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Treatment of ventricular septal defect in children: Who, when, and how? A 20-years Lebanese multicentric retrospective study

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Abstract

Introduction: Ventricular Septal Defect (VSD) is a common congenital heart disease. Three therapeutic approaches exist to treat this anomaly: observation and regular follow-up, surgical closure, and Tran's catheter intervention. We seek through this study to determine the appropriate indications for surgical and non-surgical treatment of VSD.

Methods: We conducted a retrospective multicentric study between January 1, 2000 and June 30, 2020 on 942 VSD carriers. Cases with isolated VSD were studied for age of presentation, sex, type of VSD, and VSD outcome.

Results: Majority of our patients (60.5%) had a perimembranous VSD. During 20 years of follow-up, 220 underwent an intervention for their cardiac anomaly (either surgery or catheterization) and 722 received medical treatment and were under observation. Among patients who were solely monitored, 36.7% patients had a complete spontaneous closure of their VSD, 20.9% had a partial closure, and 39.9% had an unchanged VSD size. Patients with perimembranous and inlet types were significantly more likely to undergo an intervention (p=0.018). The most common reason behind intervention was severe pulmonary arterial hypertension seen in 140 cases. Furthermore, 18 cases out of 457 unclosed VSD developed complications during follow-up.

Conclusion: We found that 36.7% of VSDs might totally close over time, particularly if VSD is of muscular type. This rate might also increase with a longer follow-up period.

Keywords: Congenital heart disease; Cardiovascular malformation; Ventricular septal defect; Spontaneous closure; Lebanon

1. Introduction

Ventricular septal defect (VSD) is the most common congenital heart disease (CHD) among children with an incidence rate of 3.071 per 1,000 child [1]. We estimate that around 200 children with this anomaly are born every year in Lebanon [2]. Its main underlying pathophysiologic mechanism is a shunt between the right and the left ventricles that usually allows blood to pass from the left to the right side of the heart. Different types of VSD exist, sorted according to the location and the defected component of the ventricular septum [3]. It can either be perimembraneous, the most frequent type, muscular, multiple (which could be perimembranous or muscular), infundibular, also called outlet type, or the atrioventricular canal type, which is known as inlet type [4]. The size of the VSD and the degree of the pulmonary vascular resistance are major factors that determine the hemodynamic significance of the VSD and contribute to the

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development of pulmonary arterial hypertension (PAH) [5]. The severity of this malformation and the delay in its diagnosis are the causes of severe complications that might lead to death [5].

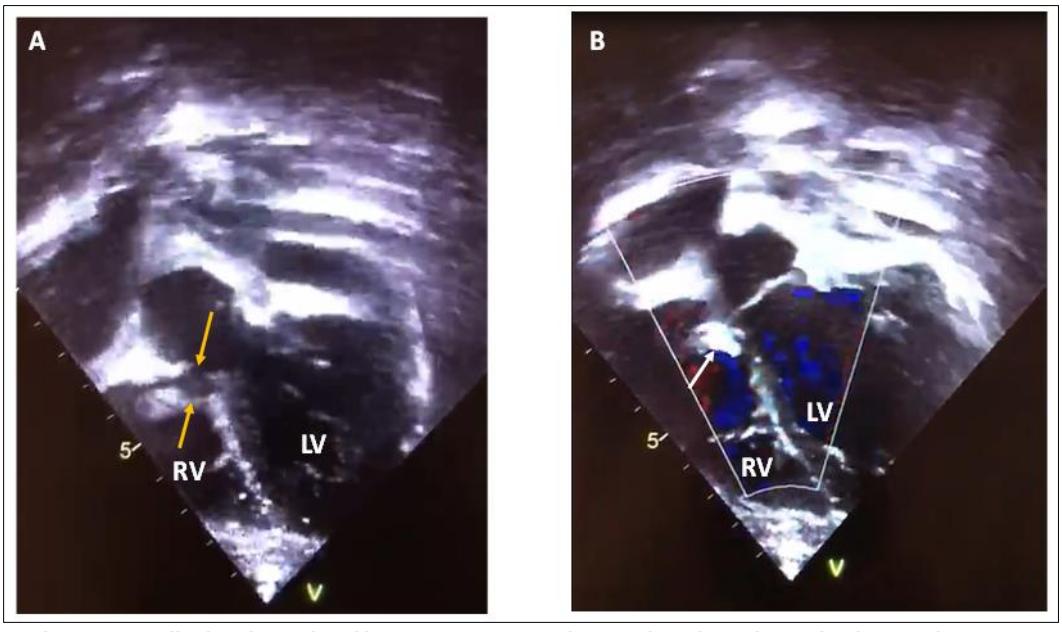
Until date, surgery is most frequently performed to close a VSD. However, operation can cause many complications [6]. In addition, such approach is associated with high costs and requires a sternotomy to grant a good exposure resulting in a surgical scar and sternotomy related-complications [7]. The trans-catheter technique is an alternative to surgery that overcomes these limitations [8], but puts the patient at risk of other complications [9]. Previous researches showed that VSDs can close spontaneously overtime, proving that patients could avoid any type of intervention and undergo simple monitoring with or without anti-congestive medications [10]. Nonetheless, the rate of spontaneous closure (SC) remains controversial, ranging from 4% to 83%, and depends on age, gender, size and site of the defect as well as many other factors [11,12].

Hence, the most suitable therapeutic approach remains a major subject of debate. Furthermore, there are only few studies internationally and no studies nationally that evaluate the natural history of neonatal VSDs over a long period of time. It is also well known, that there are no guidelines or expert consensus available to guide the frequency and duration of VSD follow-up; and, there are various opinions between pediatric cardiologists regarding the appropriate intervention time. Therefore the aim of this study is to determine, by following a group of patients with VSD, the appropriate indications for surgical and non-surgical treatment of VSD.

2. Methods

2.1. Study design and population

This was a retrospective multicentric cohort study. Subjects were followed-up over a period of 20 years: between January 1, 2000 and June 30, 2020. Eligible participants were male or female patients, born between January 2000 and December 2018, who had clinical and echocardiographic evidence of VSD and under follow-up. (Figure 1, 2, 3, 4) In addition, we enrolled patients with isolated VSD, or associated with an anomaly that is considered minimal and not interfering with the hemodynamics of the cardiovascular system, such as a very small atrial septal defect or minimal pulmonary stenosis. We excluded subjects with very small muscular VSD found in premature babies and VSD associated with significant other cardiac defects.



A-Yellow arrow indicating partially closed VSD closed by an aneurysm; B- Color Doppler echocardiography showing the same VSD (white arrow);

Figure 1 Case of large perimembranous VSD that partially closed spontaneously by an aneurysm during follow-up. This case was treated then by an Amplatzer.

Enrolled participants were then classified in 5 categories depending on the type of VSD determined by echocardiography: perimembranous, muscular, multiple (muscular or perimembranous), inlet and infundibular. Each category was further divided into 2 subcategories: intervention and observation. The purpose of these divisions and subdivisions was to determine the efficiency of each approach regarding the VSD type.

Patients who had their VSD closed, either underwent surgical closure by closing the defect, through trans-atrial approach using a patch (pericardial or goretex), or interventional catheterization, which consists of implanting a prosthesis (Amplatzer device).

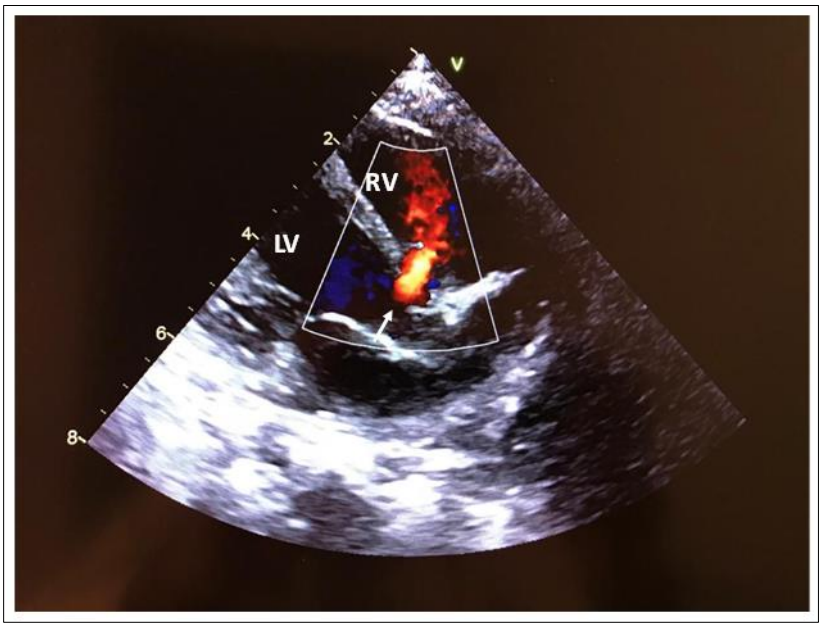


Figure 2 Case of large perimembranous VSD that partially closed spontaneously by an aneurysm becoming a restrictive type (white arrow). The case moved from class II-b to class I and is still under monitoring. White arrow indicating partially closed VSD by an aneurysm

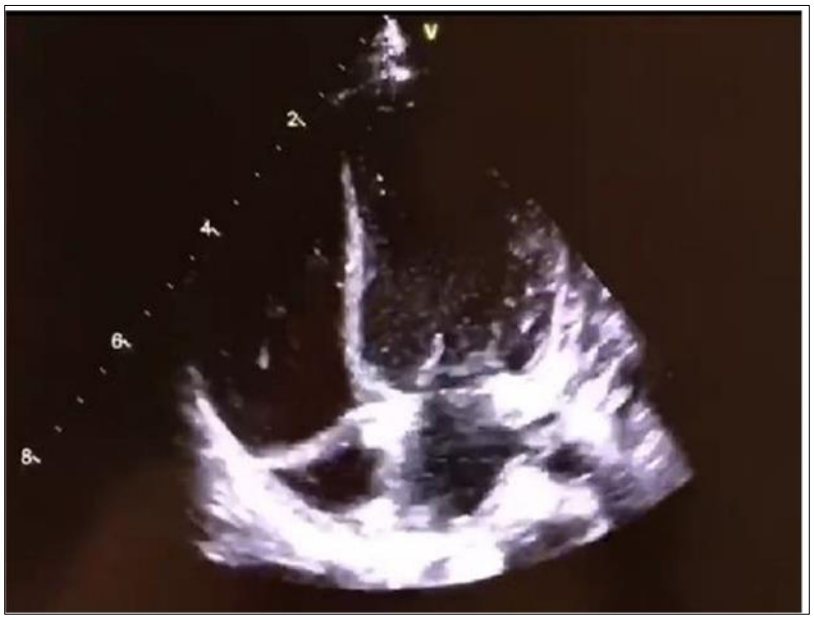


Figure 3 Case of left atrial enlargement (double the size of the right atrium) indicating an underlying large VSD with a significant left to right shunt although not visible in this cut

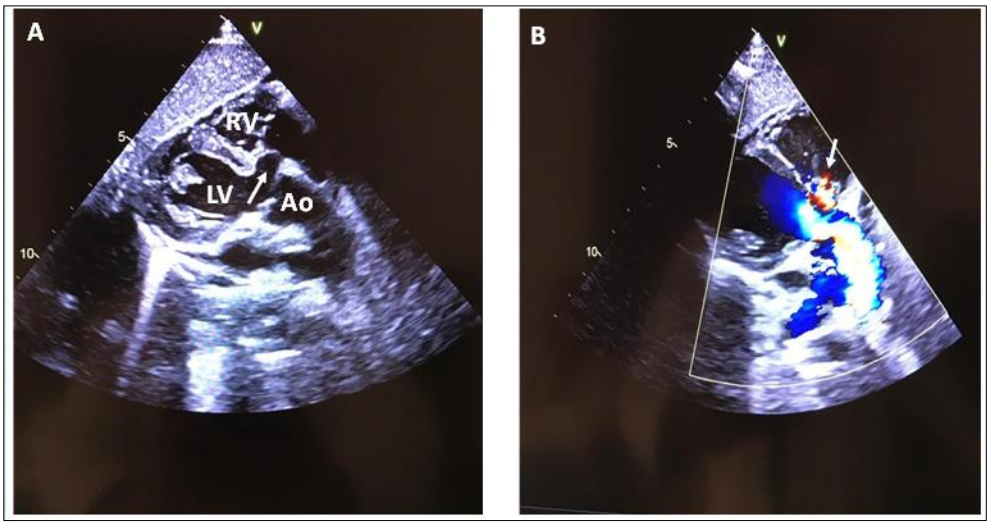


Figure 4 Case of large perimembranous VSD that completely closed spontaneously by an aneurysm (white arrow)

2.2. Data collection

We collected from patients' files regarding demographic characteristics (age at diagnosis, sex, region of residence), clinical (type of VSD, and therapeutic approach), and follow-up data (VSD outcomes).

2.3. Ethical considerations

This study was approved by The National Registry of the Pediatric and Congenital Heart Disease of the Society of Cardiology in Lebanon, Lebanese Order of Physicians. Access letter to patients' files was granted by the same society and the need for an informed consent was waived due to the retrospective nature of the study.

2.4. Statistical analysis

A descriptive analysis was enrolled, and variable were presented as per their type: categorical variables as frequency and proportion and continuous variables as the frequency and mean. We also calculated the prevalence of VSD in Lebanon between 2000 and 2018 years. Bivariate analysis was conducted to test the correlations between:

- type of VSD and age using Student t-test
- type of VSD and gender using Chi-square test
- type of VSD and intervention using Chi-square test

Data was analyzed using the IBM SPSS version 25. A statistically significant correlation was set at 5% (p-value less than 0.05).

3. Results

3.1. General characteristics of study population

The total number of registered Lebanese children between January 2000 and 2018 was 3817. During this period, prevalence rate of VSD reached 33.14%. Among 1265 VSD carriers, 942 (74.5%) were included in our study and followed regularly. (Figure 5) Our participants were mostly males (54.9%) and had a mean age of 37.3 months at diagnosis. Patients were recruited from all over the country with half of them residing in the capital Beirut (50.8%). The most frequent type of VSD was Perimembranous (60.5%), followed by Muscular (30.6%) and multiple (5.1%) VSD. Only 2.2% and 1.6% of our subjects had an Inlet and Infundibular VSD respectively. (Table 1) During 20 years of follow-ups, out of 942 patients, 220 (23.35%) required an intervention for their cardiac anomaly (either surgery or catheterization) and 722 (76.65%) received medical treatment and were under observation. At the end of the study, 265 (36.7%) patients had a complete SC of their VSD, 151 (20.9%) had a partial closure, and 288 (39.9%) had an unchanged VSD size. New findings on echocardiography were observed among 18 patients. (Figure 5).

Table 1 General characteristics of our population

Parameter	Frequency	Percent
Demographics		
Age at diagnosis		
Mean (in months)	37.3	
Minimum (in days)	1	
Maximum (in months)	182	
Sex		
Male	517	54.9%
Female	425	45.1%
Region of residence		
North	79	8.4%
Beqaa	141	15%
Beirut	479	50.8%
Mount Lebanon	161	17.1%
South	82	8.7%
Clinical Characteristics		
VSD Type		
Perimembranous	570	60.5%
Muscular	288	30.6%
Multiple	48	5.1%
Inlet	21	2.2%
Infundibular	15	1.6%

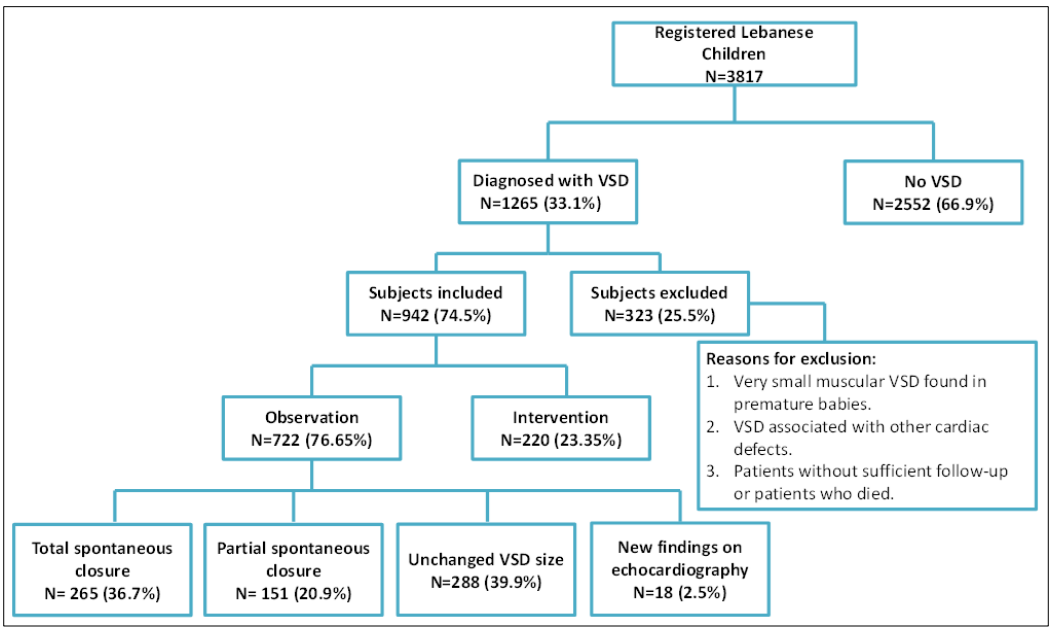


Figure 5 Flow chart summarizing the study outcomes

3.2. Epidemiology of VSD

Table 2 shows the distribution of VSD types according to age, sex and therapeutic measures. Patients with perimembranous and infundibular VSD were significantly older at time of diagnosis compared to other VSD types (respectively 43.0 months vs. 35.9 months, p<0.001, and, 76.2 months vs 27.6 months, p<0.001). In contrast, patients with muscular or multiple VSD were significantly younger at time of diagnosis when compared to other VSD categories (respectively 24.0 months vs. 40.7 months, p<0.001, and, 12.0 months vs 43.6 months, p<0.001). There was no statistically significant difference in age between inlet VSD and other VSD types (p=0.219).

As for sex distribution, females were significantly more prevalent in multiple VSD (7.1%) compared to males (3.5%) (p<0.001), as opposed to inlet and infundibular types, where males where significantly more prevailing (respectively 2.7% vs. 1.6%, p<0.001, and, 2.3% vs. 0.7%, p<0.001). There was no statistically significant difference in sex distribution in perimembranous (p=0.096) and muscular (p=0.136) types.

Regarding therapeutic measures, patients with perimembranous and inlet types were significantly more likely to undergo an intervention (respectively 86.4% vs. 52.6%, p<0.001, and 4.1% vs. 1.7% p=0.018). In comparison, patients diagnosed with muscular VSD were more likely to receive medical treatment and undergo regular follow-ups (38.8% vs. 3.6%, p<0.001). There was no statistically significant difference in therapeutic measures in multiple (p=0.130) and infundibular (p=0.177) types.

Table 2 Distribution of VSD types according to age, sex and therapeutic measures

VSD type		Age				Sex						Therapeutic measures				
		Average	Min	Max	P-value	Males		Females		Sex ratio	P-value	Intervention		observation		P-value
						N	%	N	%			N	%	N	%	
Perimembranous	Yes	43.0	0.03	65	<0.001	323	62.5	247	58.1	1.3:1	0.096	190	86.4	380	52.6	<0.001
	No	35.9	0.03	182		194	37.5	178	41.9	4:1		30	13.6	342	47.4	
Muscular	Yes	24.0	0.03	60	<0.001	150	29.0	138	32.5	1.3:1	0.136	8	3.6	280	38.8	<0.001
	No	40.7	0.03	182		367	71.0	287	67.5	4:1		212	96.4	442	61.2	
Multiple	Yes	12.0	0.03	66	<0.001	18	3.5	30	7.1	1.3:1	<0.001	8	3.6	40	5.5	0.130
	No	43.6	0.03	182		499	96.5	395	92.9	4:1		212	96.4	682	94.5	
Infundibular	Yes	76.2	0.03	182	<0.001	12	2.3	3	0.7	1.3:1	<0.001	5	2.3	10	1.4	0.177
	No	27.6	0.03	182		503	97.3%	422	99.3	4:1		215	97.7	712	98.6	
Inlet	Yes	31.4	0.03	162	0.219	14	2.7	7	1.6	1.3:1	<0.001	9	4.1	12	1.7	0.018
	No	38.8	0.03	182		503	97.3	418	98.4	4:1		211	95.9	710	98.3	

3.3. Clinical findings

Among 570 patients with perimembranous VSD, 183 (32.1%) had their VSD closed surgically with or without pulmonary artery banding and 7 (1.2%) underwent cardiac catheterization. These cardiac interventions were indicated in the cases of severe (19.6%) and moderate (4.9%) PAH, right ventricle hypertrophy (3.3%), aortic insufficiency (3.0%), sub aortic membrane (1.2%), QP/ QS> 1.8 with dilation of the left atrium and left ventricle (1.0%), and infective endocarditis (0.2%). (Table 3) During monitoring of perimembranous VSDs over the years, we noted 95 (16.7%) cases of total SC, while 108 (18.9%) subjects had partial closure. In addition, VSD size did not change over time in 162 (28.4%) individuals. Furthermore, echocardiography revealed aortic insufficiency in 7 (1.2%) patients, sub aortic membrane in 7 (1.2%) patients, and right ventricle hypertrophy in 1 (0.2%) patient. (Table 4). A 4 months year old male, suffering from type 2B perimembranous VSD with severe pulmonary hypertension, died 12 hours post-surgery of the patch due to disinsertion and developed cardiac arrest.

Table 3 Type of intervention and reason behind it according to VSD types

VSD type	Perimembranous N = 570	Muscular N = 288	Multiple N = 48	Inlet N = 21	Infundibular N = 15	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Type of intervention						
Closed by surgery with or without pulmonary artery banding	183 (32.1%)	8 (2.8%)	8 (16.7%)	9 (42.9%)	5 (33.3%)	213 (22.6%)
Closed by interventional catheterization	7 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (0.7%)
Reason behind intervention						
Severe PAH*	112 (19.6%)	8 (2.8%)	8 (16.7%)	9 (42.9%)	3 (20.0%)	140 (14.9%)
Moderate PAH	28 (4.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	28 (3.0%)
Right ventricle hypertrophy	19 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (2.0%)
Aortic Insufficiency	17 (3.0%)	0 (0%)	0 (0%)	0 (0%)	2 (13.3%)	19 (2.0%)
Sub Aortic Membrane	7 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (0.7%)
Absence of PAH, QP/ QS> 1.8† with dilation of the left atrium and left ventricle	6 (1.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (0.6%)
Infectious Endocarditis	1 (0.2%)	0	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)

*PAH: Pulmonary Arterial Hypertension; †QP/QS: pulmonary to systematic flow ratio

Table 4 Distribution of VSD outcome according to types

VSD Type	Perimembranous N = 570	Muscular N = 288	Multiple N = 48	Inlet N = 21	Infundibular N = 15	Total N=942
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Closed by intervention	190 (33.3%)	8 (2.8%)	8 (16.7%)	9 (42.9%)	5 (33.3%)	220 (23.3%)
Total Spontaneous Closure	95 (16.7%)	145 (50.3%)	21 (43.8%)	3 (14.3%)	1 (6.7%)	265 (28.1%)
Partial spontaneous closure	108 (18.9%)	22 (7.6%)	19 (39.6%)	2 (9.5%)	0 (0%)	151 (16.0%)
Unchanged VSD size	162 (28.4%)	113 (39.2%)	0 (0%)	7 (33.3%)	6 (40.0%)	288 (30.6%)
Aortic Insufficiency	7 (1.2%)	0 (0%)	0 (0%)	0 (0%)	3 (20.0%)	10 (1.1%)
Sub Aortic Membrane	7 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (0.7%)
Right ventricle hypertrophy	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)

As for muscular VSD, out of 288 patients, 8 (2.8%) underwent surgical closure of their VSD with or without pulmonary artery banding because of severe PAH. (Table 3) On follow-up, 145 (50.3%) patients had a complete SC of their VSD, 22 (7.6%) patients had a partial SC, and 113 (39.2%) had an unchanged VSD size. (Table 4).

Out of 48 patients with multiple VSD, 8 (16.7%) patients had severe PAH requiring surgical closure with or without pulmonary banding, 21 (43.8%) had total SC, and 19 (39.6%) had partial SC. (Table 3 and 4).

Regarding inlet VSD, among 21 patients, 9 (42.9%) patients had severe PAH that needed surgical closure with or without pulmonary banding, 3 (14.3%) had total SC, 2 (9.5%) had partial SC, and 7 (33.3%) had an unchanged VSD size. (Table 3 and 4).

Among 15 patients with infundibular VSD, 5 (33.3%) patients underwent surgical closure with or without pulmonary banding because of their severe PAH (3 cases) and aortic insufficiency (2 cases). (Table 3) During follow-up, 1 (6.7%) patient had total SC, and 6 (40.0%) had unchanged VSD size. On follow-up echocardiography, we noted 3 (20.0%) patients with a new aortic insufficiency. (Table 4).

4. Discussion

We conducted a 20 years retrospective descriptive study to determine the appropriate indications for surgical and non-surgical treatment of VSD. We enrolled 942 VSD carriers, among them, 220 underwent an intervention for their cardiac anomaly (either surgery or catheterization) and 722 received medical treatment and were under observation. The rate of complete and partial SC, after 20 years of follow-up, were 36.7% and 20.9% respectively.

We reported a VSD prevalence of 33.14% higher than the prevalence of 25.3% between 1997 and 2000 found by Bitar et al in Lebanon [13].This increased rate could be due to an actual increase in the prevalence of VSD, or an improvement in echocardiographic technology, availability of ultrasound in Lebanon, as well as, an increase neonatal screening [14]. In accordance with the literature, VSDs were most frequently perimembranous, and detected in males [3,15]. Previous studies proved that genetic disorders contribute to the formation of this congenital anomaly, in addition to many risk factors such as smoking, alcohol and drug usage during pregnancy, maternal diabetes mellitus, and sex of the baby [16,17]. Two dimensional echocardiography in combination with Doppler flow mapping is a non-invasive accurate tool to detect VSD at birth and its SC, and to assess hemodynamic parameters [17]. In line with many previous reports, muscular VSD had the highest rate of SC [10,18].The exact mechanism behind SC of a VSD is still uncertain and differs between VSD types. For instance, it was suggested that muscular VSD spontaneously close as a result of hypertrophy of muscular septum or superimposition of a fibrotic tissue around the defect. Whereas, perimembrenous VSD may close spontaneously by an aneurysm, prolapse of the aortic valve cusp, or adherence or reduplication of tricuspid valve [11]. Furthermore, predictors of SC varied greatly between studies depending of the population studied, research methodology, and follow-up period. Previous studies showed that the most important predictors for the probability of spontaneous closure of VSD in infants were young age (6 months to 1 year), female sex, size, and location of the defect [11,18]. In fact, isolated VSDs with small diameter (< 3mm) have a higher chance for spontaneous closure in utero or postnatal. Moreover, a muscular type VSD is more likely to close spontaneously before the 1st year of life when compared to perimembranous VSD [19,20]. A study found that 59% of muscular VSD closed during the follow up period, compared to 21% of perimembranous type of VSD [21]. Other hemodynamic independent predictors of spontaneous closure are the ratio between diameter of the defect and aortic root diameter (DVSD/DAR), left atrium and ventricle sizes, main pulmonary forward blood flow, infection scores, shunt ratio (Qp/Qs), and comorbidities including patent ductus arteriosus (PDA), and membranous septal aneurysm [22]. As for risk factors for defect persistence, Cresti et al found that perimembranous VSD in male subjects that is particularly characterized by multiple defect were less likely to close [23]. Zhao et al added that a VSD with defect size above 4mm is an independent predictor for non-closure of a VSD [10]. Moreover, close monitoring of patients with VSD is crucial because long term persistence of a large size VSD which have low rate of spontaneous closure may cause the occurrence of complications. In our study, complications of VSDs that remain unclosed were infrequent (18 cases out of 457), but most commonly occur in perimembranous VSD. Adverse events such as severe and irreversible PAH (Eisenmenger syndrome), failure to thrive, infective endocarditis, aortic insufficiency, left ventricle volume overload, right ventricle outflow tract obstruction, double chamber right ventricle, and congestive heart failure during infancy and childhood are factors that directs the decision towards surgery as a treatment. Appearance of these complications early in life is also an indication for surgery [6,12]. VSD area indexed to body surface area (BSA) and VSD indexed to aortic valve ratio were the most significant echocardiographic variables found to be independently associated with the need for surgical intervention, they are also easily obtainable and would potentially help risk-stratify asymptomatic patients with VSDs to guide surveillance, regardless of the type or location of the defect [21]. Since 2006, published data reported low mortality rates (0.0% to 2.7%) among patients undergoing primary surgical closure of VSD [24]. Post-operative course may be complicated by arrhythmias, pulmonary and

infectious events, prolonged ICU stay as well as long ventilation time [6,24]. Furthermore, scars resulting from sternotomy are major sequelae of VSD surgical repair that raises negative attitude among patients [25]. All these post-operative sequelae may impact the neurological development of the child and adolescent, cause psychosocial issues and decrease the quality of life in this group of individuals [26–28]. Transcatheter closure of VSD emerged in 1988 as an alternative to surgery. Through the years, this approach showed promising results (very low mortality rate, decreased psychological impact, short hospital stay, reduced post-operative pain, avoidance of ICU admission…) [29,30]. However, arrhythmia is a frequent adverse event reported among patient undergoing this procedure [29,30]. Notably, till date, Amplatzer™ Muscular Ventricular Septal Defect Occluder and the Amplatzer™ perimembranous ventricular septal occluder are the only two devices approved by the FDA [31,32].

Packard Children's Hospital at Stanford based their treatment protocol for VSDs on clinical, imaging data and echographic factors [21]. According to their experience, their combination is still insufficient to direct therapeutic approach and cannot be generalized In addition, the duration from diagnosis to surgery, period and intensity of follow up were unfixed. Furthermore, a Chinese experience, based their decision for treatments options on different combinations of clinical, imaging data and echocardiographic factors model, which still need validation [12]. The recommended period and intensity of follow-up were once every 1 or 2 years for small VSD and a yearly follow up for medium and large VSD. Muralidaran et al. revealed that children with moderate-sized defects and shunts greater than 1.5:1 generally have mild to moderate elevations of pulmonary artery pressure, hence, they can be followed until they are up to 5 years of age to maximize the chance of spontaneous closure. In contrast, infants with a large defect and significant CHF in whom spontaneous closure is unlikely are candidates for early closure, regardless of the patient's size [33].

Limitations

Our study presents several limitations. This is a retrospective observational research, which renders the study's findings subject to bias and confounders. We also failed to report clinical examination, echocardiography parameters (size of VSD and hemodynamic parameters), some maternal and patients' birth demographic information.

Recommendations and Perspectives

To our knowledge, this is the first research in the Middle East that describes the natural history of VSD over a very long period of time. This study also adds more data to the existing literature regarding the SC of VSD and the importance of monitoring before recurring to any interventions. Table 5 summarizes the list of recommendations and provide answers to study question. It should be also noted that adults with unrepaired VSD during childhood should also undergo regular monitoring for signs of left ventricle overload and new onset of aortic regurgitation. Despite the minimal surgery mortality risk (1%), surgical closure is only indicated in the severe VSD forms, and it is not recommended otherwise. Beside, sternal scar from an aesthetic point of view - especially for females - might have many complications such as infections, arrhythmias - mainly complete AV block - neurologic sequelae and death. If weight gain is feasible, catheter closure would be an option as soon as it becomes possible. During preparation phase, children would benefit from recent preventive measures, such as pulmonary infections prophylaxis through immunoglobulins.

Table 5 Summary of recommendations based on the findings of our study

Therapeutic approach (How?)	**Surgical Closure**	**Trans-catheter closure and/or medical treatment**	**Regular follow-up with no medical treatment**
Patient characteristics (Who?)	●Large VSD (perimembrenous or muscular) ●Failure to thrive ●Severe and moderate PAH ●Infective endocarditis ●Aortic Regurgitation ●Right mid-ventricular stenosis (Right ventricle hypertrophy)	●Large VSD partially closed that became moderate VSD because of an aneurysm ●Perimembranous or muscular moderate sized VSD	Small VSD Moderate VSD with no complications
When?	During the first year of life if severe	When weight above 10kg or by the age of 2 years	

5. Conclusion

In this study we described the natural history of 942 VSD. We found that 36.7% of VSDs may totally close over time particularly if VSD is of muscular type. This rate might also increase with a longer follow-up period. We summarized a list of recommendations for VSD treatment and follow-up, which may assist pediatrician in managing children with VSD and be implemented during counseling of patients' family regarding long term outcomes of their child disease.

Compliance with ethical standards

Acknowledgments

We would like to pay our gratitude and our respects to the late Dr Ghassan Chehab, without whom this project would never have been possible.

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

Due to the project retrospective nature, the need for informed consent was waived.

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