 7 (IQR 6, 12), unplanned surgical or catheter based reinterventions pre-discharge 10 (3%) and open sternum 14 (4%) were similar to those reported by others that used large databases of 2399 and 1917 patients [25,26].

Our study was able to demonstrate that appropriate identification of type and severity of residual lesions using TPS was able to accurately classify subjects at higher risk of not only in-hospital morbidity but also predict need for midterm reinterventions. Thus TPS can serve as a tool that identifies high risk patients, allowing physicians to appropriately determine frequency of clinic visits and additional testing. Furthermore our study was able to determine more specifically the type of residua likely to need reintervention and postoperative days on the ventilator. Early identification of progression of residua may enable optimal timing of re-repair before deterioration of cardiac and physical function. In addition, TPS can serve as a self-assessment tool and provides input on areas of repair that need modification of technique.

Study limitations and future directions

The present study represents a single center's experience with TPS using retrospective data with its inherent problems of missing and incomplete data, although only 4% of our patient population had missing qualitative data at discharge. There was much more missing quantitative data at discharge (57%). Testing the reproducibility of this tool, using both qualitative and quantitative data, across multiple centers is necessary. The strength of intraoperative TPS could not be completely validated because a large number of patients did not have routine intraoperative echocardiograms.

We are currently involved in a multicenter study to validate the TPS (now called Residual Lesion Score –RLS) prospectively in specific procedural groups, with particular attention to quantitative measures of both intraoperative and discharge/pre-reintervention echocardiograms and we anticipate that this will allow us to better weight each component of the score and determine the predictive value of each component not only for in-hospital, but also midterm and long-term outcomes. In future TPS may also serve as a self-assessment tool and provide surgeons with input on areas of repair that need modification of technique.

Conclusion

Repair of CAVSD carries low mortality, but a moderate reoperation rate, mainly on LAVV and LVOT. At our center, CAVSD repair was associated with low morbidity in-hospital and at midterm follow-up. Presence of residual lesions pre-discharge, as measured by TPS, was accurately able to identify patients who had complications, prolonged days on ventilator, and required post-discharge reinterventions.

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Supplemental Tables

Supplemental Table 5. Distribution of Technical Performance Score classes across the subcomponents of complete atrioventricular septal defect repair for cohort under study (n=350)

Subcomponent		Number
Final TPS		
	1	54
	2	218
	3	63
ASD		
	1	244
	2	24
VSD		
	1	178
	2	135
	3	4
LAVV stenosis		
	1	255
	2	26
	3	4
LAVV regurgitation		
	1	129
	2	164
	3	34
RAVV stenosis		
	1	153
	2	11
RAVV regurgitation		
	1	135
	2	165
	3	19
PDA		
	No PDA	24
	PDA open or RI	3
Conduction		
	1	319
	3	4

ASD: atrial septal defect; LAVV: left atrioventricular valve; PDA: patent ductus arteriosus; RAVV: right atrioventricular valve; RI: reintervention; TPS: technical performance score; VSD: ventricular septal defect.

Supplemental Table 6. Intraoperative revisions and pre-discharge and post-discharge reinterventions on ASD/VSD, left/right AV valve, left ventricular outflow tract and placement of permanent pacemaker based on type of repair

	n	RI (n patients)*	ASD/VSD	Left/right AV valve	PPM	LVOT	Other
Intra-operative revisions (second bypass run)							
Single patch	57 (16.2%)	1	1	1	-	-	-
Double patch	255 (72.9%)	13	3	10	-	-	-
Australian technique	38 (10.9%)	-	-	-	-	-	-
Total	350	14	4	11	-	-	-
Pre-discharge reinterventions							
Single patch	57 (16.2%)	2	1	1	1	-	1^
Double patch	255 (72.9%)	8	3	5	4	-	-
Australian technique	38 (10.9%)	-	-	-	-	-	-
Total	350	10	4	6	5	-	-
Post-discharge reinterventions							
Single patch	55 (16.0%)	2	1	1 (1.8%)	-	2 (3.6%)	-
Double patch	252 (73.3%)	25	3	20 (7.9%)	1	12 (4.8%)	-
Australian technique	37 (10.7%)	7	3	6 (16.2%)	-	2 (5.4%)	-
Total	344	34	5	27 (7.8%)	1	16 (4.7%)	-

Pre-discharge reintervention: 2 patients had >1 RI on left/right AV valve.
Post-discharge reintervention: 2 patients had > 1 RI on ASD/VSD, 10 patients had > 1 RI on left/right AV valve and 5 patients had > 1 RI on LVOT.
**Some patients had more than one post-discharge reintervention and/or more than one site intervened on.*
^ Bilateral bidirectional cavopulmonary shunts.
ASD: atrial septal defect; AV: atrioventricular; LVOT: left ventricular outflow tract; PPM: placement of permanent pacemaker; RI: reintervention; VSD: ventricular septal defect.

Supplemental Table 7. Post-discharge Surgical and Catheter Based Reintervention (n=34; 10 %)

No	Year	Age (d)	Type of repair						Subvalvar apparatus	IO TPS	DC TPS	RI (n)	Surgical RI (n)	Cath RI (n)	RI site
			(Patch) technique	VSD patch	DSBL	AP/CP	DAC	Cleft closure							
1	2000	82	Double	Dacron	-	-	-	Complete	2, well sp	-	-	1	1	-	MV, LVOT
2	2000	86	Australian	-	-	AP	-	Complete	-	-	3	4	4	-	ASD, MV, LVOT
3	2000	421	Double	Dacron	-	CP	-	Complete	2, well sp	2	3	1	1	-	LVOT
4	2000	164	Double	Dacron	-	-	-	Complete	-	3	3	1	1	-	MV, TV
5	2001	189	Australian	-	-	-	-	-	2, well sp	-	-	1	1	-	MV
6	2001	326	Single	Pericardial	+	-	-	Complete	2, well sp	-	2	1	1	-	MV, LVOT
7	2001	110	Double	Dacron	-	CP	+[1]	Complete	2, well sp	-	2	1	1	-	MV, LVOT
8	2001	217	Single	Pericardial	+	AP/CP	-	Complete	-	-	2	1	1	-	ASD, LVOT
9	2001	44	Australian	Pericardial	-	-	-	Partial	-	-	3	1	1	-	MV
10	2002	41	Double	Dacron	-	-	-	Complete	-	-	3	1	1	-	MV
11	2003	81	Australian	Pericardial	-	AP	-	Complete	2, well sp	-	3	1	1	-	VSD, MV
12	2003	39	Double	Dacron	-	CP	-	Complete	-	2	3	2	2	-	MV, LVOT
13	2004	40	Double	Dacron	+	-	-	No	1	3	3	2	2	-	VSD, MV, TV
14	2004	9	Double	Dacron	-	-	+	Complete	2, well sp	-	2	2	2	-	MV, LVOT
15	2005	99	Double	Dacron	-	AP	-	Complete	2, cl sp	-	3	1	1	-	VSD, MV, TV
16	2005	71	Double	Dacron	-	CP	-	Complete	2, well sp	3	3	1	1	-	MV
17	2005	135	Double	Goretex	-	-	-	Complete	2, well sp	2	2	2	2	-	TV, LVOT
18	2005	293	Double	Dacron	-	-	-	Complete	2, well sp	-	2	2	2	-	MV, TV
19	2005	85	Australian	-	-	-	-	Complete	2, well sp	2	2	1	-	1	ASD
20	2006	112	Double	Pericardial	-	-	-	Complete	2, well sp	2	2	1	1	-	ASD
21	2006	111	Double	Dacron	-	AP	-	Complete	-	2	2	1	-	1	TV

No	Year	Age (d)	Type of repair						Subvalvar apparatus	IO TPS	DC TPS	RI (n)	Surgical RI (n)	Cath RI (n)	RI site
22	2006	87	Double	Dacron	-	-	-	Complete	2, well sp	3	3	2	2	-	MV, LVOT
23	2006	43	Double	Dacron	-	AP	-	Complete	-	1	3	2	-	2	MV
24	2007	268	Double	Dacron	-	-	+[1]	Partial	1	2	3	2	2	-	MV, LVOT
25	2008	98	Double	Dacron	-	-	+[2]	Partial	2, well sp	1	1	1	1	-	LVOT
26	2008	89	Australian	-	-	-	-	Complete	2, well sp	2	2	1	1	-	MV, TV, LVOT
27	2009	96	Double	Pericardial	-	-	-	Complete	2, well sp	2	2	1	1	-	LVOT
28	2009	144	Australian	-	-	-	-	Complete	2, well sp	-	2	1	1	-	MV
29	2011	180	Double	Dacron	-	AP	-	Complete	2, well sp	2	2	1	1	-	MV, LVOT
30	2011	51	Double	Dacron	-	AP/CP	-	Complete	2, cl sp	2	3	2	2	-	MV, TV
31	2012	77	Double	Pericardial	-	AP	-	Complete	2, well sp	2	1	1	1	-	PPM
32	2012	32	Double	Dacron	-	-	-	Partial	2, cl sp	2	3	2	-	2	MV
33	2013	101	Double	Dacron		AP		Complete	2, well sp	2	3	1	1	-	MV, LVOT
34	2013	134	Double	Pericardial	-	-	-	Complete	2, cl sp	2	3	1	-	1	MV

+[1] LVOT muscle bar division; +[2] LVOT myotomy.

AP: annuloplasty; ASD: atrial septal defect; Cath: catheter based; cl sp: closely spaced; CP: commissuroplasty; DAC: division of accessory cords; DC: discharge; DSBL: division of superior bridging leaflet; IO: intraoperative; MV: mitral valve; PPM: placement of permanent pacemaker; RI: reintervention; TPS: technical performance score; TV: tricuspid valve; VSD: ventricular septal defect; well sp: well spaced.

Supplemental table 8. TPS and outcomes

Outcome	TPS Class 1	TPS Class 2	TPS Class 3	p value
Complications (%)	2 (3.7)	18 (8.3)	15 (23.8)	0.001
Median postoperative days on ventilator (IQR)	1 (1, 2)	2 (1, 3)	2 (2, 5)	<0.001
Median posteroperative days in ICU (IQR)	3 (2, 4)	3 (2, 5)	5 (3, 10)	<0.001
Median postoperative days in hospital (IQR)	7 (6, 10)	7 (6, 10)	11 (8, 19)	<0.001
Post-discharge reinterventions (%)	2 (3.7)	13 (6.0)	17 (29.3)	<0.001

ICU: intensive care unit; TPS: technical performance score.

Appendix 1

TECHNICAL PERFORMANCE SCORE MODULES
Complete atrioventricular canal defect

Sub-components	1	2	3
ASD repair, primum	No or trivial residual defect <2 mm	Small residual defect 2-3 mm	Reintervention or Residual defect >3 mm
ASD repair, secundum	No or trivial residual defect <2 mm	Small residual defect 2-3 mm	Reintervention or Residual defect >3 mm
VSD repair	No or trivial residual defect <2 mm	Small residual defect 2-3 mm	Reintervention or Moderate residual defect >3 mm
Left AV valve plasty	No or trivial stenosis, mean gradient <3 mmHg No or trivial regurgitation	Mild stenosis, mean gradient 3-6mm Hg Mild regurgitation	Reintervention or Moderate or severe stenosis, mean gradient >6 mm Hg Moderate or severe regurgitation
Right AV valve plasty	No or trivial stenosis, mean gradient <3 mmHg No or trivial regurgitation	Mild stenosis, mean gradient 3-6mm Hg Mild regurgitation	Reintervention or Moderate or severe stenosis, mean gradient >6 mm Hg Moderate or severe regurgitation
LVOT	No residual narrowing: peak velocity <2.2 m/sec	Mild residual narrowing: peak velocity 2.2 to 3.2 m/sec	Reintervention or Moderate to severe residual narrowing: peak velocity >3.2 m/sec
Conduction	Normal conduction		Permanent Pacemaker
Patent ductus arteriosus	No patent ductus arteriosus		Reintervention or Open patent ductus arteriosus

ASD: atrial septal defect, AV: atrioventricular, Hg: mercury, LVOT: left ventricular outflow tract, mm: millimeters, m/sec: meters per second, VSD: ventricular septal defect.

ATRIOVENTRICULAR VALVE FUNCTION PREDICTS REINTERVENTION IN COMPLETE ATRIOVENTRICULAR SEPTAL DEFECT

3

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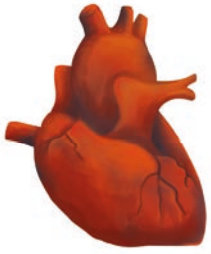

Abstract

Objective:
Technical performance score (TPS) has been associated with both early and late outcomes across a wide range of congenital cardiac procedures. A previous study has shown that the presence of residual lesions before discharge, as measured by TPS, is accurately able to identify patients who required postdischarge reinterventions after complete atrioventricular septal defect (CAVSD) repair. The aim of this study is to determine which subcomponents of TPS best predict postdischarge reinterventions after CAVSD repair.

Methods:
This was a single-center retrospective review of patients with CAVSD after repair between January 2000 and March 2016. We assigned TPS (class 1, no residua; class 2, minor residua; class 3, major residua or reintervention before discharge for residua) based on subcomponent scores from discharge echocardiograms. Outcome of interest was postdischarge reintervention.

Results:
Among 344 patients, median age was 3.2 months (interquartile range [IQR], 2.4-4.2). There were 34 (10%) postdischarge reinterventions. Median follow-up was 2.6 years (IQR, 0.09-7.9). Trisomy 21 and concomitant procedure were associated with postdischarge reinterventions. After adjusting for these factors, among the subcomponents, left atrioventricular valve stenosis and regurgitation, right atrioventricular valve regurgitation, residual ventricular septal defect, and abnormal conduction at discharge were significantly associated with postdischarge reinterventions.

Conclusions:
We demonstrated the ability of TPS to predict postdischarge reinterventions in patients who underwent CAVSD repair. Residual left and right atrioventricular valve regurgitation and abnormal conduction at discharge were among the subcomponents strongly associated with postdischarge reinterventions. Thus, TPS may aid clinicians in identifying children at higher risk for reintervention.

Better understanding of the anatomy and optimization of surgical techniques have improved early clinical outcome of surgical correction of complete atrioventricular septal defects (CAVSDs). However, several studies report a high risk of reoperation (up to 10%) (1). Technical performance score (TPS), a tool developed to determine technical adequacy of congenital cardiac repairs, has been shown to be an important predictor of both early and midterm outcomes across a wide range of congenital cardiac procedures (2). A previous study has shown that the presence of residual lesions before discharge, as measured by TPS, accurately identifies patients requiring post-discharge reinterventions (PD-RI) (3). However, in this previous study overall TPS was used to determine association between TPS and PD-RI. The association between individual subcomponents of TPS and PD-RI was not investigated. The aim of this study is to determine which subcomponents of TPS best predict PD-RI.

A review of consecutive patients with balanced CAVSDs who were operated on at a tertiary care center between 01/2000-03/2016 was performed with institutional review board approval. Demographic, echocardiographic and follow-up data were obtained. Primary complete repair of CAVSD was considered the index operation. Only patients discharged alive without heart transplantation were analyzed. Patients with associated major intracardiac anomalies or partial/transitional AVSD were excluded. Postoperative TPS was determined as previously reported (3) based on predischarge echocardiographic findings and clinical status at discharge from the index operation. The TPS for CAVSD repair included the following subcomponents: size of residual atrial septal defect (ASD), size of residual ventricular septal defect (VSD), severity of right and left atrioventricular valve (AVV) stenosis and regurgitations, status of the patent ductus arteriosus (PDA) and status of the conduction system. Each subcomponent was assigned a score of class 1 (optimal, trivial, or no residua), class 2 (adequate, minor residua), or class 3 (inadequate, major residua), based on specific echocardiographic criteria (3). The final TPS was based on the subcomponent scores and was class 1 if all subcomponents received a class 1 score, class 2 if one or more of the subcomponents were class 2 but none were class 3, and class 3 if any of the subcomponents were class 3. Any unplanned surgical or catheter-based reintervention for residua in the anatomic area repaired during the CAVSD operation or the need for permanent pacemaker (PPM) placement prior to discharge from index CAVSD surgery resulted in a class 3 (inadequate) score. The outcome variable, PD-RI, was defined as surgical or catheter-based reinterventions that occurred following discharge from index CAVSD surgery on anatomic areas repaired at CAVSD operation, including placement of PPM.

Forward selection was used to develop a multivariable Cox regression model of baseline patient factors associated with time to PD-RI; $p<0.05$ was required for retention in the final model. Qualitative TPS and its subcomponents were then added to this model. Hazard ratios were estimated with 95% confidence intervals. Statistical analysis was performed with SAS version 9.4 (SAS Institute Inc, Cary, NC).

There were 344 patients included in the analysis. There were 211 females (61%), 67 (19%) were premature, and 305 (89%) had some form of genetic anomaly. The median age at operation was 3.2 months (IQR, 2.4 to 4.2 months). There were 34 PD-RI (10%).

Trisomy 21 and concomitant procedure were associated with PD-RI. After adjusting for these

factors, among the subcomponents, left AVV stenosis and regurgitation, right AVV regurgitation, residual VSD and abnormal conduction at discharge were significantly associated with PD-RI (Table 1).

Table 1. Multivariable model; Subcomponents of TPS and post-discharge reinterventions (n=344)

		Number	Number of RI (%)	Hazard Ratio (95% CI)	P value	C index
Multivariable Model, not considering TPS (n=344)						
Trisomy 21		291	21 (7.2%)	0.29 (0.14, 0.60)	0.001	0.679
Concomitant procedure*		29	7 (24.1%)	2.71 (1.14, 6.44)	0.02	
For each model below, the results shown are adjusted for trisomy 21 and concomitant procedure						
Final TPS						0.793
	1	54	2 (3.7%)	1.00		
	2	217	13 (6.0%)	1.21 (0.27, 5.41)	0.79	
	3	60	17 (28.3%)	5.60 (1.28, 24.5)	0.02	
ASD						0.694
No defect (<2 mm)	1	244	22 (9.0%)	1.00		
Small defect (2-3 mm)	2	24	4 (16.7%)	2.91 (0.94, 8.98)	0.06	
Not reported		63	6 (9.5%)	-		
VSD						0.701
No defect (<2 mm)	1	178	13 (7.3%)	1.00		
Small defect (2-3 mm)	2	135	15 (11.1%)	1.33 (0.63, 2.80)	0.45	
RI or defect > 3 mm	3	4	2 (50.0%)	12.2 (2.51, 59.6)	0.002	
Not reported		14	2 (14.3%)	-		
LAVV stenosis						0.746
No stenosis (mean < 3 mm Hg)	1	255	16 (6.3%)	1.00		
Mild stenosis (mean 3-6 mm Hg)	2	26	9 (34.6%)	3.12 (1.24, 7.82)	0.02	
RI or ≥moderate stenosis (> 6 mmHg)	3	4	1 (25.0%)	11.0 (1.37, 88.0)	0.02	
Not reported		66	6 (9.1%)	-		
LAVV regurgitation						0.795
No/trivial regurgitation	1	129	8 (6.2%)	1.00		
Mild regurgitation	2	164	12 (7.3%)	0.84 (0.34, 2.09)	0.71	
RI or ≥moderate regurgitation	3	34	11 (32.4%)	3.98 (1.55, 10.2)	0.004	
Not reported		4	1 (25.0%)	-		
RAVV Stenosis						0.696
No stenosis (mean < 3 mm Hg)	1	153	17 (11.1%)	1.00		
Mild stenosis (mean 3-6 mm Hg)	2	11	2 (18.2%)	0.47 (0.08, 2.86)	0.42	
Not reported		167	13 (7.8%)	-		
RAVV regurgitation						0.732
No/trivial regurgitation	1	135	7 (5.2%)	1.00		
Mild regurgitation	2	165	17 (10.3%)	1.47 (0.60, 3.61)	0.40	
RI or ≥moderate regurgitation	3	19	5 (26.3%)	3.89 (1.23, 12.3)	0.02	
Not reported		12	3 (25.0%)	-		
PDA				Cannot estimate; no RI in category 3		
No PDA	1	24	2 (8.3%)			
RI or PDA open	3	3	0 (0%)			
Not reported		304	30 (9.9%)			

		Number	Number of RI (%)	Hazard Ratio (95% CI)	P value	C index
Conduction						0.699
Normal conduction	1	319	27 (8.5%)	1.00	0.002	
Permanent pacemaker	3	4	3 (75.0%)	6.68 (2.00, 22.2)		
Not reported		8	1 (12.5%)	-		

**Included: left ventricular outflow tract tissue resection, pulmonary artery band takedown, repair of coarctation of the aorta, other. Not included: patent ductus arteriosus ligation.*
ASD: atrial septal defect; LAVV: left atrioventricular valve; PDA: patent ductus arteriosus; RAVV: right atrioventricular valve; RI: reintervention; TPS: technical performance score; VSD: ventricular septal defect.

A potential limitation of this study is that it represents a single center's experience with TPS using retrospective data with its inherent problems of missing and incomplete data, although only 4 % of our patient population had missing qualitative echocardiographic data at discharge.

We demonstrated the ability of TPS to predict PD-RI in patients who underwent CAVSD repair. Residual left and right AVV regurgitation and abnormal conduction at discharge were among the subcomponents strongly associated with PD-RI. Thus TPS may aid clinicians in identifying children at higher risk for future reinterventions who may benefit from more frequent follow-up.

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ATRIOVENTRICULAR SEPTAL DEFECT SUBTYPE IS ASSOCIATED WITH TIMING OF LEFT ATRIOVENTRICULAR VALVE REPLACEMENT

4

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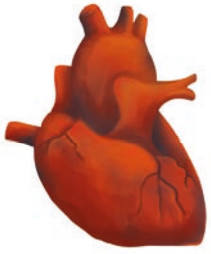


Abstract

Objectives:
Left atrioventricular valve (LAVV) reoperations are a frequent cause of morbidity and mortality after atrioventricular septal defect (AVSD) repair. Patients with AVSD may eventually face valve replacement relatively early in life. Long term freedom from LAVV replacement is not yet known. We evaluated a large patient cohort to assess this risk.

Methods:
A national multi-institutional, retrospective study was performed including patients who underwent LAVV replacement between 1979 and 2019. Patients with complete and partial AVSD were compared. Operative and follow-up data were evaluated.

Results:
LAVV replacement was performed in 64 of 1289 (5%) patients (30 (47%) with complete AVSD), the median age at LAVV replacement was 4.8 (IQR 0.7-25.8) years and 19.9 (IQR 7.1-36.6) years for complete and partial AVSD respectively ($p=0.014$). Trisomy 21 was present in 6 (9%). Thirty-one patients (16 (53%) complete and 15 (44%) partial AVSD) had a prior LAVV repair. The overall median follow-up time was 10.4 (IQR 4.5 – 23.8) years. Early death after LAVV replacement (<30 days) occurred in 1 (3%) patient with complete and in 4 (12%) with partial AVSD. Major adverse events (MAEs) occurred in 7 (23%) with complete and in 10 (29%) with partial AVSD. Follow-up reoperations on the valve prosthesis were performed in 7 (23%) patients with complete and in 10 (30%) with partial AVSD.

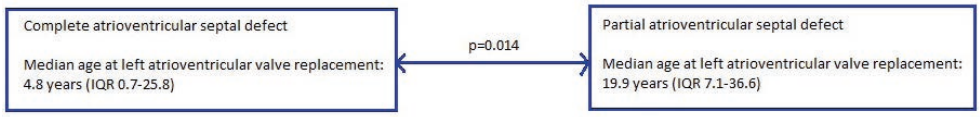
Conclusions:
LAVV replacement is frequently performed in AVSD patients. Compared to patients with partial defect, freedom from LAVV replacement was much shorter after complete AVSD repair. MAEs as well as subsequent reoperations were frequent in both groups.

Key question:
What is the incidence of LAVV replacement in AVSD patients? How do subtypes compare?

Key findings:
LAVV was replaced in 5% of AVSD patients, and occurred much later in partial than in complete AVSD.

Take-home message:
LAVV replacement is a common event in AVSD patients. Freedom from LAVV replacement is much shorter in patients with complete AVSD than in those with a partial AVSD.

Central Image:



Introduction

Inherent to atrioventricular septal defect (AVSD) repair, the left atrioventricular valve (LAVV) is at risk for dysfunction and may need to be replaced at some point in time.

Better understanding of the anatomy and improved operative and postoperative care have led to a dramatic improvement in AVSD patient outcome over the past three decades. Whilst early operative mortality once was up to 50%, current rate went down to less than 3% (1). Several studies however report a 10% risk of reoperation for residual lesions of the atrioventricular valve or left ventricular outflow tract (LVOT) (2-7). Reoperation on the LAVV for regurgitation is the most frequent indication. The LAVV is preferably spared at reoperation but replacement can eventually become unavoidable. With increasing numbers of patients surviving AVSD repair, valve replacement can be anticipated to be necessary more often.

The aim of this study is to determine the current incidence of AV valve replacement in a large national multicenter patient cohort and to compare differences between those with complete and those with partial AVSD. We compared mortality, complications and need for prosthesis replacement between the two groups.

Material and Methods

Study Population

A multicenter, national, retrospective cohort study was performed, including all patients operated on for AVSD between 1958 and 2017 who were reported to the national database. Eight institutions were involved in the care for congenital heart defects in the Netherlands over the indicated time interval (Amsterdam, Groningen, Leiden, Maastricht, Nieuwegein, Nijmegen, Rotterdam and Utrecht).

Patients

Patients were selected from our national databases of children and adults with congenital heart disease: KinCor and CONCOR registries (8,9). Approval was obtained from the local institutional review boards, with a waiver of informed consent obtained before data collection. Clinical and echocardiographic data were collected. There were 64 patients eligible for the study.

Techniques of AVSD repair (n=64)

Both single and double patch techniques were used in complete AVSD repair whereas pericardial closure only was used in all patients with partial AVSD. Full and partial closure of the zone of apposition (cleft) was performed in 30 (47%) and 7 (11%) patients respectively. In 17 (27%) patients this information was missing.

LAVV repair prior to replacement (n=31)

LAVV repair prior to replacement was performed in 31 (48%) patients (1 repair: n=28, 2 repairs: n=2, 3 repairs: n=1). Techniques included isolated cleft closure in 10 (16%), with patch augmentation in 2 (3%), valvuloplasty (both ring- and commissuroplasty) in 8 (13%), and isolated valvuloplasty in 11 (17%) patients. Concomitant procedures included right atrioventricular valve (RAVV) repair (4), closure of residual ASD (3) or VSD (3), resection of subaortic stenosis (2) and repair of stenosis in persistent left superior vena cava (1).

LAVV replacement (n=64)

LAVV replacements were performed between 1979 and 2019. Transseptal access was used in 33 (52%) patients. Incision through Waterston's groove or Guiraudon incision was performed in 14 and 3 patients respectively. In 14 patients information about LAVV access was missing. To allow prosthetic valve implantation all native valve tissue was excised in most patients, and the posterior leaflet was left intact in 14 (22 %). Annular level implantation was possible in 51 (80%) and supra-annular in 3 (5%) (missing 10). Pledget supported sutures were used in 31 patients (48%).

Systemic Anticoagulation

Systemic anticoagulation with early intravenous heparin, was used in all patients who received a mechanical prosthesis followed by coumarin therapy after removal of chest tubes and pacing wires with a target INR of 2.5 to 3.5. In patients with a biological prosthesis, coumarin therapy was replaced by antiplatelet therapy at 3 months.

Data collection

Collected data included demographic information, anatomic diagnoses, associated non-cardiac or genetic anomalies, preoperative factors, surgical procedures, surgical or follow-up complications, reinterventions and mortality. Procedural details were collected from surgery reports.

Outcomes

The primary outcomes evaluated were all-cause mortality and orthotopic heart transplantation. Other outcomes were major adverse events (MAEs), reoperation, thromboembolic/bleeding events, resource utilization (postoperative days on ventilator, length of stay (LOS) at intensive care unit (ICU) and hospital). MAEs were defined according to the STS congenital heart surgery database (10). Postoperative days on ventilator was defined as total number of days on the ventilator after the index operation and included all reintubation days. Postoperative ICU LOS was defined as total postoperative days in the ICU, including days readmitted to the ICU during hospitalization for the index operation.

Statistical Methods

Patient and procedural characteristics were summarized as frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables.
Differences in categorical patient characteristics/outcomes between patients with complete and partial AVSD were analyzed using Chi-square and Fisher's Exact tests. Differences in continu-

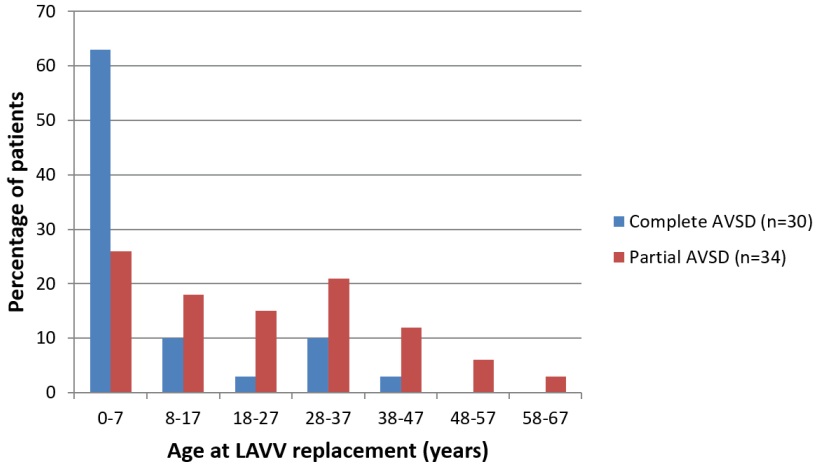
ous variables that were normally distributed and not normally distributed were analyzed using independent-samples-t-tests and Man-Whitney U tests, respectively. Normality was assessed by the Shapiro-Wilk's test ($p>0.05$). Time to reintervention was estimated using the Kaplan-Meier method. A log rank test was run to determine differences in the survival distribution of the different types of AVSD. Statistical analysis was performed with SPSS for Windows (version 25).

Results

Patients

The entire cohort of patients reported to the database that were operated on for AVSD (n=1289) included 205 patients who were reoperated on the LAVV, 64 of whom had the LAVV replaced (complete AVSD: n=30 (47%), partial: n=34 (53%)). Patient and procedural characteristics are represented in Table 1. Median age at LAVV replacement in complete AVSD patients was 4.8 (IQR 0.7-25.8) years whereas median age in those with partial AVSD was 19.9 (IQR 7.1-36.6) years ($p=0.014$) (Figure 1). Number of patients per center varied from 4 to 16. Trisomy 21 was present in 4 (13%) complete and in 2 (6%) partial AVSD patients. Indications for LAVV replacement included stenosis (moderate or severe) (2), regurgitation (moderate or severe) (51) and both (11). Endocarditis was reported in 2. LAVV repair preceded replacement in 31 (16 (53%) with complete and 15 (44%) with partial defect. Median follow-up duration was 10.4 (IQR 4.5 – 23.8) years for the entire group, 10.1 (IQR 3.7 – 24.0) years for complete and 11.0 (IQR 5.4 – 24.1) years in partial defect.

Figure 1: Left atrioventricular valve replacement rates for age.



Number of patients

	0-7	8-17	18-27	28-37	38-47	48-57	58-67
Complete AVSD	19	3	1	3	4	0	0
Partial AVSD	9	6	5	7	4	2	1

Abbreviations: AVSD=atrioventricular septal defect, LAVV=left atrioventricular valve.

Table 1. Patient and Procedural Characteristics (n=64)

Characteristic	Total (n=64)	Complete AVSD (n=30)	Partial AVSD (n=34)	P-value
Age at AVSD repair, years	2.8 (0.3 – 7.4)	0.5 (0.2 – 4.3)	4.4 (0.7 – 10.2)	**0.011**
AVSD repair before 1990	40 (62.5)	15 (50.0)	25 (73.5)	0.052
LAVV replacement during initial AVSD repair	3 (4.7)	1 (3.3)	2 (5.9)	1.000
Age at LAVV replacement, years	10.4 (1.5 – 34.8)	4.8 (0.7-25.8)	19.9 (7.1-36.6)	**0.014**
Age at LAVV replacement <18 years	37 (57.8)	22 (73.3)	15 (44.1)	**0.018**
Female sex	40 (62.5)	17 (56.7)	23 (67.6)	0.365
Weight at surgery, kg	16.0 (5.6 – 69.0)	12.7 (6.5 – 69.5)	32.0 (5.0 – 55.2)	0.867
Preoperative condition				
On ventilator support	7 (10.9)	4 (13.3)	3 (8.8)	0.697
Previous surgery				
≥1 LAVV repair	31 (48.4)	16 (53.3)	15 (44.1)	0.462
1	28 (43.8)	15 (50.0)	13 (38.2)	
2	2 (3.1)	1 (3.3)	1 (2.9)	
3	1 (1.6)	0 (0)	1 (2.9)	
Repair – replacement interval, years	2.5 (0.2 – 11.3)	1.0 (0.1 – 8.5)	2.9 (0.7 – 12.6)	0.232
Pacemaker implantation	6 (9.4)	4 (13.3)	2 (5.9)	0.407
Double orifice mitral valve	6 (9.4)	2 (6.7)	4 (11.8)	0.672
Indication for LAVV replacement				
Stenosis Regurgitation Stenosis and regurgitation Endocarditis	2 (3.1) 49 (76.6) 11 (17.2) 2 (3.1)	1 (3.3) 25 (83.3) 3 (10.0) 1 (3.3)	1 (2.9) 24 (70.6) 8 (23.5) 1 (2.9)	1.000
Genetics				
Any genetic syndrome	13 (20.3)	8 (26.7)	5 (14.7)	0.235
Trisomy 21	6 (9.4)	4 (13.3)	2 (5.9)	
Other genetic syndrome	7 (10.9)	4 (13.3)	2 (5.9)	

Values are n (%) or median (interquartile range).

LAVV replacement

Procedural details and outcomes are outlined in Table 2. Prosthetic valve sizes ranged from 15 to 33 mm (IQR 19-29).

Complete AVSD

Mortality

Death after LAVV replacement occurred early (<30 days) in 1 (3%) and late in 5 (17%) patients (cardiac n=3, non-cardiac n=2). Early death was caused by heart failure 2 weeks after LAVV replacement in a 3 months old baby, whereas late cardiac deaths were attributed to primary heart failure (2) or acute prosthetic valve thrombosis (1).

Major adverse events

Seven (23%) patients had a postoperative MAE (permanent pacemaker prior to discharge: n=5, bleeding requiring reoperation: n=2).

Follow-up prosthetic valve replacement

Seven (23%) patients needed prosthetic valve replacement within 10.0 (IQR 5.7-11.9) years after LAVV replacement in complete AVSD. Indications for subsequent replacement were: patient-prosthesis mismatch (4), endocarditis (2) and peri-prosthetic leak (1). Other reinterventions (3) on the prosthesis included surgical peri-prosthetic leak closure (1) and catheter-based reinterventions (balloon dilatation of bioprosthesis) (2).

Other reinterventions

Following primary LAVV replacement, 8 (27%) patients underwent pacemaker implantation (predischarge (5), post-discharge (3)), Ross-Konno procedure (1), RAVV repair (2) and replacement (1) and heart transplantation (3) at 7, 13 and 23 years after LAVV replacement.

Thromboembolic/bleeding events

Two (7%) patients had a bleeding event (intracerebral, ear) and 5 (17%) had a total of 6 thromboembolic events (prosthesis thrombus 2, cerebral emboli 3, myocardial infarction 1).

Table 2. Operative Outcome Data (n=64)

Variables	Total (n=64)	Complete AVSD (n=30)	Partial AVSD (n=34)	P-value
Prosthesis				1.000
Mechanical	59 (92.2)	28 (93.3)	31 (91.2)	
Biological	5 (7.8)	2 (6.7)	3 (8.8)	
Prosthesis size, mm	27 (19-29)	24 (19-29)	29 (24-31)	**<0.025**
Second bypass run	3 (4.7)	0 (0)	3 (8.8)	-
Third bypass run	2 (3.1)	1 (3.3)	1 (2.9)	
Perfusion time, min	188 (130–270)	147 (127-256)	195 (138-276)	0.664
Cross-clamp time, min	97 (75-118)	82 (70–97)	113 (91–124)	0.095
Posterior leaflet spared	14 (21.9)	6 (20.0)	8 (23.5)	0.733
Concomitant procedure[a]	25 (39.1)	10 (33.3)	15 (44.1)	0.378
Valve level implant				-
Annular	51 (79.7)	23 (76.7)	28 (82.4)	
Supra-annular	3 (4.7)	2 (6.7)	1 (2.9)	
Unknown	10 (15.6)	5 (16.7)	5 (14.7)	
Condition at discharge				
AV block requiring pacemaker	11 (17.2)	5 (16.7)	6 (17.6)	0.917
Outcome				
Major adverse events[b]	17 (26.6)	7 (23.3)	10 (29.4)	0.583
Mortality	14 (21.9)	6 (20.0)	8 (23.5)	0.733
Early death	5 (7.8)	1 (3.3)	4 (11.8)	0.360
Late death	9 (14.1)	5 (16.7)	4 (11.8)	0.723
Prosthesis replacement	17 (26.6)	7 (23.3)	10 (29.4)	0.583
First and second replacement interval, years	10.0 (5.7 – 15.0)	10.0 (5.7-11.9)	10.0 (5.2-17.0)	0.740
Days on ventilator	2.0 (1.0 – 7.0)	2.5 (1.0 -10.0)	1.0 (1.0-6.0)	0.231
ICU length of stay, days	5.0 (1.0 – 12.0)	11.0 (2.0 – 17.0)	1.5 (1.0 – 7.8)	**0.035**
Hospital length of stay, days	17.0 (9.0 – 27.0)	21.0 (10.0 – 50.0)	15.0 (7.0 – 21.0)	0.111
Follow-up, years	10.4 (4.5 – 23.8)	10.1 (3.7 – 24.0)	11.0 (5.4 – 24.1)	0.633

[a] *included variables are RAVV repair, resection of subaortic stenosis, closure of ASD, closure of VSD, aortic valve replacement, pulmonary valve replacement, maze procedure, pacemaker implantation*
[b] *arrhythmia requiring placement of permanent pacemaker, reexploration for bleeding, need for extracorporeal membrane oxygenator support, renal failure requiring dialysis, unplanned reintervention prior to discharge*
Values are n (%) or median (interquartile range).

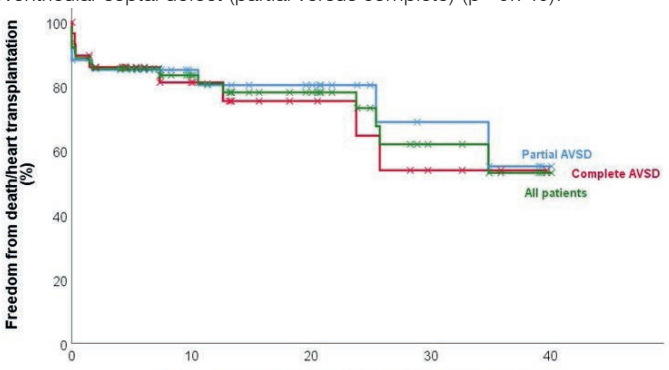
Partial AVSD

Mortality

Four (12%) patients died early and 4 (12%) late (cardiac n=5, non-cardiac n=3). All 4 early deaths were attributed to primary heart failure and late cardiac death was due to failure secondary to myocardial infarction.

Figure 2 shows transplant free survival in complete versus partial AVSD patients. A log rank test was applied to compare differences in the survival distribution between types of AVSD. There was no significant difference (p = 0.70).

Figure 2: Kaplan-Meier survival estimation of time to death/heart transplantation for the whole cohort and based on type of atrioventricular septal defect (partial versus complete) (p=0.740).



Number at risk					
All patients	64	33	21	8	1
Partial AVSD	34	18	13	5	1
Complete AVSD	30	15	8	3	0

Abbreviations: AVSD=atrioventricular septal defect, LAVV=left atrioventricular valve.

Major adverse events

Ten (29%) patients experienced 13 MAEs (permanent pacemaker prior to discharge (6), bleeding requiring reoperation (4), mechanical circulatory support (1), dialysis for renal failure (1) and unplanned reoperation (for endocarditis) prior to discharge (1). Patients had 1 (8), 2 (1) or 3 (1) MAEs.

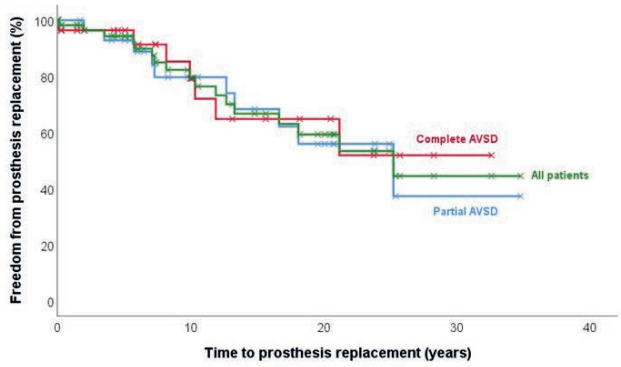
Follow-up prosthetic valve replacement

Following LAVV replacement in partial AVSD, 10 (29%) patients had their prosthesis replaced within 10.0 (IQR 5.2-17.0) years. Reasons were patient-prosthesis mismatch (5), prosthesis thrombosis (1), peri-prosthetic leak (1), endocarditis (1), degenerative bioprosthesis stenosis (1) and potential strut fracture (Bjork-Shiley) (1).

Only mechanical prostheses were used for secondary replacements in both groups (sizes 17-33).

Figure 3 shows survival freedom from prosthesis replacement for all patients (complete versus partial AVSD). The time to prosthesis replacement between groups was not significantly different (p = 0.772).

Figure 3: Kaplan-Meier survival estimation of time to prosthesis replacement for the whole cohort and based on type of atrioventricular septal defect (partial versus complete) (p=0.772).



Number at risk					
All patients	64	27	14	2	0
Partial AVSD	34	15	8	1	0
Complete AVSD	30	12	6	1	0

Abbreviations: AVSD=atrioventricular septal defect.

Other reinterventions

Seven (21%) patients underwent pacemaker implantation (prior to discharge (6), post-discharge (1)). Subaortic stenosis (1), aortic valve repair (1) and replacement (1) and RAVV repair (3).

Thromboembolic/bleeding events

Three (9%) patients had a total of 5 bleeding events (gastrointestinal tract (2), postoperative (3)) and 7 (21%) had a thromboembolic event (prosthesis thrombosis (2), cerebral embolus (4) and bone infarction (1)).

Median postoperative ventilator support was 2 (IQR 1 – 7) days for the entire cohort, median ICU and hospital LOS were 5 (IQR 1 – 12) and 17 (IQR 9 - 27) days respectively. Surviving patients were in NYHA class 1 (58) and 2 (6).

Discussion

The LAVV is the Achilles' heel of AVSD repair. We found that reoperations for LAVV replacement are already common within just 10 years of follow up. We found regurgitation to be the primary indication for reoperation and that the timing of reoperation depended on the subtype of AVSD. In complete AVSD, LAVV is typically replaced within a few years after AVSD repair whereas in patients with partial AVSD, replacement was performed much later (> 10 years after initial surgery). Apparently, end stage LAVV dysfunction develops much faster in children operated on for complete AVSD. Their morphology requires closure of two septal defects and the repair is performed at young age compared to patients with partial AVSD. Sandwiching the fragile infant AV valves between two patches may be more deleterious for LAVV than in older patients with partial AVSD in whom AV valves are supported by the ventricular septum.
Following AV valve replacement subsequent reoperations for patient prosthesis mismatch were common and equally frequent in both groups. A larger prosthesis could be inserted in all patients without operative mortality.
Interestingly, patients with trisomy 21 were relatively few compared to those reported by others (9% in our series versus > 50% in larger series (11,12)). It may indicate that trisomy 21 is protective for LAVV replacement. Perhaps this is related to more favorable morphology in these patients (13,14). Another explanation may be that before 1990 few patients with trisomy 21 were operated. Furthermore, patient counseling by the cardiologist may differ in these patients. Valve replacement may be simply not considered in syndromal patients.

Complete AVSD patients

Despite young patient age, mortality for LAVV replacement was low in complete AVSD. It approached the rate of standard MVR for degenerative mitral valve disease (15-17).
Number of pacemaker implantations in contrast was relatively high although comparable with other studies (18,19). The high incidence is probably related to the vulnerable course of the conduction tissue in AVSD patients. The risk could perhaps be modified by technical adaptations in prosthetic valve implantation like avoiding sutures in postero-inferior angle of the annulus. Prosthesis replacement at follow up (23%) is common and comparable to results reported in literature (28 – 34%) (18,19). It is inherent to outgrowth in the young patient causing patient-prosthesis mismatch. Mortality associated with these subsequent operations was low and upsizing was possible without the need of annular enlargement procedures.

Partial AVSD patients

LAVV replacement in patients with partial AVSD, had a higher early mortality than in those with complete AVSD (12% versus 3%) although not significantly different ($p=0.360$). Over-all mortality was also higher when compared to patients with MVR for degenerative disease (3.8-4.8%) (15-17). Patients with partial AVSD were much older at operation (LAVV replacement) and had a much longer follow-up (>30 years). Therefore they may have had more advanced cardiac disease. Illustrative, operations were more complex with prolonged operative and bypass times

and length of hospital stay. Furthermore, almost half the patients with partial AVSD underwent LAVV replacement during the 70s, 80s or 90s when early mortality was much higher.

Study Limitations

This is a retrospective and descriptive analysis covering a wide time span and, hence, subject to inherent deficiencies, including reporting bias, and limitations in data collection.

Conclusions

Patients with AVSD commonly require LAVV replacement. This can be carried out with acceptable risk. Freedom from LAVV replacement is much shorter in patients with complete AVSD than in those with a partial AVSD. Subsequent reoperations for prosthetic valve replacement and pacemaker implantations were common events during follow up.

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MITRAL VALVE REPLACEMENT WITH THE 15-MM MECHANICAL VALVE: A 20-YEAR MULTI-CENTER EXPERIENCE

5

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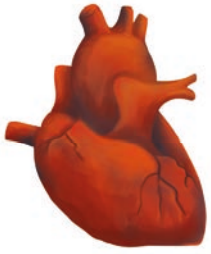


Abstract

Background:
The aim of this study was to evaluate early and long-term outcomes (mortality and prosthetic valve replacement) after mitral valve replacement with the 15-mm St. Jude Medical prosthesis.

Methods:
A multicenter, retrospective cohort study was performed among patients who underwent mitral valve replacement with a 15-mm SJM Masters prosthesis at 4 congenital cardiac centers in The Netherlands. Operative results were evaluated and echocardiographic data were studied at 0.5, 1, 2, 3, 5 and 10 years after surgery.

Results:
Surgery was performed in 17 infants. Ten patients (59%) were treated on the intensive care unit prior to surgery and 8 (47%) of them were on ventilator support. Median age at surgery was 3.2 (IQR 1.2 – 5.6) months, median weight was 5.2 (IQR 3.9 – 5.7) kg. There was 1 early cardiac death and 1 late non-cardiac death. Median follow-up time was 9.6 (IQR 2.4 – 13.2) years including 8 patients with follow-up > 10 years. First prosthetic valve explantation (n=11) occurred at median time of 2.9 (IQR 2.0 – 5.4) years. Other reinterventions were permanent pacemaker implantation (n=3), subaortic stenosis resection (n=2) and paravalvular leak repair (n=1). Prosthetic valve gradients increased from a mean of 5.0 (at discharge) to a mean of 14.3 (at 5 years follow-up) mm Hg.

Conclusions:
Mitral valve replacement with the 15-mm prosthesis can safely be performed in infants and even in neonates. Median freedom from prosthesis replacement for outgrowth is 3.5 years. Thromboembolic complications were rare.

Abbreviations

AVSD	Atrioventricular Septal Defect
FDA	Food and Drug Administration
HP	Hemodynamic Plus
ICU	Intensive Care Unit
LVF	Left Ventricular Function
LOS	Length Of Stay
MVR	Mitral Valve Replacement
NYHA	New York Heart Association
PH	Pulmonary Hypertension
SJM	St. Jude Medical

Introduction

Mitral valve replacement (MVR) may be the only bailout option in infants with irreparable atrioventricular (AV) valve stenosis or regurgitation (1).
Prosthetic valves >17 mm have long been the only available option for MVR, but these prostheses are often too large for infants and neonates. The stented bovine jugular vein graft valve (Melody; Medtronic, Minneapolis, MN) in contrast has recently been shown to be a promising alternative (2). However this valve is expensive and not designed to be surgically implanted (because it has a high profile and no sewingring) with a risk of causing left ventricular outflow tract obstruction, leaving paravalvular leak or creating pulmonary vein obstruction (3,4). Fortunately, a size reduced 15-mm bileaflet mechanical prosthesis has been introduced that is less expensive, designed for surgical use and that can be implanted with straight forward surgical techniques (5). Conceivably, this valve has a limited longevity due to increasing patient-prosthesis mismatch in the growing child and it requires the use of anticoagulants.

The dime-sized 15-mm prosthetic heart valve has been tested clinically (valve-related adverse events through 12 months post-implant in 20 subjects with mean follow-up duration of 10.4 months) and was subsequently FDA approved (Abbott SJM Masters HP 15-mm) (figure 1) (5). Long-term follow-up data are not available. However this particular prosthesis was already clinically available for off-label use in our country since 1998 (St. Jude Medical (SJM), St Paul, MN, USA). We studied our nationwide long-term experience with up to 20 years follow-up with this particular valve in mitral position in infants and neonates.

Figure 1A: Abbott SJM Masters HP 15-mm prosthesis

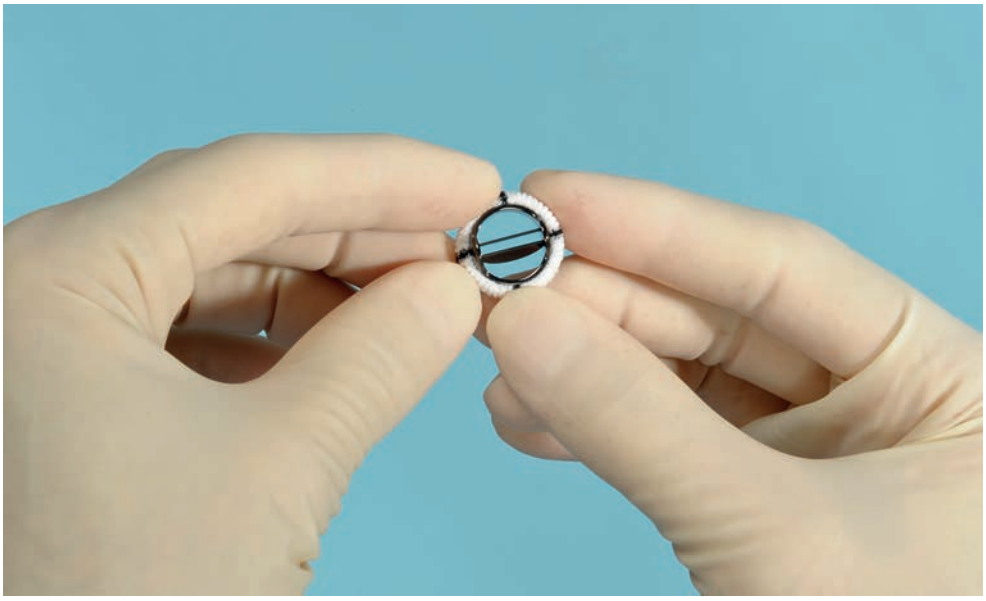
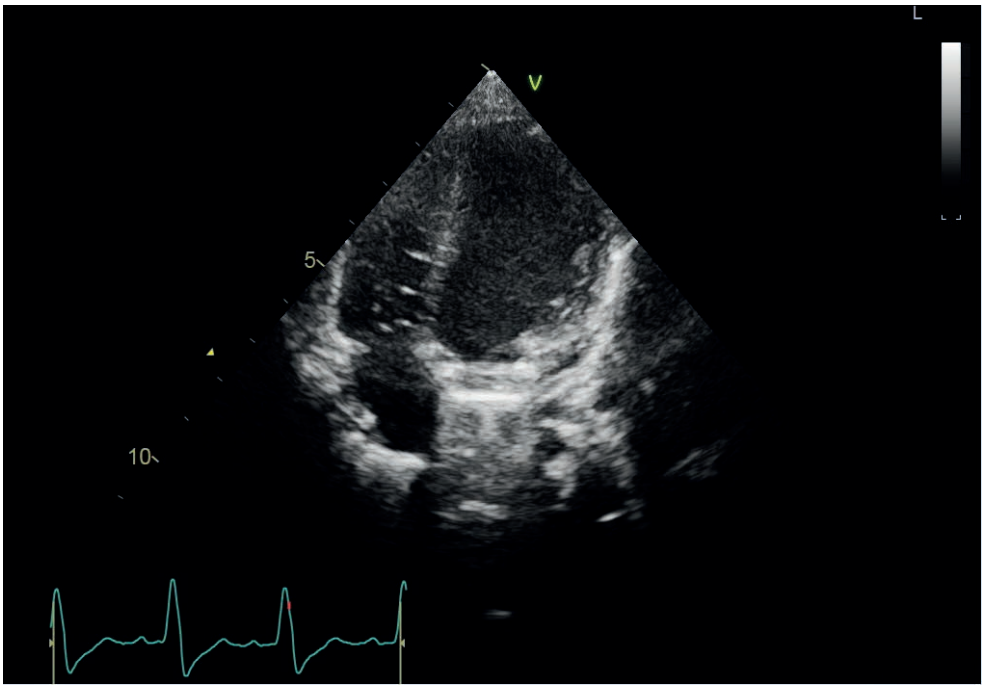


Figure 1B: echo image of 15-mm prosthesis implanted at the supra-annular level



Material and Methods

Study Design

A multicenter, retrospective cohort study was performed among patients who underwent MVR with a 15-mm SJM Masters prosthesis between January 1, 1998 and December 31, 2018. Four Dutch congenital heart centers participated including University Medical Centers in Groningen, Leiden, Nijmegen and Utrecht. Approval was obtained from the institutional review board at each center, with a waiver of informed consent obtained before data collection. Clinical and echocardiographic data were collected.

Patients

We identified 17 patients who received 18 MVRs using the 15-mm SJM Masters prosthesis. All patients were included for analysis because they met our inclusion criteria of receiving a 15-mm SJM Masters prosthesis.

Surgical Technique

Trans septal access to the left AV valve was used in the majority of patients (n=15). To prepare implantation all valve tissue (except the posterior leaflet in 4 (24%) patients) was excised including the top of papillary muscles which has shown to potentially interfere with prosthetic valve opening.

PTFE pledget supported (3x3x1.6mm) 5-0 braided polyester (Ethibond Excel, Ethicon, Somerville, New York, USA) sutures with RB-2 needle were used in 9 patients and non-pledgetted sutures were used in 8. Pledgets were positioned on the ventricular side of the annulus. A small valve ridge was left in the postero-inferior angle to avoid the AV-conduction tissue when placing sutures. Orientation of the valve was always "anti-anatomic" (90 degrees orthogonal to native orientation). Decision for level of implantation was made during surgery based on annular size. Annular implantation was possible in 14 patients and supra-annular in 3. Valve mobility was confirmed before the heart was closed and deaired.

Systemic Anticoagulation

Heparin (continuous infusion 20 units/kg/hr) was started right after surgery at the ICU with a target Activated Partial Thromboplastin Time (APTT) ratio of 1.8-2.5. Anti-factor Xa levels were measured daily from day 1 with a target range of 0.1-0.4. Coumarin therapy (acenocoumarol or phenprocoumon) was started 24 hours after surgery. Heparin was stopped when the target INR (2.5-3.5) was reached (6). The patients did not use aspirin.

Data Collection

Collected data included basic demographic information, descriptive anatomic diagnoses, associated non-cardiac or genetic anomalies, preoperative factors, echocardiographic data, surgical procedures, mortality and other clinical adverse events and reinterventions. Procedural details were obtained from operative reports.

Outcomes

The primary outcomes evaluated were mortality and prosthesis replacement. Secondary outcomes included major adverse events, thromboembolic events, resource utilization (postoperative days on ventilator, postoperative intensive care unit (ICU) length of stay (LOS) and hospital LOS) and echocardiographic function. Major adverse events were defined according to the Society of Thoracic Surgeons congenital heart surgery database (7,8).

Postoperative days on the ventilator was defined as total number of days on the ventilator after the index operation and included all reintubation days. Postoperative ICU LOS was defined as total postoperative days in the ICU, including days readmitted to the ICU during hospitalization for the index operation.

Echocardiography

All echocardiographic studies were reviewed before surgery and at discharge, and 0.5, 1, 2, 3, 5 and 10 years after MVR. Measurements of the MV annulus, gradient and degree of valvular regurgitation, tricuspid regurgitation and left ventricular function (LVF) were performed by an experienced cardiologist applying the recommendations of the American Society of Echocardiography (9,10).

Statistical Methods

Patient and procedural characteristics were summarized as frequencies and percentages for

categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Time to prosthesis replacement was estimated using the Kaplan-Meier method. Statistical analysis was performed with SPSS for Windows (version 25 (Armonk, NY: IBM Corp.)).

Results

Patients

All patients (n=17) had the 15-mm prosthesis implanted in the mitral or left AV valve position. Ten patients (59%) were treated on the ICU prior to surgery and 8 (47%) were on mechanical ventilator support. Median age at implantation was 3.2 months (IQR 1.2 – 5.6 months, full range, 1 day to 18 months). Indications for valve replacement included valvular regurgitation (moderate or greater) in 5, valvular stenosis (moderate or greater) in 2, and both in 10. Eight patients (47%) had previous attempts of repair. Median time from repair to replacement was 1.1 (IQR 0.6 – 5.7) months.

Table 1. Patient and Procedural Characteristics (n=17)

Characteristic	Value
Age at operation, months	3.2 (1.2 – 5.6)
Female sex	9 (53)
Weight at surgery, kg	5.2 (3.9 – 5.7)
Prematurity	2 (12)
Neonate	3 (18)
Preoperative condition	
On ICU	10 (59)
On ventilator support	8 (47)
Previous valve repair	
1 repair	7 (41)
2 repairs	1 (6)
Repair – replacement interval, months	1.1 (0.6 – 5.7)
Diagnosis	
Mitral regurgitation (congenital or acquired)	3 (18)
Congenital mitral stenosis	1 (6)
Congenital mitral regurgitation and stenosis	5 (29)
Hypoplastic left heart complex	4 (24)
Atrioventricular canal defect	4 (24)
Genetics	
Trisomy 21	1 (6)
Kabuki Syndrome	1 (6)

Values are n (%) or median (interquartile range).

Native echocardiographic valve size

Median preoperative lateral and anterior-posterior left atrioventricular (AV) valve diameters were 12.0 (range 8.0 – 16.6) mm and 12.6 (range 10.6 – 16.4) mm.

Surgical Technique

Procedural details and outcomes are outlined in Table 2. Median pump time was 111 (IQR 88 – 201) and median cross clamp time 78 (IQR 61 – 113) minutes. Twelve patients (71%) underwent MVR during the first bypass run and 5 patients (29%) underwent MVR as a second run procedure (failure of initial mitral valve repair (n=4), iatrogenic mitral valve regurgitation (prolapse of the anterior mitral valve leaflet) after initial resection of subaortic stenosis (n=1)).

Table 2. Operative Outcome Data

Variables	Value
Second bypass run	5 (29)
Posterior leaflet spared	4 (24)
Concomitant procedure[a]	6 (35)
Prosthetic valve level implant	
Annular	14 (82)
Supra-annular	3 (18)
Condition at discharge	
Gradient, mmHg	4.5 (3.4 – 6.0)
Absent regurgitation	17 (100)
AV block requiring pacemaker	3 (18)
Outcome	
Mortality	2 (12)
Early death	1 (6)
Late death	1 (6)
Second mitral valve replacement	11 (65)
First and second replacement interval, year	2.9 (2.0 – 5.4)
Major adverse events[b]	8 (47)
Days on ventilator	8.0 (1.5 – 9.0)
ICU length of stay, days	10.0 (6.5 – 28.5)
Hospital length of stay, days	29.0 (17.5 – 43.5)
Follow-up, years	9.6 (2.4 – 13.2)

[a] *Aortic valve repair, primary closure of ventricular septal defect, right atrioventricular valve repair, resection of subaortic stenosis, implantation of permanent pacemaker, coarctectomy with end-to-end anastomosis, Ross-Konno procedure.*

[b] *Bleeding or mediastinitis requiring reoperation, unplanned reintervention prior to discharge, arrhythmia requiring placement of permanent pacemaker, cardiac arrest requiring resuscitation, renal failure requiring dialysis Values are n (%) or median (interquartile range).*

At discharge, the median echocardiographic Doppler gradient of the SJM Masters prosthesis was 4.5 (IQR 3.4 -6.0; full range 1.4 – 11.0) mm Hg, and (para)valvular regurgitation was absent in all patients.

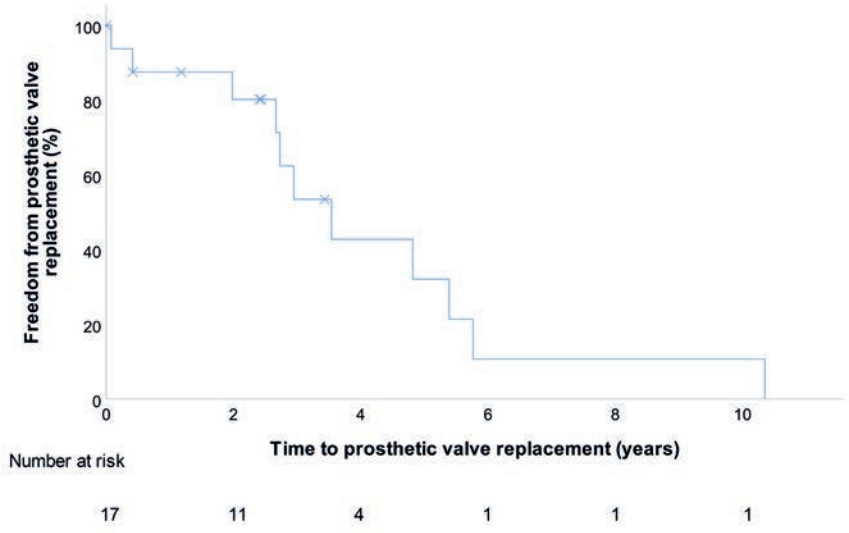
Mortality

Early cardiac death occurred in 1 patient (6%). This non-Down patient had a partial atrioventricular septal defect (AVSD) and severe AV valve regurgitation. The patient had heart failure and underwent left AV valve replacement after attempted emergency repair at 1 day of age. Patient died a few hours after surgery due to poor LV contractility despite adequate prosthetic function. Late death occurred in 1 (6%) non-Down patient 2.5 years after surgery and was attributed to pneumonia.

Prosthetic Valve Replacement

Eleven (65%) patients underwent prosthesis replacement. In all but 3 patients, 15-mm prostheses remained in place until they were found to be obstructive. This was the main indication for replacement. Median gradient prior to prosthesis replacement was 17.0 (IQR 10.0 – 20.5) mm Hg. Other indications for replacement were thrombosis in 2 and paravalvular leak in 1 patient. The median time to prosthetic valve replacement was 2.9 (IQR 2.0 – 5.4) years. Similar prostheses were used for replacement and 19 mm was the most commonly used size. Other sizes used were 15-mm (1), 17-mm (2), 21-mm (2), 23-mm (1). Bigger size prostheses during redo surgery were used in all cases except for 1 (prosthesis replacement after 1 month because of thrombosis). Figure 2 represents the Kaplan-Meier survival analysis curve for prosthetic valve replacement. Median freedom from prosthesis replacement is 3.5 years.

Figure 2: Kaplan-Meier estimate of time to prosthetic valve replacement. The number at risk at each time point is provided in the table below the graph.



Other indications for reoperation were resection of subaortic stenosis (4 in 2 patients) and aortic valve replacement (2).

Major Adverse Events

Twelve major adverse events occurred in 8 (47%) patients including permanent pacemaker implantation (3), unplanned reoperation prior to discharge (2), renal failure requiring dialysis (2), cardiac arrest requiring resuscitation (2), bleeding requiring reoperation (2), mediastinitis requiring reoperation (1). Patients had 1 (5), 2 (2) or 3 (1) major adverse events.
Unplanned reoperation prior to discharge included repair of paravalvular leak (n=1) and prosthetic valve replacement for thrombosis (n=1). In this patient, prosthetic valve impingement was seen on echo 1 week after operation. Despite optimal anticoagulant therapy the patient developed a valve thrombosis which was attributed to impeded prosthetic opening due to subvalvular tissue remnants. The stucked prosthesis was replaced 4 weeks after surgery and the patient remained free from subsequent thrombosis over the next 3 years. (Table 3, patient 1).

Table 3. Thromboembolic/bleeding events

Patient	Events	Etiology	Time since valve replacement (months)	Anticoagulation	Persisting neurological deficit
1.	Prosthesis thrombosis	Prosthesis impingement	0.9	Fenprocoumon (INR 3.1 – 4.5)	None
2.	Prosthesis thrombosis	Anticoagulation (gastroenteritis)	22	Acenocoumarol (INR 1.8 – 3.3)	Yes
3.	Stroke*	Other*	6	Other*	Yes
4.	Subdural hemorrhage	Anticoagulation (medication error)	3	Fenprocoumon (INR 7)	Yes

* *Perioperative stroke (Ross-Konno procedure with postoperative mechanical circulatory support).*

Neonatal cases

Patient 1 was diagnosed with congenital mitral stenosis and regurgitation and had respiratory insufficiency. The patient was intubated and admitted to the ICU on the day of birth and received a 15-mm MV prosthesis at 4 days of age. Resection of subaortic stenosis was performed 9 months after the index surgery. The patient was maintained with a 15-mm valve for 3.0 years, at which time a 21-mm SJM prosthesis was implanted and a second resection of subaortic stenosis was performed. The patient remains well with the 21-mm prosthesis at age 15 years with a mean gradient of 8 mm Hg. LVF is good and there are no signs of pulmonary hypertension (PH).

Patient 2 was diagnosed with congenital mitral regurgitation and heart failure. The patient was

intubated and on inotropic support immediately after birth. The patient's poor cardiac condition made us decide to give the patient a 15-mm MV prosthesis at 1 day of age. The patient underwent a reoperation because of retrocardiac bleed causing tamponade. The patient was discharged home for 5 months and readmitted with a paravalvular leak. The prosthesis was replaced by a 17 mm SJM prosthesis. The patient received a second prosthesis replacement (SJM 25-mm) 12.6 years after implantation of the 17-mm MVR. The child remains well with the 25-mm prosthesis at age 16 years with a mean gradient of 10.8 mm Hg. LVF is good and there are no signs of PH.

Patient 3 was diagnosed with a partial AVSD (non-Down) and severe AV valve regurgitation. The patient was in a poor condition (heart failure) when he went for emergency AVSD repair at 1 day of age. Attempted left AV valve repair failed and decided was to perform a MVR during second bypass run. Patient died a few hours after surgery due to poor LV contractility despite adequate prosthetic function.

Follow-up

The median follow-up time was 9.6 (IQR 2.4 – 13.2) years. Four patients experienced a thromboembolic/bleeding event (Table 3). Median postoperative days on ventilator was 8 (IQR 1.5 – 9) days, median ICU LOS was 10 (IQR 6.5 – 28.5) days. All patients were in NYHA functional class 1 at last follow-up and LVF was good in 11 (73%), slightly below normal in 3 (20%), and severely below normal in 1 (7%) patient. At last follow-up, mild to moderate PH was present in 4 (27%), severe PH in 1 (7%) patient.

Comment

The miniaturized 15-mm mechanical prosthesis may offer a favorable prospect to critically ill infants who have no further options for valve repair. This small valve can be used in the smallest hearts, be implanted with straight forward techniques and it lacks the drawbacks of the bovine jugular vein graft. It has been used in all involved Dutch centers with good early outcome with only one (6%) early death, occurring in a patient with a poor preoperative condition who died due to poor LV contractility despite adequate prosthetic function. Early (6%) and late mortality (6%) in our cohort is in line with early (11% to 42%) (11-14) and late mortality (0% to 24%) (12,14,15) reported in studies in children undergoing mechanical MVR with a slightly bigger size prosthesis. Our mortality rate is not higher compared to the rate reported by Pluchinotta and colleagues, showing death rates of 12% (early) and 8% (late) in a recent multi-center study among 59 patients who underwent MVR with a Melody valve (16).

Reinterventions

One of the concerns associated with prosthetic valve replacement in children is that a fixed-sized prosthesis is not accommodating for somatic growth of the patient. Our series shows that implantation of a 15-mm prosthesis helped infants and neonates to survive and be bridged a

median of 3.5 years ahead until patient-prosthesis mismatch required the small prosthesis to be replaced. Prosthetic valve endocarditis was not reported. No mortality was observed during the prosthesis replacement. Several studies showed expanding of the mitral ring during growth even if there is a prosthesis all around, which allowed placement of a bigger prosthesis during the following operation (17-19). This is in line with our study which shows the ability of placing bigger size prostheses during redo surgery in all cases except for 1 case (prosthesis replacement after 1 month because of thrombosis).

Another concern with MVR in small patients is the limitation posed by the small mitral annulus. In particular there is substantial concern about placement of a prosthetic valve that is larger than the annulus. Forcing too large a valve into the annulus has been associated with multiple complications, including complete heart block with the need for permanent pacemaker and compression of the circumflex coronary artery or obstruction of the left ventricular outflow tract (10,20). In our cohort, heart block requiring pacemaker (n=3) and subaortic stenosis resection (n=2) were expected complications and circumflex artery compression did not occur despite the fact that most prostheses were implanted at annular level. Prosthetic ring attachment to valve tissue in the critical area could help to prevent need for a permanent pacemaker. In our series the mean echocardiographic valve annulus diameter before 15-mm prosthesis implantation was 12.0 mm. This is smaller than the annulus measured in the study of Eltayeb and colleagues (14.8 mm) (19). Apparently it is safe to mildly oversize the prosthetic valve in infants and neonates and implant the prosthesis at annular level.

Pluchinotta and colleagues report the development of structural Melody prosthesis deterioration in a significant number (35%) of patients, requiring prosthesis replacement at median of 22 months after implantation (16). Interval to prosthesis replacement is not lower compared to our cohort. Besides differences in clinical outcomes between the Melody prosthesis and 15-mm mechanical prosthesis, the costs do significantly differ with the Melody prosthesis being 4 times as expensive.

Pannus formation and thromboembolic events

Inflammation or calcification has been noted in explanted SJM prostheses, primarily demonstrated as pannus formation. In our cohort pannus formation of SJM Masters prosthesis at time of explantation was reported in 4 (24%) patients. As opposed to pannus formation, prosthetic valve thrombosis occurs early after surgery, and results from both increased thrombogenicity and abnormal flow through the mechanical valve.

None of the patients in our cohort were on antiplatelet therapy. There is no consensus about adding antiplatelet therapy to the anticoagulant regimen. Support for the addition of antiplatelet therapy to vitamin K antagonists therapy alone comes from randomized trails showing a reduced risk of mortality and thromboembolisms with combined antiplatelet and anticoagulant therapy when compared with anticoagulant therapy alone (21,22). On the other side, these trials showed an increased risk of major hemorrhage with combined therapy when compared to anticoagulant only therapy. One of the 3 thromboembolic events in our cohort was prosthesis related (reduced cusp mobili-

ty 1 week after implantation). Prosthesis inspection during replacement revealed absent mobility of the posterior cusp and small thrombi on the cusp and in the hinge mechanism. The prosthesis was removed and a new 15-mm SJM Masters prosthesis was implanted. The other valve thrombosis was related to sub-therapeutic INR level (infection). The bleeding event was related to elevated INR level (high medication intake by mistake). The incidence of thromboembolic events due to prosthesis impingement is low in our cohort (1 of 17). Oral anticoagulant related thromboembolic events were limited (2 of 17). INR could be well targeted due to a good INR home monitoring system (INR self-testing and strict guidance from specialized thrombosis care) in our country. However, the incidence of thromboembolic complications and difficulty of managing anticoagulation in a small child are clearly downsides of the mechanical valve when compared with the Melody prosthesis, especially in countries with limited INR monitoring options.

Study Limitations

This is a nonrandomized retrospective study. Echocardiography protocols differed among the participating centers resulting in missing data for some variables. However, in order to avoid inter-observer variability, the studies were reviewed by an experienced cardiologist from the coordinating center. There is no comparison group such as the Melody prosthesis.

Conclusions

The miniaturized15-mm mechanical prosthesis has been a valuable adjunct to the armamentarium of the pediatric cardiac surgeon. It offered a chance of survival to critically ill infants and neonates. The prosthesis is relatively cheap and easy to implant in even the smallest babies. Late exchange for patient-prosthesis mismatch was required after 3.5 years median and could be carried out without the need for annular enlargement procedures. Complications of oral anticoagulant therapy were rare.

Disclosures: Authors have no disclosures

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MECHANICAL MITRAL VALVE REPLACEMENT: A MULTICENTER STUDY OF OUTCOMES WITH USE OF 15-17 MM PROSTHESES

6

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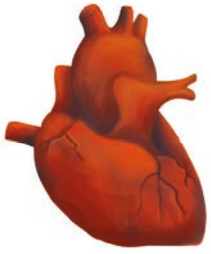


Abstract

Background:
The aim of this study was to evaluate early and mid-term outcomes (mortality and prosthetic valve reintervention) after mitral valve replacement (MVR) with 15-17 mm mechanical prostheses.

Methods:
A multicenter, retrospective cohort study was performed among patients who underwent MVR with a 15-17 mm mechanical prosthesis at 6 congenital cardiac centers: 5 in The Netherlands and 1 in the United States. Baseline, operative and follow-up data were evaluated.

Results:
MVR was performed in 61 infants (15-mm: 17 (28%), 16-mm: 18 (29%), 17-mm: 26 (43%)) of whom 27 (47%) were admitted to the ICU prior to surgery and 22 (39%) required ventilator support. Median age at surgery was 5.9 (IQR 3.2-17.4) months and median weight was 5.7 (IQR 4.5-8.8) kg. There were 13 (21%) in-hospital deaths and 8 (17%, among 48 hospital survivors) late deaths. Major adverse events occurred in 34 (56%). Median follow-up was 4.0 (IQR 0.4 – 12.5) years. First prosthetic valve replacement (n=27 (44%)) occurred at median of 3.7 (IQR 1.9-6.8) years. Risk of prosthesis replacement is greater for patients with size 15-mm valve when compared to those with 17-mm valves (p=0.009). Other reinterventions included permanent pacemaker implantation (n=9 (15%)), subaortic stenosis resection (n=4 (7%)), aortic valve repair (n=3 (5%)), and aortic valve replacement (n=6 (10%)).

Conclusions:
Mitral valve replacement with a 15-17 mm mechanical prostheses is an important alternative to save critically ill neonates and infants in whom the mitral valve cannot be repaired. Prosthesis replacement for outgrowth can be carried out with low risk.

Introduction

Mitral valve replacement (MVR) may be the only surgical option in some infants with severe congenital mitral valve (MV) stenosis or regurgitation, often after failed repair.[1] The prosthesis of choice is often a mechanical prosthesis as these are available in smaller sizes and are more durable than bioprosthetic counterparts, particularly in young pediatric patients.[2] While mechanical prostheses >17 mm have been the only available option for MVR in earlier eras, these prostheses were often too large for infants and neonates, where the normative values for lateral mitral annular diameter for neonate (weight 3 kilograms, height 50 centimeters, BSA 0.2 m^2) ranges from 8-12 mm and at 1 year (weight 7.5 kilograms, 71.5 centimeters, BSA 0.4 m^2) from 11 to 17 mm.[3]

Since 1995, mechanical prostheses have been available in 16-mm and 17-mm sizes, and the 15-mm prosthesis has been tested clinically and subsequently FDA approved in March 2018.[4] Despite the use of ≤ 17-mm mechanical valves in centers across the world, the small numbers in individual centers has resulted in few reports of outcomes in the literature.

Understanding clinical outcome in patients who have undergone MVR with a 15-17 mm mechanical prosthesis can serve as a benchmark to determine utility and benefits of bioprosthetic options, such as the stented bovine jugular vein conduits, that have recently been introduced as an alternative.[5] The availability of 15-mm mechanical prosthesis for off-label use since 1998, allows us to report a multi-institutional experience with up to 20 years' follow-up of the 15-17 mm mechanical mitral prostheses in infants and neonates, particularly mortality and valve-related morbidity.

Methods

Study Design

A multicenter, retrospective cohort study was performed in patients who underwent MVR with a 15-17 mm mechanical prosthesis between January 1, 1998 and December 31, 2018. These prostheses were implanted in five centers for congenital heart surgery in the Netherlands (University Medical Centers in Groningen, Leiden, Nijmegen, Rotterdam and Utrecht) and one in the United States (Boston Children's Hospital). Approval was obtained from the institutional review board at each center, with a waiver of informed consent, before collection of clinical and echocardiographic data.

Data Collection

Collected data included basic demographic information, descriptive anatomic diagnoses, associated non-cardiac or genetic anomalies, preoperative factors, echocardiographic data, mortality and other clinical adverse events and reinterventions. Procedural details were obtained from operative reports. Data on systemic anticoagulation post mechanical valve implant was also collected.

Outcomes

The primary outcomes evaluated were mortality and prosthesis replacement. Secondary outcomes included major adverse events during index hospitalization; thromboembolic events post valve implantation; resource utilization as measured by postoperative days on ventilator, postoperative intensive care unit (ICU) length of stay (LOS) and hospital LOS; and left ventricular function based on follow-up echocardiography post discharge. Index operation is defined as the first surgery where a 15-17 mm mechanical mitral prosthesis was inserted. Major adverse events were defined according to the Society of Thoracic Surgeons Congenital Heart Surgery Database.[6,7] Postoperative days on the ventilator was defined as total number of days on the ventilator after the index operation and included all reintubation days. Postoperative ICU LOS was defined as total postoperative days in the ICU, including days readmitted to the ICU during hospitalization for the index operation.

Echocardiography

All echocardiographic studies were reviewed before surgery, at discharge, and 0.5, 1, 2, 3, 5 and 10 years after MVR when available. Measurements of the MV annulus diameter in 2 planes, gradient and degree of valvular regurgitation and left ventricular function (LVF) were performed by an experienced cardiologist applying the recommendations of the American Society of Echocardiography.[8,9] Qualitative assessment of pulmonary artery pressures (based on pulmonary regurgitation jet), right ventricular pressures based on tricuspid regurgitation jet or septal position were also performed and resulted in scoring of pulmonary hypertension as none, mild-moderate and severe. Where echocardiographic images were not available for review, data from an echocardiographic report at the appropriate time point was used.

Statistical Methods

Patient and procedural characteristics were summarized as frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) and/or range for continuous variables. Freedom from death and prosthesis replacement following MVR was estimated using the Kaplan-Meier method, and compared between groups using the log-rank test. The Wilcoxon signed-rank test was used to evaluate change in valve size at the time of prosthesis replacement. All analysis was performed in SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patients

There were 61 patients included in the analysis (Table 1) with a median age at surgery of 5.9 months (IQR 3.2-17.4 months, range, 1 day to 5.3 years) and a median weight of 5.7 (IQR 4.5 – 8.8) kg. Primary diagnosis was isolated congenital MV stenosis/regurgitation in 29 (48%), atrioventricular septal defect in 18 (30%), Shone and hypoplastic left heart complex in 9 (15%) and other in 5 (8%). Twenty-seven patients (47%) were treated in the ICU prior to surgery and 22 (39%) were on mechanical ventilator support. Thirty-four (56%) patients had previous attempts

of repair. Median time from repair to replacement was 26 (IQR 13, 190) days. Thirteen (21%) patients underwent MVR requiring a second bypass run at index surgery after failure of initial mitral repair (n=11), iatrogenic mitral regurgitation (prolapse of the anterior MV leaflet) after initial resection of subaortic stenosis (n=1), and severe mitral regurgitation and stenosis after initial Ross-Konno procedure (n=1).

Table 1. Patient and Procedural Characteristics (n=61)

Characteristic (n=61)	**n (%) or median (IQR)**
Age at surgery, months	5.9 (3.2-17.4)
Male sex	31 (51)
Weight at surgery, kilogram	5.7 (4.5 – 8.8)
Preoperative Status	
In intensive care unit	27 (47)
On mechanical ventilator support	22 (39)
Previous surgery	
MV repair	34 (56)
Repair – replacement interval, days	26 (13, 190)
Pacemaker implantation	6 (10)
Diagnosis	
Atrioventricular septal defect	18 (30)
Shone syndrome and hypoplastic left heart complex	9 (15)
Isolated congenital MV stenosis and regurgitation	29 (48)
Other*	5 (8)
Preoperative anatomy	
Double orifice MV	1 (2)
Parachute MV	7 (11)
Arcade type MV	1 (2)
Single papillary muscle	7 (11)
Absent or short chordae	20 (33)
Basally displaced papillary muscles	3 (5)
Genetics	
Trisomy 21	3 (5)
Heterotaxy	3 (5)

IQR=interquartile range; MV=mitral valve; n=number.
** Included are parachute MV and ventricular septal defect, parachute MV with hypoplastic left ventricle and double outlet right ventricle, MV stenosis with hypoplastic left ventricle and double outlet right ventricle, straddling of MV and Taussig Bing Malformation, and Noonan Syndrome with hypertrophic cardiomyopathy.*

Surgical Technique

Procedural details and outcomes are outlined in Table 2.

Trans septal access (50 (82%) with excision of all valve tissue (except the posterior leaflet in 9 (15%) patients) with pledgets (if used) on the ventricular side of the annulus was the preferred method. Orientation of the valve was usually “anti-anatomic”. Annular implantation was possible in 47 (77%) patients and supra-annular in 14 (23%). Median pump time was 149 (IQR 110-226) minutes and median cross clamp time was 99 (IQR 73 – 141) minutes.

Systemic Anticoagulation

Systemic anticoagulation included initial intravenous heparin in all patients and was followed when clinically feasible by Coumarin therapy (acenocoumarol, phenprocoumon or warfarin) in 36 (59%), Aspirin in 4 (7%), not recorded in 21 (34%). Target INR was 2.5 to 3.5.

Hospital Course

Sixty-three major adverse events occurred in 34 (56%) patients including death prior to discharge (13, 21%), ventilator support more than 7 days (17, 28%), permanent pacemaker implantation (9, 15%), unplanned reoperation prior to discharge (6, 10%), renal failure requiring dialysis (4, 7%), mediastinitis requiring reoperation (4, 7%), postoperative ECMO support (3, 5%), bleeding requiring reoperation (3, 5%), cardiac arrest requiring resuscitation (3, 5%) and plication for paralysis or paresis of the diaphragm (1, 2%). Patients had 1 (18, 30%), 2 (11, 18%), 3 (1, 2%), 4 (1, 2%), 5 (2, 3%) or 6 (1, 2%) major adverse events. Major adverse events are depicted in Table 3.

Unplanned reoperation prior to discharge included repair of paravalvular leak (2, 3%), prosthetic valve replacement for thrombosis (2, 3%), closure of VSD and debanding of pulmonary artery (1, 2%) and implantation of left ventricular assist device (1, 2%).

Median postoperative days on ventilator and ICU was 5 (IQR 1 – 9) and 28 (IQR 12 – 56) days, respectively.

Table 2. Operative Outcome Data (n=61)

Variables (n=61)	n (%) or median (IQR)
Transseptal access	50 (82)
Posterior leaflet remained intact	9 (15)
Type of valve	
St. Jude	44 (72)
Carbomedics	16 (26)
Sorin	1 (2)
Size of valve (mm)	
15	17 (28)
16	18 (29)
17	26 (43)
Valve position	
Annular	47 (77)
Supra-annular	14 (23)
Emergency procedure	6 (10)
Second bypass run	13 (21)
Perfusion time, min	149 (110–226)
Cross-clamp time, min	99 (73-141)
Concomitant procedure[a]	21 (34)
Condition at discharge	
AV block requiring pacemaker	9 (15)
Outcome	
Major adverse events[b]	34 (56)
Prosthesis replacement	27 (44)
First to second replacement interval, years	3.7 (1.9-6.8)
Mortality	
In-hospital	13 (21)
Post-discharge[c]	8[d]
Days on ventilator	5 (1 – 9)
Intensive care unit length of stay, days	28 (12 - 56)
Hospital length of stay, days	41 (21 – 70)
Follow-up, years	4.0 (0.4 – 12.5)

IQR=interquartile range.

[a] *included variables are Ross-Konno procedure (4), right atrioventricular valve repair (3), resection of subaortic stenosis (2) with left ventricle myectomy (1), aortic valve repair (2), resection of subaortic stenosis (1), implantation of permanent pacemaker (1), coarctectomy with end-to-end anastomosis (1), coarctation repair and arterial switch (1), closure of ventricular septal defect (1) and atrial septal defect (fenestrated) (1), pulmonary vein ostial resection (1), superior vena cava/ innominate vein repair (1), repair of left lower lobe vein ostium (1).*

[b] *included variables are death prior to discharge (13), ventilator support > 7 days (17), pacemaker implantation (9), unplanned reoperation prior to discharge (6), renal failure requiring dialysis (4), mediastinitis requiring reoperation (4), postoperative ECMO support (3), cardiac arrest requiring resuscitation (3), bleeding requiring reoperation (3) and plication for paralysis or paresis of the diaphragm (1).*

[c] *Among 48 hospital survivors.*

[d] *Mortality rate among hospital survivors at 1, 2 and 5 year was 8.8%, 13.4% and 15.8%, respectively.*

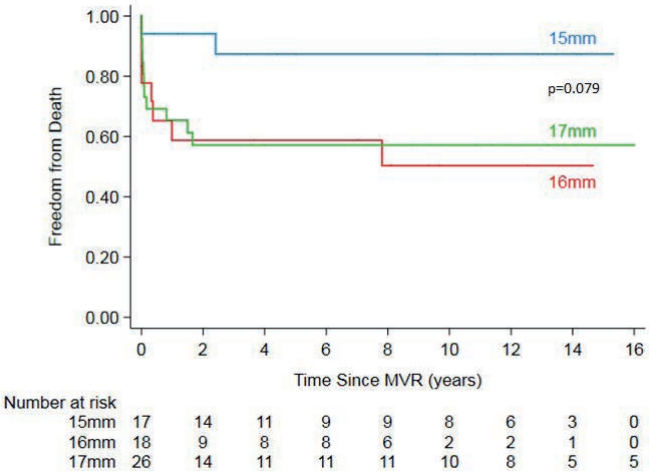
Table 3. Major Adverse Events

Patient number	Death or heart transplantation prior to discharge	Postoperative ECMO support	Bleeding requiring reoperation	Plication for paralysis or paresis of the diaphragm	Mediastinitis requiring reoperation	Ventilator support > 7 days	Cardiac arrest requiring resuscitation	Renal failure requiring dialysis	Unplanned cardiac reoperation prior to discharge	Pacemaker
1						x			x	
2						x				
3						x				
4	x									
5	x									
6	x					x				x
7	x									
8						x				
9						x				x
10	x									
11									x	x
12			x							x
13					x					x
14	x					x				
15	x									
16						x	x			
17						x		x		
18										x
19	x	x				x	x	x	x	
20						x	x	x	x	
21			x			x				
22	x									
23	x									
24				x						
25		x								
26					x	x				
27	x		x			x		x	x	
28	x				x	x			x	x
29						x				
30		x								
31					x					
32	x									
33										x
34						x				x

Mortality

In-hospital death occurred in 13 patients (21%). Death was attributed to heart failure in all patients. Post-discharge death occurred in 8 patients. Mortality rate among hospital survivors at 1, 2 and 5 year(s) was 8.8%, 13.4% and 15.8%, respectively. Death was attributed to heart failure in 2 patients and to a non-cardiac cause in 6 patients (pneumonia (2), respiratory insufficiency (2), and intracerebral bleeding (2)). Figure 1 represents the Kaplan-Meier survival curve for time from MVR to death based on size of prosthesis (Log-rank test p=0.079).

Figure 1: Kaplan-Meier survival estimation of time from MVR to death based on initial size of prosthesis. Prosthesis size of 15-mm is depicted in blue, 16-mm is depicted in red and 17-mm is depicted in green.



Abbreviations: MVR = mitral valve replacement.

Prosthetic Valve Replacement

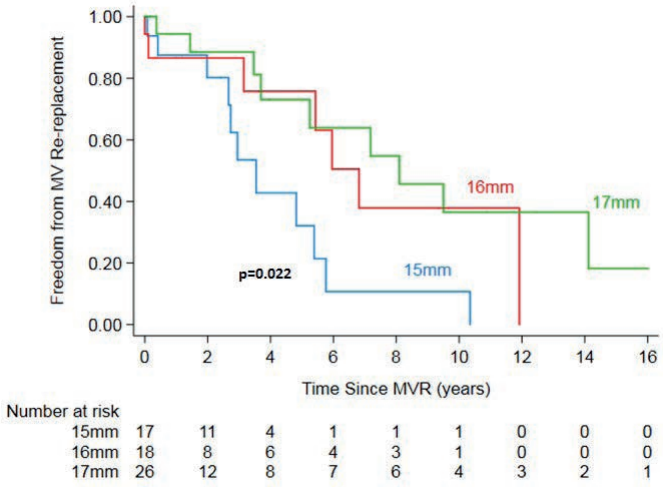
Prosthesis replacement was required in 27 (44%) patients. Main indication for prosthesis replacement was patient-prosthesis mismatch in 17 (28%). Other indications were prosthesis thrombosis in 5 (8%) and (para)valvular leak in 3 (5%), leaflet immobility and failure of prosthesis in 1 (2%), and pannus in 1 (2%). Among the 27 patients with replacement, median time to prosthetic valve replacement was 3.7 (IQR 1.9-6.8) years. Estimated freedom from prosthesis replacement at 1, 2, and 5 year(s) was 90%, 85%, and 60%, respectively. Majority of prosthesis were replaced by mechanical valves (24 (39%)). Other valves used for prosthesis replacement were porcine (2 (3%)) and pericardial valves (1 (2%)). Sizes used were 15-mm (1, 4%), 16-mm (3, 12%), 17-mm (1, 4%), 19-mm (8, 31%), 21-mm (5, 19%), 23-mm (8, 31%), 25-mm (1, 4%). Larger prostheses could be used for prosthesis replacement in all cases except for 1 (downsized 1-mm due to prosthesis thrombosis after 1.5 year) and 3 (same size due to prosthesis thrombosis (2) after 1 and 1.5 months, and due to prosthesis dysfunction after 1.5 month).

Figure 2 represents the Kaplan-Meier curves for freedom from prosthetic valve replacement based on size of prosthesis. Risk of prosthesis replacement is greater for subjects with size

15-mm valves when compared to those with larger valves (log-rank test p=0.022). In patients with initial MVR at annular and supra-annular level, prosthesis could be upsized by a median of 4 mm (signed-rank test p<0.001) and 5 mm (signed-rank test p=0.031), respectively.

Other indications for reoperation were resection of subaortic stenosis (n=4 (7%)) and aortic valve repair (n=3 (5%)) and aortic valve replacement (n=6 (10%)). One patient underwent aortic valve repair and replacement during separate procedures.

Figure 2: Kaplan-Meier survival estimation of time from MVR to prosthesis replacement based on initial size of prosthesis. Prosthesis size of 15-mm is depicted in blue, 16-mm is depicted in red and 17-mm is depicted in green.



Abbreviations: MV= mitral valve, MVR = mitral valve replacement.

Thromboembolic/bleeding events

Six (10%) patients had prosthesis thrombosis, including 1 patient with a thrombosis after prosthesis replacement with a 23-mm St. Jude Medical prosthesis, 3 of whom had persisting neurological deficit. One of these thromboembolic events was related to a malfunctioning prosthesis (reduced cusp mobility of 15-mm prosthesis 1 week after implantation). Prosthesis inspection during replacement revealed absent mobility of the posterior cusp and small thrombi on the cusp and in the hinge mechanism. The prosthesis was removed and a new 15-mm prosthesis was implanted (Table 4, patient 1). Another prosthesis thrombosis was related to sub-therapeutic INR level (infection). In the other patients, the cause of the prosthesis thrombosis remained unclear. There was a single bleeding event reported (1, 1.6%), related to elevated INR level (inadvertent intake of higher than prescribed medication dose).

Table 4. Thromboembolic/bleeding events

Patient	Thromboembolic events	Time since valve replacement (months)	Anticoagulation	Persisting (neurological) deficit
1.	Prosthesis thrombosis	0.9	Fenprocoumon (INR 3.1 – 4.5)	No
2.	Prosthesis thrombosis	3.9	Fraxiparine	Yes
3.	Prosthesis thrombosis	21.9	Acenocoumarol (INR 1.8 – 3.3)	Yes
4.	Prosthesis thrombosis^	88.7	Acenocoumarol	No
5.	Stroke	6.0	Other*	Yes
6.	Prosthesis thrombosis	6.6	Fraxiparine and Ascal	Yes
7.	Prosthesis thrombosis	17.3	Warfarin	No
Patient	**Bleeding events**	**Time since valve replacement (years)**	**Anticoagulation**	**Persisting (neurological) deficit**
1.	Subdural hemorrhage	2.8	Fenprocoumon (INR 7)	Yes

** Perioperative stroke (Ross-Konno procedure with postoperative mechanical circulatory support) during separate hospitalization.*
^ 23 mm mechanical prosthesis

Follow-up

Median follow-up time was 4.0 (IQR 0.4 – 12.5) years. Eight (13%) patients experienced a thromboembolic/bleeding event (Table 4) (7 (11%) after index surgery, 1 (2%) after prosthesis replacement with a 23 mm mechanical prosthesis). Among 25 patients with echocardiographic data at 10 years, left ventricular function was normal in 17 (68%), mildly depressed in 7 (28%) and moderately depressed in 1 (4%) patient. In a separate cohort of 22 patients with echocardiographic measurements of pulmonary/right ventricular pressures there was no evidence of pulmonary/right ventricular hypertension in 16 (73%) patients, mild to moderate in 5 (23%) and severe in 1 (4%) patient.

Comment

This multicenter retrospective review reports a 20-year experience with mechanical MVR using small prosthesis (15-17 mm) in children, with particular emphasis on mortality and valve related morbidity.

The in-hospital mortality (21%) is high but comparable to studies with similar sized mechanical prostheses (18-19%)[10,11] and is higher compared to studies where larger diameter mechanical prostheses were used (6–11 %)[12-14], albeit in older and larger patients. High mortality is likely related to the poor preoperative clinical condition of the patients in our cohort with 39% ventilated preoperatively for cardiorespiratory failure.
Mortality rates (both in-hospital (21%) and post-discharge (17%)) in our cohort are higher compared to the rates reported by Pluchinotta and colleagues, of 12% (early) and 8% (late) in a recent multi-center study among 59 slightly older and larger patients, who underwent MVR with a stented bovine jugular vein conduit.[15] High in-hospital mortality rate in our cohort may be explained by worse preoperative risk status and the greater number of concomitant procedures (21 (34%)) in our cohort. Majority of patients who suffered an early cardiac death were admitted to the ICU and on ventilator support prior to surgery indicative of compromised hemodynamics. Elevated post-discharge mortality rate in our cohort may be explained by a longer duration of follow-up in our cohort compared to the Pluchinotta's cohort (median 4.0 years versus mean 23 months). Furthermore, they have reported the development of structural bovine jugular vein conduit deterioration in a significant number (35%) of patients, requiring prosthesis replacement at median of 22 months after implantation.[15] Of note, rate of prosthesis replacement in our cohort while similar (44%) occurred later with median time to prosthesis replacement of 44 months.

Patients in our series remained free from prosthesis replacement for a median of 3.7 years, with patient-prosthesis mismatch being the most common indication for prosthesis replacement. Prosthetic valve endocarditis was not reported and there was no mortality related to prosthesis replacement. A larger prosthesis could be used in majority of patients with a median increase in prosthesis size by 4-mm during prosthesis replacement. This finding is consistent with other studies that have demonstrated mitral annular growth despite the restriction induced by a prosthetic ring as complete removal of the initial prosthesis allows the native annulus to expand.[16-18]

One of the concerns associated with prosthetic valve replacement in children with a small mitral annulus is that the annulus can rarely be surgically enlarged due to proximity to vital structures and annular implantation of larger prosthesis has been associated with heart block, compression of the circumflex coronary or left ventricular outflow tract obstruction.[19,20] Supra-annular prosthesis implantation remains an alternative option in patients with small MV annulus sizes, with poor[21] to excellent[22] results reported in small series of patients. In our cohort, heart block requiring pacemaker (n=9 (15%)) and subaortic stenosis resection (n=4 (7%)) and circumflex artery compression (n=1 (1.6%)) did occur, despite the fact that most prostheses were

implanted at annular level. We used the supra-annular technique in 14 (23%) of our patients so that an adequate sized prosthesis could be implanted while avoiding the complications of an oversized prosthesis in the true annulus. Both time to death and time to prosthesis replacement did not significantly differ between patients with prosthesis implanted at the annular and supra-annular level.

The choice of prosthesis i.e., a small mechanical prosthesis versus a bioprosthesis such as a stented bovine jugular vein conduit is best determined by the individual surgeon and cardiologist. In the short term, the morbidity and mortality risks for a 15-17 mm mechanical prosthesis are comparable to that of a bovine jugular vein contegra conduit.[15] The incidence of thromboembolic complications and difficulty of managing anticoagulation in a small child are clearly an important disadvantage with mechanical valves when compared to bioprosthetic valves such as the stented bovine jugular vein conduit, especially in countries with limited INR monitoring options where, easy access and low costs may favor the mechanical prosthesis. Long-term outcome of the stented bovine jugular vein conduit are needed and can contribute to clinical decision-making on choice of prosthesis.

Study limitations

This is a retrospective cohort study with inherent limitations of missing data. Echocardiography protocols differed among the participating centers resulting in missing data for some echocardiographic variables. However, in order to avoid inter-observer variability, the studies when available were reviewed by experienced cardiologists from the 2 coordinating centers. Furthermore, there was no bioprosthetic valve comparator group in this study.

Conclusions

Small sized mechanical prosthetic valves may be an important alternative in critically ill neonates and infants who require MVR. Inevitable prosthesis replacement for outgrowth was required at a median of 3.7 years and could be carried out with low risk. Anticoagulation and associated morbidity remains a challenge.

Conflict of Interest Statement: Authors have nothing to disclose with regard to commercial support

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LOW RATE OF LEFT ATRIOVENTRICULAR VALVE REOPERATIONS IN AUTOLOGOUS DOUBLE PERICARDIAL-PATCH REPAIR OF COMPLETE ATRIOVENTRICULAR SEPTAL DEFECT

7

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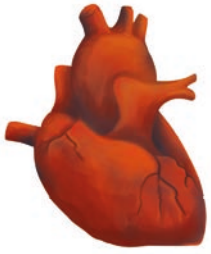


Abstract

Objectives:
Despite improved outcome in complete atrioventricular septal defect (AVSD) repair, reoperations for left atrioventricular valve (LAVV) dysfunction are common. Most of these are performed within the first months after initial repair suggesting a technical cause. During 22 years we used fresh untreated autologous pericardium for closure of both ventricular and atrial septal defect. Influence of this technical modification on AV valve function was retrospectively studied.

Methods:
Clinical and echocardiographic data were collected of patients with complete AVSD operated on with the use of autologous double patch technique between January 1, 1996, and December 31, 2017. Evaluation closed at December 2019.

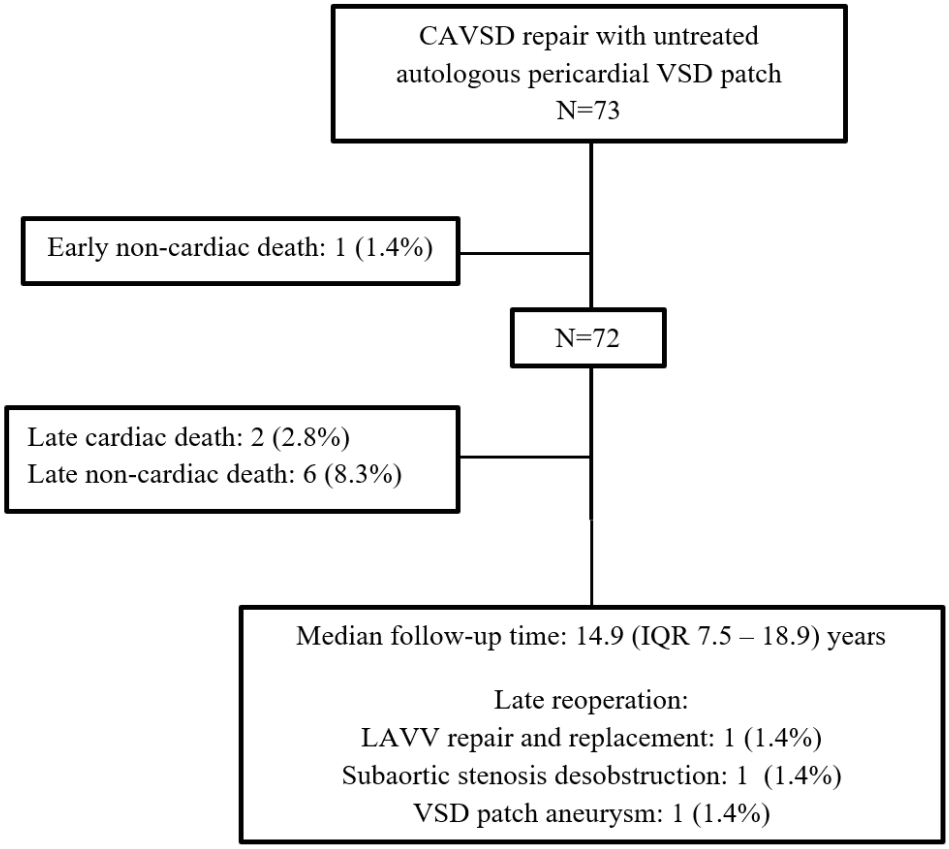
Results:
A total of 73 patients were analyzed. Median age at surgery was 3.5 (IQR 2.5 – 4.5) months and median weight was 4.5 (IQR 4.0 – 5.1) kg. Trisomy 21 was present in 65 (89%) patients. All but 1 patient survived (1.4%) and 8 patients died late (11%). Median follow-up time was 14.9 (IQR 7.5 – 18.9) years. Four patients (5%) were reoperated with a freedom from reoperation at 5, 10 and 15 years of 93%, 91% and 88% respectively. One (1.4%) patient was reoperated for LAVV regurgitation 8 months after AVSD repair, while right AV valve stenosis (1), residual VSD (1) and left ventricular outflow tract obstruction (1) were other indications for reoperation. Freedom from echocardiographic moderate/ severe LAVV regurgitation at last follow up was 83%.

Conclusions:
Infant autologous double pericardial patch repair of complete AVSD is associated with a very low incidence of reoperation on the left atrioventricular valve.

Abbreviations

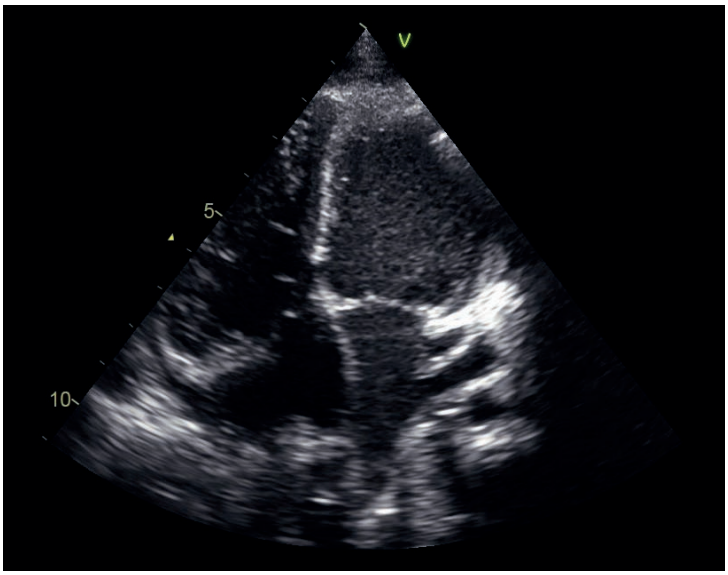
ASD	Atrial Septal Defect
AV	Atrioventricular
AVSD	Atrioventricular Septal Defect
AVV	Atrioventricular Valve
CAVSD	Complete Atrioventricular Septal Defect
ICU	Intensive Care Unit
IQR	Interquartile Range
LAVV	Left Atrioventricular Valve
LCOS	Low Cardiac Output Syndrome
LOS	Length Of Stay
LVOT	Left Ventricular Outflow Tract
MAE	Major Adverse Event
RI	Reintervention
RAVV	Right Atrioventricular Valve
VSD	Ventricular Septal defect

Graphical Abstract:



Abbreviations: CAVSD=complete atrioventricular septal defect, IQR=interquartile range, LAVV=left atrioventricular valve, VSD=ventricular septal defect.

Central Picture: Four-chamber view of echo image 10 years after repair



Central Message:

Autologous double pericardial patch repair of complete atrioventricular septal defect is associated with a very low incidence of reoperation on the left atrioventricular valve.

Perspective Statement:

The use of fresh autologous pericardium to close the ventricular septal defect component in atrioventricular septal defect repair is easy and safe. This simple surgical modification may help to reduce atrioventricular valve reoperations.

Introduction

Despite improved early outcome in primary infant complete atrioventricular septal defect (AVSD) repair, reoperations on the left atrioventricular valve (LAVV) remain an important cause of morbidity. In reported contemporary series, patients are particularly at risk for LAVV reoperation in the first year after initial surgery (1,2). Regurgitation is reported to be caused by suture dehiscence which was related to low bodyweight and AV valve tissue fragility (3). During repair, delicate bridging leaflets are immobilized on stiff artificial patch or septal crest and may become a predilection site for tears.

For 22 years we used fresh untreated autologous pericardium for ASD and VSD closure to minimize suture-traction and allow optimal AV valve dynamics. Moreover, we avoided artificial pledgets and the bridging leaflets were left intact.
We retrospectively studied these patients with particular attention to early and late AV valve function.

Methods

Patient population

Patients who underwent CAVSD repair with a VSD component that needed patch closure were included. Operations were performed between January 1, 1996, and December 31, 2017 by a single surgeon at three different sites. Patients with associated Fallot or major other cardiac anomalies were excluded. This study was performed with institutional review board approval, with a waiver of informed consent.

Early outcome variables

The primary outcome variables studied were mortality, length of stay (LOS) and major adverse events (MAE) (according to the Society of Thoracic Surgeons congenital heart surgery database) (4).
Postoperative days on the ventilator was defined as total number of days on the ventilator after the index operation including all reintubation days. Postoperative intensive care unit (ICU) LOS was defined as total postoperative days in the ICU, including days readmitted to the ICU during hospitalization for the index operation.

Follow-up

Secondary outcome variables were late mortality, late morbidity and echocardiographic findings. AVV function was assessed based on echocardiographic reports at discharge and 5, 10 and 15 years after surgery. Regurgitation was registered as a dichotomous variable; either moderate/severe or ≤ mild.

Statistical analysis

Patient and procedural characteristics were summarized as frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Time to death, reoperation, and moderate/ severe LAVV regurgitation were depicted as a Kaplan-Meier curve. Statistical analysis was performed with SPSS for Windows (version 25 (Armonk, NY: IBM Corp.)).

Results

Patients

There were 73 patients eligible for analysis (Table 1). Median age at surgery was 3.5 (2.5 – 4.5) months and median weight was 4.5 (4.0 – 5.1) kg. Thirty-eight patients were male (52%). Trisomy 21 was present in 65 (89%) patients. Six patients (8%) were admitted to the ICU and on ventilator support prior to operation. Preoperative moderate/severe AVV regurgitation was present in 11 (15%) patients (data 86% complete). Median follow-up time after surgery was 14.9 (IQR 7.5 – 18.9) years. Follow up was 100% complete.

Table 1. Patient and Procedural Characteristics (n=73)

Characteristic	Total (n=73)
Age at surgery, months	3.5 (2.5 – 4.5)
Neonate	2 (2.7)
Weight at surgery, kg	4.5 (4.0 – 5.1)
Male sex	38 (52.1)
Preoperative condition	
On ICU	6 (8.2)
On ventilator support	6 (8.2)
Moderate or greater AVV regurgitation	11 (15.1)
Missing AVV regurgitation	10 (13.7)
Genetics	
Trisomy 21	65 (89.0)

Values are n (%) or median (interquartile range).
AVV=atrioventricular valve, ICU = intensive care unit.

Surgical Technique

Standard bicaval cannulation and moderate hypothermic bypass and crystalloid cardioplegia were used. The common AV valve was approached via the right atrium. The atrial septum between primum ASD and open foramen ovale was cut and retracted for exposure. The central coaptation point of both bridging leaflets was marked with a stay-suture. Based on preoperative echo and direct inspection a boat-shaped autologous pericardial patch was tailored and

stretched out between stay-sutures. The patch was not treated with glutaraldehyde so freshly used. The convex side was fixed on the septal crest with running 6/0 Prolene. The straight side was attached to the bridging leaflets with separate 6/0 Prolene U-stitches (leaflets left intact). These sutures were also used to fix the autologous pericardial patch for ASD closure. Care was taken not to oversize the VSD patch or cause any AV valve retraction. When LAVV surface area was large enough, the zone of apposition was closed with separate single 6/0 Prolene sutures. After left AV valve was tested by filling the ventricle, the right valve was tested and repaired if necessary, the opened atrial septal bridge was subsequently reconnected and the primum ASD closed leaving the coronary sinus in the right atrium. A foramen ovale was separately closed primarily.

Table 2. Operative Outcome Data

Variables	Total (n=73)
Second bypass run	11 (15)
Perfusion time, min	120 (111–151)
Cross-clamp time, min	84 (77-104)
Concomitant procedure[a]	35 (47.9)
Condition at discharge	
AV block requiring pacemaker	0 (0)
Outcome	
Major adverse events[b]	5 (6.8)
Reintervention[c]	4 (5.5)
Mortality <30 days Late	9 (12.3) 1 (1.4) 8 (11.0)
Days on ventilator	4.0 (2.0 – 6.0)
ICU length of stay, days	6.0 (3.8 – 8.0)
Hospital length of stay, days	11.0 (8.0 – 16.8)
Follow-up, years	14.9 (7.5 – 18.9)

Values are n (%) or median (interquartile range).
AV=atrioventricular, ICU=intensive care unit, LAVV=left atrioventricular valve, RAVV=right atrioventricular valve, VSD=ventricular septal defect.
[a] *Includes duct closure (29), clipping persistent left superior vena cava (1), coarctation repair (1), rerouting (1) or clipping (1) of left superior vena cava, pulmonary artery debanding and repair (1), correction of partial anomalous pulmonary venous connection (1), repair of pulmonary vein stenosis (1). One patient had two concomitant procedures.*
[b] *cardiac arrest requiring resuscitation, bleeding requiring reoperation and unplanned reoperation prior to discharge.*
[c] *on ASD, VSD, LAVV, RAVV and LVOT.*

Procedural details and outcomes are outlined in Table 2. Second bypass run for residual lesion was performed in 11 (15%) patient. (on LAVV in 10, and for residual VSD in 1).
Duct closure (29), coarctation repair (1), rerouting (1) or clipping (1) of left superior vena cava,

pulmonary artery debanding and repair (1), correction of partial anomalous pulmonary venous connection (1), repair of pulmonary vein stenosis (1) were additional procedure performed in 35 patients (48%). The zone of apposition was closed in all but 3 patients.

Early Mortality

Death < 30 days occurred in 1 (1%) patient due to laparotomy for gastrointestinal bleeding 3 weeks after uncomplicated AVSD repair.

Major adverse events

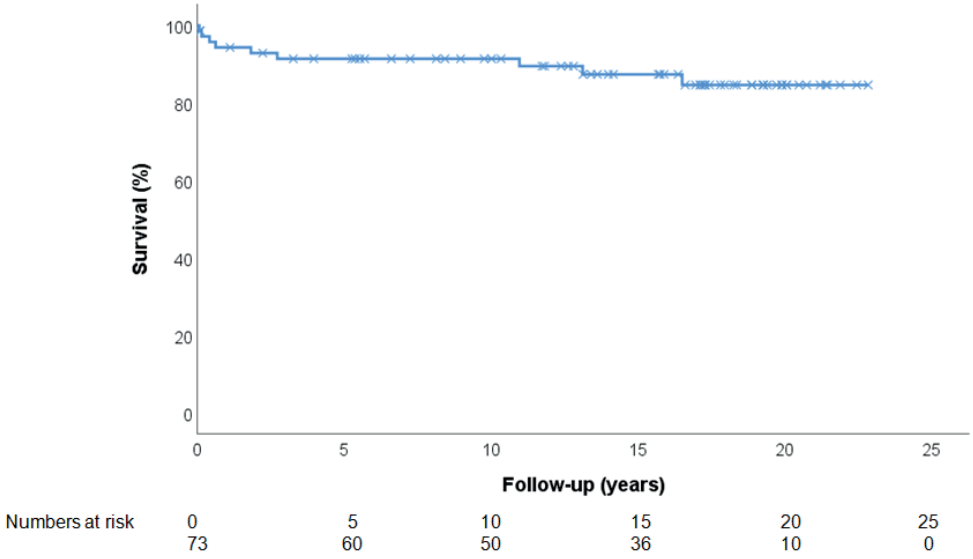
In hospital MAEs (6) occurred in 5 (7%) patients including cardiac arrest in ICU requiring resuscitation (3), reoperation for bleeding (2), unintended reoperation (1) (RAVV revision). There were no early unintended reoperations for LAVV dysfunction, nor any early pacemaker implantations.

Median duration of ventilator support was 4.0 (IQR 2.0 – 6.0) days. Median ICU LOS was 6.0 (IQR 3.8 – 8.0) days. Median postoperative hospital LOS was 11.0 (8.0 – 16.8) days.

Late mortality

Late death (Figure 1) occurred in 8 (11%) patients and was supposedly cardiac related in 2 (pulmonary hypertension (1), myocardial infarction in lymphocytic myocarditis (1)) but unrelated to AVSD repair. Other (non-cardiac) causes were pneumonia (2), gastroenteritis (1) and unknown (3).

Figure 1: Kaplan-Meier survival estimation of time to death

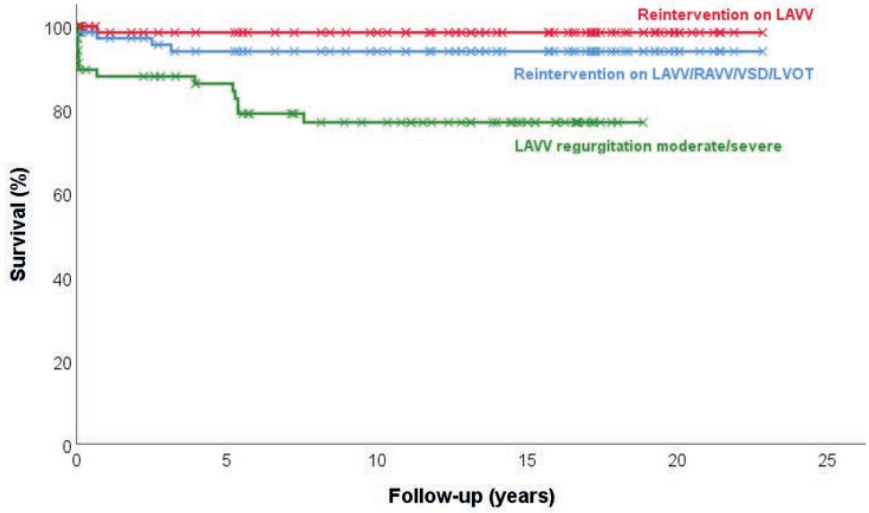


Late reoperations

Three (4%) patients were reoperated. One patient was reoperated for LAVV regurgitation at 8 months. No suture dehiscences were found and an anterosuperior leaflet indentation was closed. Eventually the valve was replaced at 13 years after AVSD repair. One patient was reoperated for LVOT obstruction and one more for VSD patch aneurysm (Figure 2). In this last patient, intraoperative echocardiography after AVSD repair showed the patch to be slightly oversized. Ballooning of the VSD patch increased at follow-up causing RAVV obstruction 2.5 years later. Excess patch was resected at reoperation and sent for pathology. The histology showed viability of smooth muscle cells on immunohistochemical staining. Extracellular collagen and newly formed elastin structures were described as shown in Figure 3.

Late pacemaker implantation was performed in 1 patient 19 years after index repair.

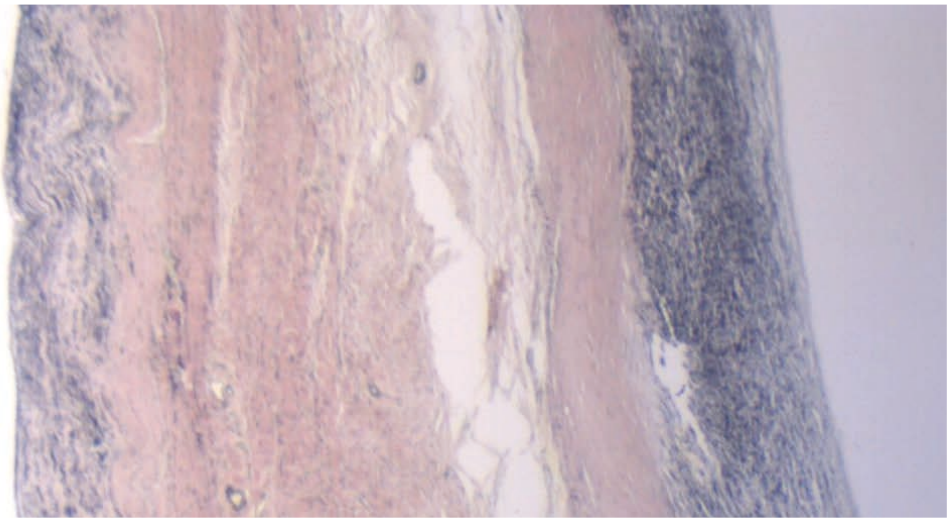
Figure 2: Kaplan-Meier survival estimation of time to reintervention on LAVV/RAVV/VSD/LVOT, reintervention on LAVV, and time to moderate/severe left AV valve regurgitation. Time to reintervention on LAVV/RAVV/VSD/LVOT is depicted in blue, time to reintervention on LAVV is depicted in red, time to moderate/severe LAVV regurgitation is depicted in green.



Numbers at risk	0	5	10	15	20	25
Reintervention	73	57	47	32	8	0
Reintervention LAVV	73	60	50	35	9	0
LAVV regurgitation	73	48	34	18	0	0

Abbreviations: LAVV=left atrioventricular valve, LVOT=left ventricular outflow tract obstruction, RAVV=right atrioventricular valve, VSD=ventricular septal defect.

Figure 3: Histology image of an untreated pericardial patch 2.5 years after implantation. Hemotoxyline-eosin staining. Cell nuclei are stained blue. Extracellular matrix and cytoplasm are stained pink.



Follow-up echocardiography

Moderate or severe AVV regurgitation at last follow-up was present in 17 (23%) patients (moderate in 16 and severe in 1) (Figure 2). All patients were in NYHA class 1, except for 1 (due to pulmonary hypertension). This patient (age 3 years) developed severe pulmonary hypertension and is on endothelin receptor antagonist, phosphodiesterase-5 inhibitor and O2 therapy. Echo showed trivial LAVV regurgitation and no residual atrial or ventricular shunt.

Discussion

While the median age at surgery for complete AVSD dropped to 3-6 months (5), reintervention rates have slightly increased over the years with reoperations on the left AV valve being the most frequent indication (rates 6.4-11.4%) and cleft and patch dehiscence a frequent operative finding (7-9). We agree with Airaksinen and colleagues that young operational age increases technical difficulties due to more fragile valve tissues and smaller dimensions (6). This may explain the persistent need for early reoperation on the AV valves. To prevent AV valve reoperations after correcting AVSD in smaller children, surgical techniques that were reliable in older children, may have to be modified. We hypothesized that with the classic surgical approach, closing the VSD with artificial patch fixes the bridging leaflets such that their dynamism is lost. This restriction may contribute to dehiscencies in delicate infant tissues.

The pericardium retained its viability on histology which supported our preferential use of this patch material. Adaptation may be assumed. Abundant elastin (normally scant) may reflect such a response on the complex dynamic environment.

Clinically, pericardial patch characteristics may have contributed to favorable AV valve function with a zero incidence of early reoperation and only 1 (1.4%) late reoperation on the LAVV during during a median follow-up of almost 15 years.
The technical use of this patch was easy and safe as long as its size was carefully tailored to the size of the VSD and insertion was performed tautly, without ballooning.

Limitations

This study is limited by its retrospective nature with the inherent problems of missing and incomplete data and concerns a single surgeon experience without control group.

Conclusion

Autologous double fresh pericardial patch repair of infant complete AVSD is associated with a very low incidence of reoperation on the left atrioventricular valve.

Disclosures: Authors have nothing to disclose with regard to commercial support

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LONG-TERM FOLLOW-UP OF PERICARDIUM FOR THE VENTRICULAR COMPONENT IN ATRIOVENTRICULAR SEPTAL DEFECT REPAIR

8

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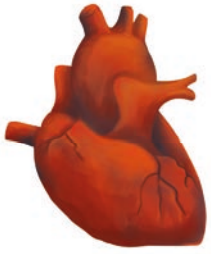


Abstract

Background:
Despite improved outcome in complete atrioventricular septal defect (AVSD) repair, reoperations for left atrioventricular valve (LAVV) dysfunction are common. The aim of this study was to evaluate the effect of fresh untreated autologous pericardium for ventricular septal defect (VSD) closure on AVV function and compare results with the use of treated bovine pericardial patch material.

Methods:
Clinical and echocardiographic data were collected of patients with complete AVSD with their VSD closed with either untreated autologous pericardial or treated bovine pericardial patch material between January 1, 1996, and December 31, 2003. Evaluation closed at September 2019.

Results:
A total of 79 patients were analyzed (untreated autologous pericardial VSD patch: 59 (75%), treated bovine pericardial VSD patch: 20 (25%)). Median age at surgery was 3.6 (IQR 2.7-4.4) months, median weight was 4.5 (IQR 3.8-5.1) kg. Trisomy 21 was present in 72 (91%) patients. Median follow-up time was 17.8 (IQR 13.1 – 19.9) years. There were 11 (14%) deaths (autologous pericardium: 9 (15%), treated bovine pericardial patch: 2 (10%, p=0.720)) and 8 (14%) reinterventions, all in the autologous pericardium group. Log rank tests showed no significant difference in mortality (p=0.728), reinterventions (p=0.199) or LAVV regurgitation (p=0.924).

Conclusions: VSD in AVSD can be safely closed with untreated autologous pericardium. Outcome on mortality, reoperation or AVV regurgitation were equal in both patch groups.

Abbreviations

ASD	Atrial Septal Defect
AV	Atrioventricular
AVSD	Atrioventricular Septal Defect
AVV	Atrioventricular Valve
CAVSD	Complete Atrioventricular Septal Defect
ICU	Intensive Care Unit
IQR	Interquartile Range
LAVV	Left Atrioventricular Valve
LCOS	Low Cardiac Output Syndrome
LOS	Length Of Stay
LVOT	Left Ventricular Outflow Tract
MAE	Major Adverse Event
RAVV	Right Atrioventricular Valve
VSD	Ventricular Septal defect

Introduction

Despite improved early outcome in primary infant complete atrioventricular septal defect (CAVSD) repair, left atrioventricular valve (LAVV) regurgitation is the most common indication for reoperation with reported rates between 10 and 20 % (1-3).

Most LAVV reoperations are performed within the first year after correction (4,5) but there is a consistent risk at follow-up which is associated with late mortality (6). Risk of LAVV reoperations has been related to valve morphology (7) as well as timing of repair (8), but was irrespective of repair mode (single or double patch) (1) whereas the mechanism of valve failure is often caused by suture dehiscence. This failure has also been related to low bodyweight and AVV tissue fragility (9). When delicate bridging leaflets are immobilized on stiff artificial patch or septal crest it may become the "Achilles heel" of AVSD repair.

We changed our repair strategy by choosing fresh autologous pericardium for septal defect repair, avoided artificial pledgets and left the bridging leaflets intact. We assumed that the elastic properties of untreated autologous pericardium could help to preserve the natural dynamics of the AVV when both atrial and ventricular septal defects are closed with two of these patches. The purpose of this study was to evaluate the effect of this modification on AVV function and compare results with those from patients in whom the VSD was closed with treated bovine pericardial patch material.

The current Covid-19 pandemic may place surgeons in a situation where the patch material of preference (xeno-pericardium, Gore-Tex, Dacron) is not available because of supply-chain interruption. This study provides insights in the use and outcomes of fresh autologous pericardium in the VSD position, which could be a valuable patch material option.

Material and Methods

Patient population

Patients who underwent CAVSD repair with a VSD component that needed patch closure were included. Operations were performed between January 1, 1996, and December 31, 2003 by two surgeons at Leiden University Medical Center. Patients with associated tetralogy of Fallot or major other cardiac anomalies were excluded. This study was performed with institutional review board approval.

Surgical Technique

Standard bi-caval cannulation and moderate hypothermic bypass and crystalloid cardioplegia were used. The common AVV was approached via the right atrium. The atrial septum between primum ASD and open foramen ovale was cut and retracted for exposure. The central coapta-

tion point of both bridging leaflets was marked with a stay-suture. The VSD was closed using a treated bovine pericardial patch in 20 (25%) (xeno-pericardium: 18, polyethylene terephthalate (Dacron): 1, polytetrafluoroethylene (Gore-Tex): 1) and an untreated autologous pericardial patch in 59 (75%) patients. Based on preoperative echo and direct inspection a boat-shaped patch was tailored and stretched out between stay-sutures. The convex side was fixed on the septal crest with running 6/0 Prolene. The straight side was attached to the bridging leaflets with separate 6/0 Prolene U-stitches (leaflets left intact). These sutures were also used to fix the patch for ASD closure (autologous pericardium: 61 (77%), xeno-pericardium: 18 (23%)). Care was taken not to oversize the VSD patch or cause any AVV retraction. When LAVV surface area was large enough, the zone of apposition was closed with separate single 6/0 Prolene sutures. After left AVV was tested by filling the ventricle, the right valve was tested and repaired if necessary. The opened atrial septal bridge was subsequently reconnected and the primum ASD closed leaving the coronary sinus in the right atrium. A foramen ovale was separately closed primarily.

Early outcome variables

The primary outcome variables studied were mortality, length of stay (LOS) and major adverse events (MAE) including reoperation for LAVV failure (according to the Society of Thoracic Surgeons congenital heart surgery database) (5). Indication for LAVV reoperation was based on LAVV function, presence of pulmonary hypertension and presence of clinical symptoms.
"Postoperative days on the ventilator" was defined as total number of days on the ventilator after the index operation including all reintubation days. Postoperative intensive care unit (ICU) LOS was defined as total postoperative days in the ICU, including days readmitted to the ICU during hospitalization for the index operation.

Follow-up

Secondary outcome variables were late mortality, late morbidity and echocardiographic findings. AVV function was assessed in echocardiographic reports at discharge and 5, 10 and 15 years after surgery. Regurgitation was registered as a dichotomous variable; either moderate/severe or ≤ mild.

Statistical analysis

Patient and procedural characteristics were summarized as frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Chi-square tests and Fisher's Exact tests were conducted to analyze differences in categorical patient characteristics/outcomes between types of VSD patch (untreated autologous pericardium or treated bovine pericardium). Normality was assessed by the Shapiro-Wilk's test ($p>0.05$). Independent-samples-t-tests and Man-Whitney U tests were run to determine any differences in characteristics and outcome between VSD patch groups for continuous variables that were normally and not normally distributed respectively. There were no outliers according to the boxplots. Homogeneity of variances was assessed by Levene's test for equality of variances. Distributions of the variables for types of VSD patch were assessed. Time to death, reintervention, and mod-

erate/severe AVV regurgitation were estimated using the Kaplan-Meier method. All necessary assumptions were met. Statistical analysis was performed with SPSS for Windows (version 25).

Results

Patients

There were 79 patients eligible for analysis (untreated autologous pericardial VSD patch: 59 (75%), treated bovine pericardial VSD patch: 20 (25%)) (Table 1). Median age at surgery was 3.6 (IQR 2.7-4.4) months and median weight was 4.5 (IQR 3.8-5.1) kg. Forty-six patients were female (58%). Trisomy 21 was present in 72 (91%) patients. Five patients (6%) were on ventilator support prior to operation. Preoperative moderate/severe AVV regurgitation was present in 9 (11%) patients (data complete 82%). Patient and procedural characteristics were comparable in both patch groups. Median follow-up time after surgery was 17.8 (IQR 13.1 – 19.9) years.

Table 1. Patient and Procedural Characteristics (n=79)

Characteristic	Total (n=79)	Untreated Pericardial patch (n=59 (75%))	Treated pericardial patch (n=20 (25%))	P-value
Age at CAVSD repair, months	3.6 (2.7 – 4.4)	3.7 (2.7 – 4.5)	3.3 (2.6 – 3.8)	0.189
Neonate	1 (1.3)	1 (1.7)	0 (0)	-
Weight at surgery, kg	4.5 (3.8 – 5.1)	4.5 (3.8 – 5.0)	4.4 (3.8 – 5.1)	0.981
Female sex	46 (58.2)	33 (55.9)	13 (65.0)	0.477
Preoperative condition				
On ICU	5 (6.3)	5 (8.5)	0 (0)	-
On ventilator support	5 (6.3)	5 (8.5)	0 (0)	-
Moderate or greater AVV regurgitation	9 (11.4)	7 (11.9)	2 (10.0)	1.000
Missing AVV regurgitation	14 (17.7)	9 (15.3)	5 (25.0)	0.328
Genetics				
Trisomy 21	72 (91.1)	54 (91.5)	18 (90.0)	1.000

Values are n (%) or median (interquartile range).
AVV=atrioventricular valve, CAVSD = complete atrioventricular septal defect, ICU = intensive care unit. Treated pericardial patch = bovine pericardium, Dacron or Goretex.

Surgical Technique

Procedural details and outcomes are outlined in Table 2. Second bypass run was used in 10 (13%) patients (residual lesion: 8, low cardiac output syndrome (LCOS): 2). Duct closure (32), clipping of left superior vena cava (1) and coarctation repair (1) were performed as additional procedure in 33 (42%) patients. The zone of apposition was closed in all but 3 patient.

Table 2. Operative and Outcome Data

Variables	Total (n=79)	Untreated Pericardial patch (n=59)	Treated pericardial patch (n=20)	P-value
Second bypass run	10 (12.7)	10 (16.9)	0 (0)	-
Perfusion time, min	119 (110–149)	120 (112-151)	114 (107-153)	0.377
Cross-clamp time, min	83 (76-101)	82 (74–102)	84 (77–102)	0.709
Concomitant procedure[a]	33 (41.8)	26 (44.1)	7 (35.0)	0.477
Condition at discharge				
AV block requiring pacemaker	0 (0)	0 (0)	0 (0)	-
Outcome				
Major adverse events[b]	10 (12.7)	9 (15.3)	1 (5.0)	0.438
Reintervention[c]	8 (10.1)	8 (13.6)	0 (0)	-
VSD[d]	4 (5.1)	4 (6.8)	0 (0)	
LAVV[e]	5 (6.3)	5 (8.5)	0 (0)	
RAVV	1 (1.3)	1 (1.7)	0 (0)	
LVOT	3 (3.8)	3 (5.1)	0 (0)	
Mortality	11 (13.9)	9 (15.3)	2 (10.0)	0.720
In hospital	3 (3.8)	3 (5.1)	0 (0)	0.567
Late	8 (10.1)	6 (10.2)	2 (10.0)	1.000
Days on ventilator	5.0 (3.0 – 9.0)	5.5 (3.3 -9.5)	5.0 (3.0-8.5)	0.446
ICU length of stay, days	7.0 (4.3 – 10.8)	7.0 (5.0 – 11.0)	6.0 (4.0 – 10.0)	0.583
Hospital length of stay, days	13.0 (9.0 – 20.0)	12.5 (9.0 – 18.0)	14.0 (10.0 – 21.0)	0.480

Values are n (%) or median (interquartile range). AV=atrioventricular, ICU=intensive care unit, LAVV=left atrioventricular valve, RAVV=right atrioventricular valve, VSD=ventricular septal defect.
[a] *Included variables are patent ductus closure (32), clipping persistent left superior vena cava (1) and coarctation repair (1).*
[b] *Included cardiac arrest requiring resuscitation, bleeding requiring reoperation, unplanned reoperation prior to discharge and low cardiac output syndrome requiring reoperation.*
[c] *Includes reoperation on LAVV and RAVV and VSD.*
[d] *reduction of VSD patch because of ballooning of patch, causing RAVV stenosis.*
[e] *Includes 1 LAVV replacement.*

Early mortality

Death < 30 days occurred in 2 (3%) patients (both autologous pericardium) due to gastrointestinal bleeding (1) and infant respiratory distress syndrome (1) at 3 and 2 weeks after uncomplicated AVSD repair respectively.

Early reoperations

AV valve reoperations prior to discharge (within 1 month) were performed in 3 patients (for RAVV repair (1) and LAVV repair with residual VSD/ASD closure (2)). Indication for LAVV repair was regurgitation due to dehiscence of initially closed zone of apposition in 1 patient. In the other patient the mechanism of LAVV regurgitation was not mentioned in the surgery report. Other in hospital MAE included cardiac arrest in ICU requiring resuscitation (5), reoperation for bleeding (5) and LCOS (1). MAEs occurred almost exclusively (all but 1) in patients operated before 2000.

Type of patch material was not a risk factor for MAEs (p= 0.438).

Median duration of ventilator support was 5.0 (IQR 3.0-9.0) days. Median ICU LOS was 7.0 (IQR 4.3-10.8) days. Median postoperative hospital LOS was 13.0 (IQR 9.0-20.0) days.

Follow-up

Late mortality

Seven patients (12%) (autologous pericardial patch) died at follow up. Causes were cardiac related (2) (pulmonary hypertension, myocardial infarction in lymphocytic myocarditis) but unrelated to AVSD repair, and non-cardiac related (5) (pneumonia (1) and unknown cause (4)). Two (10%) patients (treated bovine pericardial patch) died of subarachnoid bleeding (1) and unknown cause (1)). Patch material was not a risk factor for late death (p =1.0).

Late reoperations

Reoperations > 1 month (all autologous pericardium) were performed for LAVV regurgitation (3 (repair: 2 (after 3 and 4 months), replacement: 1 (after 17 years)), LVOT obstruction (3), residual VSD (1), patch aneurysm (1), pacemaker implantation (1). All patients who underwent LAVV reoperation have undergone closure of zone of apposition at initial AVSD repair. Mechanism of LAVV regurgitation was dehiscence of initially closed zone of apposition (1) and leaflet malcoaptation (1), and additional cleft in superior leaflet that was initially missed (1). Patch material was not a risk factor for reoperation (p= 0.199). Reoperations (all but 1) were performed in patients who underwent AVSD repair before 2000 (Figure 1).

In one patient we had the opportunity to study histology of autologous pericardial VSD patch, 2.5 years after implantation. This patient needed reoperation for patch aneurysm causing RAVV stenosis. The pericardial patch ballooning was already visible on intraoperative echo immediately after AVSD repair but was not addressed. Excessive patch was resected at reoperation and sent for pathology. Histology revealed viable smooth muscle cells (immunohistochemistry), collagen and newly formed elastin structures in the matrix (Figure 2).

The Kaplan-Meijer curve in Figure 3 shows the time to reintervention on LAVV. Similar to the survival curve, log rank test showed no difference in time to LAVV reintervention between the two treatment groups (p=0.199).

Figure 1: Overview of surgeries performed before and after 2000.

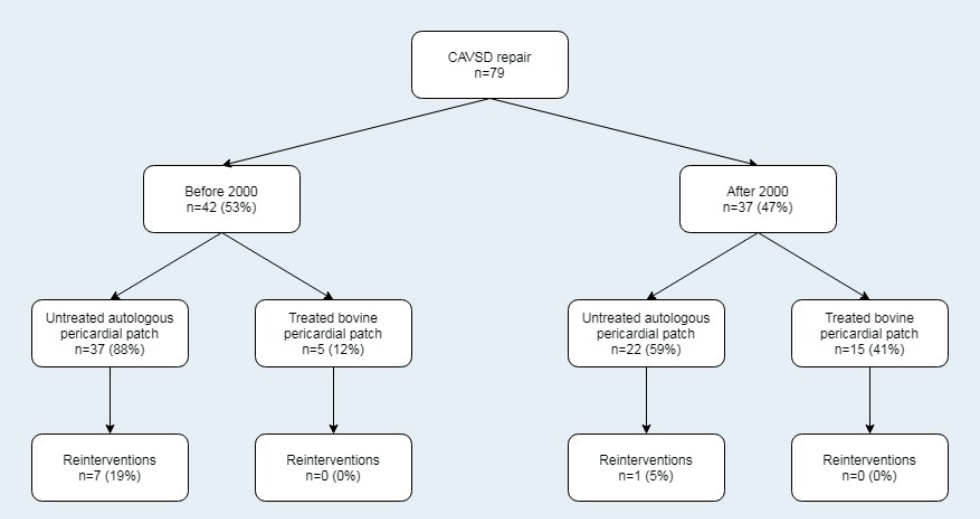


Figure 2: Histology image of an untreated pericardial patch 2.5 years after implantation.
Hemotoxyline-eosin staining. Cell nuclei are stained blue. Extracellular matrix and cytoplasm are stained pink.

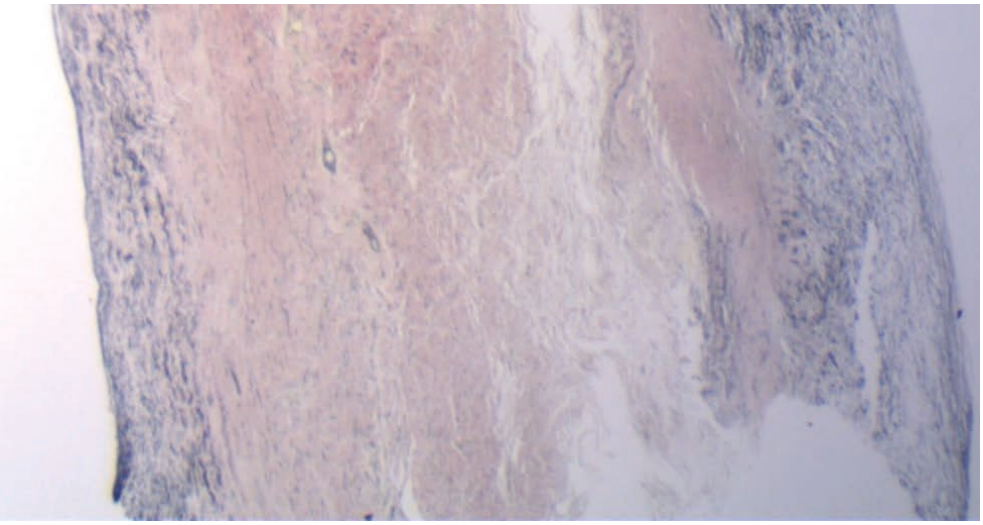
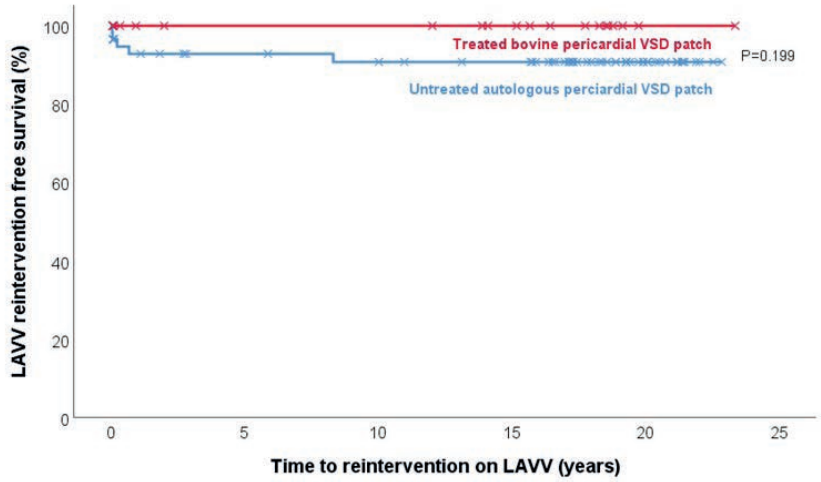


Figure 3: Kaplan-Meier survival estimation for time to reintervention on LAVV based on VSD patch (untreated autologous pericardium versus treated bovine pericardium).



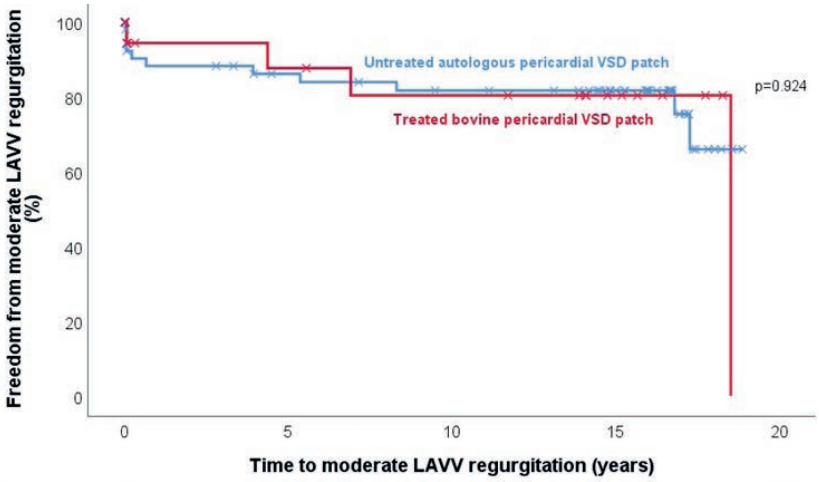
Numbers at risk	0	5	10	15	20	25
Untreated autologous pericardial patch	59	46	44	41	14	0
Treated bovine pericardial patch	20	14	14	11	1	0

Abbreviations: LAVV=left atrioventricular valve.

Echocardiographic follow-up

Expert echo assessment was performed up to 15 years after surgery. Moderate LAVV regurgitation at last follow-up was present in 15 (19%) patients with no difference between both patch groups (untreated autologous pericardium: 11 (19%), treated bovine pericardium: 4 (20%)). There were no patients with severe LAVV regurgitation. Time related incidence of moderate LAVV regurgitation was equal in both groups (p=0.924) (Figure 4).

Figure 4: Kaplan-Meier survival estimation for time to moderate LAVV regurgitation based on VSD patch (untreated autologous pericardium versus treated bovine pericardium).



Numbers at risk	0	5	10	15	20
Untreated autologous pericardial patch	59	39	35	26	0
Treated bovine pericardial patch	20	13	11	6	0

Abbreviations: LAVV= left atrioventricular valve.

Comment

This study reports on the outcomes of CAVSD double patch repair comparing untreated autologous pericardium with other patch material for VSD closure. Our report demonstrates that untreated autologous pericardium is as safe as treated bovine pericardial patch material (xenopericardium or synthetic patch). There was no significant difference in mortality, reintervention or late AVV function between either patch.

Reoperations for LAVV regurgitation were few and limited to the pericardium group although difference with the other patch group was not significant. LAVV reoperation rate (8.5%) did not exceed the incidence reported in literature (11.4%) (10).

Interestingly, all reoperations except 1 were performed on patients operated (AVSD repair) before 2000 suggesting a possible learning effect. Autologous pericardium is less user-friendly than other patch material because it is sticky and lacks stiffness. Moreover, it has to be properly sized to prevent aneurysmal dilatation. A single case of a patient with pericardial patch ballooning made us decide to avoid use of a patch larger than the size of the ventricular defect itself. It may take the surgeon some time to learn how to handle untreated pericardial tissue. We continued its use nevertheless encouraged by the demonstrated viability of the patch. This viability may potentially allow the patch to adapt to growth and to the complex spatial dynamics required for AVV function. Currently, the patch is fixed on the drapes with 2 mosquito clamps on each corner of the patch. After the first few stitches 6/0 Prolene, the patch is advanced into the heart

to complete the running suture on the septum. The AV valves are fixed on the free edge of the patch with separate U-stitches 6/0 Prolene which are stitched through the second pericardial patch for the ASD before tying. Long term echo however could not confirm any difference in LAVV regurgitation between both groups. With respect to reintervention for LVOTO, both groups were not statistically different.
Operating AVSD patients for LAVV regurgitation can be technically challenging. As our data supports, surgeons should be aware of the mechanism of LAVV regurgitation being possibly related to the cleft that was left open at initial repair or that re-opened due to suture dehiscence. Besides, use of Teflon or other synthetic patch material for septal defect closure can cause calcification of the septum or AV valve annulus. Calcification of LAVV was not seen at reoperation in patients who underwent septal defect closure with two untreated autologous pericardial patches. Using fresh pericardium may prevent calcification and may leave the valve better accessible for future surgery.
Since all reoperations for LAVV regurgitation were performed in patients operated on before 2000, it could be valuable to separately analyze outcome of patients operated on after 2000 to exclude a possible effect of learning.

The teams from the Royal Children's Hospital in Melbourne and Paediatric Cardiac Centers in Brisbane recently reported their long-term outcomes using the double patch technique for the repair of CAVSD. Xie et al. (n = 138) reported a probability of freedom from moderate or worse LAVVR of 68.7% at 8 years follow up (11). Bell et al. (n=188) reported a probability of freedom from moderate or worse LAVV regurgitation of 85% at median follow-up of 10.8 years (12).
Reported LAVV regurgitation rates in our study are similar or lower compared to previously reported findings, but the median follow-up in our study is much longer (17.8 years).

Limitations

This study is limited by its retrospective and monocentric nature with the inherent problems of missing and incomplete data especially in patients with Down syndrome who were relatively difficult to follow up. Furthermore, the control group was relatively small.

Conclusion

In AVSD, the VSD can safely be closed with untreated autologous pericardium. We found no difference in LAVV regurgitation or need for reoperation when compared to other patch material.

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MID-TERM OUTCOMES IN UNBALANCED COMPLETE ATRIOVENTRICULAR SEPTAL DEFECT: ROLE OF BIVENTRICULAR CONVERSION FROM SINGLE-VENTRICLE PALLIATION

9

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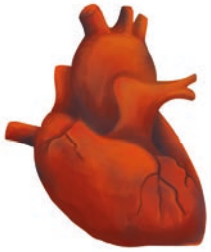


Abstract

Objectives:
Management strategy for unbalanced common atrioventricular defects (UCAVSD) includes single ventricle (SV) palliation and primary or staged biventricular (BiV) repair. More recently biventricular conversion (BiVC) from SV palliation and staged BiV recruitment (BiVR) has also been advocated. This study assesses midterm outcomes in UCAVSD grouped according to management strategy.

Methods:
Consecutive UCAVSD patients undergoing surgery at a tertiary care center from 01/2000-02/2016 with IRB approval. Index surgery is defined as first palliation procedure for SV group, biventricular repair for BiV group, and conversion or first surgery for recruitment for BiVC/R group. Kaplan Meier and Cox Regression was used for time to event analysis of mortality/transplant and unplanned reinterventions (RI) that occurred after index surgery.

Results:
There were 212 subjects; 82 (38.7%) SV; 67 (31.6%) BiV, and 63 (29.7%) BiVC/R group respectively; 50 subjects had undergone successful BiVC. There were 93 (43.9%) males, 51 (24%) with Down syndrome, and 101 (48%) with heterotaxy. For the entire cohort there were 40 (18.9%) deaths, 110 (51.9%) reinterventions, 82 (38.7%) surgical RI, 70 (33%) catheter RI, with some subjects having more than one RI. Median length of follow-up was 35 (range 1-192) months. The BiVC/R group had a similar transplant-free survival benefit as the primary BiV repair group when compared to the SV group. The BiV repair group had a lower need for catheter based reinterventions compared to the SV and BiVC/R group.

Conclusions:
BiVC/R from a SV pathway can be achieved with low mortality and morbidity in UCAVSD.

Abbreviations

AV	Atrioventricular
AVV	Atrioventricular Valve
BiV	Biventricular
BiVC	Biventricular Conversion From Single Ventricle Palliation
BiVC/R	Biventricular Conversion Or Recruitment
BiVR	Biventricular Recruitment
LV	Left Ventricle
LVEDV	Left Ventricular End Diastolic Volume
RI	Reintervention
RV	Right Ventricle
SV	Single Ventricle Palliation
UCAVSD	Unbalanced Completed Atrio Ventricular Septal Defect

Introduction

Unbalanced complete atrioventricular septal defects (CASVSDs) represent 10–15% of all atrioventricular septal defects (1, 2). This defect is characterized by underdevelopment of one of the ventricles and varying degrees of malalignment of the common atrioventricular valve (AVV) over the hypoplastic ventricle and associated hypoplasia of the outflow valve related to decreased flow (1). Management strategy includes single-ventricle (SV) palliation and primary or staged biventricular (BiV) repair (3–5). More recently, BiV conversion (BiVC) from SV palliation has been advocated, particularly in patients with trisomy 21 and heterotaxy (6, 7) who tolerate SV palliation poorly (8). Staged BiV recruitment (BiVR) has also been considered (9). The objective of this study was to assess mid-term outcomes in patients in a tertiary care centre with unbalanced CASVSDs grouped according to management strategy.

Material and Methods

Patient population

A review of consecutive patients with unbalanced CASVSDs who were operated on at a tertiary care centre between January 2000 and February 2016 was performed with institutional review board approval and waiver of consent. Patients were divided into 3 groups: (i) those who had SV palliation; (ii) those who underwent primary or staged BiV repair and (iii) those who underwent BiVC from SV palliation or planned BiVR. Demographic, clinical, imaging and follow-up data were collected by reviewing clinical charts.

Definitions

Unbalanced CASVSD: was defined as a CASVSD with an AVV override of >60% over either ventricle (or) the presence of hypoplastic, non-apex-forming ventricles or, in the case of a right dominant CASVSD, a left ventricle with indexed volumes at least 2 SDs smaller than normal and those who were deemed unbalanced and underwent SV palliation at an outside institution.

Types of repairs: SV palliation was defined as the traditional SV palliation towards a Fontan circulation. 'Primary BiV repair' was BiV repair as the primary surgery. 'Staged BiV repair' comprised of coarctation repair, aortopulmonary shunt, right ventricle to pulmonary artery shunt, pulmonary artery band or total repair of anomalous pulmonary venous return performed in the neonatal period, followed by BiV repair of unbalanced CASVSDs during infancy. 'BiV conversion' was defined as conversion to BiV circulation from prior SV palliation, which may occur at any of the 3 stages (following Stage I, superior cavopulmonary anastamosis or completion Fontan) of palliation. 'BiV recruitment' included modification of stages of palliation with a plan to recruit to a final BiV circulation; for example, restriction of the atrial septum and septation of the AVV at the time of the Stage I or superior cavopulmonary anastamosis. The techniques of BiVC and BiVR have been described previously (6, 7, 9, 10).

Index surgery: was defined as the first palliation procedure for the SV group; BiV repair for the BiV group; and BiVC from SV palliation or first surgery for BiVR for the BiVC/BiVR group.

Mortality: was defined as death any time after the index surgery.
Reintervention: included any unplanned reintervention (surgical or catheter based) that occurred after the index surgery. Planned staged procedures were not considered reinterventions.
Follow-up: All follow-up examinations were measured from the date of the index procedure. All index procedures occurred at the tertiary care centre; however, initial palliation for the BiVC/ BiVR group may have occurred at an outside institution.
Outcomes: The outcomes of interest included (i) mortality/ transplant, (ii) any reintervention, (iii) surgical reintervention and (iv) catheter reintervention.
Predictors: The primary predictor was the type of surgery (SV, BiV or BiVC/BiVR). When comparing the outcomes with the type of surgical procedure, the following variables were considered: age, gender, presence of Down syndrome, presence of heterotaxy, presence of pulmonary vein disease, presence of additional cardiac anomalies (e.g. double-outlet right ventricle, transposition of the great arteries, superior inferior venticles, or total anomalous pulmonary venous return) and dominant ventricle (right versus left).

Statistical analysis

Patient and procedural characteristics were summarized as frequencies and percentages for categorical variables and medians and ranges for continuous variables. Because we were interested in time to event and length of follow-up, which differed substantially across patients, we used the Cox regression, where relationships between risk factors and outcomes are estimated as hazard ratios, irrespective of whether data are prospective or retrospective. The times to death/transplant and to the first postdischarge reintervention were estimated using the Kaplan–Meier method with the BiV group as the reference. Cox proportional hazard models were used to evaluate the relationship between the repair groups and the outcomes of death/transplant and unplanned reinterventions after the index surgery, adjusting for clinically relevant predictor variables, and presented as hazard ratios with 95% confidence intervals. Analyses comparing the 3 management strategies were adjusted for all patient characteristics in which the groups differed (Table 1). Therefore, the hazard ratios for SV and BiVR/BiVC versus BiV can be interpreted as the relative risk between these groups, with all other factors remaining constant. Additional subgroup analysis was performed comparing the BiV to the BiVC group. Statistical analyses were performed with IBM SPSS Statistics for Windows, version 23.

Results

There were 212 patients: 82 (38.7%) in the SV group, 67 (31.6%) in the BiV group and 63 (29.7%) in the BiVC/BiVR group. Fifty patients had undergone successful BiVC. There were 93 (43.9%) boys. Fifty-one patients (24%) had Down syndrome; 101 (48%) had heterotaxy; 51 (24%) had pulmonary vein disease; 57 (26.9%) had additional complex cardiac anomalies; and 148 (69.8%) had right dominance. In the entire cohort, 40 (18.9%) patients died; 110 (51.9%) had reinterventions; 82 (38.7%) had surgical reinterventions; 70 (33%) had catheter reinterventions; some patients had more than 1 reintervention (Figure 1). The median length of follow-up was 35 months (range 1–192 months). The baseline characteristics and the outcomes of the 3 groups are shown in Table 1.

Table 1: Patient characteristics for the three management strategies for unbalanced atrioventricular septal defect

	Single Ventricle Palliation	Biventricular Repair (primary/staged)	Biventricular Recruitment/ Conversion[a]	p value (3 group comparison)[b]
N (%)	82 (38.7%)	67 (31.6%)	63 (29.7%)	
Age				**<0.001**
Neonates	56 (68.3%)	6 (9.0%)	2 (3.2%)	
Infants	23 (28.0%)	44 (65.7%)	17 (27.9%)	
Children	3 (3.7%)	17 (25.4%)	44 (69.8%)	
Gender (M)	39 (47.6%)	24 (35.8%)	30 (47.6%)	0.276
Tri 21	4 (4.9%)	29 (43.3%)	18 (28.6%)	**<0.001**
HTX	57 (69.5%)	12 (17.9%)	32 (50.8%)	**<0.001**
Pulmonary Vein Disease	26 (31.7%)	11 (16.4%)	14 (22.2%)	**<0.001**
R Dominant	71 (86.6%)	38 (56.7%)	39 (61.9%)	**<0.001**
Associated Cardiac Anomaly	36 (43.9%)	4 (6.0%)	17 (27.0%)	**<0.001**
Mortality/transplant	26 (31.7%)	7 (10.4 %)	7 (11.1%)	**0.001**
Any RI	50 (61.0%)	27 (40.3%)	35(52.4%)	**0.042**
Total number[c]	149	48	95	
Surgical RI	37 (45.1%)	23(34.3%)	22 (34.9%)	0.310
Total number[c]	60	30	26	
Catheter RI	38 (46.3%)	9 (13.4%)	23(36.5%)	**<0.001**
Total number[c]	88	18	61	

Associated cardiac anomalies include double-outlet right ventricle, congenitally corrected and dextro-transposition of the great arteries and superior–inferior ventricles. The index surgery for (i) single ventricle palliation was the Norwood/pulmonary artery banding/BTS/BDG, whichever was first; (ii) primary BiV repair was BiV repair; (iii) staged BiV repair was BiV repair; (iv) BiV recruitment was the first recruitment procedure and (v) BiV conversion was the surgical procedure where SV circulation was converted to BiV circulation.

SV: single ventricle; BiV: biventricular; BDG: bidirectional Glenn; BTS: Blalock–Taussig shunt.

[a] *There were 8 patients with balanced atrioventricular septal defect who underwent SV to BiV conversion, all of them had heterotaxy. These patients were deemed unbalanced at the outside institution that performed the SV palliation based either on the size of the ventricle or the abnormality of the atrioventricular valve.*

[b] *P-values were derived using the X2 test for patient characteristics and the log-rank test for outcomes. Significant values appear in bold.*

[c] *Some patients had more than 1 reintervention. Only unplanned reinterventions after the index procedure were included. The BDG and Fontan procedures were not included in the reintervention for the SV group.*

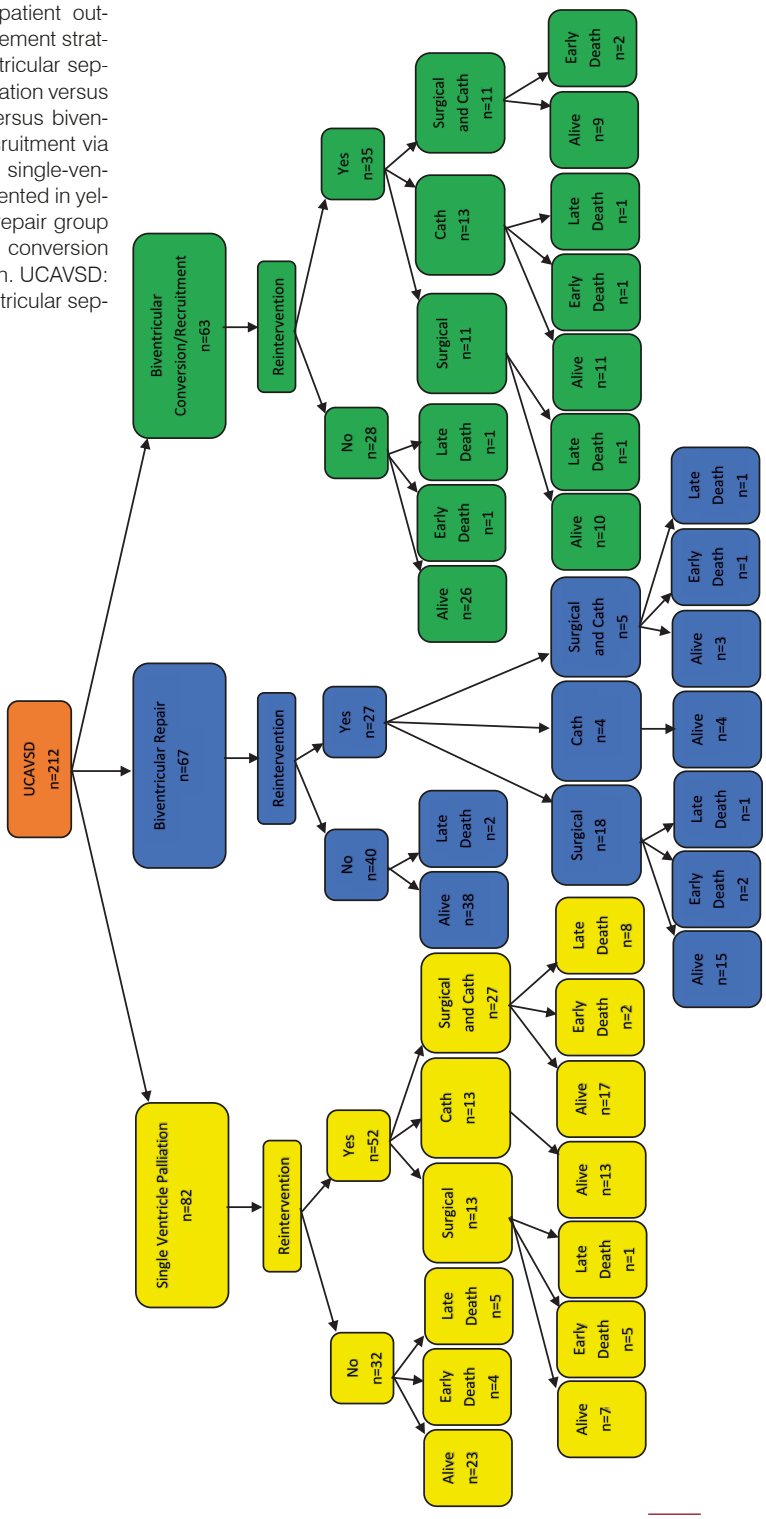


Figure 1: Flow diagram of patient outcomes based on the 3 management strategies for unbalanced atrioventricular septal defect: Single-ventricle palliation versus primary biventricular repair, versus biventricular conversion from or recruitment via single ventricle palliation. The single-ventricle palliation group is represented in yellow, the primary biventricular repair group in teal and the biventricular conversion and recruitment group in green. UCAVSD: unbalanced complete atrioventricular septal defects; cath: catheter.

On univariable analysis, age, trisomy 21, heterotaxy, pulmonary vein disease and complex cardiac anomalies were significant. The findings from the multivariable analysis for death/ transplant and reinterventions are shown in Tables 2–5. Table 6 outlines the unplanned reinterventions by groups. On multivariable modelling, the SV and BiVC groups had a higher risk for catheter-based reinterventions. There were no patients in the BiVC group who required takedown to a palliated pathway. The BiV repair group needed fewer catheter-based reinterventions compared with the SV and BiVC/BiVR groups. The BiVC/BiVR group had a survival benefit similar to that of the primary BiV repair group when compared to the SV group. Kaplan–Meier (Figure 2) estimates demonstrated a survival advantage in the BiV and BiVC/BiVR groups (log-rank P = 0.005).

On adjusted subgroup analysis, the BiVC group was remarkably similar to the BiV repair group, except for catheter-based interventions (hazard ratio 3.1; 95% confidence interval 1.3–7.3; P < 0.01). The log-rank P-value for the Kaplan–Meier estimates between the 2 groups for death/ transplant was 0.5; for any reintervention 0.2; for surgical reintervention 0.7 and for catheter-based reintervention 0.002.

The numbers were too small to make a meaningful statistical comparison between right (R) dominant and left (L) dominant CASVSD in the BiVC group; therefore, descriptive statistics are provided. In our cohort, for patients with R dominant CASVSD who underwent BiVC based on preoperative 2D echocardiogram, the median indexed left ventricular (LV) end-diastolic volume [LVEDVi = LVEDV/body surface area (BSA)1.3] was 32 ml/m2 [interquartile range (IQR) = 21 ml/m2 , 40 ml/m2]. The corresponding echocardiographic z-scores for LVEDV were as follows: median: -3.15 IQR: -3.81 to -2.44. On magnetic resonance imaging (MRI) in this cohort, the LVEDVi was 36 ml/m2 (IQR = 25–47 ml/m2). There are no z-scores currently available for LVEDV from MRI scans. On echocardiograms, the common AVV override to the right was 67% (IQR: 60-69%) and on MRI scans, it was 75% (IQR 67–82%). Rates of reintervention were as follows: R dominant CASVSD: 18 of 29 (62%) vs L dominant CASVSD: 10 of 21 (48%). Similarly, mortality rates following BiVC were as follows: R dominant CASVSD: 2/29 (7%) vs L dominant CASVSD: 2 of 21 (9.5%).

If one looks more closely at the BiVC/BiVR group, there were 7 deaths, with 4 in the BiVC group and 3 in the BiVR group. On comparing the characteristics of those who survived compared with those who died in the BiVC group, the survivors had larger LVEDVi with a median of 32 ml/m2 in the R dominant CASVSD with a median LVEDV z-score of -3.1 vs 19 ml/m2 and -3.2 in the non-survivors. In the L dominant group, severe right ventricular hypoplasia was present in 38% of survivors vs 100% of non-survivors. When we looked at the BiV recruitment group, we found no difference between survivors and nonsurvivors in the R dominant CASVSD with a median LVEDVi of 28 ml/m2.

On follow-up imaging, patients who had BiVC for R dominant CASVSD demonstrated a significant increase in LVEDVi (Supplementary Material, Figure S1). On comparing LVEDVi and LVEDV z-scores, the median LVEDVi on echocardiographic scans increased from 32 ml/m2 to 72 ml/m2. The LVEDV z-score increased from a median of -3.15 to +0.42. The LVEDVi on MRI increased from a median of 31 to 61 ml/m2. These changes were significant on paired com-

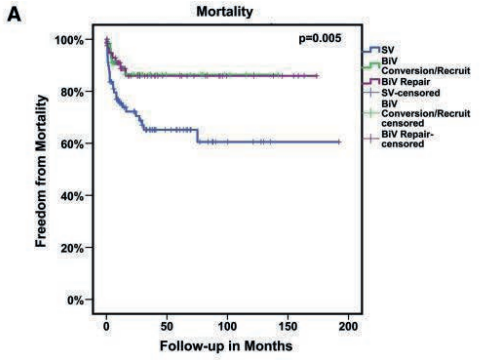
parison (Wilcoxon signed-rank test) with P-values of 0.025, 0.028 and 0.012, respectively. Of the 26 patients with heterotaxy in the BiVC group, 15 (58%) required reintervention, and there were 2 (8%) deaths, both in the reintervention group. Of the 6 patients with heterotaxy in the BiV recruit group, 5 (83%) required reintervention, with 1 (17%) death in the reintervention group. Of the 57 patients with heterotaxy in the SV group, 33 (58%) required reintervention. There were 13 (23%) deaths, of which 9 (69%) were in the reintervention group. Of the 12 heterotaxy patients in the BiV repair group, 7 (58%) required reintervention. There were 4 deaths, with 3 (75%) of the deaths occurring in the reintervention group. The majority (75%) of deaths in the heterotaxy group had some form of unplanned reintervention, likely representing greater disease complexity (Supplementary Material, Figure S2).

Table 2: Cox regression for outcome mortality/transplant in unbalanced atrio ventricular septal defect

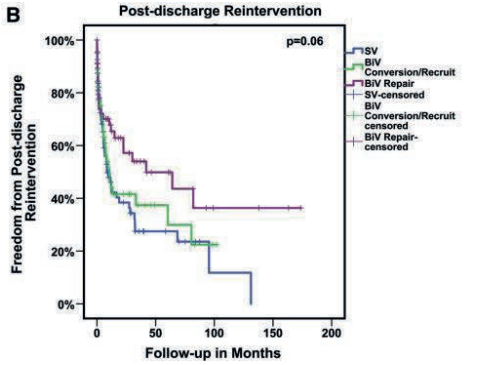
	Mortality/transplant		
	Hazard Ratio	**95% CI**	**p value**
Repair Type			
SV	1.7	0.6, 5.3	0.3
BIVR/C	1.3	0.4, 4.0	0.7
BIV	ref	-	-
Pulmonary vein disease(Y)	1.5	0.7, 3.2	0.3
R Dominant AVSD (Y)	1.3	0.5, 3.2	0.6
Other Cardiac Anomaly (Y)	1.4	0.6, 3.0	0.4
NCCA			
Trisomy 21	1.2	0.4, 3.2	0.8
Heterotaxy	0.5	0.2, 1.2	0.1
Gender	0.8	0.4, 1.5	0.4
Age			
Neonates	3.5	0.9, 12.8	0.1
Infants	1.3	0.4, 4.3	0.6
Children	ref	-	

AVSD-atrioventricular septal defect; CI-confidence interval; BIV-primary/staged biventricular repair; BIVR/C-biventricular recruitment or single ventricle to biventricular conversion; SV-single ventricle palliation; Y-yes.

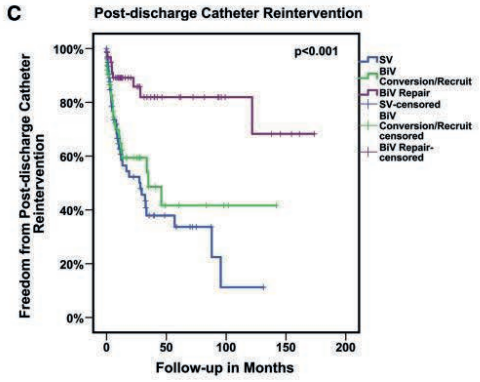
Figure 2: Kaplan Meier Estimates of transplant free survival and unplanned reinterventions for the 3 management strategies for unbalanced atrioventricular septal defect, with the single-ventricle palliation represented by the blue line, the primary biventricular group represented by the purple line and the biventricular conversion group represented by the green line. The numbers at risk for each of the 3 groups is provided as a table below each graph.



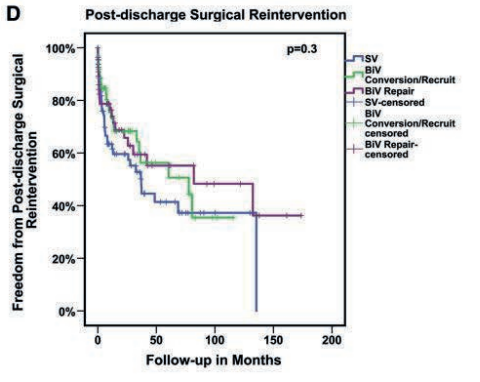
	0m	12m	24m	36m	48m	60m	72m	84m	96m	108m	120m
SV	82	49	42	30	24	20	14	10	6	5	5
BiV	67	37	28	22	17	17	14	11	8	7	7
BiVR/BiVC	63	41	29	19	14	11	9	5	5	3	2



	0m	12m	24m	36m	48m	60m	72m	84m	96m	108m	120m
SV	82	24	19	10	8	7	5	3	1	1	1
BiV	67	27	20	15	10	10	7	5	4	3	3
BiVR/BiVC	63	19	13	8	6	5	4	2	0	0	0



	0m	12m	24m	36m	48m	60m	72m	84m	96m	108m	120m
SV	82	29	24	12	10	7	5	4	1	1	1
BiV	67	33	26	19	14	14	12	10	7	6	6
BiVR/BiVC	63	25	16	8	6	5	4	3	3	1	1



	0m	12m	24m	36m	48m	60m	72m	84m	96m	108m	120m
SV	82	34	27	20	14	11	7	5	3	2	2
BiV	67	30	22	16	11	11	9	7	6	5	5
BiVR/BiVC	63	31	22	15	11	10	8	3	3	1	0

Table 3: Cox regression for outcomes of any reintervention after an index surgery in unbalanced complete atrioventricular septal defect

Any Reintervention			
	Hazard Ratio	95% CI	p value
Repair Type			
SV	1.0	0.5, 1.9	0.9
BiVR/BiVC	1.9	1.1, 3.4	**0.02**
BiV	ref	-	-
Pulmonary vein disease(Y)	1.3	0.8, 2.2	0.2
R Dominant AVSD (Y)	1.1	0.7, 1.8	0.7
Other Cardiac Anomaly (Y)	1.0	0.6, 1.5	0.8
NCCA			
Trisomy 21	0.6	0.3, 1.1	0.1
Heterotaxy	1.1	0.6, 2.0	0.7
Gender	0.9	0.6, 1.4	0.7
Age			
Neonates	2.6	1.3, 5.4	**0.008**
Infants	2.7	1.5, 4.8	**0.001**
Children	ref	-	-

AVSD: atrioventricular septal defect; CI: confidence interval; BiV: primary/staged biventricular repair; BiVR/BiVC: biventricular recruitment or single ventricle to biventricular conversion; NCCA: non-cardiac congenital abnormality; SV: single-ventricle palliation; Y: yes.
Significant P-values appear in bold.

Table 4: Cox regression for outcomes of surgical reintervention after the index surgery in complete unbalanced complete atrioventricular septal defect

Surgical Reintervention			
	Hazard Ratio	95% CI	p value
Repair Type			
SV	0.9	0.4, 1.8	0.7
BiVR/BiVC	1.3	0.7, 2.4	0.4
BiV	ref	-	-
Pulmonary vein disease(Y)	1.3	0.8, 2.4	0.3
R Dominant AVSD (Y)	1.0	0.5, 1.8	0.9
Other Cardiac Anomaly (Y)	0.9	0.5, 1.5	0.6
NCCA			
Trisomy 21	0.4	0.2, 0.8	**0.01**
Heterotaxy	1.0	0.5, 1.9	0.9
Gender	1.0	0.7, 1.7	0.8
Age			
Neonates	2.9	1.3, 6.7	**0.01**
Infants	3.9	2.0, 7.9	**<0.001**
Children	ref	-	-

AVSD: atrioventricular septal defect; CI: confidence interval; BiV: primary/staged biventricular repair; BiVR/BiVC: biventricular recruitment or single ventricle to biventricular conversion; NCCA: non-cardiac congenital abnormality; SV: single-ventricle palliation; Y: yes.
Significant P-values appear in bold.

Table 5: Cox regression for outcomes of catheter reintervention after the index surgery in unbalanced complete atrioventricular septal defect

	Catheter Reintervention		
	Hazard Ratio	**95% CI**	**p value**
Repair Type			
SV	2.9	1.1, 7.5	**0.03**
BiVR/BiVC	3.5	1.5, 8.0	**0.004**
BiV	ref	-	-
Pulmonary vein disease(Y)	2.1	1.2, 3.7	**0.01**
R Dominant AVSD (Y)	1.6	0.8, 3.2	0.1
Other Cardiac Anomaly (Y)	1.0	0.6, 1.8	0.9
NCCA			
Trisomy 21	1.0	0.4, 2.4	0.9
Heterotaxy	0.9	0.5, 1.9	0.8
Gender	0.7	0.4, 1.1	0.09
Age			
Neonates	1.3	0.5, 3.2	0.6
Infants	1.1	0.5, 2.4	0.7
Children	ref	-	-

AVSD: atrioventricular septal defect; CI: confidence interval; BiV: primary/staged biventricular repair; BiVR/BiVC: biventricular recruitment or single ventricle to biventricular conversion; NCCA: non-cardiac congenital abnormality; SV: single-ventricle palliation; Y: yes.
Significant P-values appear in bold.

Table 6: Types of reinterventions by management strategy in unbalanced complete atrioventricular septal defect: (i) single-ventricle palliation; (ii) primary biventricular repair; (iii) staged biventricular repair; (iv) biventricular conversion from single-ventricle palliation and (v) biventricular recruitment by modification of stages of single-ventricle palliation in preparation for future biventricular circulation

UCAVSD - single Ventricle Palliation: unplanned Reinterventions (149 in 50 subjects)			
Surgical reinterventions (n=60 in 37 subjects)		**Cath reinterventions (n=88 in 38 subjects)**	
AVV plasty/AVV replacement	12	APC coiling for pulmonary hemorrhage	1
Arch revision	4	Azygos Vein occlusion, VVC coil	4
Atrial septectomy	1	Baffle leak device closure	6
Additional Shunt insertion	7	BD arch	4
Epicardial pacemaker	3	BD /Stent BDG/Fontan anastomosis	4
Fontan Revision	2	BD/stent BTS/Sano	5
Main PA band/band tightening	6	BD/Stent Fontan fenestration	5
Orthotopic Heart Transplant	1	BD/stent pulmonary arteries	21
PA plasty	5	BD/stent of pulmonary veins	34
Pulmonary vein stenosis repair	9	BD/stent SVC or innominate	4
Revision /Conversion Sano/BTS	4		
Shunt/BDG/PA thrombectomy	3		
TD BDG to shunt/TD Fontan	3		
Some subjects had more than one surgical, cath or both reinterventions. Routine APC/VVC coiling at the time of pre-BDG or pre-Fontan catheterizations not listed. Uncomplicated BDG or Fontan not included as reintervention.			
UCAVSD - primary biventricular repair: unplanned reinterventions (n=25 in 15 subjects)			
Surgical reinterventions (n=17 in 14 subjects)		Cath reinterventions (n= 8 in 5 subjects)	
AVV plasty/AVV replacement	10	ASD dilation/stent	2
Epicardial pacemaker	2	BD AVV	6
Sub Aortic stenosis resection	1		
Konno/MVR	1		
Closure residual ASD/VSD	1		
CoA repair	1		
PA translocation for coronary compression	1		
Some subjects had more than one surgical or cath or both reinterventions.			
UCAVSD - SV to BiV Conversion: unplanned reinterventions (n=76 in 28 subjects)			
Surgical reinterventions (n=29 in 17 subjects)		Cath reinterventions (n= 49 in 19 subjects)	
Arch revision	1	BD arch	1
AVV plasty/AVV replacement*	17	BD/ Stent ASD	4
Epicardial pacemaker	3	BD AVV	2
Konno	1	BD/stent PA's, RV-PA conduit	10
Residual ASD/VSD	1	BD/stent of pulmonary veins	3
Sub Aortic stenosis resection	5	BD SVC/innominate vein	21
SVC augmentation	1	Left main coronary artery stent	1
		Residual Right-Left Shunt closure	2
		Residual VSD closure	1

		Transvenous pacemaker	1
		Trans catheter PVR	3
Some subjects had more than one surgical or cath or both reinterventions. Only interventions following Biventricular conversion included.			
UCAVSD - staged biventricular repair: unplanned reinterventions (n=23 in 12 subjects)			
Surgical reinterventions (n=13 in 9 subjects)		Cath reinterventions (n= 10 in 4 subjects)	
AVV plasty/AVV replacement	9	BD/stent PA's	3
Sub aortic stenosis resection	4	ASD dilation/stent	1
		BD/stent of pulmonary veins	3
		SVC BD	1
		BD AVV	2
Operations prior to staged biventricular repair included PA band, BTS shunt, and/or coarctation repair. Some subjects had more than one surgical or cath or both reinterventions. Only interventions following biventricular repair included			
UCAVSD - biventricular recruitment: unplanned reinterventions (n=19 in 7 subjects)			
Surgical reinterventions (n=7 in 5 subjects)		Cath reinterventions (n= 12 in 4 subjects)	
AVV plasty/AVV replacement	3	Aortic root thrombus TPA	1
Cryo Maze	1	ASD dilation/stent	3
Epicardial pacemaker	2	BD/stent of BTS/central shunt	2
VAD	1	BD innominate vein	1
		BD/stent PA's, RVPA conduit	1
		Radiofrequency ablation	4
Some subjects had more than one surgical or cath or both reinterventions. Only interventions following Biventricular recruitment included			

Abbreviations: APC: aortopulmonary collaterals; ASD: atrial septal defect; AVV: atrioventricular valve; BD: balloon dilation; BDG: bidirectional Glenn; BTS: Blalock–Taussig shunt; PA: pulmonary artery; PVR: pulmonary valve replacement; RVPA: right ventricle to pulmonary artery; SVC: superior vena cava; TD: takedown; TPA: tissue plasminogen activator; UCAVSD: unbalanced complete atrioventricular septal defect; VAD: ventricular assist device; VSD: ventricular septal defect; VVC: venovenous collaterals.
** Melody valve in mitral position in 3 patients. Planned BD of melody valve not included in reinterventions.*

Discussion

This study represents our experience with the management of unbalanced CASVSDs. Our institutional preference is primary BiV repair. If this is not feasible, every attempt is made towards BiVR or BiVC. We have been able to demonstrate a survival benefit in the BiV repair and the BiVC/BiVR groups compared with those receiving SV palliation, albeit at the cost of more reinterventions, particularly catheter-based interventions in the BiVC/BiVR group compared with the primary BiV repair group. Based on ventricular dominance, in the BiVC/BiVR group, the common reinterventions to anticipate for the R dominant CASVSD are AVV reintervention, followed by reintervention on the LV outflow tract. For L dominant CASVSD, the likely reinterventions would be AVV reinterventions, followed by right ventricular outflow tract reinterventions. The goal of achieving a BiV circulation is to mitigate the short- and long-term adverse effects of non-pulsatile

flow in the pulmonary circulation associated with SV palliation. Not surprisingly, SV palliation had the highest mortality/transplant rate and the highest rate of reinterventions among the 3 groups. BiVC for unbalanced CASVSDs is still an evolving field with limited data. Creation of an adequate inflow, particularly during infancy, may be the single most important factor that promotes growth of the AVV and ventricle (6, 7, 9–13). Foker et al. demonstrated that increasing atrioventricular flow could induce growth not only of the AVV but also of the associated ventricle (12). A staged approach is often required to reach the appropriate end-point. The authors reported an 87% mid-term survival rate, although about a quarter of the patients did require subsequent intervention on the AVV (13).

Children with Down syndrome are a high-risk group in whom establishing a BiV circulation primarily or by recruitment/conversion from SV physiology may be beneficial (8, 14). As demonstrated in this study, only 4 (8%) of the 51 patients with trisomy 21 underwent SV palliation, 29 (57%) underwent primary BiV repair and 18 (35%) underwent BiVR or BiVC. Recently, a greater proportion of children with heterotaxy are being managed with BiV repair/recruitment or conversion at our institution (Supplementary Material, Figure S2). As depicted in Table 1, the highest distribution of heterotaxy (69.5%) was in the SV group with a mortality/transplant rate of 32%, followed by the BiVC recruitment group (51% heterotaxy) with a mortality rate of 11%. We believe that SV circulation is tolerated poorly not only in patients with trisomy 21 but also in those with heterotaxy. It has been our institutional practice to attempt a BiV repair for both of these groups if feasible.

Deciding how to manage this complex group of patients requires an assessment of clinical, imaging and haemodynamic data (15–22). Ventricular volumes determined by 3D echocardiograms and MRI scans may guide therapy with the ability to recruit ventricles with volumes as low as 15–30 ml/m2 (6, 7, 17). The modified AVV index, the right ventricle:LV inflow angle, and the LV inflow index (15, 16, 20–22) may also aid in deciding between primary BiV repair versus staged BiVC/BiVR. At our centre, the decision to convert from prior SV palliation for R dominant CASVSD was based on the indexed LVEDV. Thus, for the R dominant CASVSD, we used a cut-off indexed LVEDV of 25–30 ml/m2. In addition, the LV should be near apex forming and the left AVV mural leaflet should be adequate. In R dominant CASVSD, an LVEDVi of less than 20 ml/m2 has been associated with non-survival at our centre, although the numbers of deaths in this group are small. For the L dominant CASVSD with a small RV, the decision is based on the ability to create sufficient right AVV inflow by appropriate septation of the common AVV and release of tethered chordae where applicable and ensuring adequate right ventricular cavity by aggressive muscle bundle resection and addition of an infundibular or transannular patch/ right ventricle–pulmonary artery conduit where appropriate. The ultimate decision is often made in the operating room, where establishment of adequate inflow and ventricular rehabilitation can be carried out based on the patient's anatomy.

Limitations

This study has some limitations. It is a retrospective study, with inherent issues of missing data, particularly in the SV group where ascertainment of reinterventions was not always possible, particularly in those followed outside our centre. The BiVC and BiVR strategies are new; thus,

duration of follow-up is shorter in this group. The number of patients in each subgroup is small. As numbers accrue, we plan to perform additional subgroup analyses of those with borderline imbalance and longitudinal analysis of changes in LV dimensions, volumes and function.

Conclusion

BiVC or BiVR from an SV pathway can be achieved with reasonably low mortality and morbidity rates, given the complexity of the diagnosis, and may provide a survival advantage. This strategy may be particularly important in high-risk groups such as patients with trisomy 21 and heterotaxy who tolerate SV palliation poorly. Early establishment of adequate inflow and outflow may be key in allowing ventricular growth and normalization of the compliance of the hypoplastic ventricular chamber with the resulting ability to sustain a BiV circulation.

Conflict of Interest: none declared

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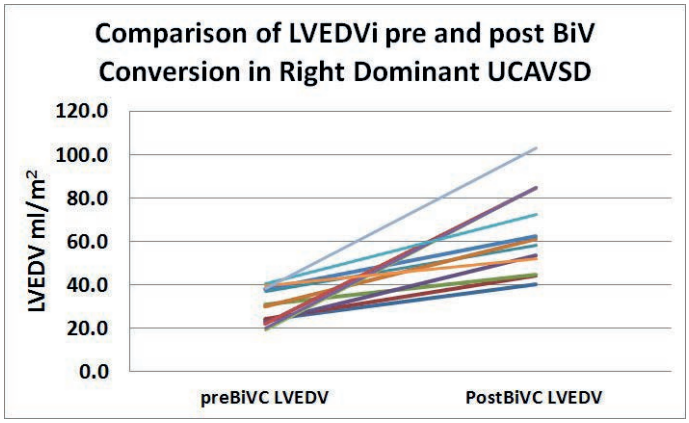
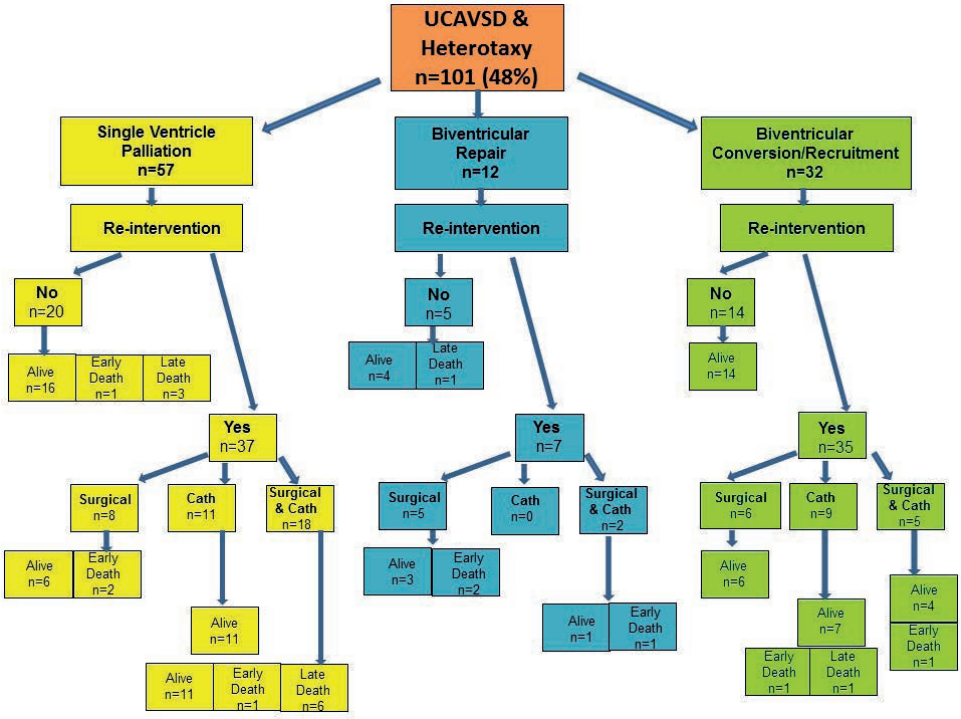
Supplemental Figures

Supplemental Figure 1S: Change in indexed left ventricular end diastolic volume following biventricular conversion from single ventricle palliation in right dominant complete atrioventricular septal defects.



Supplemental Figure 2S: Flow diagram of patient outcomes based on the three management strategies for unbalanced atrioventricular septal defect with heterotaxy: Single-ventricle palliation versus primary biventricular repair, versus biventricular conversion from or recruitment via single-ventricle palliation. The single-ventricle palliation group is represented in yellow, the primary biventricular repair group in teal and the biventricular conversion and recruitment group in green.



FOLLOW-UP AFTER BIVENTRICULAR REPAIR OF THE HYPOPLASTIC LEFT HEART COMPLEX

10

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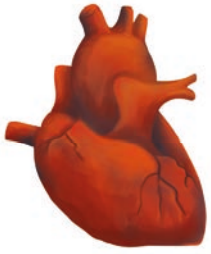


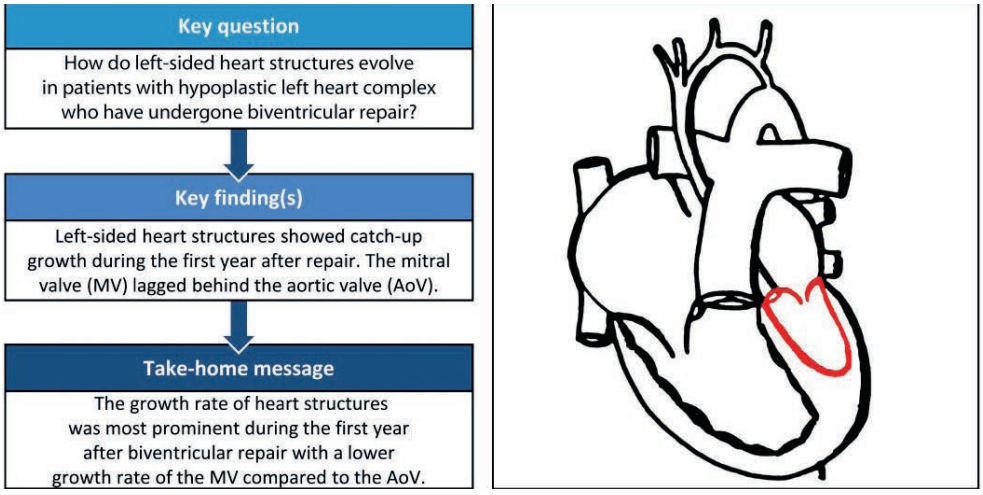
Abstract

Objectives: In hypoplastic left heart complex (HLHC) patients biventricular repair is preferred over staged-single ventricle palliation, but the number of studies is too small to support either strategy. We retrospectively characterized our patient cohort with HLHC after biventricular repair to measure left-sided heart structures and assess our treatment strategy.

Methods: Patients with HLHC who had biventricular repair between 2004 and 2018 were retrospectively reviewed. Operative results were evaluated and echocardiographic mitral valve (MV) and aortic valve (AoV) dimensions, left ventricular (LV) length and internal diastolic diameter (LVIDd) were measured preoperatively and during follow up after 0.5, 1, 3, 5 and 10 years.

Results: In 32 patients, median age at surgery was 10 (IQR 5.0) days. Median follow-up was 6.19 (IQR 6.04) years. During 10 year follow-up mean Z-scores increased from -2.82 to -1.49 and from -2.29 to 0.62 for MV and AoV respectively. ANOVA results with post-hoc paired t-tests showed that growth of left-sided heart structures was accelerated in the first year after repair, but was not equal, with the MV lagging behind the AoV ($p=0.033$), resulting in significantly smaller MV Z-scores compared to AoV Z-scores at 10 year follow-up ($p<0.001$). There were 2 (6%) early deaths. Major adverse events occurred in 4 (13%) patients. Surgical or catheter-based reintervention was required in 14 (44%) patients.

Conclusions: Growth rate of heart structures was most prominent during the first year after biventricular repair with lower growth rate of the MV compared to the AoV.



Introduction

Decision making about pursuing a single ventricle palliation or biventricular repair pathway in patients with HLHC is still dominated by controversies (1). Although outcomes of single ventricle palliation have improved significantly over the past decade, long-term outcomes remain poor, with 10 year survival rates ranging from 50% to 70% (2). The motivation for aggressive maintenance of biventricular circulation derives from the concern of poor long-term outcomes of single ventricle management. On the other hand several studies have demonstrated increased morbidity and mortality when an initial attempt of biventricular repair fails and leads to multiple surgical interventions or conversion to single ventricle palliation (3,4). Early outcome following Fontan procedure is excellent, while biventricular repair may introduce an early risk for mortality and morbidity. Outcome studies can contribute to clinical decision making to choose for either strategy.

Hypoplastic left-sided heart structures need to grow to be adequate. We measured the diameters of MV and AoV during follow up to assess the effect of biventricular repair on left sided hypoplasia and evaluated our clinical results (mortality, major adverse events and reinterventions). Part of this cohort was previously analyzed with a shorter time of follow-up (5).

Materials and Methods

Patient Population

A single-institution retrospective analysis of neonates and infants with the diagnosis of HLHC, who underwent biventricular repair between January 1, 2004, and September 1, 2018, was performed with a waiver of consent of the institutional review board. HLHC was defined according to Tchervenkov et al. as (1) MV and AoV hypoplasia without evident intrinsic stenosis, with a MV annulus and/or AoV annulus Z-score $\leq$ -2, (2) LV hypoplasia, with a left ventricular volume $<$ 20 ml/m^2 using Simpson's method, (3) ascending aorta, proximal arch and distal arch hypoplasia (Z-score $\leq$ -2), with or without aortic coarctation, (4) antegrade flow through the left heart and the ascending aorta into the vessels of the head, (5) ductus-dependent systemic blood flow (6). Figure 1 shows a flowchart of all HLHC patients operated in our center during the study period. Biventricular repair was considered as the index operation. Patients with anomalous left coronary artery from the pulmonary artery (ALCAPA) were excluded. Atrioventricular septal defect (AVSD) was not considered an exclusion criterion. Demographic, clinical, surgical, echocardiographic, and follow-up data were obtained.

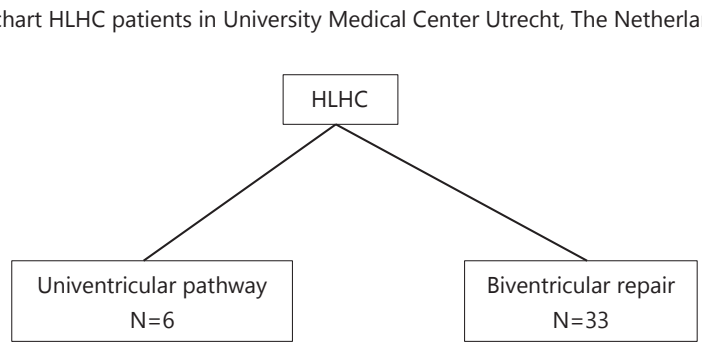
Surgical Techniques

At surgery the MV and AoV morphology was inspected and dimensions were measured by probe. All hypoplastic structures were re-assessed. The decision for biventricular repair was based on this final surgical assessment. In general, patients with a MV Z-score $\geq$ -4 were considered to be candidates for a biventricular repair.

The aortic arch/ascending aorta was reconstructed on hypothermic bypass and selective ce-

rebral perfusion with either patch angioplasty (homograft or bovine pericardium) or, in selected cases, a primary anastomosis between descending aorta and ascending aorta. Subsequently ventricular septal defects (VSD's) were closed followed by atrial septal defect (ASD) closure with a Gore-Tex (W.L. Gore, Flagstaff, AZ) patch leaving a fenestration to allow left atrial decompression and to monitor the interatrial gradient on echo. A 4 mm fenestration used in the first 5 patients was downsized in others to 2 mm to augment LV-preload.

Figure 1: Flowchart of hypoplastic left heart complex patients operated in our center during the study period.



Outcomes of Interest

The outcome variables that were analyzed were diameters and Z-scores of left-sided heart structures (MV annulus, AoV annulus, LV length and LVIDd) (primary) and additional clinical variables (mortality, major adverse events, reinterventions and length of stay (LOS)) (secondary) (7-9).

Cardiac performance and measurements

Recordings of routine 2D echocardiography, M-mode, and Doppler studies were reviewed for all eligible subjects before surgery and 6 months, 1, 3, 5 and 10 year after repair. Echocardiography studies were performed using a GE Vivid E9 or Vivid E95. Measurements of the MV annulus, AoV annulus, LV length and LVIDd were performed by an experienced cardiologist according to recommendations made by the American Society of Echocardiography (10).

BSA was calculated with the formulas of Du Bois and Boyd. The Z-score algorithm by Pettersen and colleagues, based on the Du Bois BSA calculation, was used for the MV and AoV annulus, and LVIDd (7). The algorithm by Daubeney and colleagues, based on the Boyd BSA calculation, was used to calculate the LV length Z-score (8). Mitral stenosis (MS) was defined according to the EAE/ASE Recommendations for Clinical Practice (9).

Major adverse events, reinterventions and LOS

Major adverse events were defined according to the STS congenital heart surgery database and include need for mechanical circulatory support, reexploration for bleeding, reexploration for low cardiac output syndrome, unplanned reintervention prior to discharge, mediastinitis requiring debridement, arrhythmia requiring placement of permanent pacemaker, diaphragm plication,

cardiac arrest requiring resuscitation, neurological deficit persisting at discharge, renal failure requiring dialysis, heart transplantation prior to discharge (11,12). Reinterventions were defined as surgical or catheter-based reinterventions. Postoperative days on the ventilator was defined as total number of days on the ventilator after the index operation and included all reintubation days. Postoperative intensive care unit length of stay (PICULOS) was defined as total postoperative days in the ICU, including days readmitted to the ICU during hospitalization for the index operation.

Statistical Analysis

Patient and procedural characteristics were summarized as frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Only patients alive 6 months after repair were included in analysis to assess dimensions of left-sided heart structures. For the primary outcome, we performed a two-way repeated measures analysis of variance (ANOVA) with main factors time and left-sided heart structures and the interaction between those main factors. Statistical analysis was performed with SPSS for Windows (version 25). Not all patients reached the total follow-up, so the dataset contained missing values. Therefore, we performed missing values analysis in SPSS and decided to use multiple imputation in statistical programming language R (version 3.5.1) with package 'mice' for the imputation procedure (13). More information about the missing data procedure is described in Appendix A. Before performing the two-way repeated measures ANOVA, we made sure the assumptions of continuous data, normality and sphericity were met. Normality was assessed by means of histograms and sphericity was tested with Mauchly's Test. All Z-score variables in the incomplete dataset were in the range of -3 to 3. Although the imputed datasets had 3 outliers, all of them were still within 3.5 standard deviations and were therefore not excluded from the analysis. To reduce the number of tests performed, ten post-hoc paired t-tests were carefully chosen based on the outcome of the ANOVA, the outcomes of earlier post-hoc tests and clinical relevance. For the secondary outcome Cox regression analysis was used to evaluate the relationship between preoperative MV Z-scores and reinterventions. The assumption of the proportional hazard was evaluated by using the time-dependent covariate ($p=0.086$). Time to reintervention was estimated using the Kaplan-Meier method.

Results

Patients

There were 32 patients with small left-sided heart structures and aortic coarctation and/or hypoplastic aortic arch included in the analysis. Patient and procedural characteristics are represented in Table 1. The median age at operation was 10 (IQR 5) days. There were 21 male patients (66%). Five patients had a genetic anomaly, including Kabuki syndrome in 2 (6%), Pierre Robin sequence in 1 (3%), and other in 2 (6%). A VSD was present 11 patients including 2 patients with an unbalanced AVSD. Three patients (9%) were born preterm. Median follow-up was 6.2 (IQR 6.1) years.

Table 1. Patient and Procedural Characteristics (n=32)

Characteristic	Value
Age at operation, days	10.0 (5.0)
Neonate	30 (94)
Weight at surgery, kg	3.4 (0.8)
Male sex	21 (66)
Prematurity	3 (9)
Any genetic syndrome	5 (16)
Preoperative cardiac dimensions	
MV annulus Z-score	-2.83 (1.24)
AoV annulus Z-score	-2.49 (2.08)
LV length Z-score	-2.20 (1.57)
LVIDd Z-score	-2.26 (2.08)
Surgical technique aortic arch	
Patch angioplasty	28 (87.5)
Direct anastomosis distal ascending to proximal descending aorta	4 (12.5)
Patch angioplasty material	
Pulmonary homograft	21 (66)
Bovine pericardium	6 (19)
Pulmonary homograft and bovine pericardium	1 (3)
ASD closure	
2 mm fenestrated patch	27 (84)
4 mm fenestrated patch	5 (16)
VSD closure	
Closure of perimembranous VSD	7 (22)
Closure of muscular VSD	1 (3)
Concomitant procedure[a]	6 (19)
Major adverse events[b]	4 (13)
Death prior to discharge	2 (6)
Surgical or catheter based reintervention	14 (44)
Surgical reintervention	11 (34)
Catheter based reintervention	13 (41)
Follow-up, years	6.2 (6.1)
Postoperative days on ventilator	4.0 (3.2)
Postoperative ICU length of stay, days	6.0 (4.0)
Postoperative hospital length of stay, days	11.5 (14.3)

[a] *Included variables are commissurotomy of the aortic valve, closure of left persistent superior vena cava, unroofing of sinus coronarius, correction of partial anomalous pulmonary venous connection* [b] *need for extracorporeal membrane oxygenator support, reexploration for bleeding, reexploration for low cardiac output syndrome, unplanned reintervention prior to discharge, mediastinitis requiring debridement, arrhythmia requiring placement of permanent pacemaker, diaphragm plication, cardiac arrest requiring resuscitation, persisting neurological deficit, renal failure requiring dialysis, heart transplantation prior to discharge.*
Values are n (%) or median (interquartile range). AoV=aortic valve, ASD=atrial septal defect, ICU=intensive care unit, LV=left ventricle, LVIDd=left ventricular internal diastolic diameter, MV=mitral valve, VSD=ventricular septal defect.

Surgery

Arch reconstruction was performed in all patients, using selective antegrade cerebral perfusion (ACP) in 27 patients (mean ACP time 36 (range 27-47) minutes). In 9 patients complete circulatory arrest was used (mean arrest time 26 (range 2-43) minutes). In 4 patients both ACP and circulatory arrest was used. A fenestrated ASD patch closure was performed in all patients (2 mm in 27 and 4 mm in 5). Other associated procedures were VSD closure (8), AoV valvotomy (2), persistent left superior vena cava closure (2), coronary sinus unroofing (2) and partial anomalous pulmonary venous connection repair (1). Surgical interventions on the MV were not performed; in AVSD patients we left the cleft open.

Cardiac dimensions

Median preoperative Z-scores (IQR) of the whole cohort were -2.83 (1.24) for MV; AoV -2.49 (2.08); LV length -2.20 (1.57); LVIDd -2.26 (2.08). Full ranges for MV were (-5.2, -1.1); AoV (-5.0, -0.3); LV length (-5.2, -0.2); LVIDd (-6.5, 0). The subgroup of 30 patients alive 6 months after repair were included in analysis to assess dimensions of left-sided heart structures. Information about imputation and pooling is represented in Appendix A. The pooled means and standard errors of the Z-scores are shown in Table 2. MV Z-scores increased from -2.82 to -1.49, AoV from -2.29 to 0.62, LV length from -2.09 to 0.11, LVIDd from -2.24 to -0.43 during 10 year follow-up.

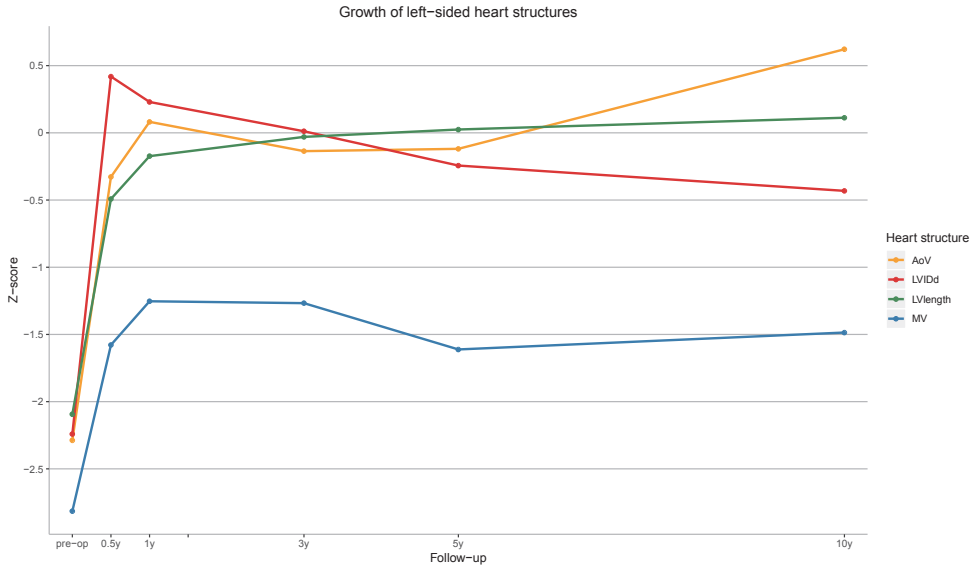
Table 2. Results Z-scores pooled data; mean (se)

Heart structure	Preoperative	6 months	1 year	3 year	5 year	10 year
MV	-2.82 (0.18)	-1.58 (0.17)	-1.25 (0.15)	-1.27 (0.13)	-1.61 (0.16)	-1.49 (0.15)
AoV	-2.29 (0.22)	-0.33 (0.19)	0.08 (0.17)	-0.14 (0.22)	-0.12 (0.25)	0.62 (0.16)
LV length	-2.09 (0.19)	-0.49 (0.21)	-0.17 (0.16)	-0.03 (0.16)	0.02 (0.17)	0.11 (0.14)
LVIDd	-2.24 (0.29)	0.42 (0.22)	0.23 (0.16)	0.01 (0.17)	-0.24 (0.42)	-0.43 (0.23)

AoV=aortic valve, LV=left ventricular, LVIDd=left ventricular internal diastolic diameter, MV=mitral valve, se=standard error

Results of the two-way repeated measures ANOVA show that the factor time of follow-up, the factor left-sided heart structures and the interaction effect are all significant on Z-scores ($p<0.001$) (Figure 2).

Figure 2: Results of two-way repeated measures ANOVA. The two main effects (time of follow-up ($p<0.001$) and left-sided heart structure ($p<0.001$)) and the interaction effect ($p<0.001$) of the two way repeated measures ANOVA are all significant.



Abbreviations: AoV=aortic valve, LV=left ventricle, LVIDd=left ventricular internal diastolic diameter, MV=mitral valve. AoV is represented in orange, LVIDd is presented in red, LV length is represented in green and MV is represented in blue.

Post-hoc tests were performed to determine between which time points the biggest change in Z-scores occurred. There was a significant difference between preoperative Z-scores and Z-scores 6 months after repair ($p<0.001$), between Z-scores 6 months and 1 year after repair ($p=0.034$), and between Z-scores 5 year and 10 year after repair ($p=0.043$). In other words, the Z-scores increased most in the first year after surgery.

Post-hoc tests for left-sided heart structure revealed that the change of the Z-scores of the mitral valve during follow-up was significantly different from the AoV ($p<0.001$), LV length ($p<0.001$) and LVIDd ($p<0.001$). Z-scores of the other 3 left-sided heart structures did not significantly differ from each other. Thus, the change of the Z-scores during follow-up is approximately similar for AoV, LV length and LVIDd, and those three are different from the MV.
To see how the Z-scores changed differently for the heart structures, we did post-hoc tests on the mean difference between preoperative Z-scores and Z-scores 1 year after repair. It turned out that there is significant less increase of MV Z-scores compared to those of the AoV ($p=0.033$). In other words, during the first year after surgery, the MV z-score shows less enlargement than the AoV z-score. At 10 year follow-up the MV remained significantly smaller than the AoV ($p<0.001$).

At last follow-up 12 patients had no MS, 8 mild, 7 moderate and 2 had severe MS. Of the 8 patients with a hypoplastic MV (Z-score $\leq$ -2) at last follow-up 3 had no MS, 2 mild, 2 moderate and 1 severe MS.

Mortality, major adverse events and reinterventions

There were 2 early deaths (6%). One patient with Kabuki syndrome and preoperative MV and AoV Z-scores of -4.14 and -4.98 respectively, died 4 days after surgery because of left and right ventricular failure, despite maximal inotropic support. Decided was to not put the patient on extracorporeal life support, since there was no prospect of transplantation. The other patient had Pierre Robin Sequence with preoperative MV and AoV Z-scores of -2.81 and -3.69, respectively, and died after 2 months, despite uneventful biventricular repair. Death in this patient was attributed to respiratory failure related to congenital brain malformation.

There were 3 patients in our cohort with preoperative MV Z-scores below -4.

Patient 1, a 1.9 kilogram neonate with Kabuki syndrome and preoperative echocardiographic MV and AoV diameter Z-scores of -4.1 and -5.0 respectively, died 4 days after surgery because of left and right ventricular failure, despite maximal inotropic support.. In this patient a morphologic normal mitral valve was found at operation which measured 5.5 mm (= Z-score of -3.5) and a normal tricuspid aortic valve. So, echocardiography underestimated the mitral valve diameter.

Patient 2 had preoperative MV and AoV Z-scores of -4.7 and -3.1 respectively and underwent biventricular repair at age of 13 days. Unintended reoperation for unrecognized VSD was performed with reopening of ASD patch fenestration. During the first 6 months after surgery the MV and AoV Z-scores increased to -2.8 and -1.5 respectively. The child remains well with MV and AoV Z-scores of -2.8 and -0.6 respectively at age 2.8 years. Echo at last follow-up showed a mean gradient of 9 mmHg across the mitral valve with signs of pulmonary hypertension (right heart pressure between 1/3-2/3 systemic blood pressure).

Patient 3 had preoperative MV and AoV Z-scores of -5.2 and -4.1 respectively and underwent biventricular repair at age of 10 days. During the first 6 months after surgery the MV and AoV Z-scores increased to -1.9 and -0.7 respectively. The child remains well with MV and AoV Z-scores of -1.4 and 0.9 respectively at age of 10 years and has a mean gradient 2.3 mmHg across the mitral valve with no signs of pulmonary hypertension.
Major adverse events occurred in 4 (13%) patients (predischarge unplanned reintervention: n=2, cardiac arrest requiring resuscitation: n=1, renal failure requiring dialysis: n=2). One patient had more than 1 major adverse event.

Reinterventions (23) were required in 14 (44%) patients for recurring or residual obstructive lesions. Surgical reinterventions were performed in 9 (28%) patients and 10 patients (31%) underwent catheter-based reinterventions. Patients underwent 1 (7), 2 (5) or 3 (2) reinterventions.
Sites of reinterventions are shown in Figure 3 and Table 3. Majority of the reinterventions were related to the aortic arch (13 (41%)) and most of these were catheter-based (11 (34%)). In some patients more than 1 site was addressed during the same procedure. Late conversion to single ventricle repair was not performed. Results of Cox regression analysis show an association between preoperative MV Z-scores and surgical and catheter-based reinterventions, hazard ratio 0.560, p = 0.026.

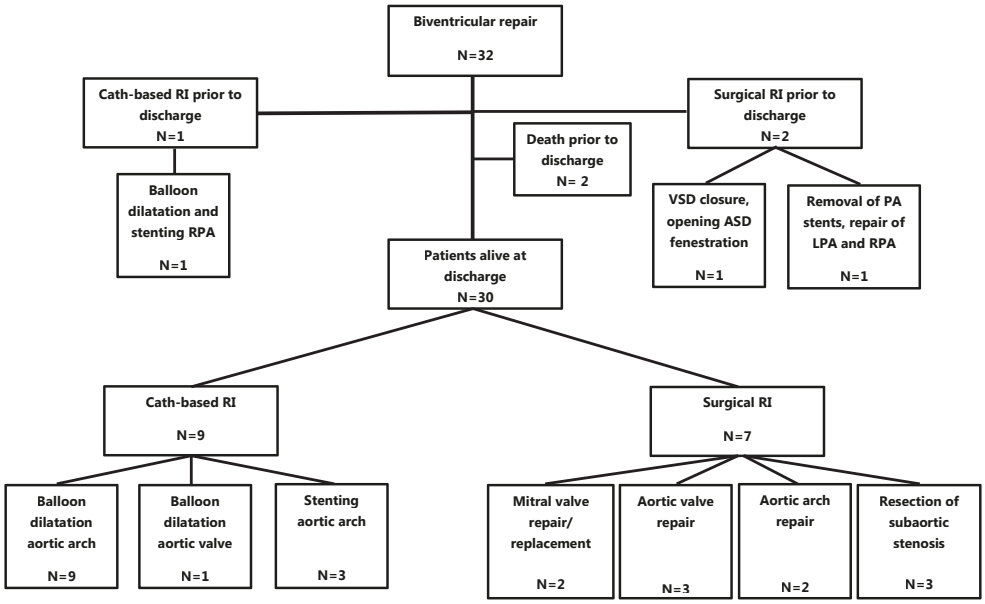
Figure 4 represents the Kaplan-Meier survival analysis curve for reinterventions based on type of reintervention (any (both surgical and catheter-based), surgical or catheter-based). All reinterventions were performed in the first 2 years after repair.

Table 3. Reinterventions

Patient	Surgical	Catheter-based
1		1. BD Re-CoA
2		1. BD Re-CoA
3	3. Valvulotomy AoV, primary closure of VSD, MVR 15 mm St. Jude	1. BD Re-CoA 2. Stenting Re-CoA
4		1. BD and stenting Re-CoA
5	3. Resection of subaortic stenosis	1. BD Re-CoA 2. BD and stenting Re-CoA
6	1. Closure VSD with Goretex patch, re-opening of ASD fenestration	
7	1. Removal of pulmonary artery stents, augmentation and repair of right and left pulmonary artery	2. Stenting right pulmonary artery
8	1. Resection of supramitral membrane 2. Resection of subaortic stenosis	
9	1. Repair of supravalvular aortic stenosis (Doty repair)	
10	2. CoA repair with patch enlargement	1. BD Re-CoA
11	2. CoA repair with patch, commissurotomy of the AoV, leaflet shaving.	1. BD Re-CoA and aortic valve
12		1. BD Re-CoA
13		1. BD Re-CoA
14	1. Resection of subaortic stenosis 2. Resection of subaortic stenosis	

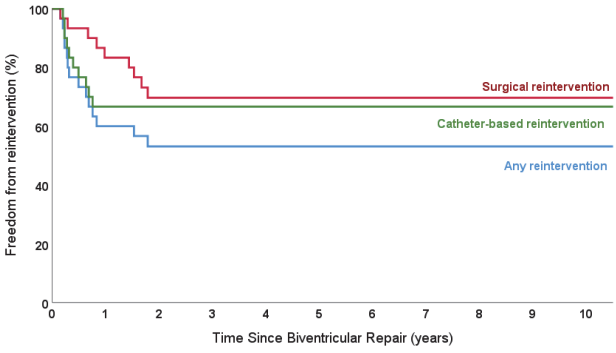
AoV=aortic valve, ASD=atrial septal defect, BD= balloon dilatation, MVR = mitral valve replacement, Re-CoA=re-coarctation, VSD=ventricular septal defect. Reinterventions are chronically numbered.

Figure 3: Sites of reinterventions after biventricular repair. Seven patients underwent a reintervention on a combination of these sites (for example: balloon dilatation and stenting of the aortic arch). ASD = atrial septal defect, LPA = left pulmonary artery, PA = pulmonary artery, RI = reintervention, RPA = right pulmonary artery, VSD = ventricular septal defect.



All patients were in NYHA functional class 1 except 3 (NYHA 2). One patient showed echocardiographic signs of pulmonary hypertension at last follow-up. Three patients were on cardiac medication at last follow-up (coumarin anticoagulant: n=1, angiotensin-converting-enzyme inhibitor: n=1, beta blocker: n=1). No patients were on medication for pulmonary hypertension.

Figure 4: Kaplan-Meier estimate of time to reintervention based on type of reintervention (any reintervention, surgical or catheter-based reintervention). Surgical reintervention is represented in red, catheter-based reintervention in green, and any reintervention in blue. The number at risk at each time point is provided in the table below the graph.



Number at risk											
Any RI	32	18	15	14	13	11	9	7	6	5	4
Surgical RI	32	25	20	19	17	14	10	8	7	6	4
Cath-based RI	32	20	19	17	16	14	12	10	9	8	6

Discussion

In the present study we analyzed the evolution of left-sided heart structures and clinical outcomes in patients with HLHC after biventricular repair.

Cardiac dimensions

We demonstrated, in accordance with other studies, the ability of the left-sided heart structures in HLHC patients to generate catch-up growth after biventricular repair (2, 14-16). In 30 patients discharged alive (with preoperative MV and AoV Z-scores up to -5.2 and -5.0 respectively) the MV and AoV diameter, LV length and LVIDd dimension showed disproportionate enlargement during the first year after repair. We interpreted this disproportionate enlargement as catch-up growth. At 10 year follow-up dimensions of AoV and LV normalized, leaving the MV somewhat behind. Our findings confirm the potential of hypoplastic left-sided heart structures to recover from hypoplasia once biventricular circulation is established.

Our study differs from others in that our study has a longer follow-up time (5). Furthermore, a two-way repeated measures ANOVA was performed with carefully chosen post-hoc tests instead of many paired samples t-tests. Multiple imputation was performed and this allowed us to use all the observed data. Even patients with shorter follow-up are included in the analysis. Because of this approach we can draw strong conclusions about the change of Z-scores during the first year after surgery. We observed incongruent growth of the mitral and aortic valve.

Our findings are in line with those of Bergonzini and associates, who found that the MV remains smaller at latest follow up when compared with AoV (Z-value of -1.44 ± 0.92 vs. -0.45 ± 1.37

respectively), although this difference was not significant (14).
Although the MV remained smaller during follow-up, majority of patients (20 (67%)) had no or mild MS at last follow-up.

We can only speculate about the reason for the limited growth potential of the MV when compared with the AoV. Since the left atrial pressure is much lower than the pressure in the left ventricle, not only increased flow, but also increased pressure may promote growth of a valve (17).

Mortality, major adverse events and reinterventions

We demonstrated, as in other studies, that biventricular repair in HLHC patients can be performed with low mortality and good clinical outcomes (5,14). One of the patients with fatal outcome died because of a non-cardiac related cause. The other patient was a patient with a genetic syndrome with preoperative MV and AoV Z-scores of -4.14 and -4.98 respectively). Given his preoperative Z-scores he was considered a candidate for univentricular palliation. However his genetic anomaly and his low birth weight (1.89 kg) made us decide to perform a biventricular repair.

Besides the good clinical and functional status at follow-up and the low incidence of extra-cardiac complications, this strategy is associated with a high incidence of reinterventions in our hands.
Fourteen patients (44%) underwent a total of 23 reinterventions. Nine (28%) patients underwent reinterventions on the aortic arch (surgical: n=2, catheter-based: n=9). Two patients underwent surgical and catheter-based reinterventions on the arch. Majority of the arch reinterventions were carried out within the first 6 months after surgery.
The higher rate of arch reinterventions in our study compared to other studies (10%) may indicate a lower threshold of percutaneous treatment (18,19). We strongly believe that an unobstructed aortic arch is key in left ventricular catch-up growth. With the recent launch of the Cook Formula Stent (535) for the pediatric population we are now able to successfully treat residual aortic obstructions in small patients using small introducer sheaths (5 French). With this introduction the threshold to treat residual lesions has come down significantly and this may explain our elevated rate of arch reinterventions (20).

Eight patients (25%) underwent reinterventions on intracardiac structures (AoV, MV, LVOT, ASD or VSD). Our findings on intracardiac reinterventions are consistent with other studies reporting a reintervention rate of 23 % to 55 % (14-16).

Although preoperative MV Z-scores were associated with reinterventions, reinterventions on the mitral valve (2) were rare. One of the patients in our cohort developed mitral valve stenosis and underwent mitral valve replacement with a 15 mm St Jude valve 17 months after biventricular repair.
In the other patient a supravalvular mitral stenosis developed which was resected 2 years after initial repair.

The role of the mitral valve as a determinant of a successful biventricular repair remains inconsistent in literature. Schwartz and colleagues show that indicators of failure of biventricular repair were, among others, smaller mitral valve dimensions and lower left ventricular end-diastolic volumes in patients with multiple left heart obstructive lesions (4). Plymale and colleagues analyzed a cohort of patients with aortic arch hypoplasia and small left-sided heart structures in which neither the MV size nor MV morphology alone were associated with outcomes, but they demonstrated that the MV in combination with other anatomic markers (AoV), can help predict the potential of the MV to support biventricular repair (21). Alternatively, Serraf and colleagues found that a morphologically abnormal, rather than hypoplastic mitral valve adversely impacted survival in patients with coarctation and left heart hypoplasia (15).

We consider the mitral valve to be a key-factor in surgical strategy decision making. Of 3 patients with preoperative MV Z-scores below -4, 1 patient died and 1 patient developed signs of pulmonary hypertension. MV Z-score of -4 appears to be the critical value.

Study limitations and future directions

This study is limited by its retrospective nature and single center experience with its inherent problems of missing and incomplete data. Ideally growth would be assessed in young adults. Due to short follow-up time only 11 (37%) patients had an echo 10 years after repair. Even though we used multiple imputation, we decided to not draw strong conclusions from post-hoc tests on differences in Z-scores between 5 year and 10 year follow-up.

Conclusion

Growth rate of heart structures was most prominent during the first year after biventricular repair with lower growth rate of the MV compared to the AoV. AoV Z-scores normalized at 10 years follow-up, in contrast to the MV.
Reinterventions are common in HLHC patients after biventricular repair, particularly on the aortic arch. Preoperative mitral valve Z-scores were significantly associated with surgical reinterventions.

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Conflict of interest: none declared

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Appendix A. Supplemental material - imputation and pooling of data

Not all patients reached the total follow-up time, so the dataset contained missing values. The missing data patterns in the dataset are represented in Supplemental Figure 1. We performed missing values analysis in SPSS and found no differences between patients with and without missing Z-scores for all patient- and peri-operative characteristics. In other words, it is most likely that the missing data occurred only because of short follow-up (recently operated).

In order to use all observed data, we imputed the incomplete variables with the statistical technique of multiple imputation (1). Multiple imputation is considered a state of the art technique that allows for the usage of all observed data without losing statistical power and accuracy (2). The imputation procedure was performed in statistical programming language R (version 3.5.1) with package 'mice', using 10 iterations and predictive mean matching as the imputation method (3,4). Supplemental Tables 1 and 2 show the predictor matrices of the mitral valve and left ventricular length and of the aortic valve and the left ventricular internal diameter respectively. In general, the preoperative and 6 months follow-up Z-scores were used as predictors to impute the missing values for the 1, 3, 5 and 10 years follow-up time points. For the aortic valve and left ventricular internal diameter, the preoperative Z-scores were also used to impute the Z-scores at 6 months follow-up. Inclusion of other variables such as the Z-scores at 1 year follow-up to impute the scores at 3 years follow-up, or baseline variables such as age and sex, generated problems of multicollinearity and convergence and were therefore not included in the imputation model.

Finally, the method resulted in 5 complete datasets. Statistical analysis was performed on each of the 5 datasets and the outcomes were pooled with package 'miceadds' (5) according to the method of Enders and colleagues (6).

Supplemental table 1: Predictor matrix of the mitral valve and ventricular length

	Predictor variable					
Imputed variable	MV preoperative	MV 6 months	MV 1 year	MV 3 years	MV 5 years	MV 10 years
MV preoperative	0	0	0	0	0	0
MV 6 months	0	0	0	0	0	0
MV 1 year	1	1	0	0	0	0
MV 3 years	1	1	0	0	0	0
MV 5 years	1	1	0	0	0	0
MV 10 years	1	1	0	0	0	0

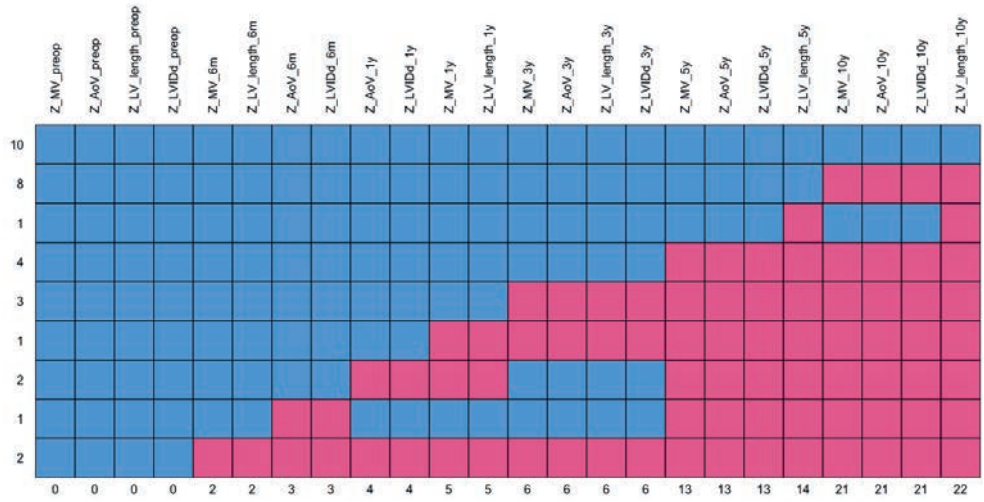
0= no predictor, 1 = predictor. MV=mitral valve. Predictor table is similar for variable left ventricle.

Supplemental table 2: Predictor matrix of the aortic valve and the left ventricular internal diameter

	Predictor variable					
Imputed variable	AoV preoperative	AoV 6 months	AoV 1 year	AoV 3 years	AoV 5 years	AoV 10 years
AoV preoperative	0	0	0	0	0	0
AoV 6 months	1	0	0	0	0	0
AoV 1 year	1	1	0	0	0	0
AoV 3 years	1	1	0	0	0	0
AoV 5 years	1	1	0	0	0	0
AoV 10 years	1	1	0	0	0	0

0= no predictor, 1 = predictor. AoV=aortic valve. Predictor table is similar for variable left ventricular internal diameter.

Supplemental figure 1: Summary of missing data patterns. Each column represents Z-scores at specific time of follow-up. Values on the left are number of patients. Values below the figure show total number of missing values. Observed values are represented in blue, missing values are represented in red.



Abbreviations: AoV = aortic valve, LV = left ventricle, LVIDd = left ventricular internal diameter, m = months, MV = mitral valve, preop = preoperative, y = years, Z = Z-score.

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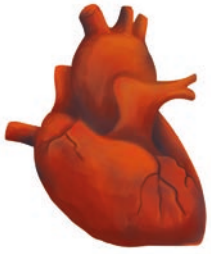
GENERAL DISCUSSION

11



General Discussion

The aim of this thesis is to report upon clinical outcomes of atrioventricular septal defect (AVSD) repair and of left atrioventricular valve (LAVV) replacement in neonates, infants and adults and to report upon clinical outcomes of repair of hypoplastic left heart complex.

Technical performance in congenital heart surgery

For children undergoing congenital heart surgery, outcomes and resource utilization vary significantly across centers and among individual surgeons (1-3). Etiologies of this variation are incompletely understood and are likely multifactorial. Gaining insight into these differences requires measurement of the specific contributions of individual care elements (4). Whereas the importance of surgeon technical skill might be assumed, the relationship between technical skill and outcomes after congenital heart surgery has not been well quantified. AVSDs are one of the congenital heart defects whose outcomes are used to assess both the pediatric heart surgeon's skill and the institution's expertise (5). Technical performance score (TPS), a tool developed to determine technical adequacy of congenital cardiac repairs, is based on residual lesions noted on postoperative echocardiograms and occurrence of pre-discharge reinterventions (5). Our experience described in **Chapter 2** shows an association between the technical performance score and complications, prolonged postoperative ventilator days and postdischarge reintervention after adjusting for covariates such as age, weight, genetic abnormality, concomitant procedure, prematurity, and second bypass run. As shown in **Chapter 3**, residual left and right AV valve regurgitation and abnormal conduction at discharge were among the subcomponents strongly associated with post-discharge reinterventions. TPS provides feedback on areas of improvement and allows identification of patients who warrant closer follow-up. However, critics of this approach have raised concerns about the use of such surrogates for technical skill, pointing to unmeasured differences in preoperative anatomy as potential confounders (6,7). This concern is supported by studies reporting preoperative severe LAVV regurgitation (8), abnormal LAVV structure (8,9) and associated cardiovascular anomalies (9) being risk factors for reinterventions. However, in order to eliminate the risk of bias, preoperative AV valve regurgitation and balance of defect (well-balanced, right or left dominant) and concomitant procedure were included in our analysis and used as surrogates for complexity of the defect.

TPS should be implemented in all congenital heart surgery centers. The ultimate goal of using performance scores is to show that measuring technical adequacy of a repair is meaningful, reproducible and rewarding for cardiac surgeons and their future patients. Use of this tool supports surgeons to have a transparent attitude towards their performance and helps them to grow from areas of improvement. This is an important step in creating an atmosphere where surgeons take care of patients with more self-awareness, share with colleagues with more openness, and learn from their weaknesses with more eagerness.

Left atrioventricular valve

Reoperations for LAVV regurgitation after AVSD repair are common, causing both early and late mortality and morbidity. With increasing numbers of patients surviving AVSD repair, valve replacement can be anticipated to be necessary more often. Replacing the LAVV in young children is challenging and puts the patient at risk for complications of anticoagulation therapy. To address the clinical problem we characterized AVSD patients with end-stage AV valve pathology who required their valve to be replaced. AVSD subtype (complete AVSD (CAVSD) versus partial AVSD (PAVSD)) was associated with patient characteristics and outcome (**Chapter 4**). LAVV replacement was indicated in children early after CAVSD repair whereas in PAVSD it was a late event in adults. Freedom from LAVV replacement is much shorter in patients with CAVSD than in those with a PAVSD. Reoperations for prosthetic valve replacement and pacemaker implantations were common in both groups. Kaza and colleagues showed AVSD subtype not being associated with postoperative LAVV regurgitation severity after adjusting for age at repair (10), but timing of LAVV reoperation was not investigated in their cohort. In our cohort of AVSD patients undergoing LAVV replacement, a relatively high number of patients had the cleft not (16%) or partially (11%) closed at initial repair. Most of these patients were operated in the earlier eras. Cleft closure is still an area of controversy, as many groups have advocated routine closure of the cleft in all patients (11,12) while other groups decide to leave the cleft open in selected cases (eg. if there is a potential parachute LAVV, if the valvular tissue is thin and fragile, and if there is satisfactory apposition, closure, and competence of the valve) (13).

The strategy to close the cleft is supported by El-Najdawi and colleagues who performed a study among 334 patients who underwent repair of PAVSD and reported closure of LAVV cleft being associated with better survival and a suggested reduced need for reoperation (14). In addition, patients who underwent suture closure of the LAVV cleft were less likely to have postoperative arrhythmias than patients who did not undergo cleft closure. It is possible that, for those patients in whom the cleft was not closed, there were associated anatomic abnormalities that precluded its closure. One of the concerns of closure of the cleft is that it may lead to a high incidence of postoperative stenosis.

Cleft closure was initially used in older children and adults, but this strategy needs to be evaluated since median age at surgery for CAVSD has dropped to 3-6 months (15). The tricuspid shape of the LAVV should maybe be respected in young infants, since cleft closure might damage the small valve and may not lead to a durable result. Comparing studies between patients with and without cleft closure at initial AVSD repair are needed in order to determine a possible association with LAVV reoperations.

Operating AVSD patients for LAVV regurgitation is technically challenging. Both adult and pediatric congenital heart surgeons should be aware of the mechanism of LAVV regurgitation being possibly related to the cleft that was left open at initial repair. Besides, Teflon or other synthetic patch material for septal defect closure is used in patients operated in earlier eras, and has shown to cause calcification of interatrial septum and AV valve. There might be a relationship between the use of those materials and the presence of LAVV regurgitation. Incision through Waterston's groove or Guiraudon incision could be a valuable option to bypass the calcified interatrial septum in these patients and prevent iatrogenic damage of the AV valve leaflets.

Small mechanical prostheses

In **Chapter 5** and **Chapter 6** outcomes of young patients undergoing mitral valve replacement (MVR) with small mechanical prostheses (15-mm and 15-17 mm) are presented, showing encouraging early and mid-term results in high-risk patients. We showed that these small prostheses will eventually become stenotic in a growing child. Reoperation for this patient-prosthesis mismatch was required at a median of 3.5 (15-mm prosthesis) and 3.7 years (15-17-mm prosthesis) and could be carried out with minimal morbidity and with no need to enlarge the annulus. Pluchinotta and colleagues have analyzed similar patients who had their MV replaced with a stented bovine jugular vein conduit (Melody valve) customized for surgical implantation. They have reported the development of structural prosthesis deterioration in a significant number (35%) of patients, requiring prosthesis replacement at median of 22 months after implantation (16). Prosthesis replacement in our cohorts (65% and 44%) occurred later with median time to prosthesis replacement of 42 and 44 months.

The choice of prosthesis i.e., a small mechanical prosthesis versus a bioprosthesis such as a stented bovine jugular vein conduit is best determined by the individual surgeon and cardiologist.
In the short term, the morbidity and mortality risks for a 15-17 mm mechanical prosthesis are comparable to that of a bovine jugular vein Contegra conduit (16). The potential of the stented bovine jugular vein conduit to be dilated to “grow” with the patient is clearly an important benefit of this valve. The incidence of thromboembolic complications and difficulty of managing anticoagulation in a small child are an important disadvantage with mechanical valves, especially in countries with limited INR monitoring options. However, easy access and low costs may favor the mechanical prosthesis. Long-term outcome of the stented bovine jugular vein conduit are needed and can contribute to clinical decision-making on choice of prosthesis. Performing randomized control studies comparing the stented bovine jugular vein conduit and small mechanical prosthesis is an important next step in improving treatment in critically ill infants requiring MVR.

Ventricular septal defect patch

The ideal patch material for septal defect closure used in congenital cardiac surgery would theoretically be compatible with growth, resistant to tearing, calcification and shrinkage, would be easy to suture, would be hemostatic, and would heal without scar formation (17). Patches to close the ventricular component are traditionally synthetic. They often cross the entire AV valve, potentially contributing to valve restriction. Long term effects may be deleterious for AV valve function. While the median age at surgery for CAVSD has dropped significantly (15), operative outcome has improved but reintervention rates have slightly increased over the years. In **Chapter 7** a retrospective review of CAVSD patients with autologous double pericardial patch repair is presented, showing a low incidence of reoperation on the LAVV (1.4%). LAVV reintervention rate in our cohort is much lower compared to studies using a synthetic patch at the VSD position (6.4-11.4%) (18-20). Adaptive properties of untreated autologous pericardium may preserve AV valve function when both the septal defects are closed with separate untreated autologous peri-

cardial patches. One of the main reasons for surgeons to avoid autologous pericardium for ventricular septal defect repair is the risk of patch aneurysm. However, only 1 (1.4%) case of patch aneurysm was seen in our cohort and occurred in a patient with an initially oversized patch. **Chapter 8** shows the results of a study comparing fresh autologous pericardium with synthetic patch material showing similar AV valve regurgitation and a similar reoperation rate in both patch groups. All but 1 patients who needed a reoperation were operated before 2000 suggesting a potential learning effect. The importance of taking into account of the learning curve when comparing different techniques is supported by previously studies showing a relationship between the date of surgery and early mortality while examining the results of AVSD operations (21,22). With the trend of earlier age at AVSD repair, surgical techniques that were reliable in older children, like use of synthetic patch material for VSD closure, may have to be modified in younger children in order to prevent LAVV reoperations. Future comparative studies on outcome after CAVSD repair with different VSD patch materials need to be performed. Ideally included patients will all be operated in the same center to avoid differences in surgical and postoperative care.

Unbalanced atrioventricular septal defects and borderline left ventricles

The major challenge faced in children with borderline left hearts (including unbalanced AVSD) is clinical decision making in pursuing either a single-ventricle pathway or a biventricular repair. Although better perioperative management has improved the long-term outcomes of the Fontan procedure, morbidity of the Fontan circulation, including protein-losing enteropathy, thromboembolism, arrhythmias, and plastic bronchitis remain a major challenge faced in this patient population and can be difficult to predict and treat (23). However, several studies have demonstrated increased morbidity and mortality when an initial attempt of biventricular repair fails and leads to multiple surgical interventions or conversion to single ventricle palliation (24,25). Three surgical approaches have been suggested for potential left ventricle recruitment in patients with borderline left hearts. In chapter 9 and 10 outcomes of two of these approaches are presented in order to contribute to clinical decision-making to choose for either strategy.

(1) The Boston group advocates an initial Norwood procedure with the radical relief of left-sided obstructive lesions and resection of endocardial fibroelastosis at the same stage or at subsequent stages of univentricular palliation before eventually deciding for biventricular repair (26,27). Kalish et al. reported short-term results in 28 patients with small LV structures undergoing biventricular repair at the median age of 3.5 years (range 4-95 months) after the initial Norwood procedure (26). Almost 90% of the patients were alive at a median follow-up of 2.6 years. Catheter-based intervention or surgical reoperation was needed in 61% of patients. The left ventricle volumes increased significantly after biventricular repair. In **Chapter 9** mid-term outcomes in 212 Boston patients with unbalanced CAVSD were assessed according to management strategy (single-ventricle palliation versus primary or staged biventricular repair) during a median follow-up of 2.9 years (range 1-192 months). Biventricular conversion or biventricular repair from a single-ventricle pathway were achieved with reasonably low mortality (11% and 10% respectively) and morbidity rates, and may provide a survival advantage over single-ventricle palliation (mortality rate 30%). Reintervention rates were 56% for biventricular conversion group and 40%

for biventricular repair group. Biventricular conversion/recruitment may be particularly important in high-risk groups such as patients with Trisomy 21 and heterotaxy who tolerate single-ventricle palliation poorly. Early establishment of adequate inflow and outflow may be key in allowing ventricular growth and normalization of the compliance of the hypoplastic ventricular chamber with the resulting ability to sustain a biventricular circulation. Patients who had biventricular conversion for right dominant CAVSD demonstrated a significant increase in the indexed left ventricular end diastolic volume on follow-up imaging.

(2) Groups in Giessen (28), Toronto (29) and Leiden (30) suggest bilateral pulmonary artery banding with or without ductal stenting in the neonatal period followed by a biventricular repair in suitable candidates. Sojak et al. (30) reported a mortality rate of 15.4% after biventricular repair after such a neonatal procedure in 26 patients with borderline left hearts. Median age at biventricular repair was 80 (range 15–371) days. During a median follow-up period of 1.8 (range 0.04–6.2) years, there were 15 (58%) surgical and 19 (73%) catheter-based interventions. Significant growth of the indexed left ventricular end diastolic volume was noted.

(3) In Utrecht a neonatal biventricular repair is performed in selected borderline left heart patients. In **Chapter 10** clinical outcome of a cohort of HLHC patients with median follow-up of 6.19 (IQR 6.04) years is demonstrated, showing a mortality rate of 6% and surgical and catheter-based reintervention rates of 28% and 31% respectively. Majority of reinterventions were performed on the aortic arch. Growth rate of left-sided heart structures was most prominent during the first year after biventricular repair with lower growth rate of the mitral valve compared to the aortic valve. Aortic valve Z-scores normalized at follow-up, in contrast to the mitral valve Z-scores.

Potential advantages of neonatal biventricular repair include complete left ventricular outflow desobstruction in the first weeks of life which may offer optimal circumstances for left ventricular recruitment. Definitive repair at a young age results in lower rates of surgical or catheter-based reinterventions when compared with neonatal bilateral pulmonary artery banding with ductal stenting prior to biventricular repair (30). As Sojak and colleagues point out, neonatal bilateral pulmonary artery banding with ductal stenting may result in ductal stent migration or in-stent stenosis requiring catheter-based reintervention and limited growth of both pulmonary arteries requiring balloon dilatation or surgical removal of 1 or both pulmonary artery bands. Potential drawbacks of the neonatal biventricular repair approach include the use of cardiopulmonary bypass, circulatory arrest and major surgical procedure during the neonatal period. Early selection of candidates for biventricular repair may therefore result in an increased risk for early mortality (30). However the Utrecht group reported only 1 (3%) early cardiac death in their cohort. Although patient characteristics among the groups may differ, clinical outcome after neonatal biventricular repair of the cohort of borderline left heart patients supports the motivation for aggressive maintenance of a biventricular circulation, promoting catch-up growth of hypoplastic heart structures.
Prospective and multicenter trials in borderline left heart patients are needed to improve clin-

ical decision making to choose for a treatment strategy. Given the relatively small number of patients, clinical care should be done according to national protocols, with echo and physical examination at the same intervals after surgery, in order to combine results and increase statistical power for analysis.

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SUMMARY / SAMENVATTING

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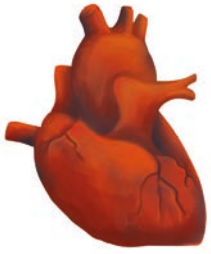

Summary

In **chapter 1** a general introduction is given. Complete atrioventricular septal defect (AVSD) consists of a ventricular septal defect (VSD) just below the plane of the atrioventricular (AV) valves, an atrial septal defect (ASD) immediately superior to the plane of the AV valves, and instead of two AV valve orifices, a single or common AV valve orifice. The partial subtype of this defect only consists of an ASD and has an intact ventricular septum. Defects can present either in a balanced form (characterized by two ventricles of equal size) or unbalanced form (characterized by underdevelopment of one of the ventricles and varying degrees of malalignment of the common AV valve over the hypoplastic ventricle). Complete AVSD is a condition requiring repair at the age of 3-5 months. The most commonly used repair technique is the double patch technique which shows similar results when compared to the (modified) single patch technique. Despite improved patient outcomes during the past three decades, reintervention rate (up to 10%) for left atrioventricular valve (LAVV) regurgitation remains a major problem that justifies further study. Management strategies for unbalanced complete AVSD include single-ventricle palliation and primary or staged biventricular repair. The challenge is to properly assign surgical strategy to the patient in question, taking into account the risk of achieving and maintaining a biventricular end state and the early and late risk associated with univentricular palliation. These clinical challenges justify a critical evaluation of outcomes in patients with unbalanced types of AVSDs who underwent repair. The aim of this thesis is to report upon clinical outcomes of AVSD repair and of LAVV replacement in neonates, infants and adults and to report upon clinical outcomes of repair of hypoplastic left heart complex.

In **chapter 2** follow-up results are presented of 350 children who underwent repair of balanced complete AVSD. Repair of complete AVSD carried a low mortality rate, but a moderate reoperation rate, mainly on the LAVV (7.3%) and left ventricular outflow tract (4.7%). A technical performance score was assigned according to pre-discharge/pre-reintervention echocardiographic findings of residual lesions and clinical status at discharge. The overall score for the procedure was based on the summation of the subcomponent scores. Presence of residual lesions before discharge, as measured by a technical performance score, was accurately able to identify patients who had complications, prolonged days on a ventilator, and required post-discharge reinterventions.

In **chapter 3** the association between individual subcomponents of the technical performance score and post-discharge reinterventions is investigated in the same patient cohort as researched in chapter 2. Residual left and right AV valve regurgitation and abnormal conduction at discharge were among the subcomponents strongly associated with post-discharge reinterventions. Technical performance score may aid clinicians in identifying children at higher risk for future reinterventions who may benefit from more frequent follow-up.

In **chapter 4** the characteristics of AVSD patients needing a LAVV replacement are investigat-

ed. A national multi-institutional, retrospective study among 64 patients (median follow-up 10.4 years) revealed that AVSD subtype (complete versus partial) is associated with timing of LAVV replacement. The median age at LAVV replacement was 4.8 (IQR 0.7-25.8) years and 19.9 (IQR 7.1-36.6) years for complete and partial AVSD respectively (p=0.014). In complete AVSD, LAVV is typically replaced within a few years after AVSD repair whereas in patients with partial AVSD, replacement was performed much later (> 10 years after initial surgery). Subsequent reoperations for prosthetic valve replacement and pacemaker implantations were common events during follow up.

One of the major limiting factors in successful LAVV replacement in neonates and infants has been the lack of appropriately sized prosthetic valves. In **chapter 5** early and long-term outcomes after mitral valve replacement (MVR) with the 15-mm mechanical prosthesis were evaluated. In 17 children with a median follow-up duration of 9.6 years, implantation of the miniaturized 15-mm mechanical prosthesis resulted in relatively good outcome (early mortality: 6%, late mortality: 6%, prosthesis replacement: 65%, oral anticoagulant related thromboembolic events: 12%). This prosthesis has shown to be a valuable adjunct to the armamentarium of the pediatric cardiac surgeon. It offered a chance of survival to critically ill infants and neonates. The prosthesis is relatively cheap and easy to implant in even the smallest babies. Late exchange for patient- prosthesis mismatch was required after a median of 3.5 years and could be carried out without the need for annular enlargement procedures. Complications of oral anticoagulant therapy were rare.

In **chapter 6** outcomes after MVR with 15-17 mm mechanical prostheses are evaluated. Analysis of outcomes in 61 infants with a median follow-up of 4.0 years revealed that small sized mechanical prosthetic valves may be an important option in critically ill neonates and infants who require MVR. There were 21% in-hospital deaths and 17% late deaths. Inevitable prosthesis replacement for outgrowth was required at a median of 3.7 years and could be carried out with low risk. Prosthesis replacement occurred in 44% of patients. Anticoagulation and associated morbidity remains a challenge. This data can serve as a benchmark to determine utility and benefits of bioprosthetic options, such as the stented bovine jugular vein conduits, that have recently been introduced as an alternative.

In **chapter 7**, outcomes in patients with balanced complete AVSD who underwent double patch repair with the use of an untreated autologous pericardial ventricular septal defect patch is described. In 73 patients with a median follow-up of 14.9 years, repair of ventricular septal defect with untreated autologous pericardial tissue in complete AVSD patients results in excellent outcomes with low rate of reoperations on LAVV (1.4%). Adequate sizing of the patch is essential, since this appears to be an important factor in preventing aneurysmal dilatation. The untreated autologous pericardial patch is assumed to be able to stretch with the growing heart over the years, having a positive impact on AV valve geometry when used by a skilled and experienced surgeon.

In **chapter 8** outcomes after double patch repair with an untreated autologous pericardial patch at the ventricular septal defect position in 59 children is compared with the use of a treated bovine pericardial patch in 20 children. Median follow-up time was 17.8 years. Ventricular septal defect in AVSD can be safely closed with untreated autologous pericardium. Outcome on mortality, reoperation or LAVV regurgitation were equal in both patch groups. Although fresh autologous pericardium is considered less user friendly we see a few potential benefits of this patch material. Using fresh pericardium may prevent calcification and leave the valve more accessible for future surgery.

In **chapter 9** mid-term outcomes in 212 patients with unbalanced complete AVSD are assessed according to management strategy. Biventricular conversion or biventricular repair from a single-ventricle pathway were achieved with reasonably low mortality and morbidity rates, given the complexity of the diagnosis, and may provide a survival advantage. This strategy may be particularly important in high-risk groups such as patients with trisomy 21 and heterotaxy who tolerate single-ventricle palliation poorly. Early establishment of adequate inflow and outflow may be key in allowing ventricular growth and normalization of the compliance of the hypoplastic ventricular chamber with the resulting ability to sustain a biventricular circulation.

In **chapter 10** the effect of biventricular repair on left-sided hypoplasia is assessed and the clinical results of 32 hypoplastic left heart complex patients after biventricular repair are evaluated (median follow-up 6.2 years). The growth rate of heart structures was most prominent during the first year after biventricular repair with lower growth rate of the mitral valve compared to the aortic valve. Aortic valve Z-scores normalized at 10-year follow-up, in contrast to the mitral valve. Reinterventions (44%) were common, particularly on the aortic arch. Preoperative mitral valve Z-scores were significantly associated with reinterventions.

Chapter 11 provides a general discussion. The results of the described studies are discussed and completed with the presently available literature data on the subject. Reoperations for LAVV regurgitation, the "Achilles' heel" of atrioventricular septal defect repair, is elaborated upon. Propositions for future research are made.

Samenvatting

Hoofdstuk 1 geeft een algemene inleiding. Een compleet atrioventriculair septumdefect (AVSD) is een aangeboren hartwijking die wordt gekenmerkt door een gemeenschappelijke atrioventriculaire (AV) klep, een ventrikel septum defect (VSD) vlak onder de AV klep en een atriaal septum defect (ASD) vlak boven de AV klep. Een partieel AVSD heeft in tegenstelling tot een compleet AVSD een intact ventriculair septum. Een AVSD kan zich presenteren in de gebalanceerde vorm (gekarakteriseerd door aanwezigheid van twee ventrikels van gelijke grootte) of in de ongebalanceerde vorm (gekarakteriseerd door onderontwikkeling van één van de ventrikels en een ongelijke verdeling van het atrioventriculaire klepoppervlak over de ventrikels). Een compleet AVSD is een afwijking die gecorrigeerd dient te worden bij een leeftijd van 3-5 maanden. De meest gebruikte techniek is de dubbele patch techniek, welke vergelijkbare resultaten laat zien als de (gemodificeerde) enkele patch techniek. De uitkomsten na chirurgische correctie zijn sterk verbeterd gedurende de laatste 3 decennia. Echter, het optreden van reoperaties voor lekkage van de linker AV klep (gerapporteerd in ongeveer 10% van de patiënten) blijft een groot probleem en vraagt om nader onderzoek.
Behandelstrategie van patiënten met een ongebalanceerd compleet AVSD bestaat uit univentriculaire palliatie, of primaire of gestageerde biventriculaire correctie. Bij het kiezen van een behandelstrategie dient een afweging gemaakt te worden tussen de risico's die ontstaan bij het bereiken en behouden van een biventriculaire circulatie en de risico's die bestaan bij een univentriculaire palliatie. Kritische evaluatie van uitkomsten bij gecorrigeerde ongebalanceerde AVSD patiënten kan helpen bij het nemen van beslissingen in deze uitdagende patiëntenpopulatie. Het doel van dit proefschrift is het evalueren van klinische uitkomsten na AVSD correctie en linker AV klepvervanging in neonaten, kinderen en volwassenen. Tevens worden de klinische uitkomsten na correctie van een hypoplastisch linkerhart complex geëvalueerd.

Hoofstuk 2 beschrijft uitkomsten van 350 kinderen die correctie van een compleet AVSD ondergingen. Correctie van een compleet AVSD resulteerde in een lage mortaliteit, maar in een aanzienlijk aantal reoperaties, vooral op de linker AV klep (7.3%) en op de linker ventrikel uitstroombaan (4.7%). Echografische bevindingen van de subcomponenten van de chirurgische correctie werden beoordeeld (bijvoorbeeld aanwezigheid van rest VSD/ASD, AV klep regurgitatie) samen met de klinische toestand bij ontslag en uitkomsten hiervan resulteerden in een *technical performance score* (technische beoordelingsscore). De uiteindelijke score was gebaseerd op het optellen van scores van de afzonderlijke subcomponenten van de chirurgische correctie. Aanwezigheid van rest-laesies voor ontslag, gemeten met deze *technical performance score*, maakte het mogelijk om patiënten met complicaties, verlengde aantal beademingsdagen en reoperaties na ontslag te identificeren.

In **hoofdstuk 3** werd onderzocht of er sprake was van een associatie tussen de afzonderlijke subcomponenten van de *technical performance score* en het optreden van reoperaties na ontslag. Het betrof hetzelfde patiënten cohort als in hoofdstuk 2. Rest-regurgitatie van de linker

en rechter AV klep en afwijkende geleiding bij ontslag waren subcomponten die sterk geassocieerd waren met het optreden van reoperaties na ontslag. Deze *technical performance score* kan artsen helpen om die patiënten te identificeren die een groter risico lopen op toekomstige reoperaties en die mogelijk baat hebben bij meer frequente controle afspraken.

Hoofdstuk 4 beschrijft de karakteristieken van AVSD patiënten die een linker AV klepvervanging hebben ondergaan. Een nationale multi-institutionele, retrospectieve studie van 64 patiënten (mediane follow-up 10.4 jaar) liet zien dat het AVSD subtype (compleet versus partieel) geassocieerd is met de timing van linker AV klepvervanging. De mediane leeftijd tijdens linker AV klepvervanging was 4.8 (interkwartielafstand 0.7-25.8) jaar en 19.9 (interkwartielafstand 7.1-3.6) jaar bij respectievelijk complete en partiele AVSD ($p=0.014$). De linker AV klep wordt doorgaans binnen een paar jaar na de initiële AVSD repair vervangen bij patiënten met het complete subtype, terwijl linker AV klepvervanging veel later plaatsvindt in partiele AVSD patiënten (> 10 jaar na de initiële AVSD correctie).

Een van de belangrijkste limiterende factoren voor een succesvolle linker AV klepvervanging bij neonaten en kinderen is het gebrek aan beschikbaarheid van geschikte maten kunstkleppen. In **hoofdstuk 5** worden de vroege en late uitkomsten na mitralisklepvervanging met een 15-mm mechanische klepprothese geëvalueerd. Implantatie van de 15-mm mechanische kunstklep laat relatief goede uitkomsten (vroege mortaliteit: 6%, late mortaliteit: 6%, kunstklepvervanging: 65%, trombo-embolische complicaties ten gevolge van antistollingsmedicatie: 12%) zien in een groep van 17 kinderen met een mediane follow-up van 9.6 jaar. Deze kunstklep is een waardevolle aanvulling op de behandelmogelijkheden van de kinderhartchirurg. Implantatie van deze kunstklep bood ernstige zieke kinderen en neonaten een kans op overleving. De kunstklep heeft een gunstige prijs-kwaliteit verhouding. Het is technisch haalbaar om deze te implanteren in zelfs de kleinste baby's. Vervanging van de kunstklep in verband met patiënt-kunstklep mismatch vond plaats na een mediane duur van 3.5 jaar. Vervangen van de kunstklep kon uitgevoerd worden zonder vergrotingsplastiek van de annulus.

Hoofdstuk 6 beschrijft de uitkomsten van patiënten die een mitralisklepvervanging ondergingen met een 15-17 mm mechanische prothese. Mediane follow-up van het cohort van 61 kinderen was 4.0 jaar. Uitkomsten waren acceptabel in deze kwetsbare patiëntengroep (vroege mortaliteit: 21%, late mortaliteit: 17%, kunstklepvervanging: 44%). Vervanging van de kunstklep in verband met patiënt-kunstklep mismatch vond plaats na een mediane duur van 3.7 jaar en kon uitgevoerd worden met lage risico's. Bijzondere aandacht verdient het gebruik van antistolling en geassocieerde morbiditeit. Dit is een uitdaging in deze kwetsbare patiëntenpopulatie. De bovenstaande data kan gebruikt worden als ijkpunt ter vergelijking met andere opties, zoals een biologisch conduit (deel van een vena jugularis van een rund) die in een stent is vastgenaaid (Melody-transkatheter-hartklep) en recent geïntroduceerd is als alternatief.

Hoofdstuk 7 geeft een overzicht van patiënten met een gebalanceerd AVSD die geopereerd zijn met de dubbele patch techniek, waarbij twee patches van onbehandeld autoloog pericard

werden gebruikt. In 73 patiënten met een mediane follow-up van 14.9 jaar zien we zeer goede uitkomsten met weinig reoperaties op de linker AV klep (1.4%). Het bepalen van de adequate grootte van de patch is essentieel in het voorkomen van dilatatie ten gevolge van een aneurysma van de patch. De onbehandelde autologe pericard patch wordt verondersteld over de eigenschap te beschikken om over de jaren mee te rekken met een groeiend hart. Wanneer deze patch gebruikt wordt door een bekwaam en ervaren chirurg heeft deze eigenschap mogelijk een positieve impact op de geometrie van de AV klep.

Hoofdstuk 8 vergelijkt de uitkomsten van AVSD patiënten waarbij het VSD gesloten is met een onbehandelde autologe pericard patch (n=59) met patiënten waarbij een patch van behandeld pericard van een rund is gebruikt (n=20). Mediane follow-up van het cohort was 17.8 jaar. Het VSD kan veilig en effectief gesloten worden met onbehandeld autoloog pericard. Uitkomsten wat betreft mortaliteit en reoperatie voor linker AV klep regurgitatie waren gelijk in beide groepen. Ondanks dat onbehandeld autoloog pericard minder makkelijk hanteerbaar is voor de chirurg, zien we een aantal potentiele voordelen van het gebruik van dit patch materiaal, zoals het voorkómen van het ontstaan van calcificatie van de klep en het toegankelijk houden van de klep voor toekomstige operaties.

In **hoofdstuk 9** worden de middellange termijn uitkomsten van verschillende behandelstrategieën onderzocht bij 212 patiënten met een ongebalanceerd AVSD. Biventriculaire conversie of biventriculaire correctie na een univentriculair traject liet relatief late mortaliteit en morbiditeit zien, zeker gezien de complexiteit van de diagnose, en laat mogelijk een overlevingsvoordeel zien. Deze strategie is met name belangrijk voor hoog risico groepen, zoals patiënten met een trisomie 21 en heterotaxie die matige uitkomsten na een univentriculaire palliatie laten zien. Vroeg tot stand brengen van een adequate instroom en uitstroom lijkt een belangrijke stimulans te zijn voor het groeien van het hypoplastische ventrikel en normalisatie van de compliantie welke resulteren in de mogelijkheid om een biventriculaire circulatie te bereiken.

In **hoofdstuk 10** wordt het effect van biventriculaire correctie op linkszijdige hypoplasie beoordeeld en worden de klinische resultaten van 32 hypoplastische linkerhart complex patiënten geevalueerd (mediane follow-up 6.2 jaar). De groeisnelheid van de linkszijdige hartstructuren was het meest uitgesproken tijdens het eerste jaar na de biventriculaire correctie, met een lagere groeisnelheid van de mitralisklep ten opzichte van de aortaklep. Aortaklep Z-scores normaliseerden gedurende 10 jaar follow-up, in tegenstelling tot de mitralisklep Z-scores. Reoperaties (44%) kwamen frequent voor, met name op de aortaboog. Lagere preoperatieve mitralisklep Z-scores waren geassocieerd met een verhoogde kans op het optreden van reoperaties.

Hoofdstuk 11 bevat een algemene discussie. De resultaten van de studies worden bediscussieerd en vergeleken met de beschikbare literatuur. Er wordt uitvoerig ingegaan op reoperaties voor lekkage van de linker AV klep, nog steeds de ‘Achilles Hiel’ van AVSD correctie. Suggesties voor toekomstig onderzoek worden gedaan.

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Curriculum Vitae

Rinske IJsselhof was born on October 21, 1991 in Polokwane, South Africa. In 2009 she finished high school at 'Bogerman College Sneek' cum laude. In the same year she entered Medical School at the University Medical Center Utrecht. In 2014 she went to Boston Children's Hospital for her elective clinical rotation under supervision of Dr. P.J. del Nido in the Department of Cardiac Surgery. During this rotation her interest for Cardiac Surgery developed. In 2015 her senior clinical rotation was done in the department of Cardiothoracic Surgery at the University Medical Center Utrecht under supervision of prof. dr. W.J.L. Suyker and dr. E.E.H.L. van Aarnhem. In 2016 she returned to Boston for her scientific research internship under supervision of Dr. M. Nathan. She worked for 6 months at Harvard Medical School in Boston Children's Hospital with specific interest in atrioventricular septal defects. During this work the first steps of this thesis were developed. In August 2016 she obtained her medical degree from the University Medical Center Utrecht. She started working as a resident – not in training – in the department of Cardiothoracic Surgery at the University Medical Center Utrecht and later at St. Antonius Hospital Nieuwegein. In September 2018 she decided to work full-time on this thesis in the Department of Pediatric Cardiac Surgery at Wilhelmina's Children Hospital Utrecht under supervision of prof. dr. P.H. Schoof, prof. dr. F. Haas and dr. M.S. Slieker.