Behavior of Unrepaired Perimembranous Ventricular Septal Defect in Young Adults

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The number of adolescents and young adults with congenital heart defects, including ventricular septal defect (VSD), increases continuously. We evaluated the mid-term outcome of small and unclosed perimembranous VSDs (pmVSDs). All patients with a known unrepaired pmVSD at 16 years of age were selected from our database. The clinical, electrocardiographic, and echocardiographic changes between baseline and the latest follow-up examination were compared. A total of 220 patients (119 males, median age 18 years, interquartile range 7) could be included. During a median follow-up of 6 years (interquartile range 4, range 38), 2 patients died (1%; 1 from sudden death and 1 from end-stage heart failure). Endocarditis occurred in 8 patients (4%). One patient required pacemaker implantation (0.5%) and one required implantable cardioverter-defibrillator implantation (1%). Fifteen patients (7%) required a closing procedure. In 8 patients (4%), the pmVSD closed spontaneously. In the remaining 203 patients (93%), the QRS morphology changed in 5% and 1% lost sinus rhythm ($p = 0.0001$ and $p = 0.015$, respectively). The left ventricular ejection fraction and stroke volume index increased from 62 ± 7% to 67 ± 8% and from 41 ± 11 to 44 ± 15 ml/m^2 ($p = 0.0001$ and $p = 0.035$, respectively), the end-systolic diameter decreased, and the end-diastolic diameter did not change. Finally, patients with an open pmVSD developed more pulmonary arterial hypertension during follow-up (from 3% to 9%, $p = 0.002$). In conclusion, mid-term follow-up of adolescents and young adults with a small and unrepaired pmVSD was not uneventful. Some patients required intervention, but in others, spontaneous closure occurred. Electrocardiographic and structural changes were noticed, for which the clinical significance needs to be determined. **(Am J Cardiol 2010;105:404–407)**

Perimembranous ventricular septal defects (pmVSDs), which include about 70% to 80% of all VSDs, involve the membranous septum and the adjacent area of the muscular septum. Spontaneous and functional closure might occur when the septal leaflet of the tricuspid valve covers the defect. Muscular VSDs are present in 15% of the cases, and 1/2 of them close spontaneously by muscular in-growth. The rare, doubly committed, VSDs, which account for 5% of all VSDs, might also close spontaneously when the right coronary cusp prolapses into the defect. Small VSDs without any hemodynamic repercussion are usually treated conservatively and remain unrepaired. The long-term results of this policy are undetermined. It is unknown whether these patients have a normal life expectancy. However, such information might be critically important with regard to future patients' employability and insurability. The objective of the present study was to determine the evolution and mid-term outcome of young adults with a perimembranous VSD (pmVSD) that was still open at 16 years of age.

Methods

All patients, registered with an unrepaired pmVSD at 16 years of age, were selected from our database of pediatric and congenital cardiology. It contains >20,000 patients with congenital heart defects. Of these patients, 7,000 are >16 years old. Our department of pediatric and congenital cardiology yearly performs >300 interventional catheterizations, and >200 patients are referred to the congenital cardiac surgeon. Only restrictive VSDs were allowed to be included. All patients in whom the pmVSD was unrepaired at 16 years of age were suggested to have a pulmonary output/systemic output (Qp/Qs) ratio of <1.5:1. Patients in whom the VSD closed spontaneously or was closed surgically before 16 years of age and patients who had associated complex congenital anomalies were not included in the present study. The institutional ethics committee of the hospital approved the study protocol.

The patient files were primarily reviewed for demographic data and events after the age of 16 years. The events were defined as death, spontaneous VSD closure, surgical VSD closure, percutaneous VSD closure, the occurrence of endocarditis, implantation of a pacemaker or implantable cardioverter-defibrillator.

Secondarily, the electrocardiographic and transthoracic echocardiographic data were collected. We looked for heart rate, atrioventricular conduction time, QRS duration, type of QRS morphology, and type of rhythm (sinus rhythm or not). The left ventricular ejection fraction (obtained by M-mode and

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Table 1
Patient characteristics at inclusion and latest follow-up

Variable	At Inclusion (n = 220)	At Latest Follow-Up (n = 220)
Gender		
Male	119	119
Female	101	101
Age (years)		
Median	18	27
Interquartile range	7	11
Length (cm)	170 ± 11	171 ± 11
Weight (kg)	66 ± 13	71 ± 14
Body surface area (m^2)	1.76 ± 0.21	1.83 ± 0.22
Systolic blood pressure (mm Hg)	125 ± 15	127 ± 16
Diastolic blood pressure (mm Hg)	76 ± 10	76 ± 11
Down syndrome	2%	
Echocardiographic data		
Bicuspid aortic valve	1%	
Aortic valve prolapse	2%	
Subaortic stenosis	1%	
Mild mitral valve prolapse	1%	
Mild double chambered right ventricle	1%	
Hemodynamic data (n = 71*)		
Right atrium (mm Hg)	4 ± 3	
Systolic pulmonary artery pressure (mm Hg)	24 ± 9	
Diastolic pulmonary artery pressure (mm Hg)	8 ± 5	
Mean pulmonary artery pressure (mm Hg)	15 ± 6	
Wedge pressure (mm Hg)	9 ± 3	
Pulmonary cardiac output/systemic cardiac output ratio	1.2 ± 0.2	

Data are presented as mean ± SD, unless otherwise noted.
* 166 patients underwent right heart catheterization, of whom 71 had data electronically available for review.

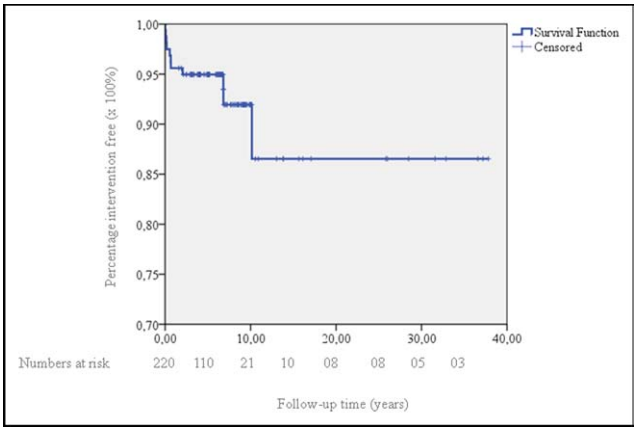

Figure 1. Kaplan-Meier curve of event-free survival, with event defined as surgical or interventional VSD closure.

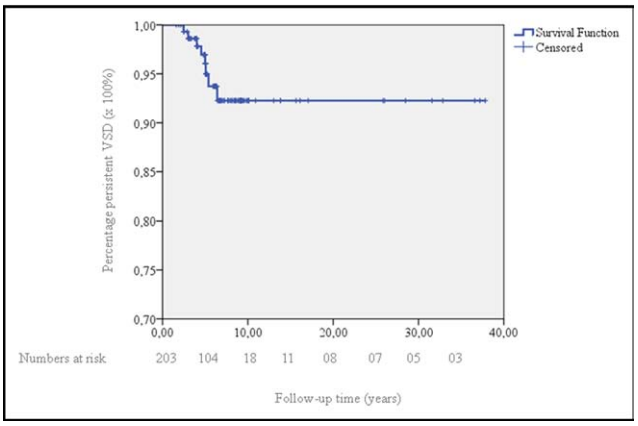

Figure 2. Kaplan-Meier curve of event-free survival, with event defined as spontaneous VSD closure.

the Teichholz formula), left ventricular diameters (obtained by M-mode through a parasternal long-axis view) and volumes (automatically calculated by the software of the echocardiographic machine from the M-mode data), stroke volume, valve function, and pulmonary hypertension (defined as a pulmonary acceleration time of <100 ms on pulsed wave Doppler or a tricuspid valve regurgitation velocity of >30 mm Hg) were assessed.

Continuous variables are reported as the mean ± SD. If a non-normal distribution was present, the data were plotted as the median and interquartile range (IQR). Proportions are reported as the numbers and percentages. Continuous variables and the proportions between baseline and the latest follow-up were compared using the paired *t* test and Fischer's exact test or chi-square test, respectively. The patient outcome is displayed using a Kaplan-Meier survival curve. p values <0.05 were considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences, for Windows, version 16 (SPSS, Chicago, Illinois).

Results

A total of 220 patients were included in the present study. The median age at inclusion was 18 years (IQR 7). The patients (119 males, male/female ratio 1.18:1) were followed for a median of 6 years (IQR 4, range 38). At the end of the study, the median age of the study cohort was 27 years (IQR 11). The demographic clinical, echocardiographic, and hemodynamic characteristics are summarized in Table 1.

Two patients (1%) died during the follow-up period. One patient, with congestive cardiomyopathy before closure, died suddenly 8 months after successful percutaneous VSD closure, with ventricular fibrillation the most likely cause of death. The second patient, with Down syndrome and congestive cardiomyopathy, died from end-stage heart failure. In 15 patients (7%), the VSD was closed (8 surgically and 7 percutaneously) because of progressive volume overload. The defect closed spontaneously in 8 patients (4%). The corresponding Kaplan-Meier curves are plotted in Figures 1 and 2. Endocarditis occurred in 8 cases (4%). All 8 cases were cured with antibiotics, and surgical intervention was not needed.

In 203 patients, the defect remained unclosed. Of these patients, 93% were in sinus rhythm at inclusion. During follow-up, 1 patient required pacemaker implantation because of atrioventricular block, and 1 developed a junctional atrioventricular rhythm. An automatic implantable cardioverter-defibrillator was implanted in 1 patient who survived ventricular fibrillation. At inclusion, 77% of the patients had normal QRS morphology. The remaining 25% were characterized by left or right bundle branch block or left or right

Table 2
Changes in electrocardiographic and echocardiographic variables in patients without spontaneous ventricular septal defect (VSD) closure (n = 203)

Variable	At Inclusion (n = 203)	At Latest Follow-Up (n = 203)	p Value
Electrocardiographic			
Heart rate (beats/min)	71 ± 16	69 ± 14	0.187*
Atrioventricular conduction time (ms)	144 ± 22	146 ± 24	0.199*
QRS duration (ms)	94 ± 14	98 ± 16	0.004*
Prevalence sinus rhythm	99%	98%	0.015†
Prevalence normal QRS morphology	77%	72%	0.0001†
Echocardiographic			
Left ventricle end-diastolic diameter (mm)	49 ± 5	49 ± 7	0.348*
Left ventricle end-systolic diameter (mm)	35 ± 5	34 ± 6	0.003*
Left ventricle end-diastolic volume index (ml/m^2)	65 ± 19	66 ± 24	0.691*
Left ventricle end-systolic volume index (ml/m^2)	25 ± 10	22 ± 11	0.017*
Left ventricle ejection fraction (%)	62 ± 7	67 ± 8	0.0001*
Stroke volume index (ml/m^2)	41 ± 11	44 ± 15	0.035*
Prevalence degree mitral valve regurgitation (x/4)			0.0001‡
0	67%	38%	
1	26%	50%	
2	4%	8%	
3	3%	2%	
4	0%	1%	
Prevalence degree aortic valve regurgitation (x/4)			0.0001‡
0	84%	74%	
1	15%	23%	
2	1%	3%	
3	0%	0%	
4	0%	0%	
Prevalence degree tricuspid valve regurgitation (x/4)			0.0001‡
0	30%	10%	
1	64%	78%	
2	4%	9%	
3	2%	3%	
4	0%	0%	
Prevalence pulmonary arterial hypertension	3%	9%	0.002†

Data are presented as mean ± SD or percentages.
* Paired *t* test.
† Fisher's exact test.
‡ Chi-square test.

hemiblock or had signs of left or right ventricular hypertrophy. The electrocardiographic changes are summarized in Table 2.

The echocardiographic changes in the group of patients with a VSD that did not close spontaneously are also summarized in Table 2. In a subgroup analysis, we found that those patients in whom the VSD did not close spontaneously and who had a increase in the end-systolic diameter (40%), the end-diastolic diameter and stroke volume index increased more than in those patients with a decrease in end-systolic diameter (60%), who were able to maintain the same stroke volume index (Table 3).

Table 3
Changes in left ventricle end-systolic diameter, left ventricle end-diastolic diameter, and stroke volume index between patients with decrease or increase in end-systolic diameter during follow-up

Change	At Inclusion	At Latest Follow-Up
Increase in left ventricle end-diastolic diameter (40% of cases)		
Left ventricle end-diastolic diameter (mm)	34 ± 5*	37 ± 5†
Left ventricle end-systolic diameter (mm)	48 ± 5	51 ± 6‡
Stroke volume index (ml/m^2)	42 ± 13	49 ± 16*
Decrease in left ventricle end-diastolic diameter (60% of cases)		
Left ventricle end-diastolic diameter (mm)	36 ± 5	32 ± 5
Left ventricle end-systolic diameter (mm)	49 ± 5	48 ± 7
Stroke volume index (ml/m^2)	40 ± 11	42 ± 15

* $p < 0.05$; † $p < 0.0001$; ‡ $p < 0.001$ vs corresponding variable in decrease in LVESD.

Discussion

We found that the course of patients with an unclosed and small pmVSD at the age of 16 years was not uneventful. Although the pmVSD closed spontaneously in some patients, others required surgical or interventional repair at later follow-up. Moreover, patients with persistent open pmVSD during follow-up developed significant echocardiographic and electrophysiologic changes.

We observed spontaneous pmVSD closure in 4% of our patients >16 years. Of all VSDs 11% to 70.8% close spontaneously during infancy.[1] This broad variation in closing rates is mainly related to the different types of VSDs. Spontaneous closure occurs more frequently in patients with muscular VSDs than in patients with pmVSDs.[2] Progressive muscularization of the left ventricle is considered the underlying mechanism of muscular VSD closure, independent of the localization of the defect.[3] The mechanism of spontaneous pmVSD closure is less well understood. However, the presence of a ventricular septal aneurysm (VSA) has been considered an early mechanism of closure.[4] It has been hypothesized that the septal leaflet of the tricuspid valve covers the defect and might explain why VSDs with a left ventricle to right atrium shunt close less frequently.[5] However, other mechanisms leading to spontaneous closure or a reduction in the size of the defect, such as prolapse of an aortic valve cusp into the VSD, have also been described. Finally, the underlying mechanism for the lower closure rates that have been reported in patients with congestive heart failure remains undetermined.[6] Spontaneous closure of VSDs during adolescence or adulthood has been described.[7,8] However, these reports were a combination of muscular, perimembranous, and doubly committed VSDs. Therefore, the incidence of spontaneous closure for each type of defect has been more difficult to delineate, compared to the rate in our study in which only pmVSDs without associated anomalies were investigated.

Two patients died during the follow-up period. Both had underlying intrinsic cardiomyopathy. Whether VSD is as-

sociated with intrinsic cardiomyopathy remains a question. However, a large, but older, study of patients with congenital VSD, in which a survival rate of 87% was reported at 25 years follow-up, showed an increased risk of severe arrhythmia and sudden death, even among patients with small defects.[9] A "ventricular septal defect cardiomyopathy" was already postulated by Bloomfield[10] in 1964. Bloomfield suggested an increased susceptibility to left ventricular disease; the defective septum was postulated to be unable to make its normal contribution to contraction, increasing the strain on the lateral wall and thus facilitating the development of ventricular disease. Others believe a long-standing VSD can lead to disturbed systolic function and a decrease of compliance of both ventricles by way of chronic pressure and volume overload. All of this could explain why a reduced left ventricular function with exercise and a subnormal working capacity could be found even in patients with small VSDs.[8] The patients who died during our study and who required implantable cardioverter-defibrillator implantation suggest that in our patient cohort, the pathophysiology was not limited to a structural septal defect. Endocarditis occurred in 4% of our patients.

Although some investigators could not find differences in left ventricular function in patients with a restrictive VSD compared to patients without echocardiographic anomalies,[11] we found that, in our patients with persistent pmVSD, the left ventricular ejection fraction and stroke volume increased with time, but the end-systolic diameter decreased and the end-diastolic diameter did not change. From these findings and the subanalysis we performed, we hypothesized that in the early phase, the stroke volumes are maintained by decreasing the end-systolic volume without changing the end-diastolic volume. When volume overload persists and is not more tolerated, the end-diastolic diameter begins to enlarge, which is an indication for late repair. The latter was needed in 7% of our patients, although they initially had a Qp/Qs ratio of $<$1.5:1. In addition, more valvular regurgitation occurred. Tricuspid valve regurgitation was more often found at later follow-up. Some people believe that a microscopically imperfect tricuspid valve, even in a healthy person, could partially explain the high incidence of tricuspid valve regurgitation in patients with pmVSD.[12] Others have attributed tricuspid valve regurgitation to VSA formation and distortion of the septal and anterior leaflets.[5] In our study, the development of aortic valve regurgitation was not uncommon. Aortic valve prolapse occurs in patients with pmVSD and frequently leads to aortic valve regurgitation.[2] This valve insufficiency might evolve, warranting surgical intervention.[13] However, none of our patients needed this surgical repair. It might be that the defects were too small to allow prolapse leading to severe valve regurgitation to occur.

Finally, the prevalence of pulmonary arterial hypertension was greater at the latest follow-up examination in patients without spontaneous VSD closure. The latter suggests that in addition to the volume overload of the left ventricle, pressure overload might not be underestimated.

The study had limitations. First, the study was retrospective with the risk of missing data. However, patients without VSD closure during childhood were systematically followed in the pediatric cardiology department, with the advantage that $>$90% of the follow-up data were complete. Second, the study was a single-center study, which implies a referral and selection bias. However, owing to the healthcare organization in Belgium, almost all children with a VSD are referred to a tertiary care center. Our hospital is 1 of the 2 main referral centers for congenital heart disease in the Flemish speaking part of Belgium; thus, the risk of data dispersion was low. Third, subanalysis of the data was not always possible because of low statistical power. However, the group of patients in whom the pmVSD remained open was large enough to perform adequate statistical analysis. Fourth, we could not study the predictors of spontaneous closure, the occurrence of endocarditis, or the loss of sinus rhythm by Cox regression analysis. We anticipated that the low number of events would not allow us to perform relevant statistical analysis. Thus, the presence of VSA was not accounted for in our analysis. Finally, the calculation of the left ventricle ejection fraction and left ventricular volumes was determined by data obtained by M-mode echocardiography. Although the latter was not ideal for volume calculations, we assumed that no regional left ventricle hypokinesia was present and that the ventricle was symmetrically contracting.

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