

Progression of aortic regurgitation after subpulmonic infundibular ventricular septal defect repair

Masashi Amano, MD¹⁾; Chisato Izumi, MD, PhD¹⁾; Sari Imamura, MD¹⁾; Naoaki Onishi, MD¹⁾; Yodo Tamaki, MD, PhD¹⁾; Soichiro Enomoto, MD, PhD¹⁾; Makoto Miyake, MD¹⁾; Toshihiro Tamura, MD, PhD¹⁾; Hirokazu Kondo, MD, PhD¹⁾; Kazuaki Kaitani, MD¹⁾; Kazuo Yamanaka, MD, PhD²⁾; Yoshihisa Nakagawa, MD, PhD¹⁾

Departments of ¹⁾Cardiology and ²⁾Cardiovascular Surgery, Tenri Hospital, Tenri, Japan

Corresponding author:

Chisato Izumi, MD, PhD

Department of Cardiology, Tenri Hospital

200 Mishima-cho, Tenri, Nara 632-8552, Japan

Tel: +81-743-63-5611, Fax: +81-743-63-1530

E-mail: izumi-ch@tenriyoroze.jp

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ABSTRACT

Objective: In patients with subpulmonic infundibular ventricular septal defect (VSD), postoperative progression of aortic regurgitation (AR) sometimes occurs despite early operation before the development of AR. The present study was aimed to identify the occurrence rate and predictors of late AR progression after VSD repair alone.

Methods: We retrospectively investigated 91 consecutive patients who underwent subpulmonic infundibular VSD repair alone and were followed up with echocardiography for >3 years postoperatively. The clinical backgrounds and chronological changes in postoperative AR were evaluated.

Results: The median follow-up period after VSD repair was 13.4 years. Among 91 patients, 7 patients showed postoperative AR progression (AR progression group) and 84 patients did not (No AR progression group). No patients in AR progression group revealed more than moderate AR preoperatively. The incidence of postoperative VSD leakage was significantly higher in AR progression group than No AR progression group (43.0% vs 2.4%, respectively; $p<0.01$). No significant differences were present in sex, age, preoperative AR severity, VSD diameter, or rate of cusp herniation. All patients in AR progression group showed deformity of the right coronary cusp or leaflet resulting in AR progression.

Conclusions: Among patients with subpulmonic infundibular VSD, the incidence of late AR progression after VSD repair alone was unexpectedly high (7.7%). Postoperative VSD leakage may be a significant risk factor for late AR progression. Long-term follow-up of postoperative AR is needed even for patients who undergo VSD repair alone.

Key questions

What is already known about this subject?

The developmental process of aortic regurgitation (AR) in patients with subpulmonic infundibular ventricular septal defect (VSD) has been well described. Therefore, an early operation is recommended before AR and/or aortic valve deformity develop, even if the pulmonary to systemic blood flow ratio is low.

What does this study add?

Few data are available regarding postoperative AR progression in patients who have no or mild AR immediately after VSD repair alone. The data indicate that cusp or leaflet deformity may be an important risk factor for postoperative AR progression and that VSD leakage is the most significant risk factor for these deformities in patients with subpulmonic infundibular VSD.

How might this impact on clinical practice?

Because of the slow progression of postoperative AR, careful long-term follow-up of postoperative AR is needed even for patients who had no or mild AR immediately after VSD repair alone. Right coronary cusp or leaflet deformities and the existence of postoperative VSD leakage should be addressed to ensure early detection of postoperative AR progression.

INTRODUCTION

Ventricular septal defect (VSD) is a common congenital heart disease with an incidence of approximately 1.5 to 6.0 per 1000 newborns.^{1,2} The incidence of aortic regurgitation (AR) is higher in patients with subpulmonic infundibular VSD than in patients with other types of VSD,^{3,4} and AR is often progressive. Therefore, in patients with subpulmonic infundibular VSD, an early operation is recommended before AR and/or deformities of the aortic valve develop, even if the pulmonary to systemic blood flow ratio (Q_p/Q_s) is low.⁵⁻⁷

Preoperative AR, a large VSD, aortic valve structural defects, and sinus of Valsalva aneurysm have been considered risk factors for AR progression after VSD repair.⁸⁻¹¹ Aortic valve surgery concomitant with VSD repair has often been performed in patients with more than moderate preoperative AR; however, it has been reported that these patients often show postoperative AR progression even when they had no or mild AR immediately after the operation.¹²⁻¹⁴ On the other hand, few long-term follow-up data are available regarding postoperative AR progression in patients who underwent VSD repair alone and had no or mild AR immediately after surgery.

The present study was aimed to identify the occurrence rate and predictors of late AR progression after VSD repair alone.

METHODS

Study population

We retrospectively investigated 122 consecutive patients who underwent surgical interventions

for subpulmonic infundibular VSD starting in 1972. Of these 122 patients, 100 underwent follow-up echocardiography for >3 years after VSD repair. Moreover, 9 patients who underwent concomitant aortic valve surgery at the time of VSD repair were excluded, and finally 91 patients were enrolled. Male patients comprised 67% of the study population (61 of 91 patients). The patients' median age at the time of VSD repair was 3 years (range, 0–38 years).

The VSDs were classified according to the system described by Soto et al.¹⁵ Subpulmonic (subarterial) infundibular VSD is defined as a defect located just beneath the aortic and pulmonary valves with fibrous continuity between both valves and an absent septal component of the subpulmonary infundibulum. The location of the VSD in each patient was confirmed by surgical findings. The study protocol was approved by the institutional ethics committee at Tenri Hospital.

Clinical characteristics and prognosis

We investigated the following clinical characteristics: sex, age at the time of surgery, follow-up period, preoperative and postoperative AR severity, incidence of VSD leakage after surgery, aortic valve surgery during the postoperative follow-up period, pressure data obtained using preoperative cardiac catheterization, and coexisting conditions such as other congenital heart diseases. The maximal diameter of the VSD was measured during VSD repair. The postoperative mortality rate and the occurrence of cardiac events were also evaluated. Cardiac events were defined as AR progression, surgical re-intervention, hospitalization due to heart failure, infectious endocarditis, or arrhythmias. Arrhythmias included ventricular tachycardia,

frequent ventricular premature contraction, atrial tachycardia, atrial fibrillation, and atrial flutter.

Echocardiographic examinations and parameters

Comprehensive echocardiographic assessments were conducted by experienced sonographers using high-quality commercially available ultrasound systems. Echocardiography was performed before and immediately after the surgical intervention as well as during the long-term follow-up period. The AR grade, ejection fraction, existence of VSD leakage after surgery, and aortic valve morphology were evaluated. AR was graded as trivial (slight under the aortic valve), mild (not reaching the tip of the mitral valve leaflet), moderate (reaching the tip of the mitral valve leaflet), or severe (beyond the tip of the mitral valve leaflet).^{16 17} The AR grade was re-evaluated by the first and second authors according to the above-described criteria. Progression of AR was defined as the development of more than moderate AR during the follow-up period in patients with no or mild AR immediately after surgery.

Cardiac catheterization

All patients except one underwent preoperative cardiac catheterization. The mean pulmonary artery pressure, systolic pressure of the right ventricle, and Qp/Qs were evaluated using the data obtained during catheterization. Moreover, the degree of preoperative AR was graded on the following semiquantitative scale of 1+ to 4+^{18 19}: mild (1+), moderate (2+), or severe (3+ and 4+). The AR grade as evaluated by cardiac catheterization was used in patients with no

available preoperative colour Doppler echocardiography data.

Statistical analyses

Statistical analyses were performed using SPSS for Windows 22.0 (IBM Corp., Armonk, NY, USA). Data are expressed as mean $\pm$ standard deviation or median (range). Differences in continuous variables between the two groups were determined using the Mann–Whitney *U*-test. Statistical significance was set at a two-tailed p-value of <0.05 .

RESULTS

Baseline characteristics of all patients

The demographic characteristics of 91 patients were described in table 1. The preoperative severity of AR in all patients except one was no or mild. With respect to concomitant cardiac anomalies, patent foramen ovale was present in 7 patients (7.7%), a double-chambered right ventricle in 3 patients (3.3%), interruption of the aortic arch complex in 2 patients (2.2%), and coarctation of the aorta in 2 patients (2.2%). No coexisting Valsalva aneurysms were present in patients during the follow-up period.

Prognosis

The median follow-up period was 13.4 years (interquartile range, 8.0–16.9 years). No all-cause death or cardiac death occurred during the follow-up period. Postoperative AR progression occurred in 7 patients (7.7%) at a mean of 13.7 ± 7.2 years after VSD closure. Moreover,

additional or re-do aortic valve surgery was performed in 3 patients (3.3%), and infectious endocarditis developed in one patient (1.1%). Atrial fibrillation developed in only one patient (1.1%) and frequent ventricular premature contraction or ventricular tachycardia was not revealed after VSD repair.

Late progression of AR after VSD closure

Among the 91 patients, 7 showed postoperative AR progression (AR progression group) and 84 did not (No AR progression group) (figure 1). No patients in AR progression group revealed more than moderate AR preoperatively. A representative case in AR progression group is shown in figure 2. The incidence of postoperative VSD leakage was significantly higher in AR progression group than No AR progression group ($p<0.01$) (table 1). On the other hand, there were no significant differences in sex, median age at surgery, preoperative AR severity, VSD diameter, rate of herniation of the right coronary cusp, Qp/Qs, preoperative ejection fraction, or mean pulmonary artery pressure. Aortic valve surgery was performed in 3 patients in AR progression group at 9, 12, and 28 years after VSD repair, respectively.

Clinical and echocardiographic characteristics of patients with postoperative AR progression after VSD repair

The clinical and echocardiographic characteristics of patients in AR progression group are listed in table 2. All patients were ≤ 6 years of age at the time of VSD closure, and 5 patients (71%) were male. They had no or mild AR immediately after VSD repair. Six patients (86%) had

preoperative herniation of the right coronary cusp, and 2 patients (29%) developed postoperative leaflet prolapse. With respect to the postoperative valve morphology, the right coronary cusp was thickened and sclerotic in all patients except one. In 3 patients (43%), the right coronary leaflet was pulled toward the left ventricle or folded. Additionally, postoperative VSD leakage was present just below the right coronary cusp in 3 patients (43%), and the cusp became deformed during the follow-up period after VSD repair. The regurgitation jet flow was eccentric in all patients; the jet direction was toward the anterior leaflet of the mitral valve in six patients and toward the interventricular septum in one patient. The echocardiographic images of aortic valve leaflet and the regurgitation jet in AR progression group and No AR progression group are shown in figure 3. Moreover, a schematic drawing illustrating representative types of aortic leaflet pathology in AR progression group is shown in figure 4.

DISCUSSION

We focused the present investigation on the progression of AR after VSD repair alone in patients with subpulmonic infundibular VSD. In previous studies, the developmental process of AR in patients with subpulmonic infundibular VSD has been well described,^{20 21} and various data regarding postoperative AR progression in patients who have undergone aortic valve surgery concomitant with VSD repair have been reported.¹²⁻¹⁴ However, few data are available regarding postoperative progression of AR in patients who have undergone VSD repair alone. This is the first study to focus on this disease entity and follow up patients during a long-term period from early childhood to adulthood.

Surgical indication for subpulmonic infundibular VSD and pathophysiology of aortic valve deformity

Subpulmonic infundibular VSD rarely closes spontaneously and is commonly associated with herniation of the aortic sinus wall of the right coronary cusp with or without AR. The development of aortic valve deformity is most strongly influenced by the Venturi effect because the superior border is more closely adjacent to the hinge point of the right coronary cusp in patients with subpulmonic infundibular VSD than in patients with other types of VSD. A large VSD is also a risk factor for aortic valve deformity because a larger jet impacts the adjacent aortic valve leaflet and results in more rapid development of aortic valve deformity and AR.²² Cusp or leaflet deformities and AR develop at the age of 5 to 8 years,²³ and preoperative AR is reported as a risk factor for postoperative residual AR.⁶ Therefore, surgical intervention for patients with subpulmonic infundibular VSD is recommended immediately after the detection of trivial AR^{6,7} or as soon after diagnosis of subpulmonic infundibular VSD as possible, regardless of shunt volume.^{24,25} In the present study, most patients underwent VSD repair alone at the age of <5 years when they had no to mild AR.

Besides leaflet deformity secondary to the Venturi effect, other proposed mechanisms leading to AR progression in patients with VSD include a lack of structural support for leaflets adjacent to the VSD, abnormal commissural suspension, lack of appositional forces, and loss of continuity between the aortic media and aortic annulus.^{21, 22, 25, 26, 27}

Progression of AR and its pathophysiology including effect of VSD leakage

As mentioned above, early surgical intervention has been recommended for patients with subpulmonic infundibular VSD to prevent AR progression. However, no long-term follow-up data of AR progression after VSD repair alone from childhood to adulthood have been available to date. In the present study, 7 (7.7%) of 91 patients who underwent VSD repair alone showed postoperative AR progression, and 3 (3.3%) required aortic valve surgery during the long-term follow-up despite the fact that AR did not develop immediately after surgery. Moreover, VSD leakage was a significant risk factor for AR progression.

Postoperative VSD leakage induces the Venturi effect because the high-velocity jet produces a drop in pressure between both ventricles. However, the blood flow of the residual VSD is too low to impact the adjacent cusp. Therefore, the Venturi effect alone may be insufficient for development of a deformity of the comparatively larger aortic valve cusp. In patients with subpulmonic infundibular VSD, the leak position is adjacent to the right coronary cusp; thus, the cusp may be gradually influenced over the years by the Venturi effect of the small residual VSD flow compared with other types of VSD. Therefore, postoperative cusp deformity and AR progression develop gradually in the long term.

In order to prevent the postoperative AR progression, residual VSD closure may be needed. Recently, transcatheter closure of postoperative VSDs were reported,^{28,29} and a good result of percutaneous device closure compared with surgical closure was reported.³⁰ At present, percutaneous device closure is adapted for perimembrous and muscular VSD; however, it may be a good option for subpulmonic VSD leakage if newly small device that does not affect aortic

valve and pulmonary valve will be invented.

On the other hand, the right coronary cusp or leaflet showed various deformities in the other 4 patients without postoperative VSD leakage, as shown in table 2. The development of these deformities may have been affected by multiple factors other than postoperative VSD leakage, and it is difficult to identify another single risk factor for postoperative AR progression. Because the postoperative AR progresses slowly, careful and very long-term follow-up of valve deformity and postoperative AR is needed even for patients with no or mild AR immediately after VSD repair alone. Deformities of the right coronary cusp or leaflet and the presence of postoperative VSD leakage should be addressed to detect postoperative AR progression in the early phase.

Study limitations

The main limitation of this study is that it was a retrospective, single-centre study with a small sample size. Moreover, for patients with no preoperative colour Doppler echocardiographic data, cardiac catheterization data were used as a substitute for echocardiographic data. The severity of AR was mainly determined by the distance of the regurgitation jet on colour Doppler echocardiography. Postoperative AR usually revealed an eccentric jet; thus, the severity may be underestimated.

CONCLUSIONS

Among patients with subpulmonic infundibular VSD, the percentage of patients with late AR

progression after VSD repair alone was unexpectedly high (7.7%). The existence of postoperative VSD leakage may be a significant risk factor for late AR progression after VSD repair alone. Long-term follow-up of postoperative AR is needed even for patients who have undergone VSD repair alone.

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FIGURE LEGENDS

Figure 1. Trial flow diagram. VSD, ventricular septal defect; AR, aortic regurgitation.

Figure 2. A representative case of late progression of aortic regurgitation (AR) after ventricular septal defect (VSD) repair. No AR was revealed just after VSD repair (A); however, AR gradually progressed until it was moderate in severity 12 years after surgery (B). LV, left ventricle; LA, left atrium; Ao, aorta.

Figure 3. Representative cases in aortic regurgitation (AR) progression group (A)-(C) and in No AR progression group (D)-(F). AR progression group; the right coronary cusp was thickened and sclerotic, and the bad coaptation of each cusps was shown in the parasternal view (A). The right coronary cusp (RCC) was thickened in the short axis view (B). The regurgitation jet was eccentric and blew toward the anterior leaflet of the mitral valve (C). No AR progression group; RCC was a little sclerotic but not thickened (D), (E). Postoperative AR was not revealed (F). LV, left ventricle; LA, left atrium; Ao, aorta.

Figure 4. A schematic drawing illustrating the representative types of aortic leaflet pathology resulting in late aortic regurgitation after ventricular septal defect repair alone. Right coronary cusp (RCC) was thickened and sclerotic (dotted arrow), and regurgitation jet direction was toward anterior leaflet of mitral valve (A). Right coronary leaflet was pulled to the left ventricle (arrow), and jet direction was toward the anterior leaflet of the mitral valve (B). RCC was

thickened and sclerotic (dotted arrow), left coronary leaflet was pulled to the left ventricle (arrow), and jet direction was toward septum (C). LV, left ventricle; LA, left atrium; Ao, aorta.

Table 1. Baseline characteristics and postoperative courses in patients who underwent VSD repair only

	All patients n=91	AR progression n=7	No AR progression n=84	p value
Age at surgery (years: range)	3 (0-38)	4 (0-6)	3 (0-38)	0.98
Male, n (%)	60 (67)	5 (71)	55 (66)	0.78
Preoperative AR severity; $\geq$ moderate n (%)	1 (1)	0	1 (1)	0.77
VSD diameter (mm)	7.7 $\pm$ 3.4	8.6 $\pm$ 4.0	7.6 $\pm$ 3.4	0.49
Herniation of right coronary cusp, n (%)	57 (63)	6 (86)	52 (63)	0.24
Qp/Qs	1.7 $\pm$ 0.9	1.9 $\pm$ 0.9	1.7 $\pm$ 0.9	0.46
Preoperative EF (%)	67.3 $\pm$ 23.8	69.5 $\pm$ 11.3	67.1 $\pm$ 24.3	0.63
Mean pulmonary artery pressure (mmHg)	20.9 $\pm$ 12.4	20.4 $\pm$ 9.2	21.0 $\pm$ 12.7	0.9
Postoperative VSD leak, n (%)	7 (7.7)	3 (43)	2 (2.4)	<0.01
Aortic valve surgery late after VSD repair, n (%)	3 (3)	3 (43)	0 (0)	—

Continuous variables are shown as mean $\pm$ SD, except for age at surgery, which is shown as median (range). All other values are shown as n (%).

VSD, ventricular septal defect; AR, aortic regurgitation; Qp/Qs, ratio of pulmonary to systemic blood flow; EF, ejection fraction.

Table 2. Clinical and echocardiographic characteristics of aortic valve in patients of AR progression group

No.	Age at VSD repair	Sex	Age at AR progression	AR before VSD repair	AR immediately after VSD repair	AR late after VSD repair	Additional aortic valve surgery	Postoperative VSD leak	Postoperative leaflet prolapse	Characteristics of valve	Regurgitant jet	Types of aortic leaflet pathology in Figure 4
1	0	M	12	none	none	moderate	+	+	–	RCL extended and was pulled to the left ventricle.	Toward backward (anterior leaflet of MV)	(B)
2	3	F	17	none	mild	severe	+	–	+	RCC was thickened and sclerotic. RCL was pulled to the left ventricle.	Toward backward	(A) + (B)
3	4	M	13	mild	mild	moderate	–	+	–	RCC was thickened and sclerotic.	Toward backward	(A)
4	4	M	16	mild	mild	moderate	–	–	–	RCC was thickened and sclerotic. RCC was fused with NCC and the motion was restricted.	Toward backward	(A)
5	5	M	12	mild	none	moderate	+	–	–	RCC was thickened and sclerotic. RCL was folded.	Toward backward	(A)
6	6	M	34	none	none	moderate	–	–	–	RCC was thickened and sclerotic.	Toward backward	(A)
7	6	F	17	mild	mild	moderate	–	+	+	RCC was thickened and sclerotic. LCL was pulled to the left ventricle.	Toward Forward (septum)	(C)

M, male; F, female; VSD, ventricular septal defect; AR, aortic regurgitation; RCL, right coronary leaflet; LCL, left coronary leaflet; MV, mitral valve; RCC, right coronary cusp; NCC, noncoronary cusp.

122 assessed for eligibility

22 excluded

(did not undergo follow-up echocardiography
for more than 3 years after VSD repair)

9 excluded

(underwent concomitant aortic valve surgery
at the time of VSD repair)

**91 enrolled
(under went VSD repair alone)**

**7 showed postoperative progression of AR
(AR progression group)**

**84 did not show postoperative progression of AR
(No AR progression group)**







