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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Increased incidence of infective endocarditis in patients with ventricular septal defect

Phong Teck Lee MBChB | Felix Maverick Uy MD | Jie Sheng Foo MBBS | Ju Le Tan MBBS

National Heart Centre, Singapore

Correspondence
Phong Teck Lee, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609.
Email: lee.phong.teck@singhealth.com.sg

Abstract

Background: Ventricular septal defect (VSD) is one of the most common congenital heart anomalies in childhood and there is an increasing prevalence of VSDs in the adult population. The long-term risk of infective endocarditis (IE) is of concern. The aim of this study was to clarify and compare the incidence of IE in adults with repaired and unrepaired VSDs.

Methods: Patients with VSDs were identified using the Adult Congenital Heart Disease registry at the National Heart Centre Singapore. Patients were divided into Group 1 (repaired VSD) and Group 2 (unrepaired VSDs). The electronic medical records were searched for hospitalization due to IE during a 10-year period (October 2, 2007—October 1, 2017).

Results: Four hundred seventy-nine patients (53% male) were identified, with a mean age of 35.0 ± 13.7 years. There were 164 patients (34.2%) in Group 1 and 315 patients (65.8%) in Group 2. In total, there were eight episodes of IE from six patients (3 male, mean age of 42.2 ± 20.7 years). Two patients had recurrent IE. The overall incidence of IE was 1.67/1000 y, and this is 11–15-fold higher compared to general adult population. The incidence of IE in Group 2 was 1.90/1000 y. There were no IE cases in Group 1.

Conclusion: Patients with VSDs, especially if unrepaired, carry a substantially increased risk of IE compared to the general population.

KEYWORDS

clinical characteristics, congenital heart disease, infective endocarditis, ventricular septal defect

1 | BACKGROUND

Ventricular septal defect (VSD) is one of the most common congenital heart disease anomalies in childhood and occur in up to 5% of infants.[1] They account for up to 40% of all congenital cardiac malformations.[2] About 85%–90% of these VSDs close spontaneously by one year of age.[3,4] Patients with large shunts are usually operated in childhood and VSDs that are small without hemodynamic compromise or ventricular remodeling are often left without intervention. The long-term prognosis of simple VSDs is generally good[5] and patients are now surviving into adulthood.[6,7] With medical advancements, contemporary data has shown an increasing prevalence of congenital VSDs in the adult population.[8]

Patients with VSDs are often asymptomatic. However, one of the main concerns with patients with congenital VSDs is the long-term risk of infective endocarditis (IE).[9] In previous studies of patients with IE, 10%–13% had underlying congenital heart disease.[10,11] The incidence of IE in patients with congenital VSD has been difficult

to ascertain due to inclusion bias and heterogeneous populations. The reported incidences were 0.24/1000 y in children,[12] and 1.45-8/1000 y in adults.[5,9,13] The aim of this study is to clarify the incidence of IE in adults with VSD and compare the IE incidence in patients with repaired and unrepaired VSDs.

2 | METHODS

This study is based on data from the Adult Congenital Heart Disease (ACHD) registry at the National Heart Centre of Singapore, which is the national cardiac referral center. The registry was started since January 2007, and included all patients who were seen at the ACHD clinic. This registry is updated routinely by ACHD specialist nurses at every clinic visit. All data collected until October 1, 2017 were included for analysis.

2.1 | Patients

The ACHD registry, at the time of data extraction, contained information of 3,030 patients. The inclusion criteria were: (1) adult patients (≥18 years of age), (2) main diagnosis of VSD, (3) at least one clinic visit, and, (4) echocardiogram performed. The exclusion criteria were: (1) patients with associated complex congenital heart defects (e.g., tetralogy of Fallot, coarctation of aorta, transposition of the great arteries, Eisenmenger physiology, pulmonary atresia requiring valve conduit and univentricular complex) and (2) syndromic conditions (e.g., Down syndrome). Simple cardiac lesions (e.g., aortic or mitral valve disease, atrial septal defects and persistent ductus arteriosus) were included. After application of these criteria, 479 patients were included for analysis. Patients were divided into two groups: Group 1 (repaired VSDs) and Group 2 (unrepaired VSDs). The study was reviewed and approved by the local Institutional Review Board (CIRB: 2017/2229).

2.2 | Diagnosis of infective endocarditis

All matching hospital discharges for the diagnosis and treatment of IE were identified in the last 10 years, from October 2, 2007 to October 1, 2017. Patients' clinical notes were retrieved and the diagnosis of IE was verified using the modified Duke's criteria.[14]

2.3 | Ventricular septal defects and additional cardiac lesions

The VSD size was defined as small: ≤5 mm, moderate: 6–10 mm and large: >10 mm.[15] Additional cardiac lesions that predisposed patients to an increased risk of infective endocarditis were obtained. These included significant valve lesions (i.e., more than mild stenosis or regurgitation), mitral valve prolapse, valve repair or replacement, bicuspid aortic valve, and atrial septal defect.

2.4 | Statistics

Statistical analysis was performed using SPSS statistical software (version 22, IBM, Armonk, New York). Descriptive statistics were presented as mean values with standard deviations for continuous variables unless specified. Continuous variables were analyzed using t-test. Categorical data was presented as absolute numbers with percentages and analyzed using chi-square test. In all tests, a *P* value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | All patients

Four hundred seventy-nine patients were identified, 254 men (53.0%) and 225 women (47.0%), with a mean age of 35.0 ± 13.7 years. One hundred and sixty-four patients (34.2%) had prior VSD repair (Group 1) and 315 patients (65.8%) had unrepaired VSDs (Group 2). Among patients with repaired VSD, there were 13 patients with residual VSD shunt (7.9%). The clinical characteristics and comparison between groups are shown in Table 1. There were no significant differences in clinical characteristics between the two groups including patient age (*P* = .07), gender (*P* = .56), height (*P* = .65), weight (*P* = .54), body mass index (*P* = .09), systolic (*P* = .93) and diastolic blood pressures (*P* = .06), left ventricular ejection fraction (*P*= .86), presence of arrhythmia (*P* = .29), presence of pacemaker or implantable cardiac defibrillators (*P* = .27), and New York Heart Association class (*P* = .25). Group 1 patients were more often associated with additional cardiac lesions compared to Group 2 patients (45.7% vs. 14.9%, *P* < .01). There were higher number of smokers and ex-smokers in Group 1 (10.9% vs. 4.1%, *P* < .01).

3.2 | Patients with infective endocarditis

Eight episodes of IE from 6 patients were identified, 3 men and 3 women, with a mean age of 42.2 ± 20.7 years at the time of IE (Table 2). Two patients had recurrent IE, each with two episodes. All episodes of IE were identified among patients in Group 2 (n = 315, 65.8%). Among patients with IE, there were five perimembranous-type VSDs and one outlet-type VSD. Four VSDs were small (<5 mm) and two were moderate (5–10 mm) in size. Two of these patients had additional cardiac lesions (moderate tricuspid regurgitation and mitral valve prolapse, respectively). Six episodes of IE presented with fever, one with chest discomfort, and one with reduced exercise tolerance. The median time from symptom onset to diagnosis was 13 days, with a range from 1 to 30 days. Blood cultures were positive for bacterial microorganisms in all cases (8 cases) and intracardiac vegetations were identified on echocardiography in four cases (50%). All patients were treated with intravenous antibiotics and were advised to undergo VSD repair. Three patients (50%) underwent elective VSD repair. None of the patients had dental procedures prior to their admission with IE.

TABLE 1 Clinical characteristics of all patients and comparison between repaired VSD and unrepaired VSD groups

	All patients (n = 479)	Repaired VSD (n = 164)	Unrepaired VSD (n = 315)	*P* value
Age (y)	35.0 ± 13.7	33.65 ± 11.9	35.8 ± 14.5	.07
Sex, n (%)				.56
Male, n (%)	254 (53.0)	90 (54.9)	164 (52.1)	
Female, n (%)	225 (47.0)	74(45.1)	151 (47.9)	
Height (cm)	163 ± 16	164 ± 10	163 ± 19	.65
Weight (kg)	63.5 ± 15.0	64.1 ± 13.9	63.2 ± 15.6	.54
BMI (kg/m^2), mean±SD	23.2 ± 5.0	23.8 ± 4.7	23.0 ± 5.1	.09
Smoking history				**<.01**
Smoker	25 (5.2)	13 (7.9)	12 (3.8)	
Nonsmoker	448 (93.5)	146 (89.0)	302 (95.9)	
Ex-smoker	6 (1.3)	5 (3.0)	1 (0.3)	
Blood pressure (mm Hg), mean±SD				
Systolic BP, mm Hg	123 ± 16	123 ± 16	123 ± 15	.93
Diastolic BP, mm Hg	67 ± 10	66 ± 9	68 ± 10	.06
LVEF (%), n (%)				.86
Normal	467 (97.5)	160 (97.6)	307 (97.5)	
Mildly impaired (40-50%)	9 (1.9)	3 (1.8)	6 (1.9)	
Mod impaired (30-40%)	2 (0.4)	1 (0.6)	1 (0.3)	
Severely impaired (<30%)	1 (0.2)	0	1 (0.3)	
Predisposing lesions[a] (yes), n (%)	123 (25.7)	75 (45.7)	47 (14.9)	**<.01**
Significant valvular lesions[b]	68 (14.2)	43 (26.2)	25 (7.9)	
Valve repair or replacement	29 (6.1)	29 (7.7)	0 (0)	
Mitral valve prolapse	31 (6.5)	14 (8.5)	17 (5.4)	
Atrial septal defect	11 (2.3)	9 (5.5)	2 (0.6)	
Bicuspid aortic valve	6 (1.3)	4 (2.4)	2 (0.6)	
Arrhythmia (yes), n (%)	25 (5.2)	11 (6.7)	14 (4.4)	.29
AF/flutter/AT	11 (2.3)	5 (3.0)	6 (1.9)	
PAC/PVC	8 (1.7)	4 (2.4)	4 (1.3)	
SVT	3 (0.6)	2 (1.2)	1 (0.3)	
Others	3 (0.6)	0 (0)	3 (1.0)	
PPM/ICD, n (%)	3 (0.6)	2 (1.2)	1 (0.3)	.27
NYHA class, n (%)				.25
NYHA I	458 (20)	160 (94.0)	307 (96.5)	
NYHA II	20 (4.2)	3 (5.4)	11 (3.5)	
NYHA III	1 (0.2)	1 (0.6)	0	

Bold value indicates statistical significance. Abbreviations: BMI: body mass index, BP: blood pressure, LVEF: left ventricular ejection fraction, AF: atrial fibrillation, AT: atrial tachycardia, PAC: premature atrial complexes, PVC: premature ventricular complexes, SVT: supraventricular tachycardia, PPM: permanent pacemaker, ICD: implantable cardiac defibrillator, IE: infective endocarditis, NYHA: New York Heart Association

[a]Multiple cardiac lesions may be present in individual patients

[b]More than mild stenosis or regurgitation

TABLE 2 Overview of the patients with infective endocarditis

Patient	Age[a]	Sex	VSD Type	VSD Size	Smoking	LVEF	Age at IE	VSD repair	Predisposing lesions	Symptoms	Time to diagnosis (d)	Microorganism	Vegetation site	PPM/ ICD	Arrhythmia	Treatment	Outcome
1	65	M	PM	Moderate	N	52	57	N	N	Fever	13	*Staphylococcus aureus*	N	N	N	Antibiotics	Alive
							59	N	N	Chest pain	1	*Viridans streptococcus*	N	Y	N	Antibiotics and elective surgery	Alive
2	63	M	O	Moderate	N	60	57	N	N	Fever	30	*Viridans streptococcus*	N	N	N	Antibiotics	Alive
							58	N	N	Fever	4	*Streptococcus anginosus*	N	N	N	Antibiotics	Alive
3	20	F	PM	Small	N	66	18	N	N	Fever	13	*Staphylococcus lugdunensis*	Right ventricle	N	N	Antibiotics	Alive
4	26	M	PM	Small	N	60	17	N	N	Fever	14	*Staphylococcus lugdunensis*	RVOT	N	SVT	Antibiotics	Alive
5	25	F	PM	Small	N	35	24	N	Mitral valve prolapse	Fever	5	*Staphylococcus aureus*	Mitral valve	N	N	Antibiotics and elective surgery	Alive
6	54	F	PM	Small	N	65	51	N	Moderate TR	Decreased effort tolerance	30	*Gemella mobiliorum*	Mitral, tricuspid valves	N	N	Antibiotics and elective surgery	Alive

Abbreviations: M: male, F: female, PM, perimembranous; O, outlet; LVEF: left ventricular ejection fraction, N: no, TR: tricuspid regurgitation, RVOT: right ventricular outflow tract, SVT: supraventricular tachycardia

Patients 1&2 had two episodes of IE within the study period. Second row shows data for second episode of IE

[a]Age is as of time of data analysis (October 2017)

3.3 | Incidence of IE

The incidence of IE was 1.67/1000 y for all patients. There was no IE cases in Group 1, and the incidence for Group 2 was 1.90/1000 y.

4 | DISCUSSION

In our study, we demonstrated an overall incidence of 1.67/1000 patient-years, and this is at least 11- to 15-fold higher compared to the general population.[16,17] In terms of ratios, 6 out of 479 patients (1.3%) were diagnosed with IE in the past 10 years. Patients with unrepaired VSD have an increased incidence of IE (1.90/1000 y) compared to patients with repaired VSD (0/1000 y). This is despite the unrepaired VSD group having significantly fewer additional cardiac lesions compared to the repaired VSD group (14.9% vs. 45.7%, $P < .01$). Our results are consistent with previous studies, which reported lower incidences of IE (0-0.6/1000 patient-years)[18-21] among patients with repaired VSDs. Of note, none of the 13 patients with residual VSD shunt after repair had IE during the study period, although this could be due to the relatively small sample size and limited study period.

The incidence of IE appeared to be highest in those with unrepaired VSD with additional cardiac lesions. In this subgroup with over 470 observed patient-years, the IE incidence was 4.26/1000 y. This is similar to IE incidences of 4-7.5/1000 y in patients with prior IE, prosthetic heart valve, or cyanotic congenital heart disease.[22-25] Of note, none of the additional cardiac lesions in this group included prosthetic valve replacement, or prosthetic materials, such as annuloplasty rings or chords, which would be categorized as high-risk for IE. Perhaps, closure of VSD or antibiotic prophylaxis may be considered in this subgroup. As our observed numbers are small, an extended follow up would be useful to determine the long-term risk of IE in this subgroup.

The risk of selection bias in our study is likely to be lower, as all patients with VSDs are routinely referred to the ACHD clinic. Our institution has a transition program, in which patient care is routinely transferred from pediatric to adult cardiology services at the age of 18. In a study from a UK tertiary center, the incidence of IE in VSD was reported to be 8/1000 patient-years.[9] This is approximately 5 times higher than our study and likely an overestimation of the risk due to selection bias of high-risk patients. Our results are comparable with previous studies, which reported an IE incidence of 2/1000 patient-years among patients with VSD,[19] and 1.61/1000 patient-years among patients with left-sided congenital cardiac lesions.[26] This suggests that the incidences of IE in VSDs are comparable in Asian and Western populations, and to the best of our knowledge, our study is the first to demonstrate this.

Poor dental hygiene and dental procedures are the most common causal factors for IE. The reported incidence of dental IE varies from 11% to 40%, depending on whether invasive procedures or poor dental hygiene is taken into consideration.[27,28] This is consistent with our study where 4 out of 8 episodes (50%) of IE were found to have causative oral microorganisms. These included Viridans group Streptococcus, *Streptococcus anginosus*, and *Gemella mobiliorum*. However, none of these patients had dental procedures prior to their admission with IE. This is possibly due to the relatively small sample size and lack of patient recall. This may also reflect the uncertainty in the direct link between dental procedure and infective endocarditis, which has been previously discussed.[29] It is unclear if antibiotic prophylaxis would have prevented these cases. The remaining 50% of IE were found to have causative skin microorganisms, and perhaps extra precautions, such as a quick assessment of skin condition during clinic visits, patient education and referral to dermatology, especially for chronic skin conditions, such as eczema or psoriasis should be considered.

Patients with a history of IE are recognized as a high risk group to develop IE.[30] Our data suggests a high risk of IE recurrence after the first episode of IE, with 2 out of the 6 patients (33%) had recurrent IE. The time intervals to IE recurrence were 13 and 31 months, respectively. VSD repair was offered to all patients with prior history of IE, in line with international guidelines.[31,32] Three patients (50%), including one with recurrent IE, underwent VSD repair and these patients had no subsequent recurrence of IE. As the follow up period is limited, it is unclear whether surgical closure of VSD reduces the risk of recurrent IE in these patients. Extended longitudinal follow up would be required to assess the risk of IE recurrence in these patients. None of the six patients died in the study period. Out of the 479 patients, there were three deaths during the study period, and these were unrelated to VSDs or IE. Of interest, patients with unrepaired VSD were less likely to smoke compared to those with repaired VSD ($P < .01$) and the significance of this finding is unclear.

The limitations of this study include the fairly small number of detected IE cases and some observations may be affected by chance. Descriptive statistics within the group of 6 patients with IE must therefore be interpreted with some caution. The follow up period of ten years is also limited when taking into account the lifetime IE risk for these patients. There is also an inherent selection bias risk within the registry, in which patients who defaulted follow up or demised in childhood were not included. The risk of the latter scenario is likely to be small. In a large Norway registry study involving 3495 children with isolated VSD who were followed up for approximately 10.1 ± 4.5 years, the mortality rates was only 0.3% with no excess mortality compared with children without CHD.[33] In our study, the prevalence of IE, however, has a narrow 95% CI (1.3%, 95% CI 0.3 to 2.3%) and the incidence reported here is in line with other studies.

Our study findings of increased incidence of IE in VSD patients serve as a reminder to have a higher index of suspicion of IE in patients with VSDs as well as better patient education on dental hygiene and IE risks. We believe that antibiotic prophylaxis should be considered in the highest risk group that is patients with unrepaired VSDs and additional cardiac lesions.

5 | CONCLUSION

In conclusion, we demonstrate that patients with simple congenital VSD have 11- to 15-fold increased risk of IE compared with the general population. Those with unrepaired VSDs have a considerably higher risk of IE and clinicians should have a higher overall index of suspicion of IE when managing these patients.

DISCLOSURE STATEMENT

There are no potential conflicts of interest, including related consultancies, shareholdings and funding grants.

AUTHOR CONTRIBUTIONS

PTL was responsible for the study design, data analysis, drafting, and revision of article. FMU was responsible for data collection and analysis. FJS and TJL were responsible for study concept and revision of article. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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