Spontaneous Closure Rates of Ventricular Septal Defects (6,750 Consecutive Neonates)

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Although ventricular septal defect (VSD) is a common and simple congenital heart disease in newborns, its true incidence and spontaneous closure (SC) rate remains topics of controversy. This study aims to provide data on the true incidence and SC rate of VSD in the Chinese neonatal population. We conducted a prospective study at 3 hospitals, all newborns underwent echocardiography. Those with a diagnosis of isolated VSD were included in the study group and underwent a 7-year follow-up period. In 6,750 newborns, VSDs were detected in 113 cases (incidence rate of 16.7%), accounting for 62.8% of congenital heart disease, of which 35 were perimembranous (5.2%), 72 were muscular (10.7%), and 6 were doubly committed juxta-arterial (0.9‰). During the 7-year follow-up period, 18 cases required surgical or transcatheter closure. The SC rate in those with perimembranous VSD and muscular VSD (mVSD) were 51.4% (18 of 35) and 97.2% (70 of 72), respectively. Excluding doubly committed juxta-arterial, perimembranous site and defects ≥4 mm are risk factors for VSD that do not spontaneously close. Independent predictive factors for perimembranous VSD which do not spontaneously close is defects ≥4 mm. There was no significant difference in the SC rate at different times between the 4 mVSD sites. In conclusion, this study provides the true incidence and SC rate for Chinese newborns with VSD. **(Am J Cardiol 2019;124:613−617)**

Although ventricular septal defect (VSD) is a common congenital heart disease (CHD) in newborns, incidence rates from studies to date are not representative of the true incidence. This is due to most previous studies not being from consecutive births screened with echocardiography.[1−5] This leads to the inevitability of missing small defects which often present with no clinical signs or symptoms. In addition, most previous studies had a follow-up period of 1 year after birth and lacked long-term follow-up data.[6−10] Given the absence of reliable evidence, no guidelines or expert consensus are available to guide the VSD follow-up frequency, especially for small defects. Differing opinions remain even between pediatric cardiologists on whether treatment is required and the latest appropriate treatment time.[11,12] This study prospectively screened consecutive births with echocardiography and had a long-term follow-up period to provide data on true incidence and long-term spontaneous closure (SC) in Chinese infants with VSD. This was done to aid clinicians in developing an appropriate follow-up or treatment plan in infants with VSD.

Methods

From February 1 until July 30, 2011, we conducted a prospective study at 3 secondary maternity facilities in Shanghai.[13] All newborns delivered during this period underwent echocardiography before discharge. Those diagnosed with isolated VSD were included in the study. This study was approved by the Ethics Committee of the Children's Hospital of Fudan University (CHFU). Verbal informed consent was obtained from parents of participating newborns.

The first author (QMZ) carried out echocardiographic scans for each participant. All echocardiographic scans were completed at the bedside with a Vivid Q (General Electric Medical Systems) ultrasound machine, interfaced with a 7S-RS Cardiac Sector Probe. Standard parasternal long-axis, short-axis, and 4-chamber view plus subcostal sagittal and coronal views were obtained. Examinations of newborns with CHD were recorded on videotape and reviewed by another doctor (CN), as a second observer. Using the classification described by Anderson et al,[14] VSDs were classified as perimembranous, muscular, and doubly committed juxta-arterial (DCJA). Muscular VSD (mVSD) were further divided into midseptal, apical, posteroinferior, and anterosuperior.[15] VSD size was categorized as follows: small defects as <4 mm, moderate as 4 to 6 mm, and large as >6 mm.

All newborns with VSD were required to undergo regular echocardiography follow-up at 3, 6, and 12 months, and annually thereafter. Children with heart failure symptoms were advised to seek care immediately. To better facilitate follow-up, a dedicated telephone line was established to

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Table 1
Type, size, and prognosis of ventricular septal defects (n = 113)

Variable	Perimembranous	Muscular					Doubly committed juxta-arterial
		Total	Midseptal	Anterosuperior	Apical	Posteroinferior	
Number	35	72	29	19	15	9	6
Size (mm)							
<4	15	52	17	14	13	8	2
4-6	14	18	10	5	2	1	3
>6	6	2	2	0	0	0	1
Outcome							
Spontaneous closure	18	70	28	18	15	9	0
Surgery/intervention	17	1	1	0	0	0	6
Patent	0	1	0	1	0	0	0

allow families to contact QMZ. Infants with VSD were provided with echocardiographic follow-up free of charge during the 6-month study period at the hospital at which they were born. After this period, the Pediatric Heart Center at CHFU was the designated site for follow-up. Children who could not attend a follow-up visit at CHFU underwent a telephone interview by QMZ. Follow-up was ended when one of the following conditions was met: (1) SC was confirmed with the absence of color flow mapping; (2) having underwent surgery or interventional therapy; (3) 7 years after birth if the defect was still present. In our hospital, only VSDs with clinical symptoms or presentation of left heart overload are treated, which can be interventional or surgical. Interventional therapy of perimembranous VSD (pVSD) generally require the patient to be at least 2 years old with a defect diameter of ≤12 mm and the distance between the upper margin of the defect and the right coronary cusp of the aorta to be at least 2 mm, whereas mVSD patients must be at least 5 kg to undergo interventional therapy. Indications for surgery include faltering growth or recurrent respiratory infections and where interventional therapy was contraindicated due to age or size of defect.

Categorical variables were expressed as number of cases and percentages. Freedom from SC was calculated using Kaplan-Meier curves and compared by log-rank test. The association of selected variables (sex, birth weight, gestational age, the defect size, and the defect position) with SC was assessed with Cox proportional hazard regression model. Hazard ratios, with the corresponding 95% confidence interval, were estimated. $p < 0.05$ was considered statistically significant.

Results

A total of 6,750 newborns were born at the 3 participating hospitals during the study period, all of whom underwent echocardiography. Median age at examination was 43 hours (2 to 97 hours). A total of 180 infants were diagnosed with CHD (incidence rate of 26.7%). VSDs were found in 113 cases (16.7%), including 35 perimembranous (5.2%), 72 muscular (10.7%), and 6 DCJA (0.9%). One mVSD had multiple defects ("Swiss cheese" type). Defect locations and sizes are summarized in Table 1. Compared with newborns without CHD, there was female preponderance in VSD and mVSD (all VSD: 67 of 113 vs 3,052 of 6,570, $p = 0.007$; mVSD: 51 of 72 vs 3,052 of 6,570, $p < 0.001$), but no significant difference in pVSD and DCJA VSD (pVSD: 15 of 35 vs 3,052 of 6,570, $p = 0.67$; DCJA VSD: 1 of 6 vs 3,052 of 6,570, $p = 0.23$). The proportion of low birth weight (<2500 g), preterm infants (<37 weeks), and older maternal (>35 years) was not significantly different between neonates without CHD and all types of VSDs.

Excluding DCJA VSD, after 7 years of follow-up, only 1 infant with mVSD was lost to follow-up after 3 years of age, a total of 88 (82.2%) VSD cases closed spontaneously (Table 1). The SC rate for pVSD and mVSD were 51.4% (18 of 35) and 97.2% (70 of 72), respectively. The SC of VSD at different sites at different times is shown in Table 2. Kaplan-Meier curves for SC showed significant differences in VSD closure between pVSDs and mVSDs (Chi-square = 32.879, $p < 0.001$) (Figure 1), but no significant difference in SC at different times between the 4 mVSD sites (Chi-square = 0.217, $p = 0.975$; Figure 1).

Table 2
Spontaneous closure of different types of VSD at different times

Location	At birth	3 months	6 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Muscular	72	42 (41.7%)	34 (52.8%)	20 (72.2%)	9 (87.5%)	6 (91.7%)	5 (93.1%)	4 (94.4%)	2 (97.2%)	2 (97.2%)
Midseptal	29	18 (37.9%)	15 (48.3%)	8 (72.4%)	4 (86.2%)	2 (93.1%)	2 (93.1%)	1 (96.6%)	1 (96.6%)	1 (96.6%)
Anterosuperior	19	11 (42.1%)	8 (57.9%)	4 (78.9%)	2 (89.5%)	2 (89.5%)*	2 (89.5%)*	2 (89.5%)*	1 (94.7%)*	1 (94.7%)*
Apical	15	8 (46.7%)	7 (53.3%)	5 (66.7%)	1 (93.3%)	1 (93.3%)	0 (100%)	-	-	-
Posteroinferior	9	5 (44.4%)	4 (55.6%)	3 (66.7%)	2 (77.8%)	1 (88.9%)	1 (88.9%)	1 (88.9%)	0 (100%)	-
Perimembranous	35	34 (2.9%)	30 (14.3%)	23 (34.3%)	20 (42.9%)	19 (45.7%)	18 (48.6%)	17 (51.4%	17 (51.4%)	17 (51.4%)
Total	107	76 (29.0%)	64 (40.2%)	43 (59.8%)	29 (72.9%)	25 (76.6%)	23 (78.5%)	21 (80.4%)	19 (82.2%)	19 (82.2%)

Numbers represent cases that remain open, percentages represent rate of spontaneous closure at given time point.
* 1 infant with mVSD was lost to follow-up after 3 years of age, who was regarded as remaining open at the end of study.

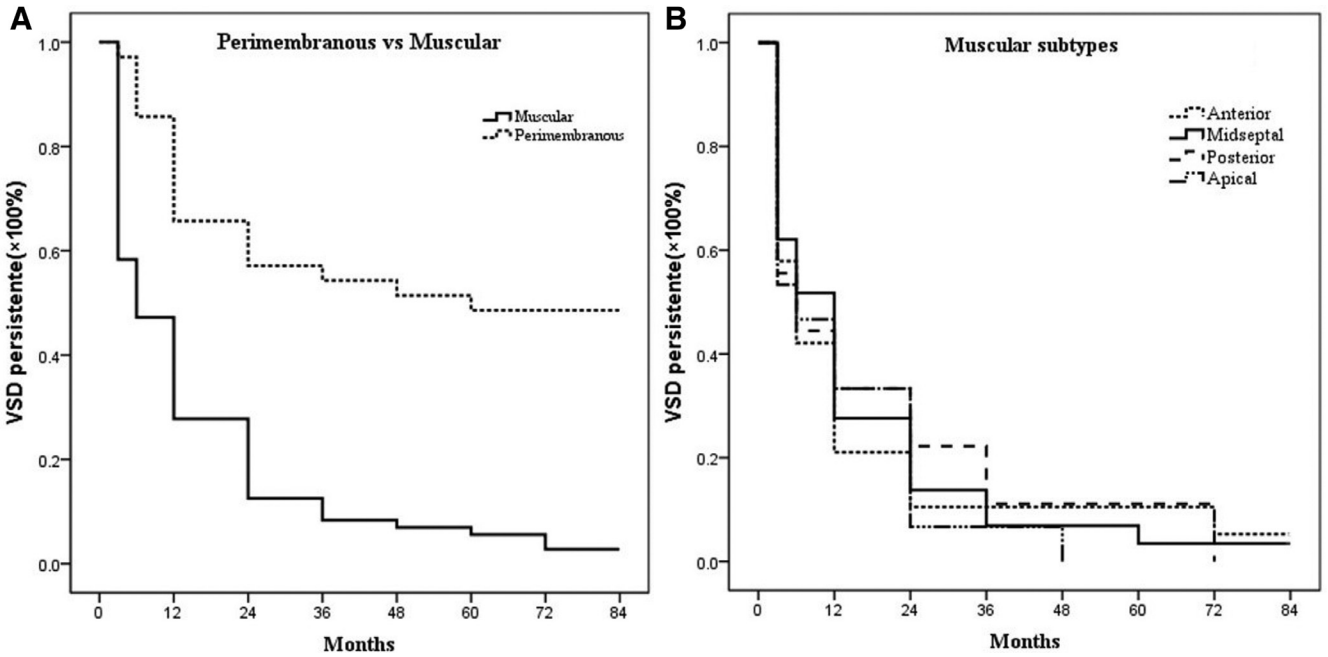

Figure 1. Kaplan-Meier curves for spontaneous closure of VSD. (*A*) Comparison of spontaneous closure in pVSD and mVSD: significant difference found. (*B*) Comparison of spontaneous closure between 4 mVSD sites: no significant difference found.

Baseline characteristics of newborns with pVSD or mVSD are presented in Table 3. For all VSDs, multivariate analysis showed that risk factors for defect persistence were perimembranous site and medium to large defects (≥4 mm) (Table 4). A defect ≥4 mm (p = 0.001; hazard ratios 5.72, 95% confidence interval 2.01 to 16.28) is also an independent predictive factor for pVSD not closing spontaneously.

Discussion

VSD is a simple CHD that is easy to diagnose and treat. However, in reality, the frequency of nonlarge VSD follow-up and the determination of the chance that SC may occur remains a clinical dilemma.[11,12] Although there have been many reports on the incidence and SC of VSD,[3–10,16–21] the results have been inevitably varied due to differences in the age, sample size, screening methods, and follow-up time. It can be argued that the only way to provide accurate VSD prevalence and SC rate is to echocardiographically screen and follow up a sufficient number of consecutive births. However, the clinical feasibility of this method is not high.

Table 4
Cox multivariate analysis of risk factors for defect persistence in isolated VSD

Variable	p	HR	95% CI	
			Inferior	Superior
Male vs Female	0.555	0.867	0.540	1.392
Gestational age (weeks) ≥37 vs <37	0.322	0.627	0.249	1.579
Birth weight (g) <2500 vs ≥2500	0.907	1.057	0.419	2.664
Defect size(mm) ≥4 vs <4	0.000	2.920	1.737	4.907
Perimembranous vs muscular	0.000	3.692	2.040	6.681

Persistence denotes not closed by the end of the study period, or having undergone surgical or interventional treatment.

Table 3
Baseline characteristics of newborns with ventricular septal defects (excluding doubly committed juxta-arterial type)

	Muscular		Perimembranous		All	
	Closed*	Open†	Closed*	Open†	Closed*	Open†
Male/female	21/49	0/2	11/7	9/8	32/56	9/10
Gestational age (weeks) <37/≥37	3/67	0/2	2/16	0/17	5/83	0/19
Birth weight (g) <2500/≥2500	4/66	0/2	1/17	1/16	5/83	1/18
Defect size (mm) <4/≥4	52/18	0/2	13/5	2/15	65/23	2/17

* Closed denotes spontaneous closure.
† Open denotes not yet closed, or having undergone surgical or interventional treatment.

After a careful review of the literature, we found that only 7 articles had findings which were obtained from consecutive births screened with echocardiography.[6–10,21,22] The study with the largest sample size of 2,891 occurred more than 20 years ago,[6] with an incidence rate of mVSD in their report of 24.9%. A recent study which included 2,067 newborns found an incidence rate of VSD and mVSD of 26.1% and 16%, respectively, but all births occurred at 1 tertiary referral hospital.[22] Three studies which were carried out in 1990, 1995, and 2003 had sample sizes of just over 1000, with mVSD incidence rates of 20%, 53.3%, and 42.8%, respectively.[7,8,10] Our study showed that the incidence rates of VSD and mVSD were 16.7% and 10.7%, respectively. Although lower than the above data, they were still significantly higher than expected rates.[23–25] Our sample size is more than double that of the previously largest study and had no selection bias in the screening population; we believe these data reflect the true incidence of VSD in Chinese newborns.

Unlike VSD incidence rates, recent studies on mVSD SC in the first year of life have drawn relatively similar conclusions, with an overall rate of 80% to 90%.[7,8,10,18] However, the pVSD SC rate, as well as longer follow-up studies are still lacking. This group ultimately had a SC rate of 97.2%, which is in line with the 6-year SC rate of 95% reported by Cresti et al.[3] There are differences in SC outcomes in various pVSD studies. Cresti et al[3] found that the SC rate of pVSD by age 6 was 81.8%, with 13.6% requiring surgical closure. Erdem et al[17] followed patients with a mean age of 6 months to 2 years of age and found the pVSD SC rate to be 58.6%, with 38.4% requiring surgery. A large Norwegian study found that in all VSDs, only 5.2% required surgical or transcatheter treatment.[26] A high rate of pVSD intervention (48.5%) in our study may be attributable to the widespread use of transcatheter treatment in China.[27]

Factors such as age, defect size, location, and follow-up time have been found to be related to the SC rate.[1–3,16,18,28] This is consistent with previous studies, with muscular and small defects, along with long follow-up time being found to be related to a higher SC rate. The effect of mVSD location on SC, however, remains controversial. Earlier reports suggested that apical VSD are more likely to close spontaneously,[10] whereas recent reports suggested that midventricular defects have a higher SC rate.[3,18] However, the reliability of these different reports may be called into question due to different sample size and mVSD classification. According to recent mVSD classification standards,[15] our results show that there is no significant difference between the 4 sites nor in the time at which SC takes place.

This study has its limitations. First, although we collected a sufficient number of echocardiographically screened newborns, the number of VSD cases in this cohort was not large, and only 1 case with multiple defects. This limits the analysis of factors which affect SC, especially in analysis of SC in mVSDs at different sites. Secondly, the task of the second observer in this study was to verify whether the diagnosis of VSD is correct through stored echocardiographic images, but there was no further verification of mVSD location. Although the 2 observers did not have conflicting diagnoses, the subjectivity of a single observer may have had some effect on the accuracy of mVSD classification. Finally, because different hospitals and doctors have their own inclinations in the timing of VSD treatment, some patients whose VSDs may have closed spontaneously might have undergone premature surgical or interventional closure, thus affecting results of this study.

In conclusion, this study, through the largest echocardiographic screening study of its type, provides the incidence rate of VSDs in Chinese newborns and provides data on SC at different time points and its influencing factors.

Disclosures

The authors have no conflicts of interest to disclose.

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