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Long term outcome after surgical ASD-closure at young age: Longitudinal follow-up up to 50 years after surgery

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ABSTRACT

Objectives: To describe the clinical outcome and quality of life up to 50 years after surgical atrial septal defect (ASD) closure at young age. Primary outcome is defined as MACE (all-cause mortality, cardiac re-interventions, ischemic stroke, endocarditis, heart failure and symptomatic arrhythmia).

Methods: Single-center, longitudinal cohort-study evaluating 135 consecutive patients who underwent ASD-closure before the age of 15 years between 1968 and 1980. Participants were invited for extensive cardiac evaluation and assessment of quality-of-life every 10 years.

Results: Eighty patients (86%) of 93 eligible survivors were included in this study (mean age 52 ± 5 years (range 41–63), 40% male). Median follow-up since surgery was 45 years (range 40–51). Cumulative survival after 50 years was 86% and comparable to the normal Dutch population. Cumulative event-free survival after 45 and 50-years was 59% and 46% respectively (re-intervention in 6, symptomatic arrhythmia in 25, and pacemaker implantation in 10 patients). Right ventricular ejection fraction on CMR was diminished in 6%. Exercise capacity was normal in 77%. There was no pulmonary hypertension. NT-proBNP was elevated in 61%. Quality of life was comparable with the general population. No predictors for late events were identified.

Conclusion: Long-term survival after surgical ASD-closure in childhood is good and not statistically different at 50 years compared to the normal Dutch population. Re-intervention rate is low, there is no pulmonary hypertension. Right ventricular function was diminished in 6%, exercise capacity was good and stable over time with quality of life comparable to the general population. However, supraventricular tachycardia is common.

1. Introduction

Atrial septal defect (ASD) is a common form of congenital heart disease (CHD), with an estimated birth prevalence of 1.6 per 1000 and a prevalence of 1 per 1000 in adults. It comprises 5–10% of all CHD [1,2]. It can cause right ventricular (RV) volume overload, pulmonary hypertension (PH), atrial arrhythmias, and paradoxical emboli. After the first successful surgical ASD-closure in 1952, the continuing innovations in surgical techniques and peri-operative care decreased the early mortality risk from 50% in the early era to 0.1% today [3]. Nowadays transcatheter closure is the preferred treatment in patients with a secundum type ASD with a suitable anatomy. However, surgical closure

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is still the treatment of choice in patients with a large or non-centrally located ASD [4].

Although prognosis after surgical ASD-closure is excellent, there are concerns on long-term morbidity, especially for arrhythmias and PH [5]. The reported prevalence of arrhythmia in patients operated at young and adult age is 16% and up to 50% respectively [5–10]. Nevertheless, data on very long-term outcome are scarce. In this study, we report on mortality, morbidity, cardiac function, and quality of life (QoL) up to 50 years after surgical ASD-closure. Our data are derived from a unique cohort that has been extensively studied every 10 years since the 1990s.

2. Methods

2.1. Study population

All consecutive patients who underwent surgical correction for a secundum type ASD or sinus venosus type (SVD) ASD in the Erasmus Medical Center, between 1968 and 1980 at <15 years of age at the time of operation were included. This cohort was previously described in 1990, 2001 and 2011 [5,11,12]. Current survival status was obtained from the Dutch National Population Registry (BRP). All patients who were alive and participated in the previous study were invited for in-hospital evaluation, including medical history, 12-lead electrocardiography (ECG), cardiopulmonary exercise testing (CPET), 24-h ambulatory ECG registration (Holter), transthoracic echocardiogram, cardiac magnetic resonance imaging (CMR) and laboratory measurements. In addition, patients underwent psychological evaluation, including the 36-item Short Form Health Survey (SF-36) questionnaire. From patients unable to participate in the in-hospital investigations, available data on morbidity and other medical data was obtained.

The study protocol was approved by the local Medical Ethics Committee (MEC 2019–0465), written informed consent was obtained from all study participants. The study was carried out according to the principles of the Declaration of Helsinki. The authors have no conflict of interest to declare.

2.2. Primary outcome

Survival status was compared to the general age-matched Dutch population by plotting expected survival of the Dutch population aged 7.5 years at the start of the inclusion period. Major cardiac events (MACE) were defined as all-cause mortality, all cardiac re-interventions (surgical or interventional), ischemic stroke, endocarditis, clinically relevant heart failure and symptomatic arrhythmia. Heart failure was considered clinically relevant when a patient was admitted for heart failure or medication was prescribed. Arrhythmia was considered symptomatic when medication was prescribed or a cardioversion or ablation procedure (either surgical or catheter based) was performed.

2.3. ECG and Holter recording

All patients underwent standard 12-lead surface ECG and 24-h ambulatory Holter recording. The analysis method was described previously [12]. ECGs with paced rhythm were excluded from conduction-interval analysis.

2.4. Cardiopulmonary exercise testing (CPET)

CPET was performed by bicycle ergometry with gradual increments of the workload by 20 W/min, assessing maximal exercise capacity and oxygen consumption (VO2max). Results were compared to reference values of matched normal individuals and to earlier measurements. Performance was considered maximal when the maximal respiratory quotient was ≥1.1. An exercise capacity and VO2max >85% of the predicted value were considered normal.

2.5. Transthoracic echocardiography

All patients underwent two-dimensional and three-dimensional echocardiography, including color-flow Doppler-imaging, pulsed-wave, and continuous-wave Doppler-echocardiography using an EPIQ7 ultrasound system (Philips Medical Systems, Best, The Netherlands) equipped with an X5–1 matrix array transducer (composed of 3040 elements with 1–5 MHz). All studies were performed by experienced technicians and analyzed according to current guidelines [13–18]. More details regarding echocardiographic methods are provided in Supplementary File 1.

2.6. Cardiac magnetic resonance imaging (CMR)

CMR imaging was performed on a clinical 1.5 T MRI system (Signa Artist 1.5 T, GE Healthcare, Milwaukee, WI, USA). Standard cine images were acquired with ECG-gating during repeated end-expiratory breath holds with the patient in supine position. Offline post-processing analyses were performed on Medis software (Medis suite version 4.0, Qmass version 8.1 and Qmap T1/T2 version 2.2.38, Medis Medical Imaging Systems, Leiden, The Netherlands).

All studies were analyzed by an experienced reviewer (JC) according to current guidelines [19,20]. Scans performed in the preceding study were re-analyzed according to current standards, both previously reported data and results according to current guidelines are reported [5]. More details regarding CMR methods are provided in Supplementary File 1.

2.7. Laboratory measurements

After at least 1 h rest, peripheral venous blood samples were collected. Commercially available assays were used to determine creatinine, NT-proBNP, HS-troponin-T, C-reactive protein, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, hemoglobin, relative distribution width, Hemoglobin A1C, thyroid stimulating hormone, and free thyroxine. Additional information regarding the used assays is provided in Supplementary Table 1.

2.8. Subjective health assessment

All patients underwent the SF-36 questionnaire. Results were compared to the age-matched Dutch population [21].

2.9. Statistical analysis

Continuous variables are presented as mean ± SD if normally distributed or as median (25th–75th percentile) in case of a non-normal distribution. Categorical variables are reported as frequencies and percentages. The paired *t*-test was used to compare normally distributed continuous variables between paired groups, while the Student's t-test was used in case of normally distributed continuous variables between independent groups. In case of a non-normal distribution, Wilcoxon signed rank test and Mann Whitney test was used, respectively.

Frequencies were compared by using the Chi-square test or Fisher's exact test when appropriate. For paired categorical data, the McNemar test was used. Associations between continuous variables were assessed by the Pearson or Spearman correlation coefficients, depending on normality of the variable distribution. Survival and event-free survival was displayed in Kaplan-Meier curves. Cox proportional hazards models were used to investigate associations with survival and MACE of the following a priori specified variables: age at operation, ASD subtype, pre-operative shunt size, cardiopulmonary bypass (CPB) time and post-operative arrhythmia. A $p < 0.05$ (two sided) was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences version 28 (SPSS Inc., Armonk, NY, USA).

3. Results

3.1. Study population

Present study participation is visualized in Supplementary Fig. 1. The original cohort consisted of 135 patients (44% male, mean age at operation 7.5 ± 3.5 years), 105 with a secundum type ASD and 30 with a SVD ASD. Survival status was obtained in 128 patients (95%). Eighty patients (86% of the approached 93) were included in the present study. Baseline characteristics are presented in Table 1. Current mean age was 52 ± 5 years (range 41–63 years, 40% male). Age at operation was 7.5 ± 3.5 years, median follow-up since surgery was 45 years (range 40–51 years, 25th–75th percentile 42–47 years). There were no statistically significant differences in baseline characteristics between participants and non-participants (Supplementary Table 2).

3.2. Survival

Survival and event-free survival is plotted in Fig. 1. Cumulative survival after ASD surgery at 10 years and 20 years, 30 years, 40 years, and 50 years was 100%, 98% (95% CI 0.931–0.992), 94% (95% CI 0.876–0.968) and 86% (95% CI 0.708–0.938) respectively. In the last decade and during the total follow-up, 6 and 11 patients died respectively (details are provided in Supplementary Table 3). Survival at 50 years is not statistically different compared to the general Dutch population ($p = 0.16$).

Cumulative event-free survival after a follow-up of 45 and 50 years was 59% and 46% respectively.

3.3. Other major cardiac events

An overview of all Major cardiac events is presented in Supplementary Table 4. In summary, 6 patients underwent a re-intervention (Supplementary Table 5), in three cases this was because of re-operation for ASD closure.

Symptomatic arrhythmia was present in 25 patients, with atrial flutter being the most common, although many patients developed atrial fibrillation subsequently. Ten patients underwent catheter ablation for supraventricular arrhythmia. The cumulative burden of symptomatic arrhythmia at 45- and 50-years follow-up was 25% and 35% respectively. During the entire follow-up, 10 patients underwent pacemaker implantation, 4 of them within 5 years after surgery. Two patients

Table 1
Patients Characteristics.

	Total	1990	2001	2011	2021
Number of patients	135	104	94	85	80
Male	44%	42%	41%	39%	40%
Cardiac catheterization at baseline					
Qp:Qs ratio	2.3:1 ± 0.8	2.3:1 ± 0.7	2.3:1 ± 0.7	2.3:1 ± 0.7	2.4:1 ± 0.7
Peak systolic PA pressure	26 ± 7	26 ± 6	26 ± 6	26 ± 7	26 ± 6
Surgical data					
Age at operation	7.5 ± 3.5	7.3 ± 3.4	7.5 ± 3.5	7.4 ± 3.5	7.5 ± 3.5
Mode of closure					
Direct closure	76%	75%	75%	72%	71%
Closure with patch	24%	25%	25%	28%	29%
Sinus venosus type ASD	22%	22%	23%	25%	26%
Follow-up since surgery (years)		15 (10–22)	26 (21–33)	35 (30–41)	45 (40–51)
Age at time of study (years)		22	33	43 ± 4.8	52 ± 5

PA = pulmonary artery, ASD = atrial septal defect.

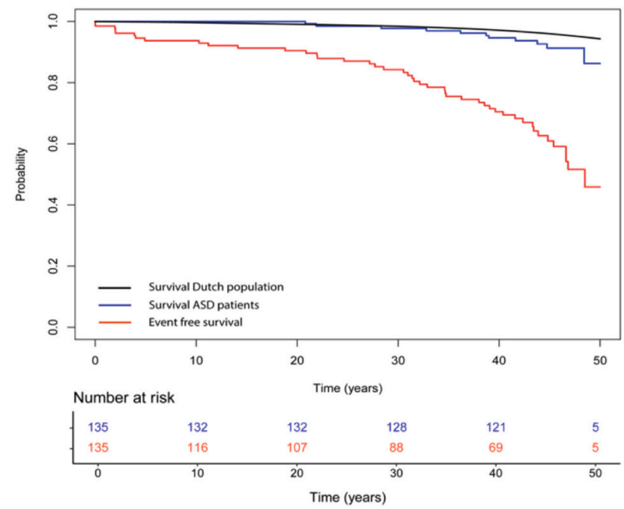

Fig. 1. Survival and survival free of major events.
Survival of the normal Dutch population is plotted from the age of 7.5, the mean age at time of surgery of the cohort at the moment of start of the inclusion.

developed endocarditis; both underwent pacemaker implantation previously. In 3 patients symptomatic heart failure developed. Finally, in 8 patients ischemic stroke occurred, in one patient a residual ASD was discovered.

3.4. Predictors for adverse outcome and late events

Univariable analysis was performed with pre-specified variables described earlier. No association between these variables and late events (all) or arrhythmias was identified (Supplementary Table 6 and 7). Multivariable analysis was not performed.

3.5. ECG and Holter monitoring

The results of ECG-reporting and Holter-findings are presented in Table 2. Sinus or atrial rhythm was present in 89%. A significant increase in QRS duration was observed in the last decade, with 13% of patients now having an QRS duration >120 ms.

Holter monitoring showed supraventricular arrhythmia in 69%, however most cases were clinically non-relevant short episodes of supraventricular tachycardia. Atrial fibrillation or flutter was seen in 2 patients (4%). Non-sustained ventricular tachycardia (3–10 complexes) was present in 4 patients (7%), while sustained ventricular tachycardia was not observed in the present study, nor in the previous studies.

3.6. CPET

CPET results are presented in Table 2. Both maximum exercise capacity and VO2max were normal in 77% of patients, with 20% having a diminished VO2max. There was no significant difference between secundum type ASD and SVD ASD patients.

There was no correlation between VO2max and age at surgery, shunt size, pulmonary artery systolic pressure or ASD type. No correlation between dimensions on CMR and diminished VO2max was found. Left ventricular ejection fraction (LVEF) on CMR was significantly lower in patients with a diminished VO2max (54% vs. 59%, $p = 0.02$). Right ventricular ejection fraction (RVEF) was not significantly different in subjects with a diminished VO2max.

3.7. Echocardiography

Echocardiography parameters are presented in Table 3. Right atrial

Table 2
standard 12-lead electrocardiogram, 24-h Holter and cardiopulmonary exercise testing findings comparing 1990, 2001, 2011 and 2021.

	1990	2001	2011	2021	*p*-value 1990 vs 2021	p-value 2011 vs 2021
ECG						
Rhythm						
Sinus	90%	89%	89%	80%	**0.04**	**0.016**
Atrial	6%	5%	4%	9%	0.69	0.45
Nodal	1%	1%	0	1%	1	–
Atrial flutter/fibrillation	0	1%	3%	3%	–	1
Pacemaker	4%	3%	4%	7%	0.25	0.25
PR interval (ms)	151 ± 30	153 ± 30	161 ± 29	162 ± 27	**0.001**	0.11
PR interval > 200 ms	3%	5%	9%	10%	**0.03**	0.5
QRS duration (ms)	88 ± 11	96 ± 13	100 ± 11	102 ± 13	**<0.001**	0.27
QRS >120 ms	0%	2%	4%	13%	–	**0.03**
LVH or RVH	4%	5%	1%	2%	1	1
24-h holter						
Supraventricular arrhythmia	45%	41%	57%	69%	**0.004**	**0.003**
Sinus node disease	39%	31%	24%	26%	0.7	0.3
SVT	6%	21%	44%	57%	**<0.01**	**0.01**
PAF	0%	0%	0%	0%	–	–
PAFl	0%	1%	0%	2%	–	–
Continuous AF/AFl	0%	1%	2%	2%	–	1
VT 3–10 complexes	3%	5%	6%	7%	–	1
VT >10 complexes	0%	0%	0%	0%	–	–
First degree AV block	15%	9%	10%	10%	0.7	1
Second degree AV block	2%	0%	3%	0%	–	–
Third degree AV block	0%	0%	0%	0%	–	–
CPET						
Maximum heartrate (% of expected)	92% ±8	92% ±9	90% ±12	91% ±12	0.16	0.93
Maximum exercise capacity (% of expected)	104% ±20	95% ±20	96% ±18	104% ±21	0.08	**0.01**
Significant arrhythmia	0%	0%	0%	0%	–	–
VO2max (% of expected)	–	–	91% [81–105]	101% [89–118]	–	**0.01**

LVH = left ventricular hypertrophy, RVH = right ventricular hypertrophy, SVT = supraventricular tachycardia, PAF = paroxysmal atrial fibrillation, PAFl = paroxysmal atrial flutter, VT = ventricular tachycardia, AV = atrioventricular, CPET = cardiopulmonary exercise testing. VO2 max *was not performed in 1990 and 2001.*

(RA) and RV dilatation was present in 23% and 45% respectively. Qualitatively, in 56%, RVEF was abnormal. Fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and tricuspid annulus maximal systolic tissue Doppler velocity (S′) were diminished in 12%, 30% and 32% respectively. LVEF was abnormal in 11%.

Mean tricuspid regurgitation velocity was 2.3 m/s. In 1 patient estimated RV systolic pressure was >35 mmHg, however, PH was ruled out during a right heart catheterization. No residual shunts were found.

S′ was significantly lower in patients with SVD ASD while FAC and TAPSE were not significantly different. There were no significant differences in RV or LV dilatation or systolic function.

3.8. Cardiac magnetic resonance imaging

CMR data are presented in Table 3 and Supplementary Table 8. In Supplementary Table 8, previously reported CMR data are presented using cut-offs used in 2011, while in Table 3 current guidelines were applied [5,19]. RV end-diastolic and end-systolic dilatation was present in 15% and 23% respectively. Mean RVEF was 52% ± 6%, 6% had a decreased RVEF. LV end-diastolic and end-systolic dilatation were present in 21% and 25% respectively. Mean LVEF was 58% ± 5%, in 10% there was a decreased LVEF. Late gadolinium enhancement was present in 33%, in 72% of these this was hingepoint fibrosis. A residual ASD was assumed in 2%. There were no significant differences in T1 ($p = 0.07$) and T2 ($p = 0.83$) mapping and ECV ($p = 0.84$) compared to healthy volunteers.

There were no significant differences in mean ventricular volumes and EF of the LV and RV between patients with a SVD ASD and secundum type ASD.

3.9. Laboratory measurements

Laboratory measurements are reported in Supplementary Table 9. NT-proBNP was elevated in 61%. There was no significant correlation between NT-proBNP and MACE or between SVD ASD and secundum type ASD.

3.10. SF-36

Mean scores of the SF-36 survey for patients and the normal age-matched Dutch population are shown in Supplementary Fig. 2 [21]. Patients with SVD ASD showed significantly higher scores on the Physical Functioning Domain compared to secundum type ASD and the normal population. Female patients showed significant higher scores on the Emotional Health domain. SF36 results over time are presented in Supplementary Fig. 3.

4. Discussion

In this prospective, longitudinal study we describe the long-term outcome of a cohort of patients following surgical closure of a hemodynamically important ASD at young age. With a follow-up period of up to 50 years after surgery and examinations repeated every 10 years, this study offers a unique opportunity to describe clinical outcome and changes over time.

4.1. Mortality and major events

Survival in this cohort is good with a cumulative survival of 86% after 50 years and is comparable to survival in the general Dutch population. There was no direct post-operative mortality. In the past decade, 6 patients died, although none were attributed to a cardiovascular cause. During the total follow-up period, two patients died suddenly where a cardiovascular cause was suspected but not proven.

To our knowledge, there are no studies with a similar long follow-up period. Two other studies reported on long-term outcome after ASD-closure. Murphy and colleagues showed that patients who were operated for an isolated ASD in childhood have a survival comparable to the normal population during a 32-years follow-up [10]. More recently, a registry-study showed that survival after ASD closure in childhood was

Table 3
Echocardiography parameters comparing 1990. 2001, 2011 and 2021 and cardiac magnetic resonance imaging (CMR). Re-analysis CMR data 2011 according to current guidelines [19].

	1990	2001	2011	2021	P-value 1990 vs 2021	P-value 2011 vs 2021
Echocardiography						
RA dilatation	5.8%	18.7%	23.5%	23.4%	**0.006**	1
RV dilatation	26,2%	23.5%	34.3%	45.3%	**0.004**	0.1
LA dilatation	1.0%	12.2%	15.7%	17.2%	**0.004**	0.8
LV dilatation	4.0%	8.8%	2.9%	4.9%	0.6	0.5
Normal LVEF	97%	96%	94%	89%	0.18	0.4
3D EF	–	–	–	57 ± 4	–	–
LV GLS	–	–	–	18.5 ± 2.5	–	–
E/A ratio	–	–	1.3 ± 0.4	1.2 ± 0.4	–	**0.02**
E/e' ratio	–	–	8.0 [5.9–9.8]	7.5 [6.3–9.6]	–	0.9
Normal RVEF	100%	100%	67%	44%	–	**0.008**
RV FAC	–	–	46.6% ±9.4	40.7% ±5.2	–	**<0.01**
TAPSE (mm)	–	–	18 ± 4	17 ± 3	–	**0.02**
S′ (mm)	–	–	10.4 ± 2.2	10.2 ± 1.7	–	0.3
RV-FWS	–	–	–	−22.8 ± 4.9	–	–
Valve insufficiency (>trace)						
AoI	0%	1%	3%	5%	–	1
MI	12%	13%	20%	13%	1	0.8
PI	44%	45%	56%	36%	0.3	**<0.001**
TI	42%	48%	56%	60%	1	0.6
Vmax TI (m/s)	2.1 ± 0.3	2.2 ± 0.2	2.3 ± 0.3	2.3 ± 0.3	**0.03**	0.6
CMR						
LV end diastolic volume/BSA (ml/m^2)	–	–	88 ± 14	85 ± 15	–	**0.04**
LV end diastolic dilatation	–	–	23%	21%	–	0.8
LV end systolic volume /BSA (ml/m^2)	–	–	40 ± 8	36 ± 8	–	**<0.001**
LV end systolic dilatation	–		50%	25%	–	**0.002**
LVEF (%)	–	–	55 ± 5	58 ± 5	–	**<0.001**
LVEF decreased	–	–	29%	10%	–	**0.04**
RV end diastolic volume/BSA (ml/m^2)	–	–	94 ± 14	97 ± 18	–	0.1
RV end diastolic dilatation	–	–	13%	15%	–	1
RV end systolic volume/BSA (ml/m2)	–	–	46 ± 10	47 ± 12	–	0.8
RV end systolic dilatation	–	–	20%	23%	–	0.5
RVEF (%)	–	–	51 ± 6	52 ± 6	–	0.07
RVEF decreased	–	–	11%	6%	–	1
Residual ASD	–	–	–	2%	–	–
LGE	–	–	–	33%	–	–
Hingepoint	–	–	–	72%	–	–
Septal T1 (msec)	–	–	–	985 ± 26	–	–
Septal T1 abnormal	–	–	–	2%	–	–

RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, LVEF = left ventricular ejection fraction, GLS = global longitudinal strain, E/A ratio = ratio early filling velocity on transmitral Doppler to early filling, E/e' ratio = ratio early filling velocity on transmitral Doppler to late filling, RVEF = right ventricular ejection fraction, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S′ = tricuspid annulus maximal systolic tissue Doppler velocity, RV-FWS = right ventricular free wall strain, AoI = aortic valve regurgitation, MI = mitral valve regurgitation, PI = pulmonary valve regurgitation, TI = tricuspid valve regurgitation.
BSA = body surface area, ASD = atrial septal defect, LGE = late gadolinium enhancement, ECV = extracellular volume fraction.
RV EF ≤ 42% ♂and ≤ 46%♀and LV EF ≤ 51% ♂and ≤ 52%♀ were considered decreased. RV end diastolic volume > 123 mL/m^2♂and ≤ 104 mL/m^2 ♀, RV end systolic volume > 59 mL/m^2♂and > 48 mL/m^2 ♀, LV end diastolic volume > 107 mL/m^2♂and > 93 mL/m^2 ♀and LV end systolic volume > 47 mL/m^2♂and > 38 mL/m^2 were considered enlarged. Normal values for T1 and T2 mapping and ECV were derived from 20 healthy volunteers without cardiovascular risk factors.

lower compared to the general population during a mean follow-up of 18.1 years, although this did not reach statistical significance after correction for Down syndrome and relevant co-morbidity (HR 1.6, 0.9–2.6) [22]. These studies and our findings show an excellent prognosis after ASD-closure during childhood, advocating the early closure of a hemodynamically relevant ASD [10,22].

Although morbidity occurred in half of the patients, severe complications are rare. The re-intervention rate was low (6 patients), with residual ASD closure in only 3 patients. During the entire follow-up period, 10 patients underwent pacemaker implantation, 4 in the early years after surgery. Post-operative bradycardia was present in half of these patients, although some of these underwent pacemaker implantations decades after surgery. Recently, similar results were published, with 7.4% of patients after surgical ASD-closure having a pacemaker implanted (70% < 16 years) during a mean follow-up of 10 ± 12 years [23]. Similar to our results, most patients underwent pacemaker implantation many years after surgical closure (average age at implantation 32 years). Therefore, long-term follow-up in patients after surgically repaired ASD is warranted. There was a low prevalence of endocarditis and both cases occurred after pacemaker implantation. This suggests an increased risk of morbidity in patients with pacemaker implantation at young age, rather than a direct association with the ASD [24].

These observations confirm previous studies and the long-term feasibility and safety of surgical ASD-closure. This procedure remains an excellent alternative for percutaneous ASD-closure, especially where minimally invasive surgery is feasible [25,26].

4.2. *Arrhythmias*

Arrhythmias were often encountered, with 69% of patients showing supraventricular arrhythmias during Holter monitoring. However, in most patients, this was caused by short episodes of supraventricular tachycardia. Atrial fibrillation was seen in only 2 cases (4%). Nonetheless, the cumulative burden of symptomatic arrhythmia after a follow-up period of 45- and 50-years was 25% and 35% respectively, with atrial fibrillation and flutter being the most common arrhythmias. This is much higher compared to a prevalence of 0.7% in the general population aged 55 to 60 years [27]. However, a prevalence of up to 50% was reported in natural history studies [9]. Previously, in patients who underwent ASD-closure at a more advanced age, a higher prevalence of atrial fibrillation was observed, indicating the beneficial effects of early closure on the development of atrial arrhythmias during long term follow-up [6–8,10]. However, in literature, no clear protective effect of early closure on the development of atrial fibrillation was observed [28]. There is an age dependent increase in the prevalence of atrial fibrillation in the general population [27]. Secondly, left atrial dilatation was present in 17% of our cohort. Left atrial dilatation and older age are independently associated with the development of new-onset atrial fibrillation in patients with an ASD, while closure was not [29]. Finally, in this aging population there was a high prevalence of other cardiovascular risk factors associated with the development of atrial fibrillation with 12% having an elevated glycated hemoglobin and 24% using anti-hypertensive medication. This increasing burden of atrial fibrillation in patients after ASD-closure at young age warrants ongoing follow-up and aggressive treatment of modifiable cardiovascular risk-factors.

4.3. Pulmonary hypertension

In only 1 patient, RV systolic pressure was >35 mmHg as assessed by echocardiography. However, PH was ruled out with an invasive measurement. There is a great variability in the reported prevalence of PH after ASD-closure, with a prevalence between 5 and 50% [30]. Our data is reliable and reassuring and showed no late development of PH in this cohort.

4.4. Ventricular function and exercise capacity

RV and RA dilatation on echocardiography was present in 45% and 23% respectively. Over the decades, a significant increase in right sided dimensions was observed. Advanced CMR imaging showed an enlarged RV end-systolic volume in 25% of the patients. In literature, conflicting results are reported. In most of these studies there was a clear bias in patient selection, as patients who were enrolled were still followed up in the outpatient clinic. De Koning et al. reported an increased RV systolic volume in 25% of patients after ASD-closure at young age (4.6 ± 2.8 years) [31]. In contrast, Bolz reported normal RV dimensions in patients after ASD-closure during childhood [32]. Although age at operation was comparable, follow-up period in this study was significantly shorter (median 22 years). Although it might be postulated that this progressive increase in right sided dimensions is related to the age at surgery and shunt fraction, this could not be demonstrated in our cohort. It could be postulated that the progressive RA and RV dilatation might be the result of the altered anatomy during childhood with progressive dilatation as a late effect. Recently, pre-operative RV end systolic volume index was identified as an independent predictor for normalization of RV volume in adults after ASD-closure [33]. RVEF was decreased on CMR in 6% of all patients with no statistically significant changes in the past decade. LV systolic function was diminished in 10%, while in literature, LVEF and global longitudinal strain are within normal range after ASD-correction in adults [34]. However, recently a reduced LV and RV systolic response to exercise was described in subjects decades after ASD correction who had normal resting function parameters [35]. Despite the observed suboptimal ventricular function in some patients, exercise capacity was normal in most patients with only 20% having a diminished VO2max. Previously, (near) normalization of exercise capacity in adults after ASD-closure has been described, enabling patients after ASD-closure to fully participate in sport activities [36,37].

There was no significant difference in survival status, occurrence of events (all) or symptomatic arrhythmias between secundum type ASD and SVD ASD. Nor was there a significant difference in PR interval, QRS duration, RV or RA dilation, LVEF or RVEF. S′ was slightly lower in SVD ASD, although there were no differences in RVEF on CMR. Finally, we did not observe any differences in exercise capacity between patients with secundum type ASD and SVD ASD.

NT-proBNP was elevated in 61% of all patients, there was no difference between SVD ASD and secundum type ASD. However, in only 16% NT-proBNP levels were > 2 times the upper reference limit. Patients with elevated NT- proBNP were older, more often showed LA dilatation and symptomatic arrhythmia, although none of these differences were statistically significant. Nevertheless, it could be postulated that the NT-proBNP elevation is partly related to atrial remodeling. Although we did not find a correlation between NT-proBNP and MACE in our cohort, in literature it has proven to be an important biomarker in risk prediction in congenital heart disease [38].

4.5. Health status assessment

Subjective QoL in this cohort was comparable to the age-matched population. Patients with SVD ASD showed significant higher scorer on Physical Functioning. However, no differences were found in echo, CMR and CPET data, and self-reported quality of life was comparable to the age-matched population. A larger study is warranted to find out if this observation is duplicable and of clinical relevance.

In literature, different findings have been published regarding self-reported QoL in patients after cardiac surgery for CHD. Lane and colleagues reported lowest self-reported QoL in patients with CHD after surgical correction who were considered surgically cured [39]. Possibly, the lifelong need for cardiac care in combination with the surgical scar and occult hemodynamic restriction can lead to a diminished self-perceived QoL. However, Moons and colleagues evaluated QoL in a large cohort of CHD patients. They concluded that the impact of an ASD has only a small effect on QoL and that the functional impact of the heart defect rather than the heart defect itself affects patients reported QoL [40]. In our cohort, 86% of all subjects were in New York Heart Association class I, the remaining 14% in class II and 80% had a normal exercise capacity, which will have contributed to the good self-perceived QoL.

5. Study limitations

Although this study has, to our knowledge, the longest longitudinal follow-up in a cohort of patients who underwent surgical ASD-closure in childhood, the sample size was relatively low and thus the results should be interpreted with caution. However, numbers lost to follow-up were low, baseline characteristics of participants did not differ from non-participants and 85% of the approached patients participated in the present study, supporting limited risk of selection bias.

6. Conclusion

Long-term outcome after surgical ASD-repair during childhood is favorable, with good survival, low re-intervention rate, good exercise capacity and a good QoL. Nevertheless, there is a high burden of symptomatic arrhythmia and need for pacemaker implantation is frequent, which warrants follow-up.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131616.

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Conflict of interest

The authors declare to have no conflict of interest.

Data availability

The anonymous data that support the findings of this study are available from the author, upon reasonable request.

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