

Progression of Aortic Regurgitation in Asian Patients with Congenital Sinus of Valsalva Aneurysm

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ABSTRACT

Background: We reviewed the experience of An Zhen and Fu Wai Hospital for congenital sinus of Valsalva aneurysm (SVA) to determine risk factors for aortic valve replacement (AVR) and postoperative progression of aortic regurgitation (AR).

Methods: Over a 7-year period, 255 patients underwent surgical repair of an SVA. Aneurysms originated from the right sinus and the noncoronary sinus in 212 patients (83.1%) and 38 patients (14.9%), respectively, and protruded into the right ventricle and right atrium in 171 patients (67.1%) and 80 patients (31.4%), respectively. AR presented in 142 patients (55.7%), 60 patients underwent AVR, and 13 patients underwent aortic valvuloplasty (3 patients eventually received AVR for valvuloplasty failure).

Results: All patients survived the operation. Late death occurred in 2 patients (0.8%), and 2 patients (0.8%) experienced anticoagulation-related complications. Logistic regression analysis revealed that infective endocarditis, the cardiothoracic ratio, and a nonruptured SVA were risk factors for AVR. Late follow-up of 150 patients by echocardiographic assessment revealed that AR improved in 17 patients and worsened in 20 patients. Cox regression analysis revealed AR at discharge to be an independent risk factor for AR aggravation at late follow-up.

Conclusions: SVA can be repaired with low mortality and excellent long-term results. AR at discharge is an important factor in determining AR aggravation at late follow-up after the operation. We recommend early diagnosis and aggressive treatment for SVA.

INTRODUCTION

Congenital sinus of Valsalva aneurysm (SVA) is a rare congenital heart disease, with an incidence ranging from 0.1% to 3.5% of all congenital heart defects [Goldberg 1990]. Aortic regurgitation (AR) is a commonly associated lesion in SVA. Although SVA can be repaired with low risk in today's cardiovascular surgery practice, aortic valve replacement (AVR) and deteriorating AR are important factors in determining long-term results after the operation [van Son 1994; Au 1998; Vural 2001; Dong 2002; Murashita 2002; Wang 2007; Yan 2008]. Based on a large patient cohort, the present study was designed to assess risk factors for AVR and postoperative progression of AR.

PATIENTS AND METHODS

Between February 2002 and December 2008, a total of 255 Chinese patients underwent surgical repair of an SVA at An Zhen and Fu Wai Hospital in Beijing. Patients with Marfan syndrome or a history of previous aortic root operation were excluded. Data collection was in accordance with the regulations and approved by the institutional review board of An Zhen and Fu Wai Hospital, and the need for patient consent for the study was waived. The severity of AR was graded according to color Doppler echocardiography [Miyatake 1984] 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), and severe (beyond the tip of the mitral valve leaflet). Diagnosis of aortic valve prolapse was made according to echocardiography and surgical findings.

The patients were followed up at our outpatient department. Patients received telephone calls and questionnaires for data collection, when necessary.

Clinical Characteristics

The study population had a mean (\pm SD) age of 32.2 \pm 12.3 years (range, 4-67 years) and a male-to-female ratio of 2.3 (178:77). At the time of admission, 194 patients (76.1%) were symptomatic (palpitations, chest pains, dyspnea, fatigue, chest distress, syncope attack); 66 of these patients (25.9%) presented with acute-onset symptoms. The mean preoperative duration of symptoms was 15.9 \pm 42.1 months (range,

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3 days to 200 months). Chest radiography results showed a mean cardiothoracic ratio of 0.56 ± 0.08 (range, 0.4-0.84), and the numbers of patients in the New York Heart Association [NYHA] cardiac functional classes were as follows: class I, 81; class II, 135; class III, 25; and class IV, 14.

Operative Procedure

Surgery was performed soon after SVA was diagnosed. Three patients (1.2%) who had uncontrolled cardiac failure underwent an emergency operation. Surgery repair was carried out with cardiopulmonary bypass with standard aortic-bicaval cannulation and moderate hypothermia, and cold blood cardioplegia was administered. In patients with significant shunting, the cardioplegic solution was cannulated directly into coronary ostia. The mean aortic cross-clamp time was 75.9 ± 40.5 minutes (range, 15-220 minutes), and the mean bypass time was 107.2 ± 49.3 minutes (range, 37-313 minutes).

Surgical Findings

A complete diagnosis was made before the operation in 217 patients (85.1%). The aneurysm originated from the right sinus, from the noncoronary sinus, and from other circumstances (2 sinuses or uncertain) in 212 patients (83.1%), 38 patients (14.9%), and 5 patients (2.0%), respectively, and protruded into the right ventricle, the right atrium, and other chambers in 171 patients (67.1%), 80 patients (31.4%), and 4 patients (1.6%), respectively. Of the 212 patients with a ruptured SVA, the aneurysm ruptured into the right ventricle in 133 patients, the right atrium in 75 patients, and other chambers in 4 patients. The mean diameter of the hole in the ruptured sac was 6.5 ± 4.2 mm (range, 2.5-28 mm). The mean diameter of the coexisting ventricular septal defect (VSD) was 11.3 ± 6.1 mm (range, 4-32 mm). Associated cardiovascular lesions included VSD (148 patients, 58%), bicuspid aortic valve (8 patients, 3.1%), mitral regurgitation (45 patients, 17.6%), tricuspid regurgitation (80 patients, 31.4%), and infective endocarditis (IE) (13 patients, 5.1%). AR presented in 142 (55.7%) of the study patients, and secondary changes presented in 92 patients (36.1%): 55 patients (21.6%) with aortic valve prolapse and 37 patients (14.5%) with a valve leaflet defect, such as fibrosis, thickening, calcification, contraction, and deformation.

Surgical Methods

Surgical approaches for SVA repair were as follows: through the chamber of termination in 152 patients (right ventriculotomy, 78 patients; right atriotomy, 74 patients), through an aortotomy in 26 patients, and via a combined approach of ventriculotomy/atriotomy and aortotomy in 77 patients. The methods of SVA repair chosen were as follows: closing the base of the fistula with a patch, 67 patients; closing the base of the fistula with a patch plus sutures to close the break, 90 patients; closing with direct sutures (simple/buttressed), 20 patients; and using no treatment, 18 patients (in some patients with a small nonruptured aneurysm and a concomitant VSD, which was repaired with a patch only). In the remaining 60 patients, SVA fistula repair and AVR were

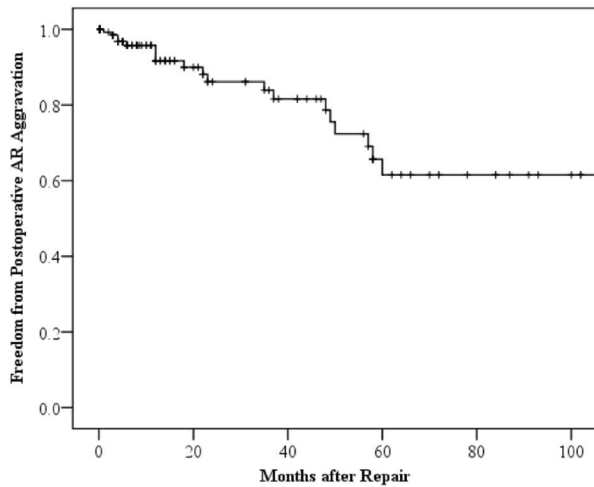
performed in the same operation. The coexisting VSD was closed via a single-patch method [Dong 2002] in 143 cases and by direct sutures in 5 cases. Aortic valvuloplasty (AVP) or AVR was performed when a preoperative evaluation showed a more-than-moderate degree of AR or when the presence of severe secondary changes was determined by the surgeon during the operation. The methods of AVP chosen included the Trusler technique, aortic cusp plication, cusp suspension, annuloplasty, and extending the aortic cusp with an autologous or bovine pericardial strip [Trusler 1973; Elgamil 1999; Rergkhang 2005]. AVR was performed if valvuloplasty had failed or if the pathologic leaflet changes were severe. Thirteen patients underwent AVP (3 of these patients eventually received AVR for AVP failure). In total, 57 mechanical valves and 3 bioprosthetic valves were implanted.

Statistical Analysis

Quantitative variables were reported as the mean \pm SD and analyzed with the independent-sample Student *t* test. Nominal variables were analyzed with the χ^2 test. A binary logistic regression model or a Cox regression model was used for the multivariate analysis of risk factors shown to be statistically significant in the univariate analyses. Statistical significance was set at a *P* value of $<.05$. The time-related freedom from events was analyzed with life tables.

RESULTS

All patients survived the operation. Of the survivors, 207 (81.2%) were followed up for a mean of 27.9 ± 25.7 months (range, 1-106 months). 191 patients were in NYHA class I, 11 patients were in class II, and 5 patients were in class III (4 underwent reoperations; 1 is under observation). Late death occurred in 2 of the patients (0.8%) who underwent AVR. Both died of anticoagulation-related complications after the operation. Reoperation was performed in 5 patients (2.0%). Three of the patients underwent AVR for more-than-moderate AR several months after AVP, the fourth patient underwent anomalous muscle bundle resection for right ventricular outlet stenosis 4 days after the operation, and the last patient underwent AVR and anomalous muscle bundle resection 5 days after the operation because of perivalvular leakage, right ventricular outlet stenosis, hemolysis, and acute renal failure. Late anticoagulation-related complications occurred in 2 patients (0.8%). One of these patients experienced hemolysis and ecchymosis on the body surface 20 months after the operation. The other patient experienced a cerebral accident 43 months after the operation, and whether the accident was caused by thromboembolic or bleeding complications remains unclear. In late follow-up, 194 patients underwent echocardiographic assessment. Forty-four of these patients had undergone AVR; of remaining 150 patients, AR improved in 17 patients. AR worsened in 20 patients: from none to trivial or mild in 13 patients, from trivial to mild in 3 patients, from mild to moderate in 1 patient, and from more-than-moderate to more severe grade after AVP in 3 patients (reoperation of AVR were performed in all 3 of these patients). The 2-year and 5-year values for actuarial freedom from events, including



Kaplan-Meier estimation of 5-year actuarial freedom from aggravation of postoperative aortic regurgitation.

reoperation and cardiac death, were $97\% \pm 1\%$ and $98\% \pm 1\%$, respectively (data not shown). The mean 2-year and 5-year values for actuarial freedom from postoperative AR aggravation were $88\% \pm 3\%$ and $67\% \pm 8\%$, respectively (Figure).

Factors for AVR

Table 1 lists clinical characteristics and comparisons of patients who did and did not undergo AVR. The univariate analysis identified IE, secondary changes, cardiac function, cardiothoracic ratio, and nonruptured SVA as risk factors for AVR; however, logistic regression analysis revealed that IE, cardiothoracic ratio, and nonruptured SVA were risk factors in the extreme. The Exp(B) values (odds ratios) were 9.6 (95% confidence interval [CI], 2.67-34.63), 1.07 (95% CI, 1.03-1.12), and 3.38 (95% CI, 1.58-7.25), respectively (all P values $<.01$).

Interestingly, patients with a nonruptured aneurysm had a higher incidence of preoperative AR (27/43, 62.8%) than those with a ruptured aneurysm (97/212, 45.8%) ($P = .048$, data not shown), and the incidence of symptoms in patients with a nonruptured aneurysm who underwent AVR (12/43, 27.9%) was significantly higher than in those who did not (6/43, 14.0%) ($P = .02$, data not shown).

Risk Factors for Late Follow-up AR Aggravation

At late follow-up, 20 of 150 patients who had undergone echocardiographic assessment showed deteriorated AR. Table 2 summarizes the clinical characteristics and compares the patients with and without AR aggravation. The univariate analysis revealed that VSD and AR at discharge were risk factors for worsening of AR. In contrast, secondary changes in the aortic

Table 1. Clinical Characteristics and Comparisons of the Patients with and without Aortic Valve Replacement*

Clinical Characteristics	Total, n (%)	Aortic Valve Replacement		P
		No	Yes	
Aortic valvuloplasty, n (%)	255 (100)			1.0
No	242 (94.9)	185 (72.5)	57 (22.4)	
Yes	13 (5.1)	10 (3.9)	3 (1.2)	
Bicuspid aortic valve, n (%)	255 (100)			.171
No	247 (96.9)	191 (74.9)	56 (22.0)	
Yes	8 (3.1)	4 (1.6)	4 (1.6)	
Infective endocarditis, n (%)	255 (100)	242 (94.9)	191 (74.9)	<.01
No	242 (94.9)	191 (74.9)	51 (20)	
Yes	13 (5.1)	4 (1.6)	9 (3.5)	
Secondary changes, n (%)	255 (100)			<.01
No	163 (63.9)	163 (63.9)	0 (0)	
Yes	92 (36.1)	32 (12.5)	60 (23.5)	
Rupture of sinus of Valsalva aneurysm	255 (100)			.007
No	43 (16.9)	26 (10.1)	17 (6.7)	
Yes	212 (83.1)	169 (66.3)	43 (16.9)	
Cardiothoracic ratio	0.564 ± 0.082	0.560 ± 0.076	0.59 ± 0.094	.001
Cardiac functional class	1.89 ± 0.79	1.83 ± 0.73	2.1 ± 0.93	.019
Age, y	32.17 ± 12.32	30.66 ± 10.93	32.98 ± 12.72	.430
Preoperative duration, min	15.92 ± 42.13	12.76 ± 33.32	26.18 ± 62.05	.113

*Data are presented as the mean \pm SD as indicated.

Table 2. Comparison of Patients with and without Aggravation of Aortic Regurgitation (AR) at Late Follow-up*

Clinical Characteristics	Total, n (%)	Aggravated AR		P
		No	Yes	
Secondary changes	150 (100)			.287
No	128 (85.3)	113 (75.3)	15 (10.0)	
Yes	22 (14.7)	17 (11.3)	5 (3.3)	
Aortic valvuloplasty	150 (100)			.125
No	142 (94.7)	125 (83.3)	17 (11.3)	
Yes	8 (5.3)	5 (3.3)	3 (2.0)	
Aortotomy	150 (100)			.259
No	116 (77.3)	103 (68.7)	13 (8.7)	
Yes	34 (22.7)	27 (18.0)	7 (4.7)	
SVA repair method	150 (100)			.175
Patch closure/ no treatment	55 (36.7)	47 (31.3)	8 (5.3)	
Patch closure plus direct suture	76 (50.7)	69 (46.0)	7 (4.7)	
Direct suture	19 (12.7)	14 (9.3)	5 (3.3)	
Ventricular septal defect	150 (100)			.019
No	74 (49.3)	69 (46.0)	5 (3.3)	
Yes	76 (50.7)	61 (40.7)	15 (10.0)	
Preoperative AR	150 (100)			.718
No	92 (61.3)	79 (52.7)	13 (8.7)	
Yes	58 (38.7)	51 (34.0)	7 (4.7)	
AR at discharge	150 (100)			.003
No	83 (55.3)	78 (52.0)	5 (3.3)	
Yes	67 (44.7)	52 (34.7)	15 (10.0)	

*SVA indicates sinus of Valsalva aneurysm.

valve, SVA repair method, aortotomy, preoperative AR, age at surgery, symptom duration, cardiothoracic ratio, cardiac function, and so forth (data not shown) showed no significant contribution to AR aggravation. Cox regression analysis, however, revealed AR at discharge to be an independent risk factor related to late postoperative aggravation of AR. The Exp(B) value (odds ratio) was 6.11 (95% CI, 1.99-18.77; $P = .001$).

DISCUSSION

The pathologic anatomy of congenital ruptured SVA, described in 1957, shows separation of the aortic media and the hinge line of the aortic annulus, which leads to a progressive expansion (to varying degrees) of the aortic wall under aortic pressure, usually in a windsock-like protrusion that can invade neighboring structures and perforate into them [Edwards 1957]. Because the aortic root occupies a central position at the base of the heart, the SVA may protrude or rupture into any of the 4 heart chambers, especially the right ventricle and the right atrium. It also can rupture (rarely) into the left ventricle, pulmonary artery, or interventricular septum [Raffa 1991; Vural 2001; Wang 2007; Honda 2009; Yang 2010]. In our series, the SVA protruded into the right ventricle in 67.1% of our patients and into the right atrium in 31.4%.

AR and VSD are common coexisting lesions in Asian patients with congenital SVA [Wang 2007], as was the case in our series, with an incidence of 55.7% and 58%, respectively. An anatomic defect and the hemodynamic Bernoulli effect are commonly considered to contribute to the form and development of AR in SVA [Chu 1990; Maruo 2003]. Our study showed that patients with nonruptured aneurysm had a higher incidence of preoperative AR than those with a ruptured aneurysm. This finding implies that the anatomic defect plays an elementary role in determining the form of AR by the above-mentioned mechanisms.

Three surgical approaches were chosen for SVA repair: through the chamber where the aneurysm terminates, through an aortotomy, or via a combined approach. Whether aortotomy should be performed routinely is still controversial [van Son 1994; Murashita 2002; Jung 2008]; however, our findings indicate that the surgical approach has no significant effect on the progression of AR. The inference is that regardless of whether aortotomy is adopted, it is crucial to avoid distorting the aortic valve.

The methods for SVA repair primarily are direct suture, patch closure, or a combination of both methods (direct suture plus patch closure). The aneurysm was small in some

of the patients with a nonruptured SVA and VSD, so the treatment of choice would be VSD repair with treatment for the aneurysm. In our series, surgical correction of an SVA was not found to have a significant effect on worsening of AR at late follow-up, although patients who underwent direct suture closure of their SVA had a significantly higher incidence of aggravated AR in the early postoperative period (data not shown).

AVP and AVR are common surgical methods for treating AR, and AVR is required in 0% to 60.9% of patients with SVA who present with concomitant AR [Murashita 2002; Moustafa 2007; Wang 2007; Yan 2008]. Because of the poor prognosis of AVP [Naka 2000; Rathore 2006] and the generally poor economic conditions of Chinese patients for allowing a second operation, replacement is preferred over valvuloplasty at our hospitals. In our study, 60 (42.3%) of the 142 patients with AR underwent AVR, whereas 10 (3.9%) underwent AVP. Because of their inherent thrombogenicity, mechanical aortic valves require lifelong oral anticoagulation therapy. Withholding or intensive anticoagulation therapy will yield an unsatisfactory or even disastrous result. Anticoagulation-related complications (thromboembolism and bleeding) are common complications after AVR and are important factors in determining the long-term results after AVR [Cannegieter 1994; Hering 2005; Taylor 2005]. In our series, 2 patients (0.8%) experienced anticoagulation-related complications. Additionally, one other patient underwent a second AVR operation for perivalvular leakage. AVR is an important factor in determining the long-term postoperative results of SVA repair. IE, the cardiothoracic ratio, and a nonruptured SVA were identified as risk factors for AVR in our study. Therefore, determining how to avoid AVR will undoubtedly be beneficial for treating SVA. These steps include an early diagnosis of nonruptured SVA and aggressive treatment before cardiac dilatation and IE can occur. Moreover, ensuring a better long-term effect via improvements in AVP technology is also a strategy for AR treatment.

Some reports have suggested that the indications for surgical treatment of symptomatic, nonruptured aneurysms included right ventricular outflow tract obstruction and acute ostial coronary artery obstruction [Warnes 1984; Faille 1985]. The optimal management of an asymptomatic, nonruptured aneurysm is less clear, however, because of the absence of a precise natural history [Takach 1999]. In our study, patients with a nonruptured aneurysm had a higher incidence of preoperative AR and a higher risk for AVR, and the patients who underwent AVR had a higher incidence of symptoms (12/43, 27.9%) than those who did not. Our experience suggests early and aggressive treatment should be recommended for a nonruptured aneurysm to prevent AR occurrence and AVR, at least before the occurrence of symptoms.

In our study, postoperative long-term survival and operative results were both excellent, as other studies have shown [Choudhary 1997; Au 1998; Vural 2001]. Unfortunately, the rate of 5-year freedom from postoperative worsening of AR was low (67%). Although few patients (1.2%) needed reoperation, AR progression was still a risk according to the late follow-up results. AR at discharge was identified as an

independent risk factor for worsening of AR at late follow-up. These findings are in accord with those of our previous study of congenital ruptured SVAs [Liu 2011] and with some opinions that consider AR a progressive disease that once present gradually increases in severity [Yacoub 1997; Sim 1999; Rergkliang 2005]. Therefore, early diagnosis and aggressive treatment should be recommended to prevent the occurrence of preoperative AR.

The limitation of this study is related to the inherent liabilities of all retrospective analyses. In addition, a low rate (81.2%) and a short time (27.9 months) of late follow-up may add a bias to the results of our study.

In conclusion, this study has shown that SVA can be repaired with low mortality. There is a high incidence (55.7%) of preoperative AR, and the AVR incidence is high (42.3%) in patients with AR. IE, the cardiothoracic ratio, and a nonruptured SVA were identified as risk factors for AVR. AR at discharge was associated with AR aggravation at late follow-up. Early diagnosis and aggressive treatment are recommended for SVA treatment.

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