Surgical Treatment of Aortic Regurgitation due to Takayasu Arteritis
Long-Term Morbidity and Mortality

Kaoru Matsuura, MD; Hitoshi Ogino, MD; Junjiro Kobayashi, MD; Hatsue Ishibashi-Ueda, MD; Hitoshi Matsuda, MD; Kenji Minatoya, MD; Hiroaki Sasaki, MD; Ko Bando, MD; Kazuo Niwaya, MD; Osumi Tagusari, MD; Hiroyuki Nakajima, MD; Toshikatsu Yagihara, MD; Soichiro Kitamura, MD

**Background**—The goal of this retrospective study was to determine the late outcome of surgical treatment for aortic valve regurgitation due to Takayasu arteritis and correlate it with evidence of inflammation on pathological examination.

**Methods and Results**—Ninety consecutive patients who underwent surgery for aortic valve regurgitation due to Takayasu arteritis between 1979 and 2003 were studied. Intraoperative pathological specimens of the aortic wall from 69 patients were retrospectively examined for inflammation. Aortic valve replacement was performed in 63 patients (group A) and composite graft repair in 27 patients (group B). The aortic root diameter was 39.9 ± 9.5 mm in group A and 54.4 ± 13.6 mm in group B (P < 0.0001). Preoperative steroid therapy was performed in 40 patients (44.4%). Hospital mortality was 4.8% (3/63) in group A and 7.4% (2/27) in group B. The overall 15-year survival rate was 76.1%. Detachment of the valve or graft occurred in 11.1% (7/63) of group A and in 3.7% (1/27) of group B patients (P = 0.43). Late dilatation (>50 mm) of the residual ascending aorta occurred in 11.1% (7/63) of group A and in 3.7% (1/27) of group B patients (P = 0.43). Active inflammation was confirmed in intraoperative pathological specimens of 10 patients, and detachment of the valve or graft occurred in 4 of these patients. Univariate analysis of background variables revealed active inflammation to be a risk factor for detachment (P = 0.0001; risk ratio 55).

**Conclusions**—Late dilatation of the ascending aorta after aortic valve replacement is a clinically important finding. Active inflammation could be related to valve or graft detachment. (Circulation. 2005;112:3707-3712.)

**Key Words:** aorta ■ complications ■ inflammation ■ surgery ■ valves

Takayasu arteritis is known as “pulseless disease,” the typical ophthalmological symptoms of which were first described by Takayasu. Although its most common lesions are in the proximal segments of arteries arising from the transverse aortic arch, the incidence of aortic valve regurgitation (AR) in patients with Takayasu arteritis is between 13% and 25%, and AR is now considered an important risk factor for mortality in patients with this disease. Furthermore, the most serious complication of aortic valve replacement (AVR) or aortic root replacement is detachment of the prosthetic valve or graft. When patients with AR and aortic root dilatation are encountered, they must be treated carefully both surgically and medically. In a previous study we reviewed the midterm results of surgical treatment for AR caused by Takayasu arteritis. In the present study intraoperative pathological specimens of resected aortic wall were retrospectively examined for inflammation. We report the late outcome of surgical treatment for AR due to Takayasu arteritis, correlate it with evidence of inflammation on pathological examination, and consider the optimal treatment for this condition.

**Methods**

The study population consisted of 90 consecutive patients who underwent surgery for AR due to Takayasu arteritis between 1979 and 2003 in our institution. Patients with Behcet disease and those who had undergone repeated surgery, allograft root replacement, or valve-sparing surgery, which was performed in 4 patients in the same period, were excluded. Institutional approval of the study was obtained, and each patient in the study gave informed consent to serve as a subject. AVR was performed in 63 patients (group A), and composite graft repair (CGR) was performed in 27 patients (group B). Preoperative and perioperative variables are shown in Table 1. Baseline demographic and clinical data were available for all of the patients. Initial data including preoperative and early postoperative variables were collected from the hospital records, and follow-up data including those related to late aortic or cardiac events were collected by contacting physicians performing close follow-up of the patients. Diagnosis was confirmed by angiography, pathological examination, or both, basically with the use of the criteria identified by the American College of Rheumatology. Age at operation was...
inferior vena cavae. Mild hypothermic cardiopulmonary bypass was enabled replacement of the entire ascending aorta, were performed and hemiarch replacement in 1 patient. Both procedures, which concomitantly included coronary artery bypass grafting in 10 patients, mitral valve replacement in 3, and cervical arterial bypass, performed simultaneously in 7 patients. We modified CGR to annular position in 2 patients. Wrapping of the ascending aorta was performed simultaneously in 7 patients. We modified CGR to prevent graft detachment; in preparing the composite graft, the artificial valve was suture-attached to the vascular prosthesis 1 cm from the edge. Implantation of the composite graft was performed by suturing of the vascular prosthesis alone with the use of a versatile technique. We used a polytetrafluoroethylene (Teflon) felt strip to reinforce the adventitial side. Finally, we also added reinforcement by continuous suturing between the adventitia and the outer side of the composite graft. This operative technique is shown schematically in Figure 2.

Coronary ostial repair was performed in 8 patients for coronary ostial stenosis due to thickening of the media and intima, by excising the thickened intima with a beaver knife circumferentially and fixing the frayed intima with anchoring sutures. Other surgeries performed concomitantly included coronary artery bypass grafting in 10 patients, mitral valve replacement in 3, and cervical arterial bypass, which was indicated because of the presence of symptoms, in 4 patients. Total aortic arch replacement was performed in 6 patients and hemiarch replacement in 1 patient. Both procedures, which enabled replacement of the entire ascending aorta, were performed under deep hypothermic circulatory arrest.

Pathological Study

Intraoperative pathological specimens of the resected aortic wall were retrospectively examined for inflammation by 1 pathologist, who was masked to the clinical follow-up of these patients. The blocks for histological study were taken intraoperatively and fixed in 4% formaldehyde, sectioned at 7 μm thickness, and stained with

### Table 1. Preoperative and Perioperative Variables

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=90)</th>
<th>AVR (n=63)</th>
<th>CGR (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>49.3±11.5</td>
<td>50.4±10.7</td>
<td>46.8±13.0</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>22 (24.4)</td>
<td>15 (23.8)</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Emergency surgery, n (%)</td>
<td>5 (5.6)</td>
<td>4 (6.3)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>18 (20.0)</td>
<td>15 (23.8)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Craniocervical vascular disease, n (%)</td>
<td>5 (5.6)</td>
<td>2 (3.2)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>2 (2.2)</td>
<td>2 (3.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>41 (45.6)</td>
<td>29 (46.0)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (6.7)</td>
<td>5 (7.9)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>8 (8.9)</td>
<td>7 (11.1)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Preoperative steroid, n (%)</td>
<td>40 (44.4)</td>
<td>28 (44.4)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Clinical evidence of inflammation, n (%)</td>
<td>4 (4.4)</td>
<td>2 (3.2)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Aortic root diameter, mm</td>
<td>44.3±12.7</td>
<td>39.9±9.5</td>
<td>54.4±13.6</td>
</tr>
<tr>
<td>Time of operation, mean±SD, min</td>
<td>356±151</td>
<td>342±125</td>
<td>403±210</td>
</tr>
<tr>
<td>CPB time, mean±SD, min</td>
<td>161±73</td>
<td>137±48</td>
<td>221±89</td>
</tr>
<tr>
<td>Aortic cross-clamp time, mean±SD, min</td>
<td>113±51</td>
<td>93±37</td>
<td>161±47</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>10 (11.1)</td>
<td>7 (11.1)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Cervical bypass grafting, n (%)</td>
<td>4 (4.4)</td>
<td>1 (1.6)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Coronary ostial repair, n (%)</td>
<td>8 (8.9)</td>
<td>7 (11.1)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Surgery after 1991, % (n/N)</td>
<td>38.9 (35/90)</td>
<td>27.0 (17/63)</td>
<td>66.7 (18/27)</td>
</tr>
</tbody>
</table>

CPB indicates cardiopulmonary bypass; CABG, coronary artery bypass grafting. Smoking indicates current smoking. Coronary artery disease and cervical vascular disease are defined as 1 or more lesions with >75% stenosis. Hypertension, diabetes mellitus, and hyperlipidemia are defined as treated medicinally.

Operation

The operation was performed through a median sternotomy. An aortic cannula was inserted into the ascending aorta or femoral artery. Two venous cannulas were inserted in the superior and inferior vena cavae. Mild hypothermic cardiopulmonary bypass was established, and the aorta was cross-clamped if possible or occluded by a balloon catheter if aortic cross-clamping was not possible because of severe calcification. Cardiac arrest was induced with blood cardioplegia infusion. Isolated AVR was performed with evertting mattress pledgeted sutures on the para-annular position in 60 patients, with mattress pledgeted sutures on the supra-annular position in 8 patients, and with interrupted sutures on the supra-annular position in 2 patients. Wrapping of the ascending aorta was performed simultaneously in 7 patients. We modified CGR to prevent graft detachment; in preparing the composite graft, the artificial valve was suture-attached to the vascular prostheses 1 cm from the edge. Implantation of the composite graft was performed by suturing of the vascular prosthesis alone with the use of a versatile technique. We used a polytetrafluoroethylene (Teflon) felt strip to reinforce the adventitial side. Finally, we also added reinforcement by continuous suturing between the adventitia and the outer side of the composite graft. This operative technique is shown schematically in Figure 2.

Pathological Study

Intraoperative pathological specimens of the resected aortic wall were retrospectively examined for inflammation by 1 pathologist, who was masked to the clinical follow-up of these patients. The blocks for histological study were taken intraoperatively and fixed in 4% formaldehyde, sectioned at 7 μm thickness, and stained with

![Figure 1. Distribution of aortic root diameter.](image)
hematoxylin-eosin, Masson trichrome, and elastica van Gieson. Active inflammation in these specimens was confirmed in 10 patients, scar stage with ongoing inflammation in 35 patients, and scar stage with no inflammation in 24 patients. The characteristic findings for each pathological category are shown in Figure 3. The distribution of these pathological conditions did not differ between the 2 operative methods.

Preoperative and Postoperative Steroid Therapy
Patients positive for C-reactive protein (CRP) (value >1.0) or whose erythrocyte sedimentation rate (ESR) rose >20 mm/h were placed on steroid therapy until these values returned to normal. For patients diagnosed with active-stage inflammation on intraoperative pathological specimens, we administered steroid therapy postoperatively until CRP or ESR values returned to normal. Nevertheless, 4 patients had serological evidence of clinical inflammation at the time of operation. The dose and duration of preoperative steroid administration were 14.5±13.7 mg (median, 10 mg; range, 2.5 to 60 mg) and 4.4±7.0 years (median, 1.25 years; range, 0.1 to 32 years), respectively.

Statistical Analysis
All data sets were reviewed retrospectively. All values are expressed as mean±SD. Differences between the groups were examined by univariate analysis ($\chi^2$ test, 2-tailed $t$ test, Fisher exact test, or Mann-Whitney $U$ test as appropriate). Values of $P<0.05$ were considered significant. The Kaplan-Meier technique was used to determine survival curves. All analyses were performed with the use of SAS Statistical Software (version 8.02, SAS Institute Inc).

Results
The percentage of surgeries performed after 1991 was 27.0% (17/63) in group A and 66.7% (18/27) in group B ($P=0.0008$). Years of operation are indicated in Figure 4. Cardiopulmonary bypass time was longer in group B (221±89 minutes) than in group A (137±48 minutes), as was aortic cross-clamp time (group B, 161±47 minutes; group A, 93±37 minutes).

Outcomes are shown in Table 2. Hospital death occurred for 3 patients (4.8%) in group A and 2 patients (7.4%) in group B. The remaining 85 patients were followed from 3 months to 24 years (mean, 9.0±6.83 years). The completeness of follow-up data collection was 94.4%. As shown by the survival curve in Figure 5, overall survival rate was 87.8% at 5 years, 78.6% at 10 years, and 76.1% at 15 years. The pathological finding for all 4 patients with serological evidence of clinical inflammation at the time of operation was scar with ongoing inflammation.
were 87.8%, 78.6%, and 76.1%, respectively.

Figure 5. Survival curves. Survival rates at 5, 10, and 15 years were 87.8%, 78.6%, and 76.1%, respectively.

Detachment of the prosthetic valve occurred in 7 patients of group A, and detachment of the proximal site of anastomosis of the prosthetic graft occurred in 1 patient of group B. A bioprosthetic valve had been used in 2 patients with valvular detachment. Evertting mattress sutures on the supra-annular position had been used in 6 patients, and mattress sutures on the para-annular position had been used in 1 patient with valvular detachment. Of these patients, only 1 had undergone first surgery after 1991 (P=0.39). Aortic specimens were studied in 6 patients who suffered detachment of valve or graft. Four of these 6 patients (67%) exhibited active inflammation (P=0.0002). The remaining 2 patients exhibited scar stage without inflammation in pathological specimens. On univariate analysis of background variables, active inflammation was found to be a risk factor for detachment of valve or graft (P=0.0001; risk ratio 55). Of the patients who had undergone preoperative steroid administration, 2 (5%) suffered valve or graft detachment.

Late dilatation of the residual ascending aorta occurred in 7 patients of group A and 1 patient of group B. All of these patients had undergone surgery before 1991. Three of them died of rupture of aortic aneurysm, and 1 underwent aortic root replacement for dilatation of the root after AVR. Aortic specimens were studied for 7 patients who suffered late dilatation of the residual aorta, and none exhibited active inflammation. Three of the 7 patients whose aortic specimens were studied (43%) exhibited scar with ongoing inflammation, the remaining 4 patients exhibited scar stage without inflammation.

Neurological complications including cerebral infarction, cerebral hemorrhage, and spinal infarction occurred in a total of 12 patients. Early postoperative complications included cerebral infarction on the fourth postoperative day in 1 patient and spinal infarction in another patient on the 17th postoperative day. Other neurological complications occurred late in the follow-up period.

Other complications included 1 superficial wound infection, 1 episode of bleeding due to gastric ulcer, and 1 formation of pseudoaneurysm at the site of cannulation of the femoral artery. These 3 patients all underwent steroid administration both preoperatively and postoperatively.

Three of 4 patients who underwent valve-sparing aortic root replacement required AVR for recurrent AR at a mean time of 35 months after operation. Two of these patients had scar with ongoing inflammation in aortic specimens, but none had evidence of inflammation in the aortic valve leaflets.

TABLE 2. Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=90)</th>
<th>AVR (n=63)</th>
<th>CGR (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital death, n (%)</td>
<td>5 (5.6)</td>
<td>3 (4.8)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Late death, n (%)</td>
<td>16 (17.8)</td>
<td>12 (19.0)</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Detachment of valve or graft, n (%)</td>
<td>8 (8.9)</td>
<td>7 (11.1)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Late dilatation of residual aorta, n (%)</td>
<td>8 (8.9)</td>
<td>7 (11.1)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Neurological complication, n (%)</td>
<td>12 (13.3)</td>
<td>9 (14.3)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Early (within 30 days after operation), n (%)</td>
<td>2 (2.2)</td>
<td>1 (1.6)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Late (&gt;30 days after operation), n (%)</td>
<td>10 (11.1)</td>
<td>8 (12.7)</td>
<td>2 (7.4)</td>
</tr>
</tbody>
</table>

Discussion

Takayasu arteritis is a chronic inflammatory arteriopathy of unknown etiology that predominantly affects young women. It was first described by Takayasu, a Japanese ophthalmologist. Although this disease was initially thought to be rare and confined to Asia, subsequent clinical reports have shown that it occurs worldwide and is more common than it was initially thought to be. It causes segmental dilatation or stenosis of the aorta and its major branches and requires surgical intervention. Diagnosis of it is based on the presence of symptoms and signs of ischemic, inflammatory large-vessel disease and supportive radiographic findings. The American College of Rheumatology has identified 6 major criteria for the diagnosis of this arterial disorder: onset at age ≤40 years, claudication of an extremity, decreased brachial artery pulse, >10 mm Hg difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. The presence of ≥3 of these 6 criteria yielded a sensitivity of 90.5% and a specificity of 97.8%. Cardiac lesions such as AR and coronary artery lesions are also often associated with Takayasu arteritis. AR in Takayasu arteritis was first described by Jervell in 1954. It is thought that AR develops primarily as a result of annular dilatation resulting from severe dilatation of the ascending aorta and that the secondary AR jet induces morphological change of the aortic valve leaflets such as fibrous thickening and enrolling and thereby worsens the AR itself. AR sometimes requires surgical treatment, whether or not an arterial lesion is present. Talwar et al reported that myocardial involvement other than valvular or coronary pathology is uncommon, especially in children. Although in our series no patients had been diagnosed with myocarditis, the possibility of chronic heart failure due to myocardial lesions must also be considered in patients with Takayasu disease.

Pathological specimens of arterial lesions in Takayasu arteritis exhibit a panarteritis characterized by severe thickening of the adventitia, media, and intima. Nasu provided a detailed review of the pathology of this arteritis. The
main pathological finding is severe destruction of the medial elastic fibers that maintain the strength of the aortic wall. In the early and active inflammatory phases, granulomatous inflammation is present, with various cellular infiltrations in the adventitia and the outer part of the media, along with marked inflammation of the vasa vasorum. Subsequently, in the scar stage, severe intimal thickening occurs in the areas that overlie granulomatous and fibrotic lesions in the media and adventitia. This severe fibrous thickening of the arterial wall makes the diseased aorta stenotic or occluded and also causes coronary ostial stenosis. Even at this stage, some patients have residual inflammatory changes including lymphocyte infiltration, as we have described.

Recently, surgical outcomes have improved dramatically because of the development of not only surgical equipment and technologies but also preoperative evaluation and postoperative management.6,22 However, surgical treatment of this disorder is difficult because of the need to manipulate fragile and inflamed tissue. Valve detachment after AVR or anastomotic aneurysm after CGR may still occur as a result of fragility of the aortic wall or annular tissue caused by Takayasu arteritis.4–6,12,22 Miyata et al12 reported that the incidence of anastomotic aneurysm in Takayasu arteritis is 8.5%. In their study the occurrence of anastomotic aneurysm was found not to be related to the presence of inflammation, preoperative use of steroids, or pathological stage. In the present study we found that the presence of active inflammation may be a predictor of pseudoaneurysm. For patients whose aortic wall is suspected to have active inflammation, aggressive postoperative control of inflammation is necessary to prevent this complication.5,12 As previous reports from our institution have noted, we believe that preoperative steroid administration to improve inflammation and its postoperative use to control inflammation may be important.5 In the present series, 40 patients who had steroid administration preoperatively, 2 patients suffered anastomotic complications in late follow-up. There was no difference in incidence of anastomotic complications between patients who did and those who did not undergo preoperative use of steroid therapy. In the present study the pathological finding for all patients who had serological evidence of clinical inflammation (CRP positive or ESR >20 mm/h) at the time of operation was scar with ongoing inflammation. These serological findings are useful for controlling not only systemic but also local inflammation. We administered steroid when CRP was positive or ESR rose >20 mm/h and continued it until these values returned to normal.

The present study was not designed to be a comparative study of 2 methods of surgery. Aortic root diameter and year of surgery each differed significantly between the 2 groups, indicating that these groups differed in patient population. When we encountered AR with Takayasu arteritis, we chose the method of surgery on the basis of the presence or absence of other underlying disorders, including dilatation of the ascending aorta. Indeed, we prefer CGR for patients with AR and dilatation of the aortic root. Furthermore, to prevent surgical detachment of a valve or graft, we have made use of various technical improvements, including placement of a thick, belt-like Teflon felt strip on the lateral side of the aortic wall for reinforcement, translocated implantation of artificial valve to the composite graft, and reinforcement by continuous suturing between the adventitia and outer side of the composite graft. The purpose of Teflon felt reinforcement is not only to reinforce the suture line but also to reduce the tension on the suture line and aortic annulus.

The present study yielded other important findings with regard to late aortic events. This study was unable to confirm a higher incidence of late aortic events in AVR patients than in CGR patients because the difference between these groups in such events was not statistically significant and our patient population was small. In addition, the follow-up period for AVR patients was longer than for CGR patients, and AVR patients were older than CGR patients at the time of surgery. However, it is clearly important to monitor postoperative patients closely to prevent life-threatening events related to the residual aorta with the use of either surgical technique.

Neurological symptoms or deficits are not always present, even in patients who have craniocervical vascular lesions due to the development of collateral circulation.14 Our strategy for preoperative craniocervical vascular lesions due to Takayasu arteritis is to consider cervical bypass indicated only for patients who are symptomatic. Moreover, both early and late postoperative cerebral complications can be serious in patients with Takayasu disease. The present study confirmed a high incidence of postoperative cerebrovascular complications after surgical treatment for this disease. Close postoperative follow-up for this complication is also mandatory.

It is doubtful that the patients in our series could have been managed with valve-sparing aortic root replacement. We performed this procedure in 4 patients, 3 of whom (75%) subsequently required AVR for recurrent AR in the follow-up period. The pathological specimens of aortic valve leaflets resected at the time of reoperation exhibited no evidence of inflammation but did exhibit severe secondary change due to AR, including curling and thickening of the free margins of the valve leaflets. We believe that valve-sparing aortic root replacement is not contraindicated, although it is challenging, for this type of disease.

Limitations of the present study are that we examined only a small number of patients and that it was retrospective. In addition, operations were performed by many surgeons, and pathological specimens could not be collected from all patients.

Conclusion
The late outcome of surgical treatment of AR due to Takayasu arteritis has thus far been favorable. Active inflammation may be a risk factor for anastomotic aneurysm. Although we found the outcome of patients with AVR to be comparable to that of patients with CGR, late dilatation of the residual ascending aorta is the major concern in long-term follow-up.

Disclosure
None.

References


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