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Supracristal ventricular septal defect in adults: Is it time for a paradigm shift?

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ABSTRACT

Background: To determine the risk and predictors of progression of aortic regurgitation (AR) and other adverse events (AE) in adults with supracristal ventricular septal defect (VSD).
Methods: Retrospective observational study of 62 adults with supracristal VSD followed at the Mayo Clinic from 1994 to 2013. Freedom from AR progression was compared by age and racial groups (Asian vs non-Asian). Predictors of AR progression were determined using Cox proportional hazard model. Composite AE endpoint was defined as AR progression, endocarditis, aneurysm of sinus of Valsalva (aSOV), and rupture of aSOV. Risk of AE was compared between group 1 (no surgical intervention) and group 2 (surgical intervention).
Results: Sixty-two patients aged 47(SD 12) years were followed for 13 (SD 5) years. Group 1 = 42/62 and group = 20/62. Endpoint of AR progression and aSOV occurred in 13% and 20% respectively. Freedom from AR progression for the entire cohort was 88%, 86% and 86% at 5, 10 and 15 years respectively. Risk of AR progression was significantly lower in patients (aged ≤40 years, $p = 0.008$) but similar between Asians and non-Asians ($p = 0.57$). Age ≤40 years was an independent predictor of AR progression (hazard ratio [HR] 3.5, 95% CI 2.3–5.4, $p = 0.001$). Composite AE endpoint occurred in 33% and 40% of group1 and 2 cohorts respectively, $p = 0.69$.
Conclusion: Adults with supracristal VSD are at lower risk for AR progression but higher risk for aSOV formation compared to historical pediatric cohorts. Younger age was a predictor of AR progression. Surgical intervention had no protective effect on complication rate.

1. Introduction

Ventricular septal defect (VSD) is one of the most common congenital heart defects and is sub-classified based on the location of the defect in the ventricular septum [1–3]. Supracristal VSD is relatively uncommon, comprising about 2–3% of all VSDs in the United States with significantly higher prevalence in Asians [2]. Although supracristal VSD is more common among Asians, there are no studies about racial differences in complications rates in this population. Supracristal VSD is a deficiency in the infundibular septum resulting in lack of continuity between aortic annulus, media and ventricular septum [1]. It is associated with aortic valve prolapse (AVP), aortic regurgitation (AR), and aneurysm of the sinus of Valsava (aSOV) [4–9]. Proposed mechanisms for these complications are lack of structural support for the aortic cusp adjacent to the VSD, abnormal commissural suspension, and deformity of the aortic cusp because of the Venturi effect [10,11]. Published data suggest that AVP and AR in supracristal VSD is progressive and prophylactic surgical intervention is recommended to halt progression of disease [12–14]. Data supporting early or prophylactic surgical intervention is based on natural history studies of pediatric cohorts, and has been applied to the general supracristal VSD population regardless of age. We hypothesized that adults with supracristal VSD without significant AR are a self-selected population at low risk of AR progression and as a result should be managed conservatively without prophylactic surgery.

Abbreviations: AR, aortic regurgitation; ASOV, aneurysm of sinus of Valsava; AVP, aortic valve prolapse; VSD, ventricular septal defect; SOV, sinus of Valsava.

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[1] All authors take full responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2. Methods

2.1. Patient selection

We identified 71 consecutive patients, aged ≥21 years, with supracristal VSD followed at the Mayo Clinic from January 1994 to December 2013. We excluded patients with

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associated congenital heart disease (bicuspid aortic valve, n = 2) and patients without follow-up data (n = 7). Sixty-two patients were included in our final cohort. None of the patients in the final cohort had Marfan syndrome or any connective tissue disease associated with aortopathy. The Mayo Clinic Institutional Review Board approved this study.

2.2. Data collection

Clinical, echocardiographic, and surgical data were abstracted. Forty-six patients (74%) had race data documented in their medical record. We divided these 46 patients into two groups: 'Asian' and 'non-Asian'. For the purpose of our study, our Asian group comprised of patients with the word 'Asian' or any country within the Asian continent documented in their medical record. The non-Asian group comprised all other patients with available race data in their medical record. Our rationale for this racial classification was because supracristal VSD is known to be associated with Asian ancestry and we intended to compare freedom from AR progression between Asians and non-Asians. Echocardiographic data collected include VSD size, AVP, severity of AR, left ventricular dimensions and mass, left ventricular systolic and diastolic function, qualitative assessment of left-right shunt, left atrial size, sinus of Valsalva (SOV) dimension, right ventricular size, function, and systolic pressure.

2.3. Definitions and classifications

We divided our cohort into two groups based on whether they underwent surgical intervention during follow-up (Group1 = no surgical intervention; group 2 = underwent surgical intervention). Severity of AR was categorized into 4 ordinal groups: none, mild, moderate, and severe as documented in the echo report, and we defined AR progression as progression from one ordinal group to the next.

Composite adverse event was defined as AR progression, endocarditis, development of new aSOV, and rupture of aSOV. For the purpose of our study, we defined aSOV as SOV dimension >45 mm. Left ventricular enlargement was defined as left ventricular end-diastolic dimension >32 mm/m^2 based on published normal values for gender and body surface area [15]. In order to compare adverse event rates between groups, we calculated duration of follow-up from the time of initial presentation to last hospital visit for group 1 cohort, and from the time of surgical intervention to last hospital visit for group 2 cohort. Patients were followed every 2 to 3 years with echocardiogram and follow up was complete in all patients.

Our primary endpoint was to determine the freedom from AR progression and identify predictors of AR progression. Our secondary endpoint was to compare freedom from composite adverse events between surgical and non-surgical groups.

2.4. Statistical analysis

All statistical calculations were performed with the JMP version 10.0 software (SAS Institute Inc., Cary, NC, USA). Categorical variables were expressed as percentages while continuous variables were expressed as mean (SD) or median (interquartile range, IQR) for skewed data. Comparison of categorical variables was performed using Fisher exact test, while comparison of continuous variables was performed with two-sided unpaired Student t-test or Wilcoxon rank sum test as appropriate. Cox proportional-hazard model was used to identify predictors of AR progression and expressed as hazard ratio (HR) and 95% confidence interval (CI). Event-free survival curves were generated with Kaplan–Meier method, and compared with log-rank test. All p values were two sided, and p values < 0.05 were considered significant.

3. Results

3.1. Progression of AR

Sixty-two adults with supracristal VSD were followed at the Mayo clinic from 1994–2013. Mean age at initial presentation was 47(SD 12) years, median age was 41 (IQR14) years and follow-up was 13 (SD 5) years. Thirty-nine patients (61%) were followed for more than 10 years. Thirty-seven percent (17/46) were Asians, 42 patients (68%) had AVP, and 36 patients (58%) had AR at baseline (Table 1).

Freedom from AR progression for the entire cohort was 88%, 86% and 86% at 5, 10 and 15 years respectively. Age at presentation as a continuous variable was not predictive of AR progression on univariate analysis. However age as a dichotomous variable (≤40 or >40 years) was predictive of AR progression both on univariate and multivariate analysis. Freedom from AR progression was significantly higher in patients older than 40 years (96%, at 5, 10 and 15 years) compared to patients younger than 40 years at time presentation (76%, 71% and 71% at 5, 10 and 15 years), p = 0.008. Freedom from AR progression was similar in Asians and non-Asians, p = 0.57(Fig. 1). Younger age at presentation (≤40 years) was the only independent predictor of AR progression (HR 3.51, CI 2.32–5.43, p = 0.001), Table 2.

Table 1
Baseline characteristics of entire cohort at presentation.

n	62
Male	39 (63%)
Age (years)	47 (SD12)
NYHA III/IV	2(3%)
Follow-up (years)	13(SD 5)
Race (Asians/non-Asians)*	17/29
Echocardiographic data	
Small VSD	60(97%)
Moderate VSD	2(3%)
LVEDD index (mm/m^2)	27(SD 3)
Mild LVE**	36 (58%)
Mod LVE	1(1.6%)
LVEF (%)	60 (SD 5)
LA volume index	29 (SD 3)
RVSP (mmHg)	35 (IQR: 28–42)
SOV (mm)	36(SD 8)
Aneurysm of SOV¶	5 (8%)
Aortic valve prolapse	42(68%)
AR	36(58%)
Mild AR	33(53%)
Mod AR	3(5%)

NYHA: New York Heart Association.
LVEDD: Left ventricular end-diastolic dimension.
LVEF: Left ventricular ejection fraction.
LA: Left atrium.
SOV: Sinus of Valsalva.
LVE: Left ventricular enlargement.
VSD: Ventricular septal defect.
AR: Aortic regurgitation.
RVSP: Right ventricular systolic pressure.
Aneurysm of SOV = SOV dimension > 45 mm.
* Race data was available in only 46 patients.
** Based on LVEDD normogram published by Lang et al.[15].

3.2. Surgical cohort

Twenty patients (32%) underwent 21 surgical interventions during follow-up. There was no surgical mortality. Indications and types of surgical interventions are shown in Table 3. Four patients underwent surgical intervention because of rupture of aSOV and all 4 cases involved rupture of the right aSOV into the right ventricle. Eighty percent (16/20) of all surgical interventions occurred within the first year of presentation. Patient #7 underwent 2 surgical interventions. He initially underwent surgical VSD closure after 4 years of follow-up because of AR progression. The patient developed endocarditis 10 months postoperatively resulting in rapid progression to severe AR. He subsequently underwent aortic valve replacement with CarboMedics mechanical prosthesis at 5 years of follow-up (1 year after initial surgical VSD closure). Prior to surgical intervention, 14/20 had mild AR and 3/20 had moderate AR. Postoperatively 16/20 had mild AR while 1/20 continued to have moderate AR, Fig. 2.

3.3. Composite adverse event

In group 1, 5 patients (12%) showed AR progression while 9 patients (21%) developed new aSOV within14 (SD 3) years of follow up. Baseline characteristics of group 2 patients (based on echocardiographic assessment performed postoperatively) showed mild AR in 16 patients and moderate AR in 1 patient. In the course of 11(SD 5) years of follow up, 2 patients (10%) showed AR progression, 4 patients (20%) developed new aSOV, and 2 patients (10%) developed endocarditis. No patient experienced SOV rupture postoperatively. Composite adverse event endpoint occurred in 33% of group 1 and 40% of group 2 cohort (Table 4). Freedom from composite adverse event was similar in both groups (63%, 55% and 55% at 5, 10 and 15 years in group 1 vs 58%, 51% and 48% at 5, 10 and 15 years in group 2, p = 0.69), Fig. 3. Interestingly the most frequent adverse event in the entire cohort was development