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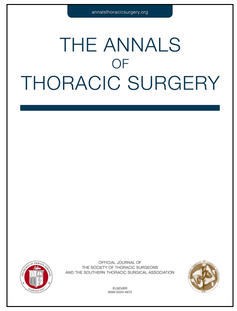

Complete Atrioventricular Septal Defect – Evolution of Results in a Single Center during 50 years

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Complete Atrioventricular Septal Defect – Evolution of Results in a Single Center during 50 years

Running Head: Unicenter Evolution of cAVSD Surgery

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Abstract

Background: Operative mortality after complete atrioventricular septal defect (cAVSD) repair has improved vastly. Less improvement has been demonstrated regarding late mortality and reoperation rates. There is evident lack of comprehensive population-based studies analyzing the history and progress of the ever-changing operative results.

Methods: This is a 5-million population-based retrospective study of consecutive 388 cAVSD patients operated in Finland between 1962 and 2014. Data was collected using Children's Cardiac Surgical Registry of Children's Hospital at the Helsinki University Hospital, Finland. Mortality data and reoperation rates were analyzed on a decade-by-decade basis.

Results: During the early era, overall mortality was 17.4%, operative mortality comprising 10.9%. The operative results have improved significantly over the decades, and eventually, the last decade showed no mortality. Total of 23 late deaths occurred; of these, 20 were directly heart-related. Half of the late mortality occurred during the first postoperative year. The only significant risk factor for overall mortality was an earlier decade of operation ($p<0.001$). Reoperation rates have not decreased but slightly increased over decades ($p=0.621$), and reoperations have been performed mainly during the first year after the primary operation. Actuarial freedom from left side AV valve reoperation at 15 years was 90,9%.

Conclusions: There has been an outstanding improvement in surgical results through years even though the general operative approach has remained the same. Rates of reoperation have not been declining, but the reoperations are dated to early childhood years. The improvement in results has been ongoing.

Abstract word count: 243

Abbreviations

cAVSD, complete atrioventricular septal defect

LAVV, left atrioventricular valve

SD, standard deviation

ICU, intensive care unit

PA, pulmonary artery

CPB, cardiopulmonary bypass

MI, mitral insufficiency

PH, pulmonary hypertension

CHF, congestive heart failure

MS, mitral stenosis

MOF, multi-organ failure

NEC, necrotizing enterocolitis

CI, cerebral infarction

SVT, supraventricular tachycardia

DCM, dilating cardiomyopathy

The early decades of complete atrioventricular septal defect (cAVSD) repair surgery were associated with high perioperative mortality after the first successful repair performed by C. Walton Lillehei and associates in the 1950's. Later, significant improvements in perioperative and late mortality have been demonstrated (1, 2, 3, 4). The early and long-term results of cAVSD patients are readily connected to the technical achievement at the surgery and, in particular, achieved left atrioventricular valve (LAVV) function. However, at the same time, there is a steady improvement in early survival after cAVSD repair and a concomitant regularity or a slight increase in the need for recurrent left AV valve plasty (1). A complete population analysis of the operative results of cAVSD could thereby show the evolution of the of surgical treatment in a single center setting.

The cardiac surgery patient registry of the Children's Hospital at the Helsinki University Hospital in Finland is particularly comprehensive and includes all corrective cAVSD operations performed in Finland since the beginning of corrective surgery in the 1960s with comprehensive follow-up of all operated patients. Patients' survival status has been crosschecked with Statistics Finland's causes-of-death registry. Finnish health care system is based on a social welfare model which limits no treatments from personal funds or health insurance, which makes the treatments available to all in need. Thus, our study includes a nationwide cohort of patients and is the first of its kind to examine all reparative operations for cAVSD since the beginning of corrective surgery in a single nation.

The purpose of this study was to determine the long-term outcome, atrioventricular valve reoperation rate, and risk factors of mortality and reoperation during the 50 years of corrective surgery of cAVSD at a single institution.

Patients and Methods

Data collection

Data were acquired using the surgical patient registry of the Children's Hospital, Helsinki University Hospital, which includes all children's heart operations performed since the beginning of pediatric cardiac surgery in Finland. The registry and the study protocol were approved by the local ethics review board at Helsinki University Hospital. A registry search was performed to identify all two-ventricle repairs for complete atrioventricular septal defect between 1962-2014. Patients with unbalanced ventricles, operated by a single ventricle line, were not included in this cohort. Criteria for the single ventricle palliation has been determined by left ventricular volume, inflow and outflow measurements according the standards of time being. Following variables were collected and analyzed to determine possible preoperative and perioperative risk factors for mortality and need for reoperation: trisomy-21, age at operation, gender, concurrent cardiac anomalies, the decade of procedure and perioperative complications.

Late survival data were acquired using the Central Population Register of Finland with patients' social security number. This register includes mortality data on all Finnish nationals. Death certificate data were acquired for those who had died during the follow-up period. Other methods of data collection were questionnaires sent to patients during the follow-up period at a few years' intervals and medical history records sent us by the patients' attending physicians. In the end, three patients (0.7%) of the primary study cohort were excluded from the analysis, all of them because of emigration and thus failure to acquire late survival data. Mean follow-up for all patients was 11.6 years (median 10.6, range 0-40.5). Mean follow-up for all hospital survivors was 13.0 years (median 12.0, range 0.1-40.5).

Study Endpoints

Primary outcomes for this study included survival and need for LAVV-related reoperation after initial two-ventricle complete AVSD repair. Mortality was further classified as operative (within the first 30 days of the primary surgery) and late (after the first 30-day postoperative period). For the causes of late death analysis, late deaths were further categorized into two groups. One was those patients who suffered mortality between 30 days and one year after primary repair and the other for those who died more than one year after primary repair. Reoperation was defined as any corrective surgery of the LAVV after the initial repair for the complete atrioventricular septal defect. The indication of LAVV reoperation was significant residual insufficiency leading to enlargement of the left ventricle and left atrium of more than +2 standard deviations (SD), with or without symptoms including arrhythmias. Criteria for the single ventricle palliation has been determined by left ventricular volume, inflow and outflow measurements according to the standards of time being.

Statistical Analysis

Continuous variables are reported as mean and median with range. Categorical variables are reported as frequencies and percentages of the total. Risk factors for mortality and need for reoperation were assessed using the binary logistic regression analysis. Actuarial survival and freedom from reoperation were estimated using the Kaplan-Meier method and groups were compared using the Mantel-Cox (log-rank) test when needed. Decade by decade trends for hospital and intensive care unit (ICU) length-of-stay were analyzed using one-way ANOVA. Levene's test for homogeneity of variances was used to assess equality of variances. Post hoc testing was performed using the Tukey's HSD test. Statistical significance was assumed with a p-value lower than 0.05.

Data were analyzed using IBM SPSS Statistics, version 23 (International Business Machines Corp, Armonk, New York).

Results

Patient characteristics

We identified a total of 388 patients who underwent a biventricular repair for complete atrioventricular septal defect between 1962-2014. Patient characteristics are summarized by a decade of operation in Table 1. The overall study cohort included 228 female (58.8%) and 160 male (41.2%) patients of whom 285 (73.3%) had trisomy 21 (Down's syndrome). Patients with Down's syndrome were not operated before the1980s. The median age at the time of operation decreased decade by decade from 14.5 years in the 1960s to 0.32 years in the 2000s (range 0.2-2.7 years).

Associated cardiac anomalies included ventricular septal defect in 13 patients (3.4%), coarctation of the aorta in 15 patients (3.9%), claimed patent ductus arteriosus in 64 patients (17.5%; yet routine ligation of the ductus arteriosus is the norm), double-outlet right ventricle in 2 patients (0.5%), pulmonary valve stenosis in 9 patients (2.3%), total anomalous pulmonary venous connection in 1 patient (0.3%) and tetralogy of Fallot in 15 patients (3.9%). Eight patients had exposed to previous cardiac operations before cAVSD repair. Six of these patients had had a prior corrective cardiac surgery for coarctation of the aorta, 2 of these patients for patent ductus arteriosus. Seventeen patients (4.4%) had undergone prior palliation with pulmonary artery banding, primarily in the 1980s. As a surgical method, the two-patch technique was used almost uniformly since the early 1980s.

Overall mortality

During the follow-up period, a total of 67 patients (17.4%) died. Of these, there were 42 operative deaths (62.7% of all deaths) and 25 late deaths (37.3%). Overall mortality showed improvements decade by decade. This improvement is illustrated in Table 2. No operative deaths have occurred after the year 2002.

The actuarial survival for all patients (n=388) was 85.8% (+/- 1.8%) at 1 year, 84.3% (+/- 1.9%) at 5 years and 82.8% (+/- 2.0%) at 15 years of follow-up. When comparing actuarial survival by a decade of operation using a Kaplan-Meier method the mortality was decreasing every decade. This finding was statistically significant ($p<0.001$). The results are illustrated in Figure 1.

Predictors of overall mortality

We analyzed obtained patient variables for the risk of total mortality using univariate binary logistic regression analysis. Only the decade of operation showed a statistically significant effect on all mortality. Down's syndrome and higher age at operation showed a trend towards lower risk of mortality, although the difference was not statistically significant ($p=0.122$ and $p=0.121$ respectively). Pulmonary artery (PA) banding was associated with a tendency towards higher risk of death, but the difference lacked statistical significance ($p=0.145$). Patients sex and required reoperation had no association with postoperative mortality ($p>0.05$).

In the multivariate binary logistic regression analysis for the mortality risk, based on the potential risk factors in the univariate analysis, only the decade of operation showed statistical significance with an odds ratio (OR) of 0.34 (0.23-0.49, $p<0.001$). Results of the logistic regression analysis are presented in Table 3.

Causes of late mortality

A total of 23 late deaths occurred during the follow-up. Actuarial survival was analyzed with a Kaplan-Meier analysis. Differences between the decades of operation were not statistically significant ($p=0.328$). About half of the late deaths (11 of 23, 47.8%) occurred during the first postoperative year. As shown in Figure 2, all except three late deaths were due to either a cardiac cause or an infection. Sixteen of the deaths were cardiac related (69,6%), four were due to infectious causes (17.4%). One patient suffered a late death due to cerebral infarction after surgery for scoliosis (4.3%). For the remaining two, the cause of death could not be identified (8.7%).

Reoperations

After the initial biventricular repair of the complete AVSD, a total of 31 reoperations, were performed on 29 patients. Ten (32.2%) of these were early reoperations during the first 30-day postoperative period.

Twenty-nine patients (7.5%) had reoperation because of atrioventricular valve insufficiency, two of these patients needed more than one reoperation (one patient with secondary AV-valvuloplasty and one patient with secondary AV-valve prosthesis). Five of these patients had a concurrent residual ventricular septal defect which was corrected on the same session.

In addition to these LAVV reoperations 15 other reoperations were performed on 15 patients. A total of 13 patients needed a permanent cardiac pacemaker. One patient was reoperated for right ventricular outflow tract restenosis, and one patient was reoperated for subvalvular aortic stenosis.

Actuarial freedom from LAVV-related reoperation was assessed using the Kaplan-Meier method. Kaplan-Meier estimates for freedom from reoperation were 94.8% (+- 1.2%) at 1 year, 92.9% (+/- 1.4%) at 5 years and 90.9% (+/- 1.6%) at 15 years. Decade by decade Kaplan-Meier analysis among all patients did not reveal any statistically significant difference in reoperation rates through the decades (p=0.621, Figure 3).

Predictors of the need for reoperation

We tested different variables for the risk of the need for reoperation using univariate binary logistic regression analysis. No statistically significant risk factors were identified. No patients with a prior PA banding had been reoperated, and thus we excluded the previous PA banding variable from the analysis.

A multivariate logistic regression analysis was performed with the most promising patient variables in the model. No statistically significant risk factors were identified. Results of the binary logistic regression analysis are demonstrated in Table 4.

Freedom from reoperation and death combined

Because there seemed to be a trend towards increasing reoperation rate (and thus it might be that some patients in need of reoperation died instead of reoperation), data about survival and need for reoperation were combined and analyzed same as above.

During the follow-up, 92 patients (23.7%) died or underwent reoperation for AV regurgitation, four of whom belonged to both categories (died after reoperation). The actuarial freedom from reoperation and death was 82.0% (+/- 2.0%) at one year, 79.1% (+/- 2.1%) at 5 years and 76.0% (+/- 2.3%) at 15 years of follow-up for the whole cohort. When we compared the results by a decade of operation using the Kaplan-Meier method, there was a statistically significant (Figure 4) trend towards better results every decade.

Predictors of the need for reoperation and death combined

We used binary logistic regression to analyze possible risk factors for the combined endpoint. Only the later decade of operation was a statistically significant protective factor against reoperation and death with a per decade OR of 0.52 (0.39-0.68, p<0.001). Results of the analysis are presented in Table 5. Associated anomalies did not show predictive value, probably due to the low incidence.

Hospitalization

Length-of-stays at the ICU and in the hospital were acquired. Time at the ICU could be obtained for all except 15 patients. Median of ICU stay was six days (0-59, mean 6.8). Median of ICU stay for those who survived the hospital was six days (0-59, mean 6.7). There was a statistically significant difference in the length of ICU stay when we compared the length of stay decade by decade (One-way ANOVA, F=3.484, p=0.004). Post hoc testing showed a decreasing trend in length of ICU stay in a decade by decade analysis.

Length of hospital stay data could not be acquired on 67 patients, mainly from the early decades. Median of hospital stay was 12 days (0-71, mean 13.9). Median of hospital stay for those who survived the hospital was 12 days (5-71, mean 14.5). There was a statistically significant difference in the length of hospital stay when we compared the length of stay decade by decade (One-way ANOVA, F=2.786, p=0.018). Post hoc testing showed a decreasing trend in the length of hospital stay in a decade by decade analysis.

Comment

This study is a 5-million population-based analysis of the results of cAVSD repair in Finland during the whole surgical treatment era of more than 50 years. With 99.3% follow-up coverage of operated patients, this study features particular comprehensiveness of a nationwide cohort of 388 consecutive patients. Operative mortality showed a steadily decreasing trend when assessed decade by decade, a finding still evident in the latest decades. No operative deaths have occurred since 2002. However, the improvement in late mortality has been less apparent.

Previous data show a significant improvement in both early and late results among pediatric cardiac surgery patients (4). This has also been acknowledged in AVSD patients, which is especially interesting since the operative approach has been practically unchanged, i.e., shunt closure with mainly two-patch technique with the closure of the LAVV cleft whenever possible. A widespread reduction in operative mortality is observable in analyses done using the extensive North American STS database (5,6,7), and similar results have been shown in single centers (1-3,8).

The decrease in operative mortality represents an improvement in perioperative care as well as a change in patient characteristics. Risk factors for operative death include pulmonary hypertensive crises (10) and severe LAVV regurgitation in the immediate postoperative period (3, 10). In this long-term study, factors contributing to the improvement in operative mortality might be the advances in intensive care and perfusion techniques. New medications to treat pulmonary hypertension appeared during the 1990s, including standard inhaled nitrous oxide in 1993 and milrinone in 1998, amrinone a few years earlier. Additionally, availability of around-the-clock children's cardiac anesthesiologist in the pediatric ICU since the end of the 1990s has improved postoperative care at our institution. During the 1990s increasing operation frequency brought surgical refinements and standardization. At that time, institutional learning must have improved all levels of treatment. Most importantly, the age at the time of complete repair has decreased and – at present – repair is performed at the median age of about 0.32 years (under four months) at our institution. This might be the major factor contributing to the decrease in operative mortality: the earlier repair prevents the development of permanent changes in the pulmonary vasculature and thus reduces the risk for pulmonary hypertensive crises previously shown to be a risk factor for operative mortality. We have kept the operative age on the late side of the spectrum with an idea to gain more tissue strength at the operation.

The improvement in late survival has been subtler. In our cohort, about half of the late deaths occurred during the first postoperative year. Late death among those patients who survive the first postoperative year is uncommon in the scope of our follow-up period. We could see a small improvement in late survival when we compared the results decade by decade. In our material, late deaths are almost uniformly cardiac of origin with usually a complicating infection causing the acute worsening. It can be argued that these deaths could be prevented be it that cardiac condition was treated more aggressively.

The late survival goes hand in hand with LAVV function: the main factor affecting the late mortality is LAVV regurgitation (2, 9). As Crawford (1) concluded in the analysis of his personally operated 20-year cohort, the late incidence of LAVV-related reoperation seems to have stayed constant. Our data support the studies implying (1) that there has been little improvement regarding the need for LAVV reoperation decade by decade, as the rates for reoperation due to LAVV incompetence have stayed around 10% at ten years for the last decades, and we saw a small but statistically insignificant trend towards increasing reoperation rates. Young operational age increases technical difficulties due to more fragile valve tissues and smaller dimensions. This may contribute to unsatisfactory surgical results, which might eventually partly explain the remaining need for early reoperations. As previously proposed (1), the risk for reoperation seems to be highest in the early postoperative period with no reoperations performed after more than a 9-year follow-up after the initial repair in our patient material. The mean time for LAVV-related reoperation was at 1.79 years of follow-up after primary repair (median 0.53 years). As shown above, the insufficiency of the LAVV could most commonly be managed with a repair of the LAVV rather than valve replacement, which is in line with previous research (2).

We analyzed the combined end-point of freedom from LAVV reoperation and overall mortality and saw statistically significant stepwise improvement in results through the decades. The analysis showed that although there was a slightly increasing trend in the reoperations due to LAVV insufficiency through the decades, the overall results have still improved significantly. Our contemporary mortality and reoperation rates are in line with the previous single-center results (1-3, 8) and strengthen the fact that the results have improved considerably from the early days of corrective AVSD surgery.

This study included a large nationwide cohort of patients with surgically corrected cAVSD with practically complete follow-up, but it has its limitations. Firstly, although we selected all patients with a two-ventricle repair, we cannot rule out the fact that there might have been some included patients with borderline ventricles as the retrospective design of this study does not allow us to collect all possibly relevant data. However, we have no conversions to the univentricular line, according to the reoperations data. Secondly, the analyses were only performed using hard clinical data on survival and reoperations, which might not reflect the differences in quality of life or functional status of the patients. The primary diagnostic studies at the time of repair were unavailable for all patients and therefore were not used in risk factor analysis. The registry was created in the late 1980s and thus does not include all data for prior operations. Finally, the study comprised of a relatively small number of different operating surgeons at one institution and might not take into account the possible differences in operating techniques and care strategies used in other centers.

In this study, we have shown the evolution in the treatment results of cAVSD patients in a true nationwide cohort of more than 50 years. There has been a tremendous change in the surgical results of cAVSD repair when the results are assessed decade by decade. The improvement has been stepwise and has been continuing even in the latest decades. Most of the mortality in the scope of our follow-up is LAVV-related and is observed in the early period after primary repair. The marked improvement in survival from the early era of hypothermic arrest without cardiopulmonary bypass is underlined by the fact that, in our series, the last perioperative death occurred in 2002. As we are now approaching better and better survival of the patients on each decade, morbidity studies are necessary to optimize the treatment protocols for patients with cAVSD. Nevertheless, according to our results, modern cAVSD surgery is safe, and LAVV re-repair is warranted in the early phase when indicated.

References

1. Crawford F, Stroud M. Surgical repair of complete atrioventricular septal defect. Ann Thorac Surg. 2001;72:1621-9.

2. Ginde S, Lam J, Hill GD, et al. Long-term outcomes after surgical repair of complete atrioventricular septal defect. Journal of Thoracic & Cardiovascular Surgery. 2015;150:369-74.

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

4. Raissadati A, Nieminen H, Jokinen E et al. Progress in Late Results Among Pediatric Cardiac Surgery Patients. Circulation. 2015;131:347-353.

5. Fudge JC, Shuang L, Jaggers J, et al. Congenital Heart Surgery Outcomes in Down Syndrome: Analysis of a National Clinical Database. Pediatrics. 2010;126:315-22.

6. Jacobs JP, Jacobs ML, Mavroudis C, et al. Atrioventricular septal defects: Lessons learned about patterns of practice and outcomes from the congenital heart surgery database of the society of thoracic surgeons. World J Pediatr Congenit Heart Surg. 2010;1:68-77.

7. St Louis JD, Jodhka U, Jacobs JP, He X, Hill KD, Pasquali SK, Jacobs ML. Contemporary outcomes of complete atrioventricular septal defect repair: Analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. J Thorac Cardiovasc Surg. 2014 Dec;148(6):2526-31.

8. Lange R, Guenther T, Busch R, Hess J, Schreiber C. The presence of down syndrome is not a risk factor in complete atrioventricular septal defect repair. Journal of Thoracic & Cardiovascular Surgery. 2007;134:304-10.

9. Hanley FL, Fenton KN, Jonas RA, et al. Surgical repair of complete atrioventricular canal defects in infancy. twenty-year trends. J Thorac Cardiovasc Surg. 1993;106:387-94.

10. Bando K, Turrentine MW, Sun K, et al. Surgical management of complete atrioventricular septal defects. A twenty-year experience. Journal of Thoracic & Cardiovascular Surgery.

1995;110:1543-52.

Table 1. Patient and operative characteristics by decade of operation

	All	1960's	1970's	1980's	1990's	2000's	2010's
n	388	1	12	60	149	120	46
Females, n(%)	228 (58.8%)	1 (100%)	6 (50%)	37 (61.7%)	89 (59.7%)	65 (54.2%)	30 (65.2%)
Down's, n(%)	285 (73.3%)	0 (0%)	0 (0%)	37 (61.7%)	121 (80.7%)	92 (76.7%)	35 (76.1%)
Reoperations, n(%)	38 (9.8%)	0 (0%)	1 (8.3%)	3 (5.0%)	13 (8.7%)	14 (11.7%)	7 (15.2%)
LAVV-reoperations, n(%)	29 (7.5%)	0 (0%)	1 (8.3%)	3 (5.0%)	9 (6.0%)	11 (9.2%)	5 (10.9%)
Complications, n(%)	172 (47.9%)	1 (100%)	5 (41.7%)	30 (50.0%)	81 (54.4%)	39 (32.5%)	16 (34.8%)
Mortality, n(%)	69 (18.5%)	1 (100%)	7 (58.3%)	18 (30.0%)	33 (22.1%)	8 (6.7%)	0 (0%)
Age, mean (yrs)	0.95	14.49*	4.04	1.70	0.90	0.43	0.43
Age, median (yrs)	0.40	14.49*	2.65	0.77	0.35	0.32	0.38
Hospital stay, mean (d)	14.05	5*	6.5*	16.4 *	16.0	12.5	11.8
ICU stay, mean (d)	6.72	5*	6.6	7.7	8.0	5.7	4.4

Aortic xclamp (min)	77.1	NA	NA	NA	74.4	78.2	77.3
CPB (min)	115.4	NA	NA	NA	118.0	115.1	113.5

ICU, intensive care unit; xclamp, cross-clamp; CPB, cardiopulmonary bypass: LAVV, left atrioventricular valve.

*) low number of patients with data

Table 2. Postoperative mortality by decade of operation

	1960's	1970's	1980's	1990's	2000's	2010's
All operated, n	1	12	60	149	119	45
Operative mortality, n (%)	1 (100%)	5 (41.7%)	11 (18.3%)	21 (14.0%)	4 (3.3%)	0
Late mortality, n (%)	0	2 (16.7%)	7 (12.1%)	12 (8.3%)	4 (3.3%)	0
All mortality, n (%)	1 (100%)	7 (58.4%)	18 (30.4%)	33 (22.3%)	8 (6.6%)	0 (0%)

Table 3. Analysis of potential risk factors associated with postoperative mortality

	Univariate model		Multivariate model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Decade of operation	0.38 (0.28-0.52)	<0.001	0.34 (0.23-0.49)	<0.001
Female sex	1.31 (0.76-2.25)	0.340		
Down's syndrome	0.64 (0.36-1.13)	0.122	0.96 (0.49-1.86)	0.895
Age at operation (per year)	1.10 (0.98-1.23)	0.121	0.88 (0.75-1.04)	0.127
Required reoperation	0.75 (0.25-2.22)	0.599		
Prior PA banding	2.25 (0.76-6.71)	0.145	2.56 (0.79-8.35)	0.118

Table 4. Analysis of potential risk factors associated with LAVV reoperation

	Univariate model		Multivariate model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female sex	0.73 (0.34-1.57)	0.425	0.74 (0.34-1.58)	0.433
Decade of operation	1.30 (0.88-1.93)	0.194	1.34 (0.91-1.98)	0.141
Down's syndrome	0.67 (0.30-1.50)	0.330	0.61 (0.27-1.37)	0.232
Age at operation (per year)	0.94 (0.73-1.21)	0.619		

Table 5. Analysis of potential risk factors associated with the combined end point

	Univariate model		Multivariate model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Down's syndrome	0.69 (0.41-1.14)	0.146	0.89 (0.51-1.55)	0.670
Female sex	1.12 (0.70-1.81)	0.638		
Decade of operation	0.53 (0.41-0.69)	<0.001	0.52 (0.39-0.68)	<0.001
Age at operation (per year)	1.08 (0.96-1.20)	0.194	0,95 (0.83-1.08)	0.410
Prior PA banding	1.49 (0.50-4.40)	0.472		

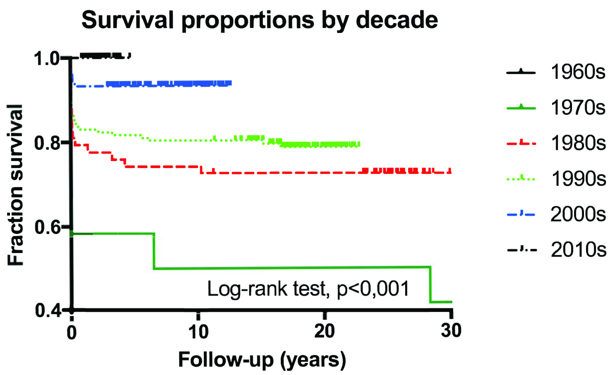
Figure legends

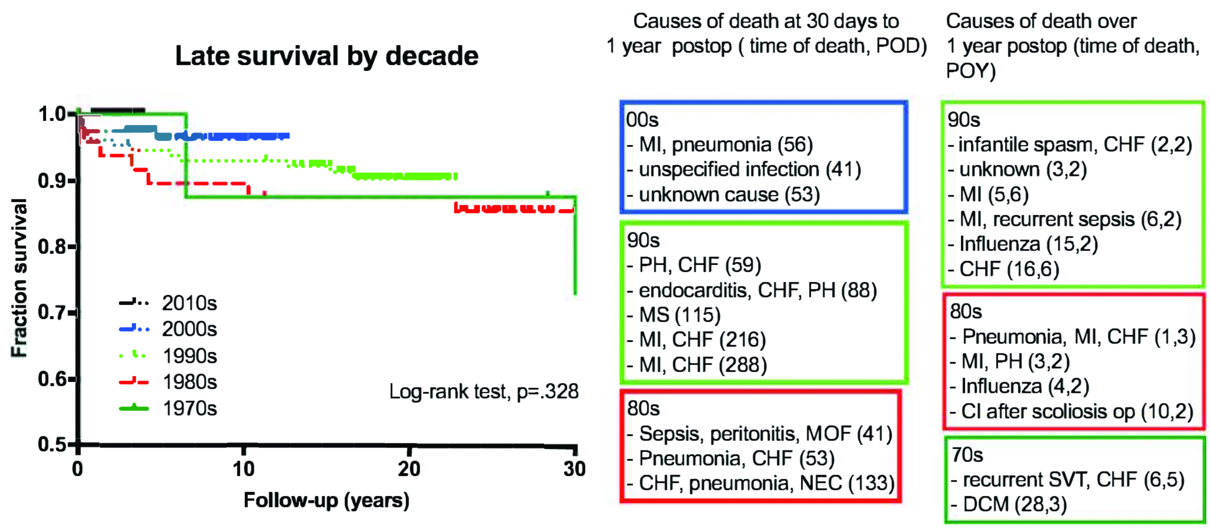
Figure 1. Kaplan-Meier estimates of actuarial survival by decade of operation. The mortality has decreased in a consistent manner when compared decade by decade.

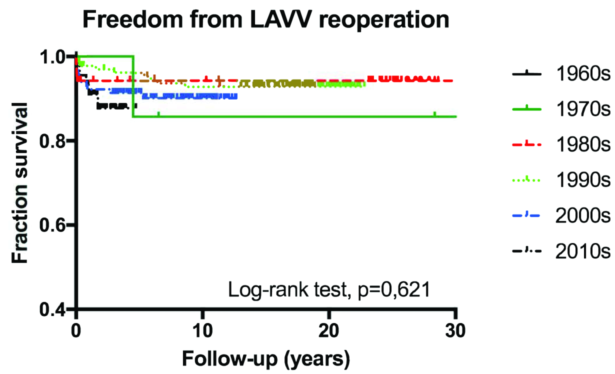
Figure 2. Kaplan-Meier estimates of actuarial late survival by decade of operation. Late survival has shown a decreasing, yet statistically insignificant trend through the decades. MI, mitral insufficiency, PH, pulmonary hypertension, CHF, congestive heart failure, MS, mitral stenosis, MOF, multi-organ failure, NEC, necrotizing enterocolitis, CI, cerebral infarction, SVT, supraventricular tachycardia, DCM, dilating cardiomyopathy.

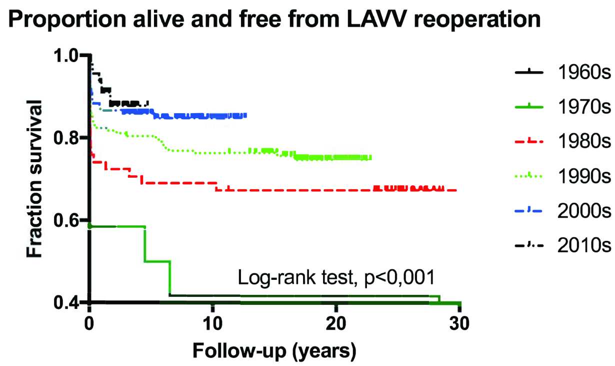
Figure 3. Kaplan-Meier estimates of actuarial freedom from LAVV reoperation by decade of primary operation. Reoperation rate has shown a slightly increasing trend through the decades. This difference is not statistically significant. Reoperations are situated in the early postoperative period.

Figure 4. Kaplan-Meier estimates of actuarial portion of patients alive and free from reoperation by decade of primary operation. The results have improved in a consistent manner when the end points have been combined. The latest decades show no difference.


Survival proportions by decade
Fraction survival
1.0
0.8
0.6
0.4
0
10
20
30
Follow-up (years)
Log-rank test, p<0,001
1960s
1970s
1980s
1990s
2000s
2010s


Late survival by decade
Fraction survival
1.0
0.9
0.8
0.7
0.6
0.5
0
10
20
30
Follow-up (years)
2010s
2000s
1990s
1980s
1970s
Log-rank test, p=.328
Causes of death at 30 days to 1 year postop (time of death, POD)
00s
- MI, pneumonia (56)
- unspecified infection (41)
- unknown cause (53)
90s
- PH, CHF (59)
- endocarditis, CHF, PH (88)
- MS (115)
- MI, CHF (216)
- MI, CHF (288)
80s
- Sepsis, peritonitis, MOF (41)
- Pneumonia, CHF (53)
- CHF, pneumonia, NEC (133)
Causes of death over 1 year postop (time of death, POY)
90s
- infantile spasm, CHF (2,2)
- unknown (3,2)
- MI (5,6)
- MI, recurrent sepsis (6,2)
- Influenza (15,2)
- CHF (16,6)
80s
- Pneumonia, MI, CHF (1,3)
- MI, PH (3,2)
- Influenza (4,2)
- CI after scoliosis op (10,2)
70s
- recurrent SVT, CHF (6,5)
- DCM (28,3)


Freedom from LAVV reoperation
Fraction survival
1.0
0.8
0.6
0.4
0
10
20
30
Follow-up (years)
Log-rank test, p=0,621
1960s
1970s
1980s
1990s
2000s
2010s



Proportion alive and free from LAVV reoperation
1.0
0.8
0.6
0.4
Fraction survival
0
10
20
30
Follow-up (years)
Log-rank test, p<0,001
1960s
1970s
1980s
1990s
2000s
2010s