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ORIGINAL ARTICLE

Spontaneous Closure of Isolated Ventricular Septal Defect in the First Year

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Abstract

Background/Aim: Ventricular septal defect (VSD) is the most common congenital heart anomaly that in many cases closes spontaneously. The spontaneous closure (SC) rate of VSD varies widely between studies. The aim of this study was to identify clinical and echocardiographic factors influencing SC of isolated VSD in the first year of life among a group of patients presented at the Paediatric Clinic.
Methods: Prospective study was performed in 60 consecutive patients with trivial, small or medium isolated VSD during the first year of life. Patients were divided into groups, according to gender and gestational age of the patient, type, number and the size of the defect and persistence of pulmonary hypertension. The size of defect was described in comparison to the diameter of the aortic annulus (VSD/Ao ratio).
Results: At the time of diagnosis, the mean VSD/Ao ratio was 0.33 mm. Muscular VSD was more common (76.7 %) than perimembranous (23.3 %). SC of VSD occurred in 60 % of all patients, in case of muscular defect in 73.9 % and in case of perimembranous in 14.3 %. There was a negative correlation between defect size and SC rate. SC probability for a given defect size was described by the formula: probability = -1.82933X+1.20145. None defect with pulmonary hypertension closed.
Conclusion: It was found that type and size of VSD and the persistence of pulmonary hypertension were significant predictors for SC, while gender and gestational age of the patient and the number of defects were not. This study can be useful in predicting the natural outcome of the VSD to make proper follow-up and management plans.

Key words: Ventricular septal defect; Spontaneous closure; Probability; The first year of life.

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Introduction

Ventricular septal defect (VSD) is an abnormal congenital communication between the two ventricles.[1] With an estimated a prevalence of 2 to 3.94 per 1000 live births, it is the most common congenital heart anomaly.[2-5] Since many cases are asymptomatic and a large number of defects close spontaneously before coming to the attention of physicians, the true prevalence is probably even higher. VSD is more common in premature infants with prevalence of 4.5 - 7 per 1000 live births.[6-9] It can occur as an isolated anomaly or with other congenital heart defects and as a component of complex congenital heart diseases. The isolated form of VSD is the most common and accounts for almost 50 % of all heart anomalies.[10] These defects are mostly classified according to their lo-

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cation, size and number. In terms of phenotypic features, VSD can be placed into one of three primary types. The first type, named muscular VSD, is made up of a defect that has exclusively muscular borders. In the second type, membranous VSD, the posteroinferior quadrant of the defect is made up of fibrous tissue. Since borders of this type of defect usually are partly made of muscular tissue, it is usually named perimembranous.[10] In the third type, the fibrous continuity is present between the leaflets of the aortic and pulmonary valves in the cranial margin of the defect. This type of defect is doubly committed and directly juxta-arterial because of the absence of any muscular subpulmonary infundibulum.

The most objective estimate of defect size is based on the ratio of the maximum diameter of the VSD and the diameter of aortic annulus (VSD/Ao ratio).[11] Usually, defects are considered small if their diameter is less than one-third, medium if it is between one and two-thirds and large if it is greater than two-thirds of the aortic annulus diameter. Trivial defects are small defects with a diameter less than one-quarter of the aortic annulus diameter. In some cases, there is more than one defect, mostly located in the apical part of the septum, which is called multiple VSD. The clinical manifestation of an isolated VSD is related to its size and the relationship between systemic and pulmonary vascular resistances. The symptoms typically become manifest in term infants between the fourth and eighth week, concomitant with the decrease in pulmonary vascular resistance. In premature infants the onset of symptoms is much earlier.[1] Today, echocardiography has a major role in diagnosis, monitoring and planning the appropriate treatment.

It has long been recognised that VSD in many cases closes spontaneously and there is a number of observation follow-up studies about this topic. Spontaneous closure (SC) rate of the defect depends on multiple factors, of which, the well-known are defects type, location and size. The mechanism of closure depends on the location, respectively on the type of VSD. The usual mechanism of SC of muscular VSD is thought to be muscular encroachment plus superimposed fibrosis or physical hypertrophy of the septal myocardium or by fibrous tissue around the margins leading to apposition of the edge of the defect.[12] The most considered mechanism of closure of perimembranous VSD is the adherence of tricuspid valve leaflets which create an aneurysm that closes the defect.[13] Doubly committed defects, on the other hand, usually always require surgical closure since they persistence courts the risk of development of aortic valvular prolapse.[1, 14] The SC rate of VSD varies widely between studies, from 12 % to 84 %, depending to the age of the patients, the location, size and type of VSD, diagnostic methods and the length of the follow-up period.[12, 15-17] The overall reported rate of SC of isolated VSD is between 44 % and 73 % by the end of the first year of life.[13, 14, 16, 18] After that age, the rate declines, especially after 3.5 years.[13] The size of the defect is one of the major predicting factors for SC, especially in muscular defects.[8] Defects greater than 66 % of the aortic annulus diameter mostly need surgical closure.[17]

The aim of the study was to identify clinical and echocardiographic factors influencing SC of VSD and to summarise a prediction formula including contributing factors.

Methods

Study design and subjects

Prospective study was performed in 60 consecutive patients born between June 2017 and July 2019 who presented with isolated VSD at the Paediatric Clinic of the University Clinical Centre of the Republic of Srpska. Only patients with isolated VSD or VSD in combination with an open *foramen ovale* were included in the study. Those with additional cardiac and other anomalies and with chromosomal abnormalities were excluded. Patients were divided into groups, according to gender (male or female), gestational age (mature or premature), type of VSD (muscular or perimembranous), number of defects (single or multiple), size of the defect (trivial, small or medium) and persistence of pulmonary hypertension.

The size of VSD was described in comparison to the diameter of the aortic annulus (VSD/Ao ratio) in order to negate the influence of weight and gestational age on the absolute VSD size. VSD was considered trivial if it measures less or equal to 25 % of the aortic annulus diameter, small if it measures more than 25 % but less or equal to 33 % and medium if it is more than 33 % but less or equal to 66 % of the aortic annulus diameter. This study did not include patients with large defects and patients with doubly committed and direct-

ly juxta-arterial VSD, since these usually always require surgical treatment, rather than follow-up observation.

Diagnostic procedure

VSD was detected with conventional two-dimensional colour Doppler echocardiography. Indications for performing echocardiography was auscultation of a heart murmur during a regular physical examination of the newborn. The ventricular septum was completely scanned and the position, number and size of the defects were determined. Defect size was measured in all planes and the largest diameter of VSD was recorded and the diameter of the aortic annulus was measured at the level of the valve (Figure 1).

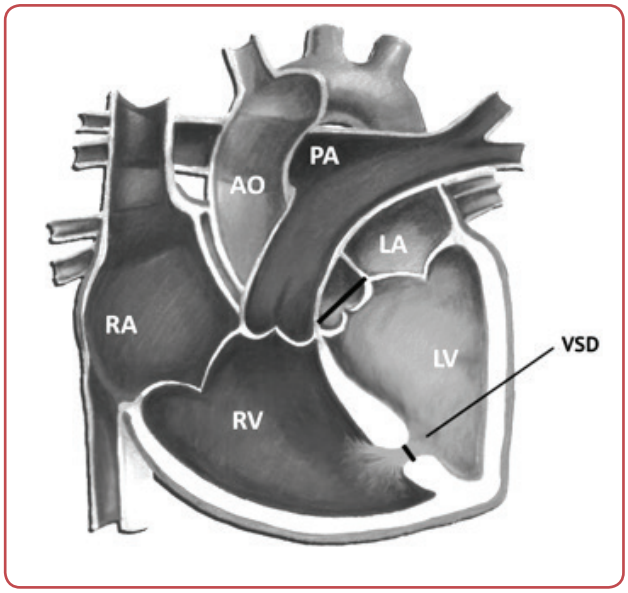

Figure 1: Picture of the heart with VSD illustrating the measurement of the VSD/Ao;

RV - right ventricle, LV - left ventricle; RA – right atrium; LA - left atrium; Ao - aorta; PA - pulmonary artery; VSD - ventricular septal defect;

In the case of multiple defects, the size of the largest one was studied, as it was considered that its natural course most faithfully reflects the course of the entire defect. Additional cardiac anomalies were excluded. All patients were followed up periodically, every three to six months depending on the size of the defect, till its closure or the end of the first year of life. This follow-up period was considered sufficient for the study since most of the defects were expected to close during the first year. The VSD was considered closed if the echocardiogram of the ventricular septum was normal, confirmed by colour Doppler mapping. Doppler echocardiography measurements were used also to estimate pulmonary artery pressure with peak tricuspid regurgitation velocity and adding right atrial pressure. Other sign of pulmonary hypertension, as right ventricle size and pressure overload, pulmonary artery acceleration time and pulmonary artery diameter, were also searched.[19]

Statistical analysis

The Chi-square test was used to compare the differences in SC of VSD between groups. A p-value of less than 0.05 was regarded as statistically significant. To estimate the SC probability for a given statistically significant variable(s), logistic regression analysis was used. The logistic regression model was generated with SC as a dependent variable (SC as 1, no closure as 0) and defect size that was described in comparison to the diameter of the aortic annulus (X) as an independent variable.

Ethics statement

The study was conducted according to the principles expressed in the Declaration of Helsinki. All parents of studied patients provided written informed consent. Ethical authorisation was obtained from the Ethics Committee of the University Clinical Centre of the Republic of Srpska (decision No 01-9-396-2/17).

Results

Out of 60 patients born with isolated VSD, 31 (51.67 %) were males and 29 (48.33 %) were females, 46 (76.67 %) were born on term and 14 (23.33 %) were born prematurely. The mean age of the patients at the time of diagnosis was 31.62 ± 58.55 days (range 1-240 days).

Muscular defect was found in 46 patients (76.67 %) and perimembranous in 14 patients (23.33 %). Among patients with muscular VSD, 26 (56.52 %) had defect in apical part, 16 (34.78 %) in middle part and 4 (8.70 %) in anterior part of muscular septum. None of patients had a defect in the posterior part of the muscular septum. At the time of diagnosis, the mean size of VSD was 2.5 ± 1.15 mm (range 1-6 mm) and the mean VSD/Ao ratio was 0.33 ± 0.14 mm (range 0.09–0.66 mm). The mean VSD/Ao ratio for muscular defects was 0.28 ± 0.08 mm and for perimembranous 0.55 ± 0.13 mm. Trivial defect was found in 22 (36.67 %), small defect in 16 (26.67 %) and medium defect in 22 (36.67 %) patients. SC of VSD till the end

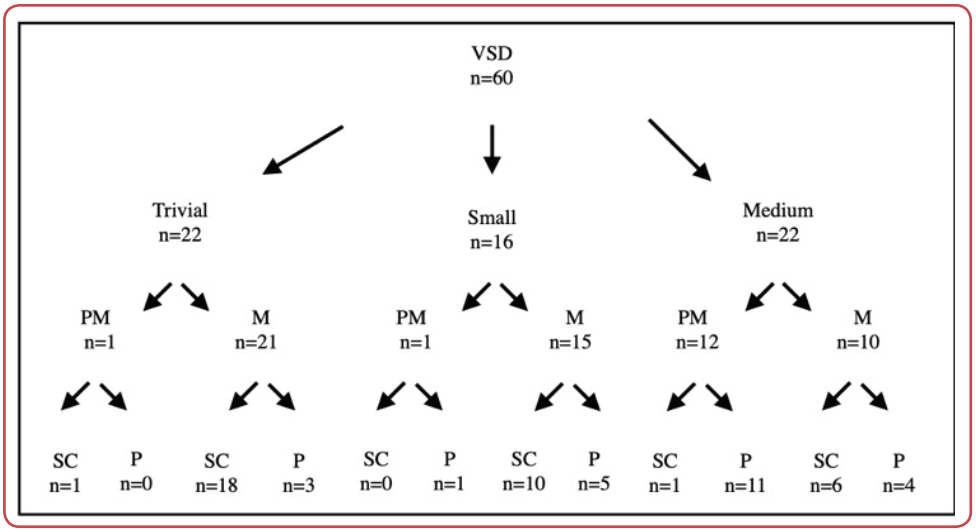

Figure 2: Flow chart showing the distribution of the studied VSDs according to size, type and natural outcome of defect

n - number; PM - perimembranous; M - muscular; SC - spontaneous closure; P - persistent; VSD - ventricular septal defect;

of the first year of life occurred in 36 (60 %) patients. The distribution of the 60 studied VSDs, according to size, type and natural outcome, is shown in Figure 2.

Table 1: Distribution of the patients according to clinical and echocardiographic indicators between the group with and the group without SC of VSD

Indicator	SC of VSD	No SC of VSD	p-value
Total, n (%)	36 (60.00 %)	24 (40.00 %)	-
Gender			
Male	21 (67.74 %)	10 (32.26 %)	0.316
Female	15 (51.72 %)	14 (48.28 %)	
Gestational age			
Mature	27 (58.70 %)	19 (31.30 %)	0.709
Premature	9 (64.29 %)	5 (35.71 %)	
Number of defect			
Single	31 (64.58 %)	17 (35.42 %)	0.263
Multiple	5 (41.67 %)	7 (58.33 %)	
Type of defect			
Perimembranous	2 (14.29 %)	12 (85.71 %)	< 0.001*
Muscular	34 (73.91 %)	12 (26.09 %)	
Size of defect			
Trivial	19 (86.36 %)	3 (13.64 %)	0.001*
Small	10 (62.50 %)	6 (37.50 %)	
Medium	7 (31.82 %)	15 (68.18 %)	
Pulmonary hypertension	0 (0.00 %)	4 (100.00 %)	-

*VSD - ventricular septal defect; SC - spontaneous closure; n - number; *p < 0.05;*

Significantly different closure rates were found for defects that differ in type ($p < 0.001$) and size ($p = 0.001$). Muscular VSD had a higher closure rate (73.91 %) compared to perimembranous VSD (26.09 %). Defects in apical and middle part had higher closure rates (76.92 % and 75 %, respectively) than defects in anterior part of the muscular septum (50 %), but this difference was not statistically significant. According to defect size, the highest closure rate was in the group with trivial VSD (86.36 %). Of 19 trivial defects that closed spontaneously, one was perimembranous and 18 were muscular defects. Three cases of trivial VSDs, all muscular, did not close. Small defects spontaneously closed in 62.50 % and medium in 31.82 % of cases. VSD closure rate was slightly higher in males (67.74 %) compared to females (51.72 %), in prematurely born patients (64.29 %) compared to those born on term (58.70 %), and in the case of a single defect (64.58 %) compared to multiple defects (41.67 %), but these differences were not statistically significant. Four patients (6.66 %) had pulmonary hypertension. In none of them, the defect was spontaneously closed till the end of the first year. Differences of results between patients with and without SC of VSD are summarised in the Table 1 and Table 2.

Table 2: Distribution of the patients with muscular VSD according to defect localisation between the group with and the group without SC of VSD

Location	SC of VSD	No SC of VSD	Total
Apical	20 (76.92 %)	6 (23.08 %)	26 (56.52 %)
Middle	12 (75.00 %)	4 (25.00 %)	16 (34.78 %)
Anterior	2 (50.00 %)	2 (50.00 %)	4 (8.70 %)
Total, n (%)	**34 (73.91 %)**	**12 (26.09 %)**	**46 (100.00 %)**

VSD - ventricular septal defect; SC - spontaneous closure; n - number; Chi-Square: 1.318; p-value: 0.517 (p > 0.05); Location: Muscular defect according to location in muscular part of ventricular septum;

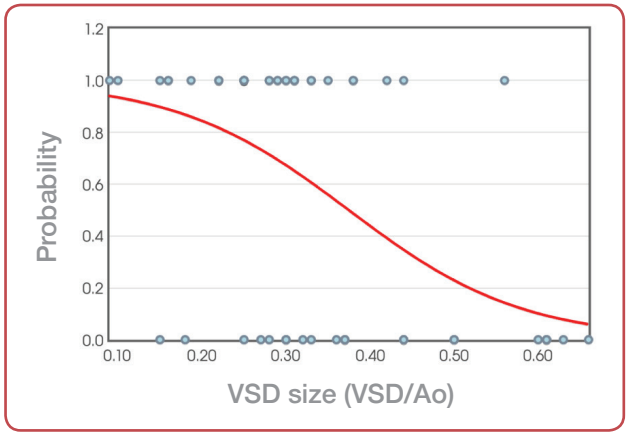

Figure 3: Logistic regression line shows the probability of SC of VSD depending on the size of the defect (VSD/Ao ratio);

1: closed VSD, 0: persistent VSD; Chi-Square: 16.765, p =0.0009; VSD - ventricular septal defect; SC - spontaneous closure; Ao - aorta;

The SC probability for a given defect size, as a statistically significant variable, was estimated using logistic regression analysis (Figure 3). The relationship between defect size (VSD/Ao ratio) and SC probability was described by the following prediction formula:

probability = - 1.82933X + 1.20145.

Discussion

The present study was conducted in order to evaluate the SC rate of isolated VSD during the first year of life. From 60 consecutively enrolled patients with isolated VSD, there was almost the same number of male and female patients, consistent with the well-established fact that there is no gender predilection in VSD.[20] Preterm born patients account for 23.33 %. Since the average incidence of preterm birth rate in Europe is 10.6 %, this result is in line with known fact that VSD is more common in premature than in term born infants.[8, 9, 21, 22] The mean age of the patient in this study at the time of diagnosis was 31.62 days, when the onset of symptoms in the case of a smaller defect, such as was studied, is usually not yet expected.[11] The explanation for this early finding is that echocardiography was performed because of the auscultation of a heart murmur as an isolated sign.

In presented study, the frequency of muscular VSD was higher than of perimembranous (76.67 % compared to 23.33 %), that differs from studies that include wide paediatric population and classically report that perimembranous defects account for approximately 75 % of total VSDs.[6, 7] This difference likely reflects the facts that the vast majority of prenatally diagnosed VSDs are muscular and that the rate of SC in the postnatal period is higher in muscular than in perimembranous defects and probably combined with the high number of muscular defects that are undiagnosed due to the common absence of clinical signs.[7, 14, 22, 23] This predominance of muscular defects in this study is consistent with the results of studies in which VSDs were screened in non-selected populations using echocardiography.[22, 23]

It was found that 60 % of all studied VSDs were closed by the end of the first year of life, which is within the range of results of many previous reports.[6, 13, 14, 18] The closure rate was significantly higher in muscular (73.91 %) compared to perimembranous VSD (14.29 %), which generally could be explained by different closing mechanisms and, in this study, with a much smaller mean size of muscular compared to perimembranous VSD. Other studies reported a similar SC rate for muscular VSD (69 % to 74 %), but higher for perimembranous VSD (22 % to 28 %) compared to presented results.[22, 23] A possible explanation for this difference in results is the relatively larger average size of the perimembranous defect in presented patients and the shorter follow-up period compared to other studies. The location of the defect within the muscular part of the septum seems that also affects the CS rate. Other studies state that it is slightly higher in defects located in the central part of the muscular septum compared to those in its apical, anterior and posterior parts.[16, 24] In this study, defects in the middle and apical parts of the septum had approximately similar SC rate (76.9 % and 75 %), which was higher than the SC rate of defects in the anterior part of the muscular septum (50 %), although this difference was not statistically significant. This difference in rates of spontaneous closure of defects in different parts of the muscular septum between this and other studies could be explained by presented small patient sample. The results of this and other studies indicating that the SC rate of VSD depends on its localisation are particularly useful for predicting the natural outcome of VSD in newly diagnosed patients.

The SC rate in this study, as in many previous studies, shows negative correlation with the size of the defect.[8, 17] The trivial VSD had, expectative, the highest closure rate (86.36 %), but in three

cases these defects have not closed till the end of the follow-up period. This is particularly unusual because they all were muscular and were not accompanied by pulmonary hypertension. This result leads us to a conclusion that other unknown factors also influence defect closure, which could be a subject of future studies. With data of the natural outcome of studied VSDs for a given defect size, the linear regression model obtained a formula for calculating the probability of SC that could be useful in predicting the natural outcome of this anomaly.

In general, multiple VSD, because of a larger shunt, has a lower SC rate than single VSD. According to one report, multiple VSD closes spontaneously in the first year only in 20 % of the cases.[16] In this study, multiple defects closed spontaneously in 41.67 % of the cases, which is not statistically significantly different from the SC rate of a single defect.

Pulmonary hypertension is a negative factor for SC of VSD according to many previous studies.[8, 12, 16] Although there were only four patients with VSD who had pulmonary hypertension in this study, it is significant to point out that in none of them defect spontaneously closed.

It seems that gender and gestational age does not affect the incidence of SC. In this study, the SC of VSD rate was slightly higher in males (67.74 %) compare to females (51.72 %), in accordance with Li et al report and opposite to Farina et al report, although these differences did not reach statistical significance in either study.[12, 25] The rate of SC in premature infants in presented study was almost similar to those born on the term, in line with other reports.[12, 17]

There were some limitations in this study. Because of small the number of patients and short the follow-up time, the results can be useful in predicting the natural outcome of the anomaly, but they do not have a diagnostic value. Only those factors that are found to be significant predictors of the outcome were examined, but other unmeasured factors could also influence defect closure and, therefore, the result. A simplified classification of VSDs was used. Determining the size of septal defects is not always easy, and therefore, results reported in relation to the size of the defect should be interpreted with caution. Finally, VSDs that were considered isolated according to the clinical findings during a follow-up time were studied, which is insufficient for detection of the possible delay in psychomotor development or growth, so some syndromic cases could have been missed.

Conclusion

It was found that type and size of VSD and the persistence of pulmonary hypertension were significant predictors for SC, while gender and gestational age of the patient and the number of defects were not. This study can be useful in predicting the natural outcome of the VSD to make proper follow-up and management plans.

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Conflict of interest

None.

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