

# Follow-up Study of Aortic-Valve Replacement Surgery in Patients With Takayasu's Disease Complicated by Aortic Regurgitation

Satoshi Nishimura, MD; Tetsuya Toubaru, MD;  
Eiji Ootaki, MD; Tetsuya Sumiyoshi, MD

Aortic regurgitation (AR) is not a rare complication of Takayasu's disease and is now considered as an important risk factor related to mortality. Aortic-valve replacement surgery is the only curative treatment, but cardiac function and mortality after surgery have not been reported, so a follow-up study in 10 patients with Takayasu's disease complicated by AR was performed. Six patients underwent aortic-valve replacement surgery and all had improvement of the ejection fraction and a decrease in the size of the left ventricle size on echocardiography. Three of the 6 cases had a remote cardiovascular event. Detailed pathological examination carried out in one case of the aortic valve and aortic specimen from surgery showed only lymphoid cell infiltration around the capillary in the ascending aorta, and no other inflammatory change. Inflammation was well controlled at surgery by pre-operative steroid therapy, so early and aggressive aortic-valve replacement surgery with peri-operative immunosuppressive therapy should be considered for patients with Takayasu's disease. (*Circ J* 2002; **66**: 564–566)

**Key Words:** Aortic regurgitation; Aortic valve replacement; Aortitis syndrome; Takayasu's disease

**T**he incidence of aortic regurgitation (AR) with Takayasu's disease is between 13% and 25%<sup>1,2</sup> and is now considered as an important risk factor for mortality.<sup>3</sup> Aortic-valve replacement surgery is the only curative treatment, but postoperative cardiac function and mortality have not been reported, so we conducted a follow-up study of patients after aortic-valve replacement surgery for Takayasu's disease complicated by AR, and carried out detailed pathological examination of one case.

## Methods

### Patients

Fourteen patients admitted to hospital between 1980 and 2000 with the diagnosis of Takayasu's disease confirmed by clinical, angiographic, and pathological data were enrolled and of these, 10 had moderate or severe AR diagnosed by echocardiography. There were 2 males and 8 females with ages ranging from 27 to 62 years at the onset (Table 1); the mean follow-up period was 12 years.

### Echocardiography

Aortic root diameter, and the left ventricular end-diastolic (LVDD) and end-systolic dimensions (LVDs) were measured from standard M-mode echocardiographic images, and the ejection fraction was determined from the end-diastolic and end-systolic volumes of the left ventricle. The primary endpoint was a cardiovascular event, and the secondary endpoint was the left ventricular dimension and ejection fraction measured on echocardiography.

(Received December 25, 2001; revised manuscript received February 5, 2002; accepted February 20, 2002)

Department of Cardiovascular Medicine, The Sakakibara Heart Institute, Tokyo, Japan

Mailing address: Satoshi Nishimura, MD, 2-5-4 Yoyogi, Shibuya-ku, Tokyo 151-0053, Japan. E-mail: snishi-ty@umin.ac.jp

### Histology

A detailed histological examination was performed on one other case, a 29-year-old female.

### Statistical Analysis

Continuous variables are reported as the mean  $\pm$  1 standard deviation.

## Results

The 10 patients were separated into 3 groups (Table 1): aortic-valve replacement surgery was performed in 6 patients (AVR group), 2 patients were observed only, because of good left ventricular function and mild symptoms of congestive heart failure (the observational group) and surgery was also not performed in the remaining 2 patients because of their high risk of peri-operative mortality (the inoperable group). Patient 7 in the inoperable group, had uncontrollable inflammation despite steroid treatment, and the severe hypertension was also refractory despite full medication. Her renal function gradually deteriorated and she died from renal failure 12 years after onset. Patient 8 in the same group underwent aorta–aorta bypass surgery for severe aortic stenosis, but severe hypertension caused by the AR worsened, her congestive heart failure deteriorated and she died 17 years after onset.

Aortic-valve replacement surgery was performed for symptoms of congestive heart failure and reduced ejection fraction in AVR group. The left ventricle was enlarged at surgery in all 6 cases, but the dimensions decreased at follow-up visits with improvement in systolic function (LVDD decreased from  $63 \pm 4.5$  to  $49 \pm 5.9$ , and ejection fraction increased from  $52 \pm 9.1$  to  $63 \pm 7.9$ ; Fig 1). In contrast to the good improvement in left ventricular function, there was a high incidence of remote cardiovascular events (3 of 6 cases). In patient 1 Warfarin therapy was started post-

**Table 1 Patient Characteristics at Onset and Remote Cardiovascular Events**

Patient no.	Age (years) /sex	AR	MR	NYHA	LVDd/Ds	AoD	EF	Steroid therapy (pre/post)	Follow-up & event
<i>AVR group</i>									
1	27/F	sev	–	I	61/43	39	50	–/+	14y SAH, 15y alive
2	32/M	sev	–	II	61/43	39	56	–/+	15y alive
3	39/M	sev	–	II	58/38	40	69	–/–	17y re-AVR for leakage, 22y alive
4*	49/F	sev	mod	II	70/52	33	49	–/+	12y alive
5	62/F	mod	–	II	60/47	39	46	+/+	4y alive
6	62/F	sev	mild	II	66/55	48	44	–/+	7y die from IE
<i>Inoperable group</i>									
7	40/F	sev	–	III	48/37	29	56	+	12y die from CRF
8	41/F	sev	mild	III	53/35	36	74	–	3y Ao-Ao bypass, 17y die from CHF
<i>Observational group</i>									
9	44/F	mod	mod	I	44/37	26	64	+	10y alive
10	45/F	mod	–	I	46/34	28	65	–	5y alive

age, age at onset; AR, aortic regurgitation; MR, mitral regurgitation; mod, moderate; sev, severe; NYHA, New York Heart Association class; LVDd/Ds left ventricular end-diastolic/end-systolic dimension; AoD, aortic root diameter; EF, ejection fraction; Steroid therapy, pre-/post-operative steroid treatment; SAH, subarachnoid hemorrhage; IE, infective endocarditis; CRF, chronic renal failure; Ao-Ao bypass, aorta-aorta bypass surgery; CHF, congestive heart failure. \*Mitral valve replacement was also performed in this patient.

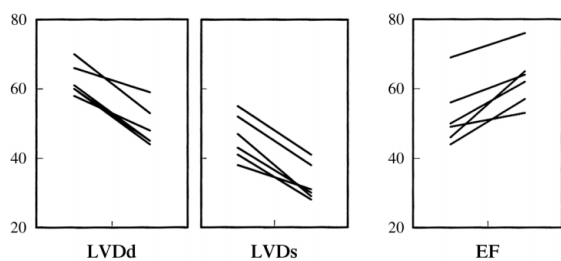


Fig 1. Changes in the left ventricular end-diastolic (LVDd) and end-systolic (LVDs) dimensions and ejection fraction (EF) on echocardiography during the follow-up period in the 'AVR group'.

operatively and was well controlled at the outpatient visits. A subarachnoid hemorrhage was diagnosed 14 years after surgery and she has mild neurological sequela. In patient 3 severe congestive heart failure abruptly appeared 17 years after surgery. Para-valvular leakage was diagnosed and the valve replacement surgery was repeated. Her postoperative course was good and peri-operative steroid treatment was not required because there was no active inflammation. The other case was fatal infective endocarditis in patient 6. Her inflammatory status had been controlled by postoperative steroid treatment, but she was admitted with acute congestive heart failure 7 years after surgery. Destruction of the prosthetic valve because of infective endocarditis was diagnosed, and she died from sepsis despite antibiotics and surgery. We could not find any relationship between these remote cardiovascular events and the peri- and/or post-operative treatment including steroid therapy.

The inoperable group was followed up until they both died. The observational group was followed at outpatient visits and the dimensions of the left ventricle and the severity of symptoms were unchanged at the end of follow-up (data not shown).

Detailed histological examination was carried out on the surgical samples from a 29-year-old female who developed congestive heart failure because of severe AR with annuloaortic ectasia and severe hypertension during delivery of her first child. An emergency cesarean section was performed, and she was later diagnosed by angiography as

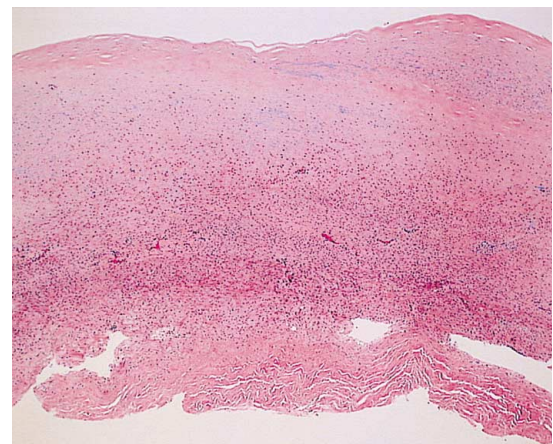


Fig 2. Surgical specimen of the ascending aorta (H&E, x8).



Fig 3. Surgical specimen of the aortic valve (H&E, x8).

having Takayasu's disease. The left ventricle was enlarged (LVDd 71 mm, LVDs 53 mm), and the ejection fraction was decreased (47%) at onset. An erythrocyte sedimentation rate of 47 mm/h and a C-reactive protein concentration of 2.6 mg/dl (normal range, <0.3) suggested active inflam-

mation. She was HLA-BW52-negative. Multiple pulmonary infarctions, bilateral subclavian artery stenoses, bilateral common carotid artery stenoses and ascending aortic dilatation were observed on angiography. She was treated with prednisolone (0.5 mg/kg per day) and the inflammation was well controlled. Aortic-valve replacement, using a mechanical valve (St Jude Medical (SJM) 25 mm), was performed under medication of prednisolone 0.25 mg/kg per day. The ascending aorta was thickened macroscopically and a specimen stained with hematoxylin-eosin showed marked thickening of all layers (Fig 2). Slight lymphoid cell infiltration around the capillaries in the adventitia was observed, but no other evidence of active inflammation, such as giant cell and epithelioid cell infiltration. Marked myxoid degeneration was observed in the aortic specimen and the aortic valve (Fig 3), which could have been caused by the AR as there were no other signs of inflammation in the aortic valve. She had a good postoperative clinical course and is now on steroid therapy with outpatient visits.

### Discussion

Takayasu's disease is not uncommonly complicated by AR and it is now recognized as a major factor contributing to mortality!<sup>1-3</sup> Aortic-valve replacement surgery is considered as the only curative treatment, but frequent remote cardiovascular complications, including detachment of the prosthetic valve, infective endocarditis, pseudoaneurysmal formation and cerebrovascular disease, make clinicians hesitant to perform this therapy!<sup>4-6</sup>

In the 6 patients treated by aortic-valve replacement surgery, there was a reduction in the size of the left ventricle and improvement in the ejection fraction at follow-up, similar to previous reports of aortic valve replacement surgery in patients with AR of other etiologies!<sup>7,8</sup> None of the present cases had evidence of postoperative cerebral ischemia and preoperative hypertension resolved soon after surgery. Hypertension is related to the high prevalence of heart failure and high mortality in patients with Takayasu's disease and AR!<sup>9,10</sup> and the reduction in blood pressure and volume overload after surgery might result in improvement of the left ventricle dimensions and ejection fraction.

We found some minor inflammatory changes in the adventitia of the ascending aorta and myxoid change in the aortic valve and aorta, which could be secondary changes related to the severe AR. The mechanism of AR in patients with Takayasu's disease is generally thought to be a combination of dilatation of the aortic root at the aortic valve and thickening of the valve cusps!<sup>4,5</sup> and both were present in

this case. Absence of active inflammatory change in the aortic specimen and aortic valve leads us to speculate that the inflammatory status was controlled well by the preoperative immunosuppressive therapy and encourages us to perform early and aggressive surgical treatment of the AR with appropriate immunosuppressive therapy in patients with Takayasu's disease.

In contrast to the improvement in cardiac function, the incidence of postoperative remote cardiovascular events was high as 50% (3/6 cases). In one report of Japanese patients with AR of other etiologies, a SJM valve prosthesis resulted in a 12-year freedom from re-operation of 99.5%!<sup>1</sup> and another reported a 10-year freedom rate from re-operation for valve-related complications of an aortic SJM of 92.1%!<sup>2</sup> Because of the high frequency of remote cardiovascular events in Takayasu's arteritis, careful observation, including postoperative steroid treatment, is vital.

### References

1. Koide K. Takayasu arteritis in Japan. *Heart Vessels Suppl* 1992; **7**: 48-54.
2. Deyu Z, Guozhang L. Clinical study of aortic regurgitation in patients with aortoarteritis. *Int J Cardiol* 2000; **75**(Suppl 1): S141-S145.
3. Morii S. Follow-up study of Takayasu arteritis with aortic regurgitation. *J Cardiol* 1995; **26**: 293-298 (in Japanese with English abstract).
4. Aoyagi S, Fukunaga S, Tayama E, Hayashida N, Akashi H, Kawara T. Aortic valve replacement for aortic regurgitation caused by aortitis. *Jpn Circ J* 1999; **63**: 885-888.
5. Ando M, Kosakai Y, Okita Y, Nakano K, Kitamura S. Surgical treatment for aortic regurgitation caused by Takayasu's arteritis. *J Card Surg* 1998; **13**: 202-207.
6. Isomura T, Hisatomi K, Yanagi I, Shimada S, Uruguchi K, Aoyagi S, et al. The surgical treatment of aortic regurgitation secondary to aortitis. *Ann Thorac Surg* 1988; **45**: 181-185.
7. Bonow RO, Dodd JT, Maron BJ, O'Gara PT, White GG, McIntosh CL, et al. Long-term serial changes in left ventricular function and reversal of ventricular dilatation after valve replacement for chronic aortic regurgitation. *Circulation* 1988; **78**: 1108-1120.
8. Roman MJ, Klein L, Devereux RB, Kligfield P, Niles NW, Hochreiter C, et al. Reversal of left ventricular dilatation, hypertrophy, and dysfunction by valve replacement in aortic regurgitation. *Am Heart J* 1989; **118**: 553-563.
9. Subramanian R, Joy J, Balakrishnan KG. Natural history of aortoarteritis (Takayasu's disease). *Circulation* 1989; **80**: 429-437.
10. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease: Clinical and statistical analyses of related prognostic factors. *Circulation* 1994; **90**: 1855-1860.
11. Nakano K, Koyanagi H, Hashimoto A, Kitamura M, Endo M, Nagashima M, et al. Twelve years' experience with the St Jude Medical valve prosthesis. *Ann Thorac Surg* 1994; **57**: 697-702; discussion 702-703.
12. Kratz JM, Crawford FA Jr, Sade RM, Crumbley AJ, Stroud MR. St Jude prosthesis for aortic and mitral valve replacement: A ten-year experience. *Ann Thorac Surg* 1993; **56**: 462-468.