Failure to Prevent Progressive Dilation of Ascending Aorta by Aortic Valve Replacement in Patients With Bicuspid Aortic Valve: Comparison With Tricuspid Aortic Valve

Hisayo Yasuda, MD; Satoshi Nakatani, MD, PhD; Marie Stugaard, MD, PhD; Yuko Tsujita-Kuroda, MD, PhD; Ko Bando, MD, PhD; Junjiro Kobayashi, MD, PhD; Masakazu Yamagishi, MD, PhD; Masafumi Kitakaze, MD, PhD; Soichiro Kitamura, MD, PhD; Kunio Miyatake, MD, PhD

Background—Patients with bicuspid aortic valve (BAV) have been frequently complicated with ascending aortic dilation possibly because of hemodynamic burdens by aortic stenosis (AS) or regurgitation (AR) or congenital fragility of the aortic wall.

Methods and Results—To clarify if the aortic dilation could be prevented by aortic valve replacement (AVR) in BAV patients, we studied 13 BAV (8 AR dominant, 5 AS dominant) and 14 tricuspid aortic valve (TAV) patients (7 AR, 7 AS) by echocardiography before and after AVR (9.7 ± 4.8 years). We also studied 18 BAV (11 AR, 7 AS) without AVR. Diameters of the sinuses of Valsalva, sinotubular junction and the proximal aorta were measured. The annual dilation rate was calculated by dividing changes of diameters during the follow-up period by the body surface area and the observation interval. We found that aortic dilation in BAV patients tended to be faster than that in TAV patients, although a significant difference was found only at the proximal aorta (0.18 ± 0.08 versus −0.08 ± 0.08 mm/(m²/year), P = 0.03). BAV patients with and without AVR showed similar progressive dilation. AR dominant group showed tendency of more progressive dilation than AS dominant group in BAV, although it did not reach statistical significance. TAV patients did not show further aortic dilation after AVR.

Conclusions—AVR could not prevent progressive aortic dilation in BAV. Since the aorta did not dilate in TAV, progressive aortic dilation in BAV seems mainly due to the fragility of the aortic wall rather than hemodynamic factors. (Circulation. 2003;108[suppl II]:II-291-II-294.)

Key Words: aortic valve ■ heart valve prosthesis ■ aneurysms

Bicuspid aortic valve (BAV) is one of the most common congenital heart malformations found in adults. Although BAV is frequently associated with ascending aortic dilation, the cause of the association has not been fully elucidated. There are 2 hypotheses for this significant association. One is aortic dilation because of hemodynamic burdens caused by aortic stenosis (AS) or aortic regurgitation (AR) that associated with BAV. Forceful ejection jet by AS (poststenotic dilation) or increased stroke volume by AR may dilate the aorta. The other is congenital aortic fragility. In 1972, Mckusick reported the coexistence of BAV and Erdheim's cystic medial necrosis. He suggested that the association was not coincidental and those were the expression of a developmental defect of the arterial tree. The significant association was confirmed by other authors and the concept of an underlying congenital defect of patients with BAV have been given. Further, recent investigations have suggested that BAV is associated with accelerated degeneration of the aortic media. The fact that BAV is sometimes associated with other aortic abnormalities including aortic coarctation, Marfan's syndrome and even aortic dissection may support this hypothesis.

Patients with BAV sometimes require aortic surgery for their dilated aorta such as aortic replacement or wrapping concomitant with aortic valve replacement (AVR). However, there is still controversy regarding when and how to treat the dilated aorta with BAV and it is not known whether the dilation of aorta continues after AVR. If aortic dilation is due to the hemodynamic burdens, AVR may prevent the further dilation of the aorta. On the other hand, if the dilation is because of the congenital aortic fragility, it may continue despite AVR. To clarify if the aortic dilation could be prevented by AVR, we studied patients with BAV by echocardiography before and after AVR comparing those with tricuspid aortic valves.
Methods

Patients
We retrospectively assessed 13 BAV patients with AVR (BAV-OP), 18 BAV patients without AVR (BAV-NOP), and 14 tricuspid aortic valve (TAV) patients with AVR (TAV-OP) who were referred to our echocardiography laboratory from May 1983 to February 2002. The average age of the patients were 50±14, 52±13, and 44±11 years old for BAV-OP, TAV-OP, and BAV-NOP groups, respectively (Table 1). No members of the patient’s family in this study had congenital heart anomalies. The valve morphology of the patients with AVR was confirmed by the pathological examination at operation and that of patients without AVR was confirmed by reviewing echocardiography videotapes by a single reviewer (H.Y.).

We divided the patients based on echocardiographic findings into AR dominant group who had grade 3 or 4 AR and AS dominant group who had transaortic pressure gradient of 75 mm Hg or more just before AVR or at the latest examination in patients without AVR. Then, 8 patients were AR dominant and 5 patients were AS dominant in the 13 BAV-OP patients, and 7 were AR dominant and 7 were AS dominant in the 14 TAV-OP patients. In the 18 BAV-NOP patients, 11 were AR dominant, and 7 were AS dominant. We excluded patients with suboptimal echocardiographic images, a short follow-up period (less than 2 years), Marfan’s syndrome, Bentall’s operation, ventricular or atrial septal defect, infective endocarditis, dilated ascending aorta (larger than 44 mm), prosthetic valve dysfunction, or decreased left ventricular function (% fractional shortening lower than 30%).

Surgery
All AVR patients had mechanical valves. The types included St. Jude Medical valve (SJM) in 5, Omnicarbon (OC) in 2, Björk-Shiley (BS) in 2, ATS in 2, CarboMedicus (CM) in 2 in BAV-OP patients. Concomitant mitral valve plasty was performed in 3 BAV-OP patients. In TAV-OP patients, there are 8 SJM, 3 OC, 1 BS, 1 ATS, 1 CM, and 3 had concomitant mitral valve replacement, 2 had tricuspid valve annuloplasty and 1 had tricuspid valve replacement and coronary artery bypass grafting.

Echocardiographic Measurements
The patients who underwent AVR had serial transthoracic echocardiography before and after AVR (9.7±4.8 years) (Table 1). The BAV-OP patients were assessed at the baseline and after a long follow-up period (8.0±4.0 years). Echocardiographic data were obtained with the use of commercially available ultrasound systems and standard techniques. Besides the standard echocardiographic measurements, we measured diameters of the sinuses of Valsalva, the sinotubular junction, and the proximal ascending aorta 1 cm above the sinotubular junction at the early systole.* Measurements were done from videotapes. An average of at least 3 beats was reported for each diameter. The annual dilation rate was calculated as the change of diameters divided by the body surface area and the follow-up period. We measured blood pressure and heart rate at the echocardiography examination.

Statistical Analysis
Analysis was performed with the use of StatView version 5.0 (SAS Institute Inc, Cary, NC). Data were presented as absolute numbers and percentages or as mean value ± standard error for annual dilation rates and mean value±SD for the other parameters. Comparisons of categorical data among 3 groups were performed using the chi-square test. Statistical differences between groups were evaluated by the unpaired t-test. Univariate and multivariate analyses were performed to identify the hemodynamic and echocardiographic parameters that correlated with the annual dilation rate in each group. Age, systolic, and diastolic blood pressures, and left ventricular systolic and diastolic diameters, fractional shortening and wall thickness were entered as possible variables for these analyses. A probability value less than 0.05 was considered statistically significant.

Results
Annual Dilation Rate
Table 1 shows the characteristics of the patients. There were no differences in age, blood pressure and the follow-up period among BAV-OP, BAV-NOP, and TAV-OP groups. Figure 1 shows the annual dilation rate in each group. We found that aortic dilation in BAV patients tended to be faster than that in TAV patients, although a significant difference was found only at the ascending aorta (0.18±0.08 versus -0.08±0.08 mm/(m²/years); P=0.03). BAV-OP and BAV-NOP patients showed the similar rates of aortic dilation (0.03±0.06 versus 0.02±0.13 mm/(m²/years)) at the sinuses of Valsalva, 0.10±0.06 versus 0.08±0.06 mm/(m²/years) at the sinotubular junction, 0.18±0.08 versus 0.09±0.09 mm/(m²/years) at the proximal ascending aorta, all, P=ns). That is, the BAV patients showed progressive dilation of the aorta even after operation. In contrast, the TAV patients did not show...
significant dilation at any levels of the aorta, suggesting the preventing effect of AVR on aortic dilation.

**Effect of AR or AS on Dilation**

Next, we compared the dilation rate between the AR dominant group and the AS dominant group (Figure 2). In the BAV-OP patients, the AR dominant group tended to show more progressive dilation than the AS dominant group, except the diameter of the sinuses of Valsalva. In the BAV-NOP patients, the AR dominant group showed progressive dilation especially at the level of the proximal aorta, whereas the AS dominant group did not show dilation at any level. The TAV-OP patients did not show such progression.

**Predictors of Aortic Dilation**

We investigated risk factors of rapid dilation using a linear regression model. In the BAV-OP patients, we found no significant relationship between the dilation rate at any level and echocardiographic parameters. In the BAV-NOP patients, diastolic blood pressure at the follow-up period showed a weak correlation with the dilation rate of the sinuses of Valsalva \((P<0.05)\). In the TAV-OP patients, diastolic blood pressure at the follow-up period, and the baseline fractional shortening showed positive correlations with the dilation rate of the proximal ascending aorta \((P<0.05)\).

The significant correlates from univariate analysis were included in a multivariate linear regression model to predict aortic dilation. Then, in the BAV-OP patients and the BAV-NOP patients, no factors were significantly associated with the dilation rate. On the other hand, in the TAV-OP patients, diastolic blood pressure at the follow-up (DBP) and the baseline fractional shortening (FS) showed a significant association with the dilation rate of the proximal ascending aorta \((y = -1.45 + 0.30 \times \text{DBP} + 0.55 \times \text{FS}, \ r = 0.74, \ P<0.05)\). Thus, the aortic dilation rate in TAV patients, although it was small, seemed to be mostly influenced by hemodynamic factors, such as blood pressure or fractional shortening, whereas in BAV patients, the cause of dilation was not explained by hemodynamic factors only.

**Discussion**

**Hemodynamic Factors**

Previous studies have compared aortic diameters in BAV patients and TAV patients without AVR or assessed diameters only in BAV patients. Pachulski et al measured the aortic diameter at the sinuses of Valsalva level in 101 patients with a normally functioning or minimally stenotic BAV.\(^5\) They found that aortic diameters in BAV patients were significantly greater than those obtained in the age and sex matched control group.\(^5\) Nistri et al reported the aortic root was significantly larger in young men with a normally functioning BAV than in normal controls.\(^6\) Hahn et al showed a high prevalence of aortic root enlargement in BAV patients irrespective of altered hemodynamics or age.\(^12\)

In the present study, we found the BAV patients, especially AR dominant patients, showed progressive ascending aortic dilation after AVR even though their aortas were not dilated before operation. Because the dilation rate of the aorta in BAV-OP patients was similar to that of BAV-NOP patients, we concluded the aortic mechanical valve replacement cannot prevent aortic dilation in BAV patients. On the other hand, the aortic diameters did not dilate significantly in TAV-OP patients.

**The Pathological Features of BAV**

In this study, we demonstrated the different aortic dilation rates between BAV and TAV patients. Such a difference may be based on the histological features of BAV. Bonderman et al have advocated that premature medial smooth muscle cells apoptosis could be a part of a genetic program underlying aortic disease in patients with aortic valve malformation.\(^11\) They observed massive focal apoptosis of smooth muscle cells in the medial layers of the aorta not only in BAV and TAV patients with the dilated aorta but also in BAV patients without aortic dilation. Fedak et al suggested that matrix metalloproteinases (MMPs) activity may be elevated in the aorta of BAV patients, degrading the structural support of the aorta and resulting in aortic dilation.\(^9\) Other investigations have indicated that focal abnormalities within the aortic media such as matrix disruption and smooth muscle cell loss are similar in BAV patients and in patients with Marfan syndrome who suffer from abnormal fibrillin-1 content\(^16\) and
that MMPs become activated in fibrillin-1 deficient tissues.13,14 These findings may be helpful to understand the pathophysiology of the aortic complications in patients with BAV. Recently, Keane et al showed the differences in aortic diameters between BAV and TAV patients using echocardiography.15 They reported the aortic diameters were larger in BAV patients than in TAV patients with comparable degrees of aortic valve disease, suggesting intrinsic pathology appeared to be responsible for aortic dilation beyond that predicted by hemodynamic factors in BAV.15

Clinical Implications
From the present results, we suggest the possibility of increasing diameter of the aorta even after AVR in patients with BAV. Thus, when the BAV patients with dilated aortic root are operated, attention should be paid to the aortic fragility. Some investigations have recommended the combined application of valve reconstruction and remodeling of the dilated aorta in surgery for BAV patients.21–23 In our series, we excluded patients with the dilated aorta at the operation and no patients showed aortic dissection or aortic aneurysms during the follow-up period.

Study Limitations
We examined only a small number of patients. This was partly because of our strict patient exclusion criteria. For instance, we had to exclude some patients who had suboptimal echocardiographic images on videotapes in this retrospective study. However, because of the strict criteria, we believe that we could demonstrate clinically meaningful data. It seems that extended follow-up of a larger number of patients will be desirable to establish the differences of the time course of aortic dilation after AVR. Further, the effect of histological changes in the aortic wall on the aortic dilation rate would be interesting.

We found the progressive dilation of the aorta in BAV patients even after AVR. This may lead to the concept of prophylactic operation for the aorta at AVR. However, in the present study, we did not aim to determine the definite value of aortic diameter which required such prophylactic operation.

Conclusions
The patients with bicuspid aortic valve showed progressive dilation of the proximal ascending aorta even after AVR. Thus, AVR could not prevent progressive aortic dilation in those patients. Since the aorta did not dilate in patients with tricuspid aortic valve undergoing AVR, aortic dilation in patients with bicuspid aortic valve seems mainly due to the fragility of the aortic wall rather than hemodynamic factors caused by aortic stenosis or aortic regurgitation.

References
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