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Long-Term Outcome of Patients with Perimembranous Ventricular Septal Defect: Results from the Belgian Registry on Adult Congenital Heart Disease

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Key Words
Ventricular septal defect · Adult congenital heart disease · Hemodynamics · Transthoracic echocardiography · Left ventricular outflow tract obstruction

Abstract
Objectives: Studies evaluating the long-term outcome of adults with ventricular septal defect (VSD) are important to inform patients about prognosis. This study investigated the long-term outcome of patients with perimembranous VSD (pmVSD) followed in the Belgian Registry on Adult Congenital Heart Disease. ***Methods:*** All pmVSD patients in the registry were analyzed. ***Results:*** Two hundred and sixty-six patients were studied. Fifteen patients had Eisenmenger syndrome. One hundred and seventy-three had isolated pmVSD and 78 had pmVSD with concomitant lesions. Of the patients with isolated pmVSD, 52% were male, median age was 29 years (IQR 24–35 years) and median follow-up duration was 18 years (IQR 10–25 years). Fifty-three (31%) patients underwent VSD closure and 10 (19%) had a residual shunt. Most (93%) patients were in NYHA class I. No patients died. Two (4%) patients developed atrial arrhythmia and 2 (4%) required pacemaker implantation. Seven (14%) developed left ventricular outflow tract obstruction (LVOTO). In the unrepaired pmVSD group, 4 developed endocarditis. In the entire group, moderate or severe aortic regurgitation (AR) occurred in 9 (5%) patients. ***Conclusions:*** Long-term survival in patients with isolated pmVSD was not uneventful. Moderate or severe AR might develop and endocarditis occurred in patients without VSD repair. Complications after VSD closure included atrial arrhythmia, pacemaker implantation and LVOTO.

Introduction

Isolated ventricular septal defect (VSD) is the most common congenital heart defect, apart from bicuspid aortic valve, accounting for 30–40% of all congenital cardiac malformations [1, 2]. Spontaneous closure in the first years of life is common in cases of small defects. VSD is generally diagnosed and, if necessary, treated in childhood. Four subgroups have been defined in the guidelines, according to defect location: perimembranous, muscular,

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outlet and inlet type [1]. The perimembranous type is the most common in adults (about 80% of all VSDs) [1]. The clinical presentation and natural history can vary from small VSD with insignificant left-to-right shunt to VSD with significant left-to-right shunt with left ventricular (LV) volume overload and right ventricular (RV) pressure overload, which, if unrepaired, may cause pulmonary vascular disease and even Eisenmenger syndrome [1, 3–5]. Patients with a small VSD and insignificant left-to-right shunt or with a repaired VSD usually remain event-free during follow-up. However, several problems may still develop later in life, with the most important being endocarditis, LV dilatation due to volume overload, double-chambered right ventricle, LV outflow tract obstruction (LVOTO), aortic valve regurgitation (AR) and complete heart block (especially in the earlier years of cardiac surgery) [1].

Recent studies evaluating the long-term outcome of adult patients with VSD are scarce but are important for evaluating current VSD management and informing patients about prognosis and professional and health insurance issues. The aim of this study was to determine the long-term outcome of patients with perimembranous VSD (pmVSD) included in the Belgian Registry on Adult Congenital Heart Disease (ACHD), from the first diagnosis in childhood until the latest follow-up visit. There was specific interest in pmVSD because it is the largest VSD subpopulation and also due to the proximity of the aortic valve. Aortic valve complications in pmVSD were studied in detail.

Methods

Patient Selection

All patients with pmVSD were selected from the Belgian Registry on ACHD. This registry was initiated in 2005 via the collaboration of 10 university/academic centers in Belgium. It currently includes almost all adult patients, i.e. aged ≥16 years, in our country, with congenital shunt lesions and who are in follow-up. Analysis was done on the cohort of patients in the registry in April 2013. Only a minority of patients with ACHD in Belgium are followed at peripheral centers. Patients dismissed from follow-up in the 1970s and 1980s after closure of small isolated shunt lesions are currently being contacted for check-ups and scheduled for further inclusion in the registry. Demographic, clinical and biochemical data, electrocardiographic, echocardiographic and invasive hemodynamic measurements and, if applicable, data on closure were obtained from the patient's records. Follow-up consisted of systematic evaluations in each participating center. Each participant signed an informed consent for registry inclusion. The Ethics Committee of each hospital approved the follow-up protocol (Belgian protocol No. B32220071280; approval date: 19 November 2007. http://www.uzleuven.be/commissie-medische-ethiek). An independent data-manager (Alabus AG, Switzerland) maintained the registry from 2005 until 2014. Since 2015, the registry is maintained independently by the Leuven Coordinating Center, University of Leuven.

Patients with Eisenmenger syndrome or with concomitant congenital heart lesions were analyzed separately from patients with isolated pmVSD. All records were reviewed for the presence of LVOT malformations, which predispose to the development of progressive LVOTO or AR. Such malformations included bicuspid aortic valve, asymmetric tricuspid aortic valve, dysplastic aortic valve, severe coronary cusp prolapse, subaortic membrane and supravalvular aortic stenosis (AS).

Data were reviewed for all patients and 4 time points were considered: (1) the first visit or baseline, i.e. the first patient contact with the physician who diagnosed the defect, (2) heart catheterization, (3) the VSD closure time point (if applicable) and (4) the latest follow-up visit.

Echocardiography

All patients underwent transthoracic and/or transesophageal echocardiography (TTE/TEE) at baseline, mainly focusing on anatomical and shunt characteristics. Defect size was defined as the maximal VSD diameter, obtained from parasternal long-axis view, parasternal short-axis view and/or apical 5-chamber view. At the latest follow-up, TTE was analyzed according to the 2006 guidelines for chamber quantification [6]. TTE included 2-dimensional, M-mode, pulsed-wave, continuous-wave and color-flow Doppler measurements. Atrial and ventricular dimensions were graded as normal, mild, moderate or severe, based on absolute measurements and/or observer impression. Tricuspid valve regurgitation and AR were graded semiquantitatively on color-flow Doppler echocardiography. The pulmonary hypertension (PH) probability in patients with repaired VSD without residual shunt was estimated by means of the tricuspid regurgitation velocity (TRV), obtained by TTE. Three different PH categories, i.e. unlikely, possible and likely, were defined, following the ESC/ERS guidelines on PH [7]. PH was considered unlikely if TRV ≤2.8 m/s, possible if TRV ≥2.9 and ≤3.4 m/s and likely if TRV >3.4 m/s. Patients with no or only trivial tricuspid valve regurgitation were assumed to have no PH, based on the absence of indirect echocardiographic signs of PH [7, 8]. In patients without VSD closure or in the presence of a residual shunt, PH was estimated by means of the peak pressure gradient across the VSD (i.e. the difference between LV and RV systolic pressure, estimated by 4 times the VSD peak velocity squared, with a cut-off of 4 m/s) and the pulmonary artery acceleration time (with a cut-off of 100 ms [9]), obtained by TTE. LVOTO was defined by a peak systolic pressure gradient across the LVOT of >10 mm Hg. LVOTO was subdivided into valvular, supravalvular or subvalvular AS, based on the continuous-wave Doppler echocardiographic velocity in the LVOT and the location of flow acceleration/turbulence with color-flow Doppler.

Invasive Evaluation

In patients who underwent invasive hemodynamic measurements prior to VSD closure, pulmonary artery pressure (PAP) was measured and shunt ratio (Qp/Qs) was calculated via an oxygen saturation series by the Fick method. PH at baseline was defined as mean PAP ≥25 mm Hg, according to the PH guidelines [7].

Follow-Up

Patients without VSD closure were usually followed on a yearly basis or, in the absence of comorbidities, every 3–5 years. Pa-

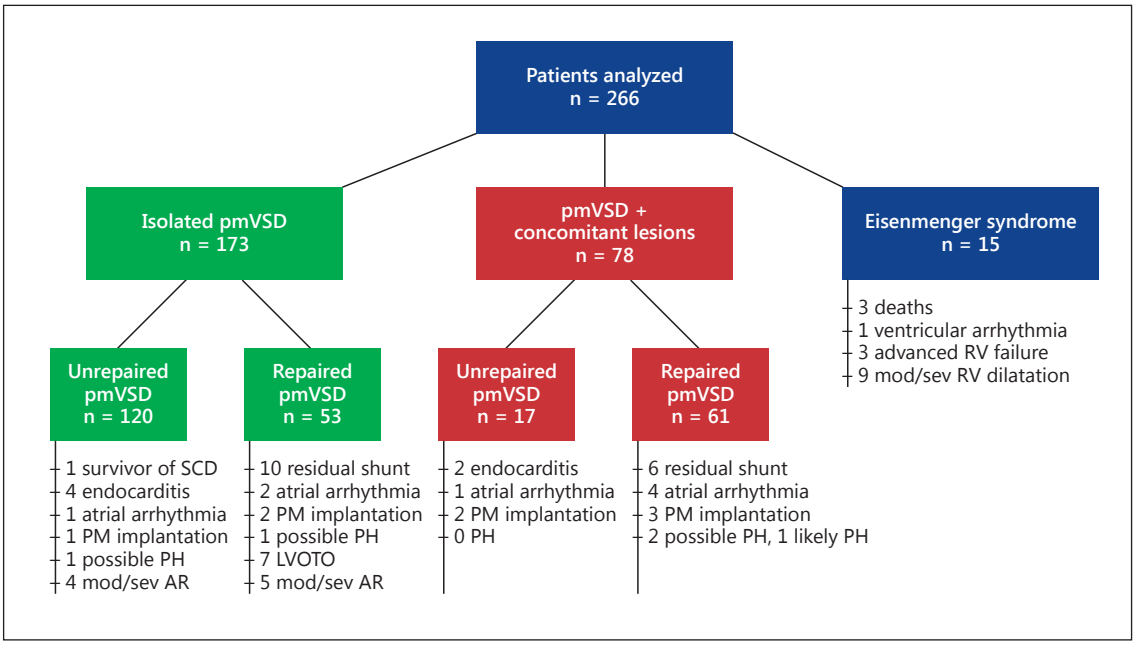

Fig. 1. Flowchart of patient inclusion and subdivision. mod/sev = Moderate or severe; PM = pacemaker; SCD = sudden cardiac death.

tients with closure were reassessed at 1 day, 1 month and 6 months after VSD closure and every 3–5 years thereafter, unless abnormal evolution was noted. Follow-up was mainly done by noninvasive examinations (clinical examination, electrocardiography, TTE and exercise testing).

Statistical Analysis

Statistical analyses were performed with SPSS software v22.0 (SPSS, Chicago, Ill., USA). For continuous variables, data are reported as means ± standard deviation (SD) or median + interquartile range (IQR) if a normal assumption was not valid. Discrete variables are presented as frequencies and/or proportions. Comparison of 2 means was done by 2-tailed Student's t test or, when normality was not assumed, by Mann-Whitney U test. Levene's test was performed to assess for equal variances. Proportions were compared by the χ^2 test (or Fisher's exact test in the case of a small sample size). Cox regression analysis was performed to identify predictors of AR development. LVOTO-free and AR-free survival were plotted by the Kaplan-Meier method, with comparisons made by log-rank statistics. All tests were 2-sided and $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Data of 268 adult patients with pmVSD were collected from the Belgian Registry on ACHD. Two patients were excluded due to a lack of data. Finally, 266 patients were analyzed (fig. 1). After detailed review of the records, pmVSD could be confirmed with certainty in 257 (97%) patients. Fifteen (6%) patients with pmVSD evolved to Eisenmenger syndrome. Concomitant congenital heart lesions were present in 78 patients (table 1).

The remaining 173 patients had isolated VSD. Of these, 90 (52%) were male. Median age at latest follow-up was 29 (IQR 24–35) years. Median follow-up duration was 18 (IQR 10–25) years. Nine (5%) patients were diagnosed with Down syndrome. Most (91%) patients had one single pmVSD and the other 9% had 2 VSDs (i.e. a muscular or outlet type next to the pmVSD). Median VSD size at baseline was 7 (IQR 4–10) mm. Fifty-three (31%) patients underwent VSD repair; this was closed surgically in 49 and percutaneously in 4. Repair took place between November 1971 and January 2005. Median age at initial VSD repair was 2.6 (IQR 0.5–6.9) years. Thirty-nine (74%) patients underwent invasive hemodynamic measurements by heart catheterization prior to closure. Median Qp/Qs ratio before closure was 1.9 (IQR 1.5–2.9). Twenty-six (49%) patients had a mean PAP ≥25 mm Hg before closure.

Outcome of the Patients with Isolated VSD

At the latest follow-up, 93% of the patients functioned in NYHA class I and the remainder in NYHA II. No patient developed heart failure or died. One male patient

Table 1. Concomitant congenital heart lesions

Congenital heart lesion	Patients, n (%)
ASD-type secundum	17 (6.4)
LVOTO	16 (6.0)
PS	15 (5.6)
DCRV	15 (5.6)
Patent ductus arteriosus	9 (3.4)
Aortic coarctation	9 (3.4)
Bicuspid aortic valve	8 (3.0)
CCTGA	2 (0.8)
Ebstein's anomaly	1 (0.4)
AV septal defect	1 (0.4)

ASD = Atrial septal defect; CCTGA = congenitally corrected transposition of the great arteries; DCRV = double-chambered right ventricle; PS = pulmonary stenosis.

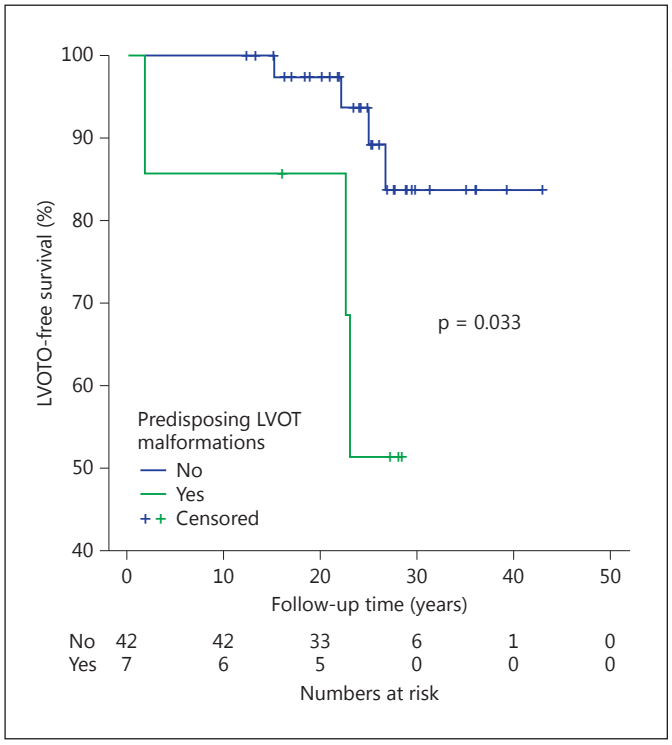

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Fig. 2. Kaplan-Meier curve of LVOTO-free survival after VSD repair.

survived a witnessed sudden cardiac arrest at the age of 36 years. The initial heart rhythm was not clear. Evaluation after cardiac arrest showed a small VSD with a hemodynamically irrelevant left-to-right shunt. Magnetic resonance imaging showed biventricular dilatation. No genetic mutation in genes known to be associated with cardiac arrhythmia was found. The patient received an implantable cardioverter defibrillator.

Sequelae in Patients with Unrepaired Isolated VSD

In the unrepaired isolated VSD group (n = 120), 4 (3%) patients developed endocarditis (table 2). Fifteen (13%) spontaneous closures occurred. One (1%) patient developed paroxysmal atrial arrhythmia during follow-up, at the age of 37 years, 1 required pacemaker implantation for high-degree atrioventricular (AV) block at the age of 48 years and 1 developed possible PH (TRV was 2.92 m/s). Twenty-five (21%) patients evolved to mild and 4 (3%) to moderate or severe AR during follow-up (none of the 4 presented with congenital LVOT malformations).

Sequelae in Patients with Repaired Isolated VSD

In the repaired isolated VSD group (n = 53), a residual shunt was present in 10 (19%) patients. Four underwent suture closure and 6 underwent patch closure of the VSD. No patients needed redo VSD surgery. No patient developed endocarditis. In 2 (4%) patients, atrial arrhythmia (atrial flutter) was detected, 15 and 24 years after surgical VSD closure performed by atriotomy and aortotomy, respectively. One of them suffered a stroke. Two (4%) patients required pacemaker implantation for high-degree AV block, late after surgical VSD closure. One developed high-degree AV block shortly after aortic valve intervention at the age of 23 years. The other received a pacemaker 28 years after VSD repair, at the age of 32 years. One (2%) patient developed possible PH during follow-up after VSD closure (TRV 2.96 m/s).

Interestingly, 7 (14%) patients (3 males and 4 females) presented some degree of LVOTO during follow-up after surgical VSD repair. All 7 functioned in NYHA class I and were asymptomatic. Peak systolic pressure gradient across the LVOT ranged from 11 to 41 mm Hg. Mean peak systolic LVOT pressure gradient was 19 mm Hg. Associated AR was mostly absent or mild. Two patients developed moderate AR; one had aortic valve intervention at the moment of VSD closure and the other had an asymmetric tricuspid aortic valve.

Congenital LVOT malformations were present in 3 patients. Two underwent aortic valve interventions through aortotomy at the moment of VSD closure, because of important coronary cusp prolapse or dysplastic aortic valve. One patient had an asymmetric tricuspid aortic valve.

Table 2. Endocarditis in patients with unrepaired isolated VSD

Gender	Age, years	Location of vegetation	Organism	Circumstances
Female	27	TV	*Streptococcus viridans*	tooth extraction
Male	25	VSD	*Streptococcus salivarius*	–
Female	1	VSD and TV	*S. viridans*	acute EBV infection
Male	7/19	VSD and TV	*S. viridans*	tooth extraction

EBV = Epstein-Barr virus; TV = tricuspid valve.

The remaining 4 patients did not have any predisposing LVOT malformations. Three developed membranous subvalvular AS with a mean interval of 22 years after VSD closure; VSD repair took place by right atriotomy (no aortotomy) in 2and the approach in the other one is not known. One patient developed valvular AS without known etiology.

The Kaplan-Meier curve of LVOTO-free survival, in the presence and absence of congenital LVOT malformations, is plotted in figure 2.

Seventeen (35%) patients with surgical VSD repair evolved to mild and 5 (10%) to moderate or severe AR. Analyzing the patients with moderate or severe AR in more detail, 3 (60%) had predisposing LVOT malformations (asymmetric tricuspid aortic valve in 2 and dysplastic aortic valve in 1) and 2 developed LVOTO during follow-up. In 2 (40%) patients, no predisposing LVOT malformations were present.

Compared to the patients with repaired isolated VSD, those with unrepaired VSD had a significantly smaller median VSD size, 5 (4–8) versus 8 (8–10) mm ($p < 0.001$) and a significantly smaller median Qp/Qs ratio, 1.3 (1.2–1.4) versus 1.9 (1.5–2.9) ($p < 0.001$).

Development of Moderate or Severe AR in Patients with Isolated VSD (Repaired and Unrepaired)

A total of 9 (5%) patients with isolated VSD developed moderate or severe AR, and 6 of these did not have predisposing LVOT malformations. Cox regression analysis was performed to identify predictors of development of moderate or severe AR. Two patients who had undergone aortic valve surgery, isolated or together with VSD repair, were excluded from this analysis (1 with mild AR and 1 with moderate AR during follow-up). A total of 171 patients remained, 8 of whom developed moderate or severe AR (7 males and 1 female). Median age at development of moderate or severe AR was 20 (IQR 18–27) years. Four cases had undergone surgical VSD repair, 2 with suture closure and 2 with patch closure. Variables studied by the Cox regression analysis included gender, the presence of predisposing LVOT malformations, VSD repair and mode of surgical repair (suture versus patch closure). In univariate and multivariate analysis, the only significant predictor of moderate or severe AR was the presence of predisposing LVOT malformations (table 3). The Kaplan-Meier curve of AR-free survival, in the presence and absence of predisposing LVOT malformations, is plotted in figure 3. The Kaplan-Meier curve of AR-free survival, stratified by gender, is plotted in figure 4.

Table 3. Cox regression analysis to identify predictors of moderate or severe AR development

	HR	95% CI	p value
Univariate analysis			
Male gender	6.9	0.9–56.2	0.071
Predisposing LVOT malformations	13.6	2.7–68.4	0.002
VSD repair	2.6	0.7–10.6	0.171
Mode of surgical repair	3.0	0.4–21.2	0.274
Multivariate analysis			
Male gender	5.2	0.6–44.4	0.133
Predisposing LVOT malformations	8.0	1.5–41.9	0.013

CI = Confidence interval; HR = hazard ratio.

Outcome in Patients with VSD and Concomitant Congenital Heart Lesions

A total of 78 patients, 54% male with a median age at the latest follow-up of 28 (24–33) years, had concomitant congenital heart lesions. At the latest follow-up, 90% of the patients functioned in NYHA class I and the remainder in NYHA II. No patients developed heart failure or died.

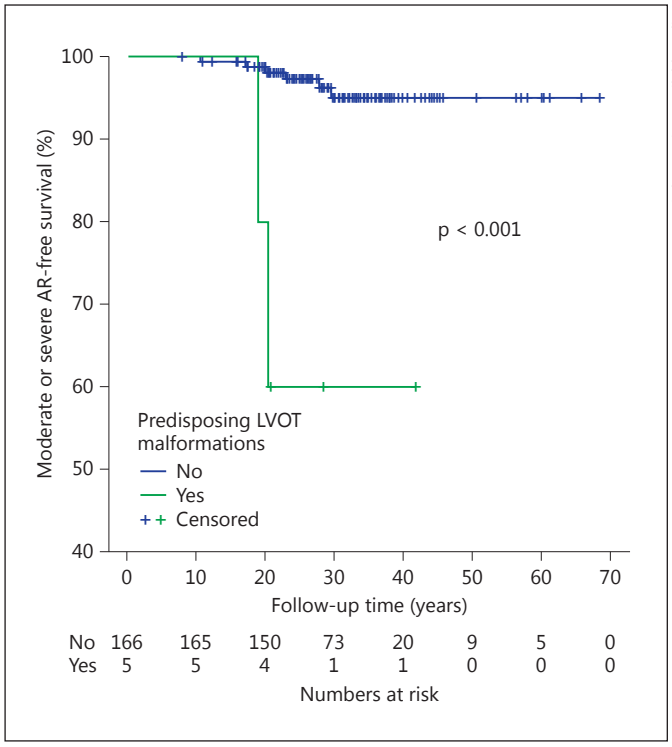

Fig. 3. Kaplan-Meier curve of moderate or severe AR-free survival for the entire group of unrepaired and repaired pmVSD, stratified by the presence of predisposing LVOT malformations. Follow-up time since birth in years.

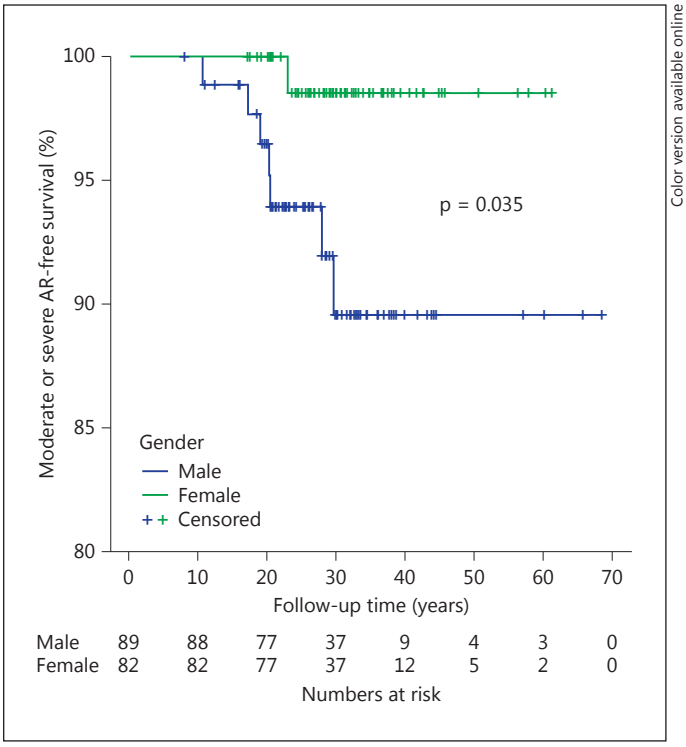

Fig. 4. Kaplan-Meier curve of moderate or severe AR-free survival for the entire group of unrepaired and repaired pmVSD, stratified by gender.

In the unrepaired group (n = 17), 4 (24%) spontaneous closures occurred. Two (12%) patients with unrepaired VSD developed endocarditis, at the age of 19 and 21 years. One, who developed endocarditis at the right ventricular outflow tract, underwent VSD closure after the endocarditis episode. Two (12%) patients required pacemaker implantation for high-degree AV-block, at the age of 23 and 45 years, respectively. One of these was known with a congenitally corrected transposition of the great arteries.

Sixty-one (78%) patients underwent surgical VSD repair. Median Qp/Qs ratio before closure was 2 (IQR 1.5–3). Ten (16%) underwent resection of a subaortic membrane during VSD surgery. In 4, LVOTO by a subaortic membrane reoccurred, between 6 and 22 years postoperatively, implying a recurrence rate of 40% in our pmVSD population. Two patients developed possible PH (TRV 2.96 and 3 m/s) and 1 developed likely PH (TRV 3.42 m/s) during follow-up after repair. Four (7%) developed atrial arrhythmia, 1 immediately postoperatively, 1 at 6 months postoperatively and the remaining 2 at 15 and 27 years, respectively, after VSD repair. Three of them underwent surgical VSD closure by atriotomy. Three (5%) patients required pacemaker implantation for high-degree AV-block, 2 early postoperatively and 1 at the age of almost 3 years, at the moment of reintervention for resection of a subaortic membrane.

Outcome in Patients with VSD and Eisenmenger Syndrome

Fifteen patients (73% female with a mean age at the latest follow-up of 44 ± 14 years) with isolated VSD evolved to Eisenmenger syndrome. Mean follow-up duration was 10 ± 5 years, meaning that 12 (80%) had already reached adulthood before their first visit to a university center. Six (40%) patients had Down syndrome. Mean VSD size was 18 ± 8 mm, which was significantly higher than in the group of unrepaired isolated VSD who did not develop Eisenmenger syndrome (mean VSD size 6 ± 3 mm; p = 0.002).

At the latest follow-up, 13 (87%) patients functioned in NYHA class II, 1 (7%) in NYHA III and 1 (7%) in

NYHA IV. Median oxygen saturation by pulse oximetry was 82% (76–84%). TTE showed moderate or severe right atrial dilatation in 7 (47%) and moderate or severe RV dilatation in 9 (60%). Mean TRV was 4.2 ± 0.7 m/s.

Seven (47%) patients were on selective pulmonary vasodilator therapy, 2 (13%) needed long-term oxygen treatment and 3 (20%) received iron supplements. Three (20%) evolved to advanced right heart failure, 3 suffered a stroke and 3 died from end-stage heart failure, at the age of 39, 53 and 62 years, respectively. One patient survived a ventricular arrhythmia by successful cardiopulmonary resuscitation, at the age of 60 years.

Discussion

The patients with isolated pmVSD included in the Belgian Registry on ACHD seem to have a quite good overall survival, but not uneventful. Fifteen (6%) developed Eisenmenger syndrome, 3 of whom died. In the unrepaired isolated VSD group, 3% developed endocarditis. In the repaired isolated VSD group, the main complications during follow-up included the development of atrial arrhythmia, pacemaker implantation for high-degree AV block and the development of some degree of LVOTO, even in the absence of predisposing anatomical defects. In the entire isolated VSD group, moderate or severe AR developed in 9 (5%) patients. In patients with concomitant congenital heart lesions, the event rates of endocarditis, atrial arrhythmia development and pacemaker implantation were higher.

Survival of the Entire VSD Population

No patient with isolated VSD or with concomitant congenital heart lesions died. Overall survival has greatly improved in the past decades, due to the earlier diagnosis of VSD, the advancements in surgical techniques and the postoperative care [1, 10–12]. The mortality rate was low in our study compared to 2 other studies [13, 14]. This could partly be explained by the fact that their patients were diagnosed or operated on in an earlier era. In one study, they were diagnosed between 1958 and 1969, and in the other, they underwent VSD surgery between 1968 and 1980. In our study, patients underwent VSD repair between 1971 and 2005. Furthermore, the different mortality rate could also be related to immortal time bias. Immortal time refers to a span of time in the follow-up period of a cohort during which the outcome of interest (here: death) could not have occurred [15]. The patients had to remain alive until the start of the Belgian Registry on ACHD (2005) in order to give their informed consent for registry inclusion. This means that patients who died before 2005 were not included in the analyses. However, our data suggest that the patients who transferred from pediatric cardiology to ACHD had good outcomes. This validates the treatment strategy in childhood and offers more information for professional and health insurance issues.

Three patients with Eisenmenger syndrome died during follow-up. The survival of patients with Eisenmenger syndrome is known to be reduced compared with the general population, although many survive into their third or fourth decade [1].

Outcome in Patients with Unrepaired Isolated VSD

Fifteen (13%) spontaneous closures occurred. This is a rather high percentage compared to the 6% in a follow-up study of 222 patients with VSD [16], but similar percentages, i.e. 10–15%, have been reported by other study groups [13, 17]. Four (3%) patients developed endocarditis, all at the VSD and/or tricuspid valve level, which is the most typical location in VSD patients without associated valvular disease. The VSD was not closed afterwards in any of the patients. This seems contradictory to current guidelines, stating a class IIa indication for VSD closure after infective endocarditis [1]. A possible explanation may be that the episodes of endocarditis dated from 1977 to 1996, when more conservative management was common. The occurrence of endocarditis reported in other studies varies from 2 to 15% [16, 18, 19]. Although these were single-center studies and not registry data, they were performed in large tertiary university centers, with the number of patients equal to or greater than in the registry analysis. The development of atrial arrhythmia and high-degree AV block were rare.

Outcome in Patients with Repaired Isolated VSD

There were no postoperative deaths in our study group. Other studies have reported an early postoperative mortality of 0–13% and a late postoperative mortality of around 4–5% [11, 14, 20, 21]. The studies referred to are all single-center studies, but were performed in large tertiary university centers, specialized in pediatric and/or ACHD, enabling a comparison with our registry data. A residual shunt was present in 10 (19%) patients compared to other studies which documented this 8–23% [14, 21]. No reoperations for VSD occurred. Two (4%) patients developed atrial arrhythmia during follow-up after surgical VSD closure. The prevalence of atrial arrhythmia after

VSD closure reported in the literature varies from 0 to 23% [10, 14, 21]. It appears to be more prevalent after VSD surgery compared to unrepaired VSD [16]. This is possibly linked to the surgical access via atriotomy. Two (4%) patients required pacemaker implantation for high-degree AV block after surgical VSD repair. Similar numbers have been documented by other study groups [10, 14]. Only 1 (2%) patient developed PH, confirming that early VSD repair successfully prevents progressive pulmonary vascular disease [10, 14].

LVOTO in Patients after Surgical Repair of Isolated VSD

Seven (14%) patients presented some degree of LVOTO during follow-up after surgical VSD repair. Associated AR was mostly absent or mild. Predisposing congenital LVOT malformations were present in 3 patients. Three without predisposing LVOT malformations developed membranous subvalvular AS, with a mean of 22 years after VSD closure. Various studies in the literature document the development of subvalvular AS after surgical VSD repair [22, 23], and it is associated with CHD in 20–50% of the cases reported, mainly VSD and aortic coarctation [22, 24, 25]. Subvalvular AS is believed to be acquired over time, presumably secondary to the altered flow patterns caused by structural LVOT abnormalities [26]. It is sometimes difficult to diagnose, but failure to remove a subaortic membrane at the time of VSD repair may lead to the progression and development of severe subaortic obstruction or the development of AR [23, 27].

Development of Moderate or Severe AR in Patients with Isolated VSD (Repaired and Unrepaired)

Nine (5%) patients developed moderate or severe AR. The prevalence of moderate AR during follow-up after surgical VSD repair ranges from 2 to 17% in the literature, depending mainly on the type of VSD studied and the presence or absence of associated aortic valve malformations and/or surgery [10, 14, 21, 28]. In unrepaired VSD, there is also a wide range of AR development, of between 2 and 20% [16].

In univariate and multivariate analysis, the only significant predictor of moderate or severe AR was the presence of predisposing LVOT malformations. The presence or absence of VSD repair and mode of surgical repair do not seem to influence the severity of AR, at least not in the limited number of cases studied here. Similar observations were made by others [16]. However, some studies describe VSD surgery as being associated with a substantial risk of coronary cusp prolapse of the aortic valve, with subsequent AR development [1]. A large (88%), but not significant, number of patients with moderate or severe AR were male.

Outcome in Patients with VSD and Concomitant Congenital Heart Lesions

In patients with concomitant congenital heart lesions, the event rates of endocarditis, the development of atrial arrhythmia and pacemaker implantation were higher than in patients with isolated pmVSD. The recurrence rate after surgical resection of a subaortic membrane was rather high (40%) [22]; these are important findings to take into account when following these patients in clinical practice.

Limitations

The retrospective and multicenter study design makes this study subject to missing data and a lack of management uniformity. Furthermore, in the 1970s and 1980s, it was common after VSD closure to dismiss patients with small isolated VSD from follow-up. Such patients were consequently not included in the Belgian Registry, possibly inducing a selection bias, but they are currently contacted for check-ups. Their data will be compared to the data of our study population. Moreover, the catheterization and echocardiographic data were not reanalyzed in a blinded way but were retrospectively obtained from the final study protocols; however, if available, echocardiographic images were retrospectively reviewed. Lastly, the mortality rate was low in our study. Different mechanisms may have been involved here, keeping a possible immortal time bias in mind.

Conclusions

Overall long-term survival in patients with isolated pmVSD seems to be good, but not uneventful. Some patients developed moderate or severe AR, irrespective of VSD repair and 3% without VSD repair developed endocarditis. Complications after VSD closure included atrial arrhythmia, pacemaker implantation and the development of LVOTO, even in the absence of predisposing anatomical defects.

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Conflict of Interest

No funding resource was involved in the study design, collection and interpretation of data or writing and submission of this study.

References

1 Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E; (ESC) TFotMoG-uCH-DotESoC, (AEPC) AfEPC, (CPG) ECfPG: ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010;31:2915–2957.

2 Moons P, Sluysmans T, De Wolf D, Massin M, Suys B, Benatar A, Gewillig M: Congenital heart disease in 111,225 births in Belgium: birth prevalence, treatment and survival in the 21st century. Acta Paediatr 2009;98:472–477.

3 Penny DJ, Vick GW: Ventricular septal defect. Lancet 2011;377:1103–1112.

4 Van Hare GF, Soffer LJ, Sivakoff MC, Liebman J: Twenty-five-year experience with ventricular septal defect in infants and children. Am Heart J 1987;114:606–614.

5 Soufflet V, Van de Bruaene A, Troost E, Gewillig M, Moons P, Post MC, Budts W: Behavior of unrepaired perimembranous ventricular septal defect in young adults. Am J Cardiol 2010;105:404–407.

6 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W; Committee ASoEsNaS, Quantification TFoC, Committee ACoCE, Association AH, European Association of Echocardiography ErSoC: Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79–108.

7 Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G; (CPG) ECfPG: Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–2537.

8 De Meester P, Van De Bruaene A, Herijgers P, Voigt JU, Delcroix M, Budts W: Geometry of the right heart and tricuspid regurgitation to exclude elevated pulmonary artery pressure: new insights. Int J Cardiol 2013;168:3866–3871.

9 Granstam SO, Björklund E, Wikström G, Roos MW: Use of echocardiographic pulmonary acceleration time and estimated vascular resistance for the evaluation of possible pulmonary hypertension. Cardiovasc Ultrasound 2013;11:7.

10 Meijboom F, Szatmari A, Utens E, Deckers JW, Roelandt JR, Bos E, Hess J: Long-term follow-up after surgical closure of ventricular septal defect in infancy and childhood. J Am Coll Cardiol 1994;24:1358–1364.

11 Nygren A, Sunnegårdh J, Berggren H: Preoperative evaluation and surgery in isolated ventricular septal defects: a 21-year perspective. Heart 2000;83:198–204.

12 Moons P, Bovijn L, Budts W, Belmans A, Gewillig M: Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. Circulation 2010;122:2264–2272.

13 Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM, Pieroni DR, Wolfe RR, Weidman WH: Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. Circulation 1993;87:I38–51.

14 Roos-Hesselink JW, Meijboom FJ, Spitaels SE, Van Domburg R, Van Rijen EH, Utens EM, Bogers AJ, Simoons ML: Outcome of patients after surgical closure of ventricular septal defect at a young age: longitudinal follow-up of 22–34 years. Eur Heart J 2004;25:1057–1062.

15 Suissa S: Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167:492–499.

16 Gabriel HM, Heger M, Innerhofer P, Zehetgruber M, Mundigler G, Wimmer M, Maurer G, Baumgartner H: Long-term outcome of patients with ventricular septal defect considered not to require surgical closure during childhood. J Am Coll Cardiol 2002;39:1066–1071.

17 Neumayer U, Stone S, Somerville J: Small ventricular septal defects in adults. Eur Heart J 1998;19:1573–1582.

18 Otterstad JE, Nitter-Hauge S, Myhre E: Isolated ventricular septal defect in adults. Clinical and haemodynamic findings. Br Heart J 1983;50:343–348.

19 Corone P, Doyon F, Gaudeau S, Guérin F, Vernant P, Ducam H, Rumeau-Rouquette C, Gaudeul P: Natural history of ventricular septal defect. A study involving 790 cases. Circulation 1977;55:908–915.

20 Aydemir NA, Harmandar B, Karaci AR, Sasmazel A, Bolukcu A, Saritas T, Yucel IK, Coskun FI, Bilal MS, Yekeler I: Results for surgical closure of isolated ventricular septal defects in patients under one year of age. J Card Surg 2013;28:174–179.

21 Mongeon FP, Burkhart HM, Ammash NM, Dearani JA, Li Z, Warnes CA, Connolly HM: Indications and outcomes of surgical closure of ventricular septal defect in adults. JACC Cardiovasc Interv 2010;3:290–297.

22 Lampros TD, Cobanoglu A: Discrete subaortic stenosis: an acquired heart disease. Eur J Cardiothorac Surg 1998;14:296–303.

23 Firpo C, Maitre Azcárate MJ, Quero Jiménez M, Saravalli O: Discrete subaortic stenosis (DSS) in childhood: a congenital or acquired disease? Follow-up in 65 patients. Eur Heart J 1990;11:1033–1040.

24 Vogel M, Freedom RM, Brand A, Trusler GA, Williams WG, Rowe RD: Ventricular septal defect and subaortic stenosis: an analysis of 41 patients. Am J Cardiol 1983;52:1258–1263.

25 Zielinsky P, Rossi M, Haertel JC, Vitola D, Lucchese FA, Rodrigues R: Subaortic fibrous ridge and ventricular septal defect: role of septal malalignment. Circulation 1987;75:1124–1129.

26 Cape EG, Vanauker MD, Sigfússon G, Tacy TA, del Nido PJ: Potential role of mechanical stress in the etiology of pediatric heart disease: septal shear stress in subaortic stenosis. J Am Coll Cardiol 1997;30:247–254.

27 Fisher DJ, Snider AR, Silverman NH, Stanger P: Ventricular septal defect with silent discrete subaortic stenosis. Pediatr Cardiol 1982;2:265–269.

28 Gabriels C, Gewillig M, Meyns B, Troost E, Van De Bruaene A, Van Damme S, Budts W: Doubly committed ventricular septal defect: single-centre experience and midterm follow-up. Cardiology 2011;120:149–156.