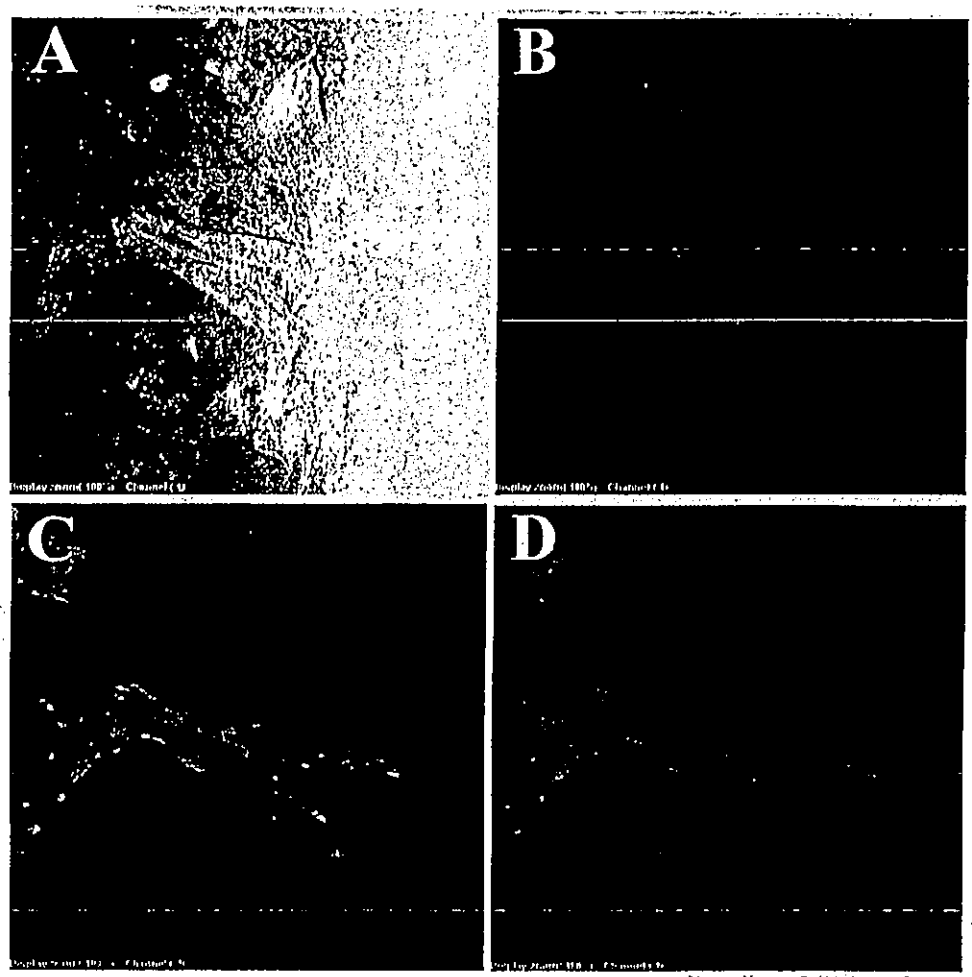


**Figure 5. Myogenic differentiation of GFP-BMCs. Cells were stained with a first antibody against MHC. A was photographed during the contrast phase. B and C were photographed during the fluorescent phase (B, green, excitation at 515-540 nm; C, red, excitation at 574-640 nm). D was the double-labeled cell superposition of B and C. Positive cells showed a cross-striated pattern. Combined green and red fluorescence represented myogenic cells derived from BMCs. (Original magnification 400×.)**

and the great vessels were discarded, hearts were minced into 1-$mm^3$ pieces with fine scissors, transferred to a sterile tube, and washed once in cold phosphate-buffered saline solution (PBS: NaCl, 136.9 mmol/L; KCl, 2.7 mmol/L; $Na_2HPO_4$, 8.1 mmol/L; and $KH_2PO_4$, 1.5 mmol/L [pH 7.3]) to remove any blood and clots. The minced tissue was digested in a PBS solution supplemented with 0.5% trypsin, 0.1% collagenase, and 0.02% glucose for 2 minutes at 37°C. The cell suspension was transferred into a tube containing 20 mL of complete medium and centrifuged at 1000 rpm for 5 minutes. The cell pellet was resuspended in complete medium and plated on 35-mm dishes (Falcon; Becton, Dickinson and Company, Franklin Lakes, NJ) at a density of $1.25 \times 10^4/cm^2$ and cultured at 37°C in 5% carbon dioxide and 95% air.

## Experimental Culture Systems

GFP-BMCs and cardiomyocytes were prepared as described above, and $1 \times 10^5$ cells/dish were plated as follows (Figure 1). In group 1 only GFP-BMCs were plated on 35-mm dishes (Falcon) as control specimens (n = 5). In group 2 cardiomyocytes were plated onto cell culture inserts (Falcon), which we applied to 35-mm dishes seeded with GFP-BMCs 2 days later (n = 5). In group 3, cardiomyocytes were plated on 35-mm dishes, followed by additional plating of GFP-BMCs 2 days later to make up a coculture (n = 5). They were incubated at 37°C in 5% carbon dioxide and 95% air until further processing. All the dishes were then evaluated for 1 week with a fluorescent microscope (Nikon TE300, Nihon Kogaku, Tokyo, Japan) equipped with a heated plate (37°C), a digital video camera, and a confocal microscope (Olympus Fluoview, Tokyo, Japan).

## Immunohistochemistry

The cultured cells were immunohistochemically stained. In brief, the cells were washed with PBS and fixed with 4% paraformaldehyde for 5 minutes at room temperature, whereas the dishes for staining against anticonnexin 43 were fixed for 10 minutes at 4°C. A mouse monoclonal antibody against myosin heavy chain

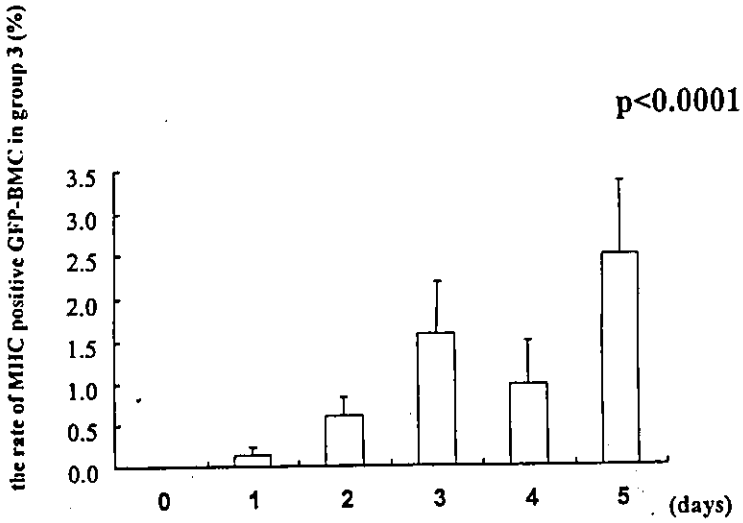


Figure 6. The percentage of MHC–positive BMCs from day 0 through day 5 in group 3. The *bar* represents mean and SE. MHC-positive GFP-BMCs appeared from day 1. There was a significant difference among days in group 3 ($P < .0001$). As the days passed, the expression of MHC-slow significantly increased to 2.5% on day 5.

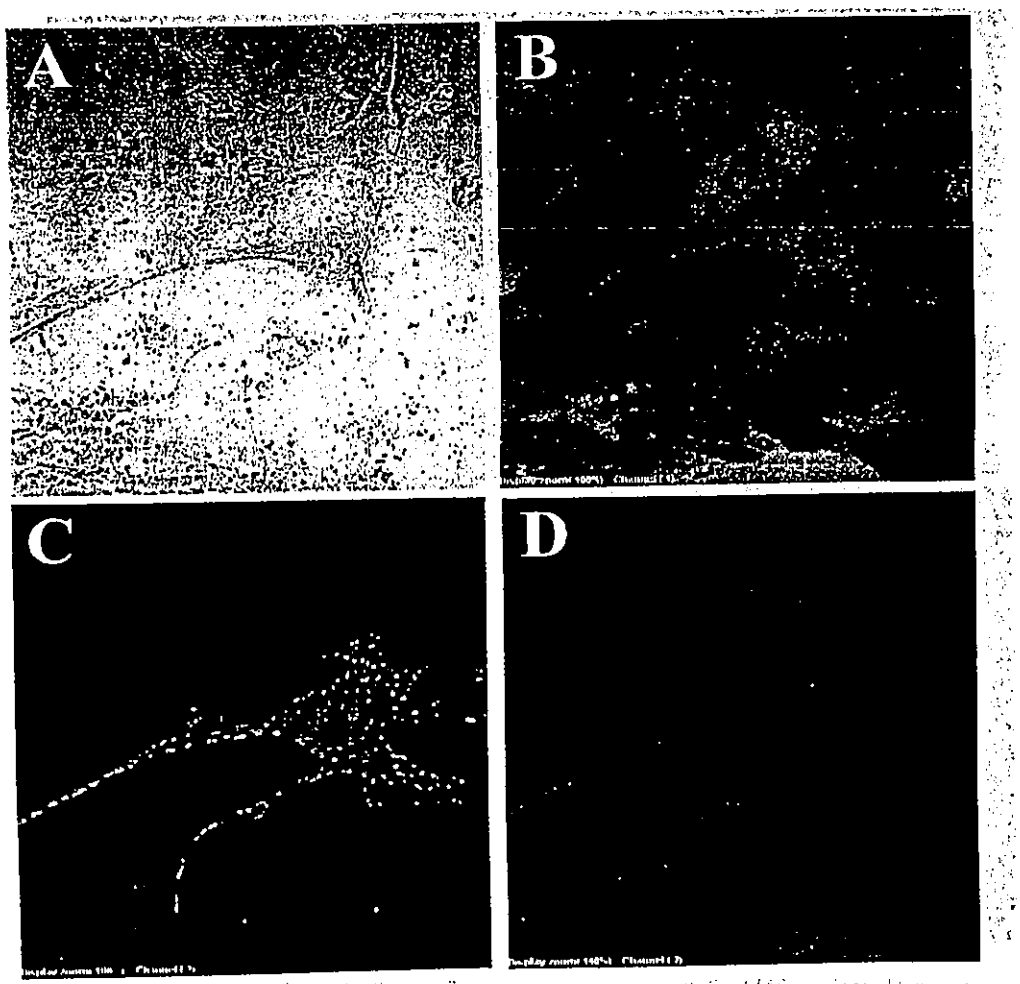


Figure 7. ANP-positive BMCs. Cells were stained with a first antibody against ANP. The phases (A-D) were the same microscopic conditions seen in Figure 5. (Original magnification 400×.)

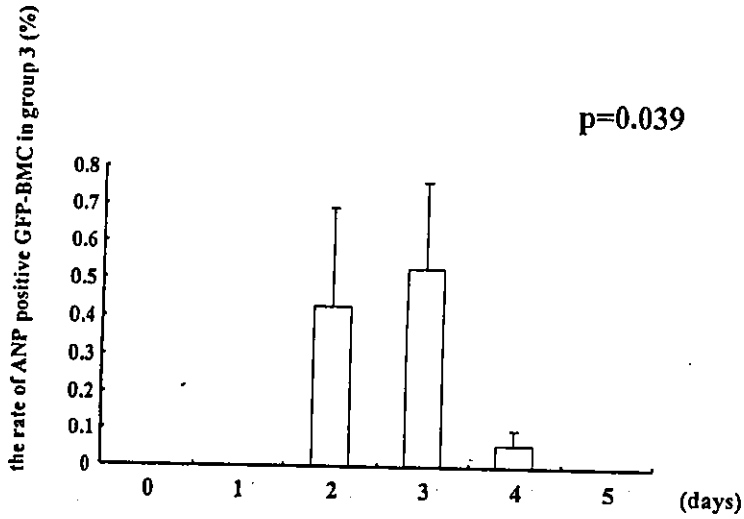


Figure 8. The percentage of ANP-positive BMCs in group 3. The *bar* represents mean and SE. Positive cells appeared on days 2, 3, and 4. Among days, the difference in the percentages were recognized as significant ($P = .039$).

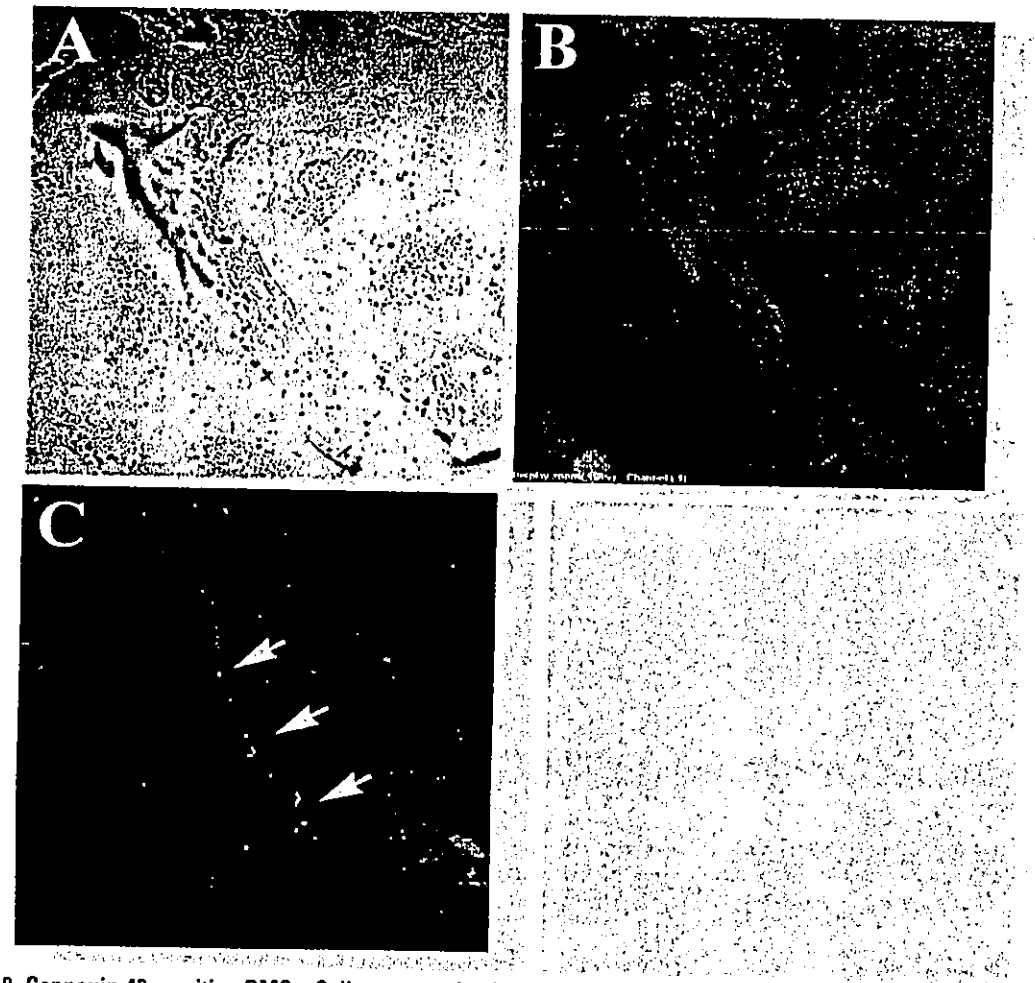


Figure 9. Connexin 43–positive BMCs. Cells were stained with a first antibody against connexin 43. Phases A and B were the same microscopic conditions as in Figure 5. Connexin 43 was detected at the margin of BMCs in phase C. (Original magnification 600×.)

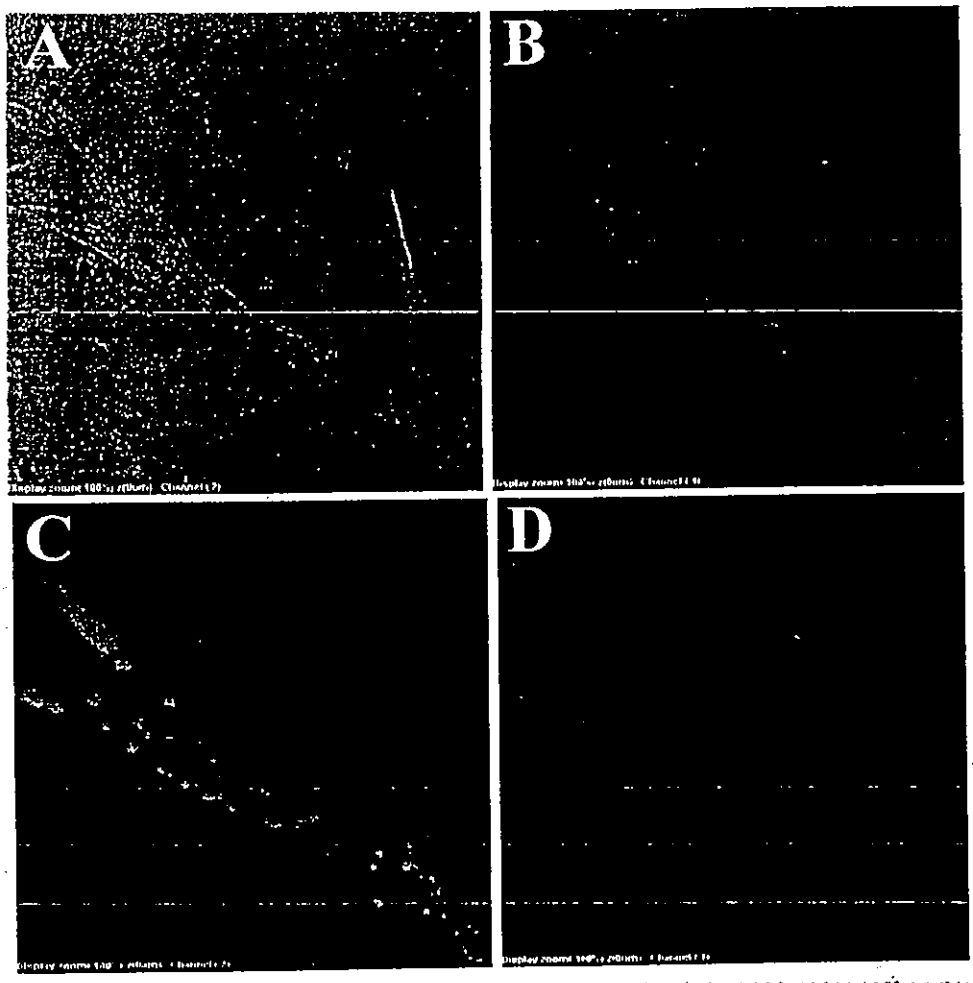


**Figure 10. TnI–positive BMCs. Cells were stained with a first antibody against TnI. The phases (A-D) were the same microscopic conditions as in Figure 5. Some BMCs stained positively and showed myofibrils lengthwise along the cell. The expression of TnI corresponded to green fluorescence derived from BMCs. (Original magnification 400×.)**

(MHC)-slow (Sigma, St Louis, Mo) diluted 1:1000 was used to evaluate the differentiation of striated muscle. A rabbit monoclonal antibody against atrial natriuretic peptide (ANP; Protos Biotech Corp, New York, NY) diluted 1:1000 was used to determine the cardiac-specific expression. Connexin 43 was detected by using a rabbit polyclonal antibody (Santa Cruz Biotechnology Inc, Santa Cruz, Calif) diluted 1:1000 and a mouse monoclonal antibody against cardiac-specific troponin I (TnI; Hytest, 4C2, Euro City, Finland) diluted 1:200 to detect mature cardiomyocytes. The dishes were incubated with the first antibodies at 4°C overnight. The culture dishes were washed with PBS 3 times to remove unbound antibodies. The primary antibodies anti-MHC-slow and anti-TnI were detected with a goat anti-mouse IgG antibody (Alexa Fluor 568, Molecular Probes, Wako, Osaka, Japan), and anti-ANP and anti-connexin 43 were detected with a goat anti-rabbit IgG antibody (Alexa fluor 568, Molecular Probes, Wako, Osaka, Japan). After incubation, the culture dishes were rinsed with PBS. The cells were then evaluated and photographed with a Fluoview FV300 confocal laser scanning microscope equipped with a z-stepping system (Olympus, Tokyo, Japan).

### Quantitative Analysis

The percentage of positively stained cells was determined by using a fluorescent microscope, and the structure of the differentiated GFP-BMCs was observed in detail by means of confocal microscopy. In briefly, the total cell number was counted in the bright field. GFP-BMCs were detected with a band beam splitter for simultaneous excitation at 515 to 540 nm and counted. Alexa dye, which conjugated the cells, was visualized with a band beam splitter for simultaneous excitation at 574 to 640 nm. The percentage of positively stained cells was calculated in 4 randomly selected fields of 5 culture dishes from the initial plating (day 0) through the seventh day (day 7).

### Statistical Analysis

Statistical analysis was performed with StatView 5.0 software (SAS Institute, Inc, Cary, NC). All values are expressed as means ± SE. Comparison of the growth rate between 2 distinct groups was analyzed by using the Mann-Whitney *U* test. Comparison of the data among days in each group was performed with the Kruskal-Wallis test.

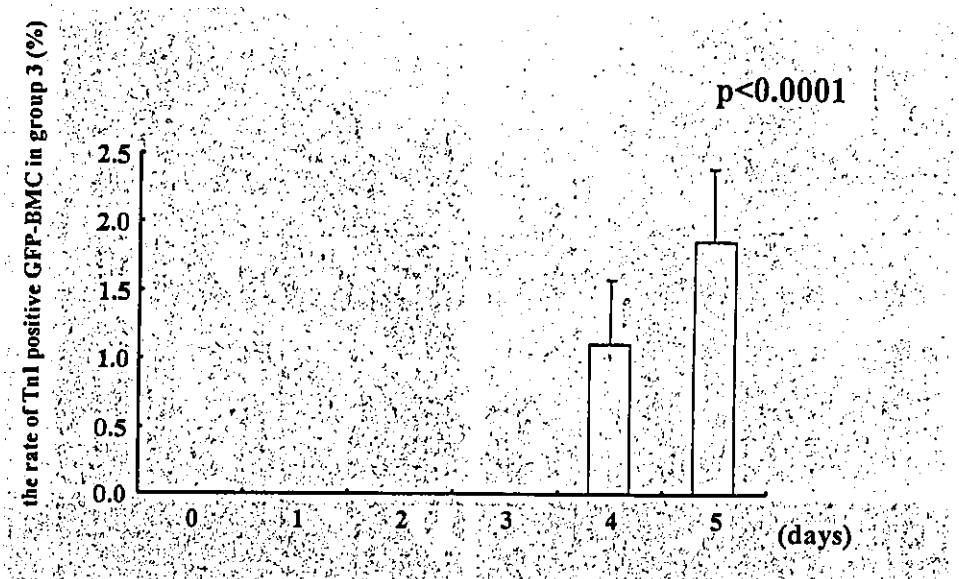


**Figure 11. The percentage of cardiac-specific TnI–positive BMCs in group 3. The *bar* represents mean and SE. Positive cells appeared on day 4 and increased to 1.9% on day 5. The differences of the positive BMCs were recognized to be significant among days ($P < .0001$).**

## Results

### Morphologic Changes of GFP-BMCs and Cardiomyocytes

Although GFP-BMCs were cultured and passaged, nonadherent cells were eliminated, and spindle-shaped cells formed colonies and proliferated rapidly. All of the GFP-BMCs but red blood cells expressed bright green fluorescence (Figure 2). Contracting cardiomyocytes were identified on day 1. Contracting frequency per minute of beating cardiomyocytes was 60 to 70. On day 2, a few neonatal cardiomyocytes connected each other, and the beating rate was 70 to 80 per minute. None of the cardiomyocytes was visible under the fluorescent condition (Figure 2). In group 1 the shapes of these cells varied (ie, spindle, oval, wedge, or sheet), and they did not show any contraction. In group 2 GFP-BMCs did not contract. The shape and proliferation of GFP-BMCs were not different from those in group 1. In group 3, however, on day 1, part of the spindle-shaped GFP-BMCs attached in parallel to the colony of contracting cardiomyocytes (12.5% ± 1.8%), whereas flattened GFP-BMCs covered the cardiomyocyte layer at random. On day 2, we found that GFP-BMCs attached to nonfluorescent contracting cells (cardiomyocytes) started to contract synhronously with cardiomyocytes (5.6% ± 2.3%, Figure 3). he beating rate was almost 60 to 80 per minute. On day 5, FP-BMCs began forming colonies and maintained synhronous contraction (15.6% ± 4.2%). As time passed, the ontracting cells communicated, and almost all the fields ontracted synchronously. The proliferation of the GFP-MCs between groups 1 and 3 was not different in this study (Figure 4). After day 6, the cultured cells were peeled off, and we could not evaluate them immunocytologically.

### Phenotypic Changes of GFP-BMCs

In groups 1 and 2 GFP-BMCs did not express any type of myogenic or gap junction proteins. In contrast, in group 3 GFP-BMCs started to express MHC at 0.14% ± 0.09% of the total GFP-BMCs on day 1. The MHC-positive BMCs increased day by day and were recognized at 2.49% ± 0.87% on day 5 (Figures 5 and 6). The double-labeled cells indicated that striated muscles originated from GFP-BMCs, and almost all of these cells had dinuclei. The ANP-positive BMCs were detected mainly on days 2 and 3 (0.78% ± 0.56%, Figures 7 and 8). As the days passed, the ANP-positive BMCs decreased on day 4 and disappeared on day 5. Connexin 43 was identified between GFP-BMCs and unlabeled cardiomyocytes from day 2 through day 5 (Figure 9). The cardiac-specific TnI-positive BMCs appeared at 1.11% ± 0.42% on day 4 and increased to 1.86% ± 0.53% on day 5 (Figures 10 and 11). The results are summarized in Table 1. Groups 1 and 2 did not show any myogenic differentiation of GFP-BMCs. In contrast, GFP-BMCs in group 3 expressed MHC first, followed by the expression of connexin 43 and ANP. Finally, GFP-BMCs expressed TnI. Some GFP-BMCs stained positive against myogenic proteins attached directly to cardiomyocytes and some attached to cardiomyocytes through nonmyogenic cells.

## Discussion

The evidence of cardiomyogenic differentiation of bone marrow cells in vivo suggests the existence of environmental factors.[2,4-6] However, these factors are not well known because they are in vivo phenomena, making investigation difficult. Possible factors might include cell-cell interaction,

**Table 1. The trend of time-dependent expression of proteins**

| | | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|
| Group 1 | | — | — | — | — | — | — |
| Group 2 | | — | — | — | — | — | — |
| Group 3 | MHC | — | + | + | + | + | + |
| | connexin43 | — | — | + | + | + | + |
| | ANP | — | — | + | + | + | — |
| | TnI | — | — | — | — | + | + |

MHC: Myosin heavy chain slow. ANP: Atrial natriuretic peptide. TnI: Troponin I. +: some cells expressed protein. —: negative.

electrical and mechanical stimulation, and unknown growth factors.

We hypothesized the cell-cell interaction was a cardiogenic inducer for stem cells and set up a coculture to simulate the in vivo phenomena by using GFP-BMCs and cardiomyocytes, which have 2 advantages. First, GFP-BMCs are visible because the cells are alive. Contraction is a typical characteristic of myogenic cells, which is only seen in living cells. We can see the interaction between GFP-positive cells and GFP-negative cells dynamically. Second, GFP-BMCs facilitated 100% labeling efficiency, which enabled us to differentiate GFP-BMCs from cardiomyocytes. In other words it was possible to perform quantitative analysis of GFP-BMCs without false-negative and false-positive contamination. The cultured GFP-BMCs maintained green fluorescence strongly for at least 8 weeks. GFP-BMCs proliferated as C57 mouse-derived BMCs.

This study also has a characteristic: the simulation of xenogeneic cell transplantation from mice to rats in vitro. Even if xenogeneic cell transplantation has several issues, it might provide commercial availability in the future if immunologic problems are solved.[7]

Reinecke and colleagues[13] reported that some skeletal myoblasts contracted synchronously with adjacent cardiomyocytes in vitro. However, skeletal myoblasts did not differentiate into cardiomyocytes. Makino and associates[14] and ourselves[2] reported that BMCs were induced into cardiomyogenic cells with chemicals. In contrast, in this study we did not use any chemicals and only cocultured with cardiomyocytes. We showed here that multinuclei GFP-BMCs differentiated into cardiomyogenic cells. GFP-BMCs started to contract synchronously with cardiomyocytes. Isoproterenol (25 nmol/L) increased the heart rate of the GFP-BMCs and the cardiomyocytes from 80 to 100 per minute (unpublished data). This mechanism could also happen in vivo.[4,7]

There are some possible reasons why groups 1 and 2 did not show the cardiac differentiation of GFP-BMCs. Although BMCs have the capacity for cardiac differentiation, they might need some triggers, such as 5-azacytidine.[2,14] Furthermore, unknown soluble inducers might not exist or might exist only at low concentrations. We regarded the direct attachment with cardiomyocytes as one of the important triggers for the cardiogenic differentiation of GFP-BMCs.

Our results indicated that GFP-BMCs cocultured with cardiomyocytes expressed myogenic protein as the first step, gap junction protein and ANP as the second step, and TnI as the final step. In contrast to increasing MHC and TnI values, ANP vanished on day 5. ANP is important for proliferation in embryonal cardiac development.[15] Cardiomyogenic (CMG) cells from bone marrow stroma also expressed ANP.[16] The myogenic cells might have lost ANP as a result of ventricular phenotypic change.

Although we observed the differentiation of GFP-BMCs, the percentage of differentiated cells was low. We considered the possible reasons. We did not purify specific cell types, such as CD34, in this study. Therefore, cultured cells were heterogeneously populated, and only a very small percentage of the BMCs were pluripotent stem cells, whereas most others were lineage-destined progenitor cells.

In this study we evaluated this coculture for only 1 week because the cultured cells were detached from the bottom of dishes as a result of overconfluency. Given the time-dependent increase of MHC- and TnI-positive cells, the percentage of cardiomyogenic cells from GFP-BMCs might increase if a longer culture is possible. We simulated BMC transplantation into the normal myocardium in this study. Stem cells are thought to be subtle in the normal tissue. On the other hand, injury, including ischemia, might trigger these cells to be active.

Cell fusion was suggested as an explanation for stem cell plasticity.[17,18] In contrast, another group[19] was against the fusion theory because single euploid multipotent adult progenitor cells differentiated into cells of 3 germ layers in vitro. They showed a high frequency of chimerism in comparison with the results of the previous study.[17] Some in vivo studies have reported a robust (30%-50%) level of transdifferentiation.[20] Although we cannot exclude the possibility of cell fusion, our conversion rate (2.5%) was much higher than the frequency of spontaneous fusion (2-11 clones out of $10^6$ BMCs; 0.0002%-0.0011%).[17] The mech-

anism of differentiation of stem cells should be investigated more deeply in future studies.

We used neonatal cardiomyocytes because we wanted to see contractions not seen in adult cardiomyocytes in vitro. The combination of adult cardiomyocytes and GFP-BMCs might be evaluated later.

The present study provides the first demonstration, to our knowledge, of the cardiomyogenic differentiation of BMCs without any chemicals in vitro. Using this coculture, we might be able to identify specific substances regulating cardiac development in the future.

We thank Ms K. Hattori for her help in breeding the GFP mice.

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## Discussion

**Dr Frank W. Sellke** *(Boston, Mass).* How do you know that it is due to direct cell-to-cell contact or interaction and that there is not some substance secreted that causes this effect?

**Dr Tomita.** Of course, from only the observation under the microscope, we do not know about that in detail. Some unknown soluble factors might go through gap junctions, and we speculated another mechanism of induction. We saw some TnI–positive cells derived from GFP-BMCs attached to GFP-negative cells, which were TnI negative. This observation suggested that some BMCs differentiated to cardiomyocytes by means of mechanical stretching. Therefore, there are several inducers in this system.

**Dr Henry M. Spotnitz** *(New York, NY).* What do you think the mediators are of this effect that are passing through the gap junctions?

**Dr Tomita.** Thus far I have no concrete evidence.

**Dr Spotnitz.** You are sure that these cells are being transformed and that they are not really myocytes?

**Dr Tomita.** Do you mean that the phenomenon is due to fusion?

**Dr Spotnitz.** Yes.

**Dr Tomita.** There were landmark articles regarding fusion between embryonic stem cells and BMCs published in the journal *Nature* in April. They include a warning that reported differentiation might be due to fusion.But in this study we just cultured cardiomyocytes and BMCs and not embryonic stem cells. Of course there are some possibilities, but embryonic stem cells are very energetic and immature. They are easy to communicate, and in the in vivo situation we put BMCs in the adult heart. They are not embryonic stem cells. Therefore, it is a different story.

**Dr Marcio Scorsin** *(Curitiba, Brazil).* I have some doubts concerning the fate of transplanted BMCs into a myocardial infarction scar. It is widely accepted that those cells might have a milieu-dependent differentiation (becoming cardiomyocytes) in normal myocardium. However, if you inject those cells into a myocardial scar, according to some studies, they would produce angiogenesis and differentiate into fibroblasts instead of cardiomyocytes. My question is whether you think that it is important to differentiate BMCs before transplantation.

**Dr Tomita.** For the in vivo study, it is not necessary to convert all BMCs into cardiomyocytes. For example, if you put BMCs into the scar, they might go in like myofibroblasts, but the myofibroblasts are also important to prevent extension of the scar. I saw some TnI–positive cells from transplanted BMCs in the scar tissue in the previous study. I agree to the hypothesis that fibroblasts are strong inducers for BMCs to transform to fibroblasts.

In terms of the strategy for the differentiation with BMCs, I do not know which is stronger for the differentiation, either the in vitro condition or the in vivo condition. However, when we think about the cell process for the clinical reality, it might be difficult to control preferable cell types in vitro under GMP regulation. Therefore, it might be more practical to manipulate cells in the in vivo environment.

**Dr Marc J. H. Hendrikx** *(Hasselt, Belgium).* If you did not use a coculture but just differentiated your BMCs by using 5-azacytidine, would you get the same expression of cardiac markers? Do you have any ideas about that?

**Dr Tomita.** We reported the BMC differentiation using 5-azacytidine in the journal *Circulation* in 1999, but in this study I just cultured in the cardiac environmental setting. Therefore, I did not use 5-azacytidine in this study. In the next step, we are considering using 5-azacytidine. It might increase the number of induced cardio-specific cells in the coculture system.

# Durability and Outcome of Aortic Valve Replacement With Mitral Valve Repair Versus Double Valve Replacement

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*Background.* The purpose of this study was to evaluate morbidity and mortality after double valve replacement (DVR) and aortic valve replacement with mitral valve repair (AVR + MVP).

*Methods.* From 1977 to 2000, 379 patients underwent DVR (n = 299) or AVR + MVP (n = 80). Actuarial survival and freedom from reoperation were determined by the Kaplan-Meier method. Potential predictors of mortality and reoperation were entered into a Cox multiple regression model. Propensity score was introduced for the multivariable regression modeling for adjustment of a selection bias.

*Results.* Survival 15 years after surgery was similar between the groups (DVR, 81% ± 3%; AVR + MVP, 79% ± 7%; $p = 0.44$). Freedom from thromboembolic event at 15 years was similar between the groups ($p = 0.25$). Freedom from mitral valve reoperation at 15 years was significantly better for the DVR group (54% ± 5%) as compared with the AVR + MVP group (15% ± 6%; $p = 0.0006$), primarily due to progression of mitral valve pathology and early structural deterioration of bioprosthetic aortic valve used for patients with AVR + MVP. After AVR + MVP, freedom from mitral reoperation at 15 years was 63% ± 16% for nonrheumatic heart diseases, and 5% ± 5% for rheumatic disease ($p = 0.04$).

*Conclusions.* Although both DVR and AVR + MVP provided excellent survival, DVR with mechanical valves should be the procedure of choice for the majority of patients because of lower incidence of valve failure and similar rate of thromboembolic complications compared with AVR + MVP. MVP should not be performed in patients with rheumatic disease because of higher incidence of late failure.

(Ann Thorac Surg 2003;75:28–34)


For patients with aortic and mitral valve disease, double valve replacement (DVR) has been advocated as a standard surgical option, which has been safely performed even in elderly populations in recent years. In these patients, a majority of aortic valve disease required valve replacement because the early and late results of aortic valve repair have not been satisfactory [1,2]. In contrast, valve repair has been advocated in mitral valve disease [3, 4]. However, the durability and outcome of combined aortic valve replacement and mitral valve repair versus double valve replacement remain to be determined. The purpose of this study was to evaluate survival and late outcome after DVR and aortic valve replacement and mitral valve repair (AVR + MVP) for double valve disease.

## Patients and Methods

From 1977 to 2000, 379 patients underwent AVR with either mitral valve replacement (MVR) (DVR group; n = 299) or MVP (n = 80). The cases of concomitant procedure with coronary artery bypass grafting or aortic surgery were excluded from the study. The preoperative clinical characteristics of each group are shown in Table 1. The DVR group was more common in patients with atrial fibrillation (Af) ($p < 0.0001$). The AVR + MVP group was more common in patients with pure mitral regurgitation (MR) ($p < 0.0001$). The age of patients having bioprosthetic valve was 52 ± 12 years old in the AVR + MVP group and 50 ± 9 years old in the DVR group. The proportion of New York Heart Association (NYHA) functional class III and IV was similar between the two groups. In the DVR group, follow-up ranged from 6 months to 20.1 years (8.6 ± 6.1 years), with a total of 2,561 patient-years. In the AVR + MVP group, follow-up ranged from 6 months to 21.7 years (9.4 ± 7.1 years), with a total of 752 patient-years.

### *Surgical Procedure*

The majority of patients with DVR had mechanical valve prostheses in both aortic (219/299 patients, 73%) and mitral (215/299, 72%) position. In contrast, a bioprosthetic valve was more frequently used in the AVR + MVP group (49/80, 61%) ($p < 0.0001$). In both groups, an Ionescu-Shiley valve (58/84 [69%] in the DVR group,

Presented at the Thirty-eighth Annual Meeting of The Society of Thoracic Surgeons, Fort Lauderdale, FL, Jan 28–30, 2002.

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Published by Elsevier Science Inc

0003-4975/03/$30.00
PII S0003-4975(02)04405-3

*Table 1. Patient Characteristics*

| | DVR | AVR + MVP | *p* |
|---|---|---|---|
| n | 299 | 80 | |
| Age (years; mean ± SD) | 54.1 ± 9.7 (27–75) | 53.0 ± 12.0 (29–78) | 0.32 |
| Female | 158 (53%) | 27 (34%) | 0.002 |
| NYHA class III + IV | 144 (48%) | 35 (44%) | 0.67 |
| AF | 228 (76%) | 39 (49%) | <0.0001 |
| Past history | | | |
| Rheumatic fever | 65 (22%) | 11 (14%) | 0.11 |
| CHF | 103 (34%) | 24 (30%) | 0.71 |
| TIA | 41 (14%) | 9 (1%) | 0.69 |
| MI | 5 (2) | 2 (0.3) | 0.64 |
| IE (medication) | 6 (2%) | 5 (6%) | 0.06 |
| Etiology | | | |
| Rheumatic | 182 (61%) | 43 (54%) | 0.31 |
| Degenerative | 17 (5%) | 20 (25%) | 0.001 |
| Endocarditis | 26 (9%) | 4 (5%) | 0.36 |
| Unknown | 74 (25%) | 13 (16%) | 0.15 |
| Mitral valve lesion | | | |
| Stenosis | 42 (14%) | 11 (13.7%) | 0.67 |
| Regurgitation | 39 (13%) | 44 (55%) | <0.0001 |
| Stenosis and regurgitation | 218 (73%) | 25 (31%) | <0.0001 |
| Follow-up periods (months) | 102.8 ± 73.3 (6–271) | 112.7 ± 84.8 (6–266) | 0.30 |
| Patient-years | 2,561 | 752 | |

AF = Atrial fibrillation; CHF = chronic heart failure; DVR = double valve replacement; NYHA = New York Heart Association; TIA = transient ischemic attack; MI = myocardial infarction; IE = infective endocarditis.

28/49 [57%] in the AVR + MVP group) was primarily used as a bioprosthetic valve between 1981 and 1984 for all generations. Since then, the Carpentier Edwards valve was commonly used for the patients more than 70 years of age, and most recently, the Mosaic valve was introduced in 1999. In patients who received mechanical valves, the St. Jude Medical valve (135/215 patients, 63%) was the most frequently used in both aortic and mitral positions. The Maze procedure was more common with the DVR group as compared with the AVR + MVP group because the rate of preoperative Af rhythm was more frequently associated with the DVR group as compared with the AVR + MVP group (DVR, 228/299 [76%] vs AVR + MVP, 39/80 [49%]; $p = 0.02$). Several different techniques were used for MVP, including commissurotomy (36 patients, 45%), Kay procedure (33 patients, 41.3%), ring annuloplasty (10 patients, 12.5%) use of Duran or Carpentier-Edwards ring and leaflet resection (5 patients, 6.3%), or a combination of these techniques.

### *Data Collection and Follow-Up*

We retrospectively reviewed the data from the operation notes, anesthesia records, clinical histories, laboratory investigations, and cardiac catheterization. This retrospective study was approved by the Internal Review Board of National Cardiovascular Center. Follow-up data were collected from National Cardiovascular Center records of outpatient visits and correspondence with referring physicians. All clinical characteristics were accumulated as a computerized database and analyzed in the Appendix. The definitions of morbidity and mortality were based on the published guidelines of Society of Thoracic Surgeons and American Association for Thoracic Surgery "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations" [5].

### *Statistical Methods*

Statistical analysis of the two groups were performed using the Pearson chi square test with Yates' correction or Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Unadjusted survival curves for the two groups were generated using the Kaplan-Meier method. The log-rank test was used for the comparison of the unadjusted survival curves. Cox's multivariate regression model with the propensity score method [6] was performed to assess the influence of surgical method on the probability of survival or reoperation. The incorporation of a propensity score balances the weight of covariates between the two groups on each patient level so that the comparisons of these two groups of patients were more significant. Hazards ratio and 95% confidence intervals (CI) were provided. All statistical analyses were performed using the software package SPSS 10.0 for Windows (SPSS Inc., Chicago, IL). Differences were considered statistically significant when $p$ was less than 0.05.

## Results

### *Early and Late Mortality*

Overall hospital mortality was 4.5% (17/379), which declined to 2.9% (2/69) during the last 5 years. The major

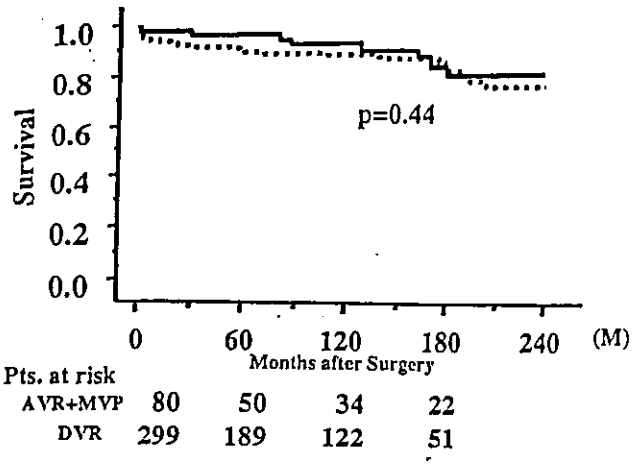


*Fig 1. Long-term actuarial survival for the subgroups of patients with AVR + MVP and DVR.* Solid line = *AVR + MVP;* dotted line = *DVR.* (AVR = *aortic valve replacement;* DVR = *double valve replacement;* MVP = *mitral valve repair;* Pts. = *patients.*)

causes of hospital death were postoperative low cardiac output (LOS) (5/17, 31%) or multiple organ failure (MOF) (6/17, 31%). Three deaths (0.8%) were related to the prosthetic valve failure. There were 36 late deaths, 27 in the DVR group and 9 in the AVR + MVP group ($p = 0.70$). Cardiac-related late deaths were observed in 5 patients in the DVR group, whereas only 1 patient died in the AVR + MVP group. Actuarial survival at 5, 10, and 15 years was 96% ± 2%, 92% ± 4%, and 79% ± 7% for the AVR + MVP group versus 89% ± 2%, 87% ± 2%, and 81% ± 3% for the DVR group, respectively ($p = 0.44$) (Fig 1).

Valve-related death occurred in 5 patients in the DVR group (5/299, 1.7%): valve thrombus (1), cerebral infarction (1), stuck valve (1), acute subdural hematoma (1), and prosthetic endocarditis (1). In contrast, there was only one valve-related death in the AVR + MVP group (1/80, 1.3%): anticoagulant-related cerebral hemorrhage. Actuarial freedom from valve-related death at 5, 10, and 15 years was 100%, 98% ± 2%, and 98% ± 2% in the AVR + MVP group versus 99% ± 1%, 99% ± 1%, and 97% ± 2% in the DVR group ($p = 0.73$).

### *Valve-Related Complications*

The actuarial estimates of freedom from overall valve-related complications at 15 years were 45% ± 5% and 18% ± 7% for the DVR group and the AVR + MVP group, respectively, with significance ($p = 0.02$) (Table 2). This was probably related to the fact that 61% of patients with AVR + MVP received bioprosthetic valves, whereas only 28% of the patients with DVR had bioprosthetic valves ($p < 0.0001$). Subsequently, structural valvular deterioration (SVD) of the bioprosthetic valve developed in 28 of 80 patients (35%) in the AVR + MVP group compared with 50 of 299 (17%) patients in the DVR group ($p = 0.0006$). Actuarial freedom from SVD at 15 years in the AVR + MVP group (26% ± 8%) was significantly lower than that of the DVR group (67% ± 4%) ($p = 0.002$). When stratified by the type of prosthesis, DVR as well as AVR + MVP using bioprosthetic valve resulted in lower freedom from SVD at 15 years (27.7% ± 5.8% and 18.5% ± 7.7%, respectively) compared with both groups using mechanical valves (both 100%) (Fig 2).

*Table 2. Freedom From Valve-Related Complications*

| Complication | Freedom at 15 Years (%) DVR | AVR + MVP | $p$ |
|---|---|---|---|
| Total number | 45.1 ± 5.0 | 17.8 ± 6.7 | 0.02 |
| Structural valve deterioration | 66.5 ± 4.3 | 26.2 ± 8.4 | 0.002 |
| Nonstructural dysfunction | 92.0 ± 2.5 | 92.9 ± 4.2 | 0.83 |
| Valvular thrombosis | 98.4 ± 1.2 | 100 | — |
| Thromboembolism (neurological) | 97.4 ± 1.2 | 94.7 ± 3.1 | 0.26 |
| Bleeding event | 97.5 ± 1.3 | 98.7 ± 1.3 | 0.94 |
| Prosthetic valve endocarditis | 92.8 ± 2.5 | 97.2 ± 2.7 | 0.17 |

AVR = aortic valve replacement; MVP = mitral valve repair; DVR = double valve replacement.

### *Anticoagulant-Related Complications*

The systemic anticoagulant therapy with warfarin sodium was initiated in all patients immediately after the extubation. The warfarin sodium was adjusted from 1.8 to 2.8 of INR for the MVR and from 1.5 to 2.5 for the AVR [7]. Three months later, warfarin sodium was discontinued in the patients having only bioprosthetic valve without atrial fibrillation. However, the patients who received a mechanical valve or remained in atrial fibrillation after valve surgery continued to take warfarin sodium. The Maze procedure has been done for 7 of 80 patients (9%) with AVR + MVP, and 60 of 299 patients (20%) with DVR since 1994. Return to sinus rhythm was obtained for 4 of 7 patients (57%) in the AVR + MVP group and 45 of 60 patients (75%) in the DVR group. Ultimately, sinus rhythm was maintained in the postoperative periods for 63% (50/80) of patients in the AVR + MVP group and 33% (98/299) of patients in the DVR group, respectively. Freedom from systemic anticoagulant therapy at 10 years was 58% for the AVR + MVP group and 23% for DVR group ($p = 0.0006$). All patients with atrial fibrillation

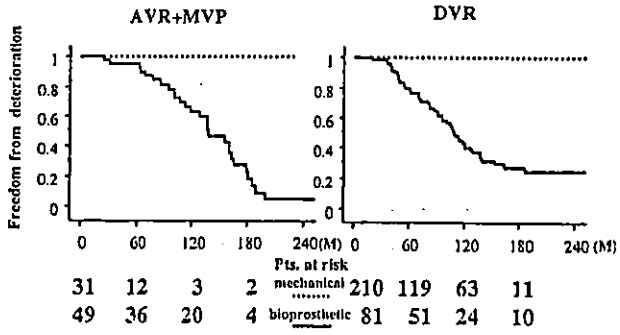


*Fig 2. Freedom from structural valve deterioration for the subgroups of patients with AVR + MVP and DVR stratified by the type of prosthesis.* (AVR = *aortic valve replacement;* DVR = *double valve replacement;* MVP = *mitral valve repair;* Pts. = *patients.*)

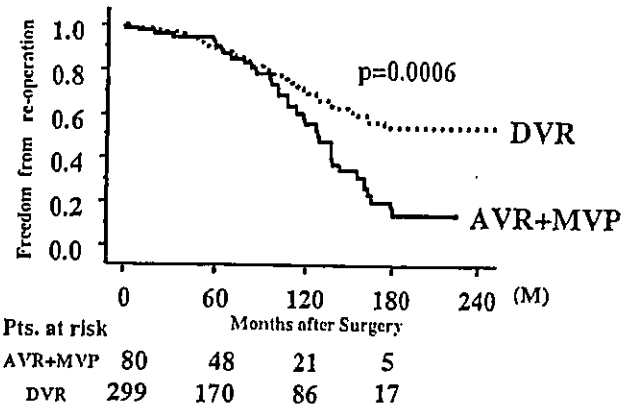


*Fig 3. Freedom from mitral reoperation for the subgroups of patients with AVR + MVP and DVR. (AVR = aortic valve replacement; DVR = double valve replacement; MVP = mitral valve repair; Pts. = patients.)*

after surgery continued to have warfarin sodium regardless of the type of valve received.

Postoperative thromboembolic complication was observed in 3 of 80 (3.8%) patients with the AVR + MVP group and 5 of 299 (1.7%) patients in the DVR group. All these thromboembolic events occurred in the cerebral lesion, but not in the other organs. Estimates of freedom from thromboembolism at 15 years was 95% ± 3% in the AVR + MVP group versus 97% ± 1% in the DVR group ($p = 0.26$).

There was only one bleeding event (1.3%) in patients with the AVR + MVP group, whereas four episodes (1.3%) occurred in the DVR group and one resulted in a fatality. Estimates of freedom from bleeding events at 15 years were 99% ± 1% in the AVR + MVP group and 98% ± 1% in the DVR group ($p = 0.94$).

### *Reoperations*

Reoperation was required in 39 of 80 patients (49%) in the AVR + MVP group, and 69 of 299 patients (23%) in the DVR group ($p < 0.0001$). All these patients underwent mitral valve reoperations with or without second AVR. In the AVR + MVP group, the major cause of reoperation was progression of mitral stenosis or regurgitation (39/39) with the structural deterioration of bioprosthetic valves in the aortic position (32/39), or associated with the pannus formation after AVR with mechanical valves (2/39). Thus, the remaining 5 patients had only MVR without aortic valve surgery. In this group, reoperation was required for 22 of 28 patients (78.6%) with an Ionescu-Shiley valve 15 years after surgery, whereas 4 of 10 patients with the Carpentier-Edwards valve required reoperation during the same time period. In the DVR group, the SVD of bioprosthetic valve in either aortic or mitral position (54/69, 78%) was a primary cause of reoperation. Freedom from mitral reoperation in the AVR + MVP group was significantly lower as compared with that of the DVR group ($p = 0.0006$)(Fig 3). Although the AVR + MVP group had a higher incidence of reoperation, the mortality in reoperation was similar between the two groups: 13% (5/39) in the AVR + MVP group versus 9% (6/69) in the DVR group ($p = 0.78$).

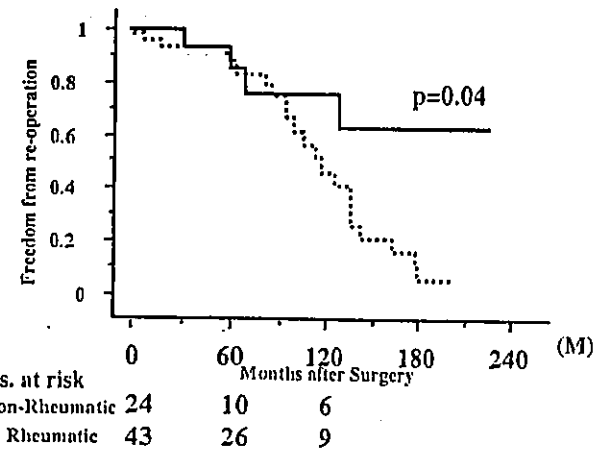


*Fig 4. Freedom from mitral reoperation after AVR + MVP stratified by the rheumatic etiology.* Solid line = *nonrheumatic;* dotted line = *rheumatic.* (AVR = *aortic valve replacement;* DVR = *double valve replacement;* MVP = *mitral valve repair;* Pts. = *patients.*)

*Table 3. Univariate Risk Factor Analysis for Early and Late Mortality*

| Variable | *p* Value | Hazard Ratio | Lower | Upper |
|---|---|---|---|---|
| Age (10-year increment) | 0.01 | 1.49 | 1.10 | 2.00 |
| Male | 0.79 | 1.08 | 0.63 | 1.84 |
| Atrial fibliration | 0.96 | 1.02 | 0.56 | 1.85 |
| Past history | | | | |
| MI | 0.06 | 3.06 | 0.95 | 9.82 |
| TIA | 0.48 | 0.72 | 0.29 | 1.81 |
| CHF | 0.72 | 1.11 | 0.63 | 1.94 |
| RF | 0.54 | 1.22 | 0.65 | 2.27 |
| NYHA class IV | <0.001 | 4.39 | 2.33 | 8.29 |
| Year of operation | 0.06 | 0.95 | 0.89 | 1.00 |
| Method (AVR + MVP or DVR) | 0.47 | 0.78 | 0.39 | 1.54 |
| Maze | 0.74 | 0.85 | 0.33 | 2.19 |
| CPB time | <0.001 | 1.35 | 1.20 | 1.43 |
| ACC time | 0.02 | 1.52 | 1.06 | 2.17 |

MI = myocardial infarction; TIA = transient ischemic attack; CHF = chronic heart failure; RF = rheumatic fever; AVR = aortic valve replacement; MVP = mitral valve repair; DVR = double valve replacement; CPB = cardiopulmonary bypass; ACC = aortic cross-cramp; NYHA = New York Heart Association.

### *Reoperation in the AVR + MVP Group Stratified by Etiology of the Valve Disease*

In the AVR + MVP group, when freedom from survival was stratified by the etiology of the valve disease, freedom from reoperation at 5, 10, and 15 years was 85% ± 10%, 76% ± 13%, and 63% ± 16% for nonrheumatic heart disease, and 89% ± 5%, 46% ± 11%, and 5% ± 5% for rheumatic heart disease, respectively ($p = 0.04$) (Fig 4).

### *Risk Factor Analysis for Survival*

By univariate analysis, significant predictors of poor survival included older age, past history of myocardial

*Table 4. Multivariate Risk Factor Analysis Using Propensity Score for Early and Late Death*

| Variable | p Value | Hazard Ratio | Lower | Upper |
|---|---|---|---|---|
| Method (AVR + MVP or DVR) | 0.945 | 0.98 | 0.47 | 2.01 |
| Propensity score | 0.71 | 1.58 | 0.15 | 16.98 |
| Age (10-year increment) | | 1.74 | 1.24 | 2.41 |
| Past history | | | | |
| MI | 0.04 | 3.56 | 1.07 | 11.88 |
| NYHA class IV | <0.001 | 4.84 | 2.50 | 9.38 |
| Year of operation | | 0.89 | 0.83 | 0.95 |
| CPB time | <0.001 | 1.43 | 1.27 | 1.61 |

AVR = aortic valve replacement; MVP = mitral valve repair; DVR = double valve replacement; MI = myocardial infarction; CPB = cardiopulmonary bypass; NYHA = New York Heart Association.

infarction, preoperative NYHA class IV, and longer cardiopulmonary bypass (CPB) time and aortic cross-clamp time (Table 3). By multivariate analysis using propensity score, significant predictors for early and late mortality included older age, past history of myocardial infarction, NYHA class IV, early year of operation, and longer CPB time (Table 4).

### *Risk Factor Analysis for Reoperation*

By univariate analysis, risk for reoperation included early year of operation, mitral repair as the first operation, omission of Maze procedure for the patients with Af, and the use of bioprosthetic valve (Table 5). By multivariate analysis using propensity score, early year of operation and the use of bioprosthetic valve were predictors for reoperation (Table 6).

*Table 5. Results of Univariate Risk Factor Analysis for Reoperation*

| Variable | p Value | Hazard Ratio | Lower | Upper |
|---|---|---|---|---|
| Age (10-year increment) | 0.21 | 0.88 | 0.71 | 1.07 |
| Male | 0.22 | 0.78 | 0.53 | 1.15 |
| Atrial fibllriation | 0.56 | 0.89 | 0.59 | 1.34 |
| Past history | | | | |
| MI | 0.32 | 1.66 | 0.61 | 4.51 |
| TIA | 0.84 | 0.94 | 0.53 | 1.69 |
| CHF | 0.19 | 1.30 | 0.88 | 1.91 |
| RF | 0.72 | 0.92 | 0.56 | 1.49 |
| NYHA class IV | 0.15 | 0.55 | 0.24 | 1.25 |
| Year of operation | <0.001 | 0.85 | 0.81 | 0.90 |
| Type of prosthesis (mechanical) | <0.001 | 0.11 | 0.06 | 0.19 |
| Maze | 0.05 | 0.13 | 0.02 | 0.96 |
| CPB time | 0.44 | 0.89 | 0.66 | 1.20 |
| ACC time | 0.65 | 0.94 | 0.62 | 1.35 |

MI = myocardial infarction; TIA = transient ischemic attack; CHF = chronic heart failure; RF = rheumatic fever; AVR = aortic valve replacement; MVP = mitral valve repair; DVR = double valve replacement; CPB = cardiopulmonary bypass; ACC = aortic cross-cramp; NYHA = New York Heart Association.

*Table 6. Variables in the Reoperation Model Using Propensity Score*

| Variable | p Value | Hazard Ratio | Lower | Upper |
|---|---|---|---|---|
| Method (AVR + MVP or DVR) | 0.06 | 1.50 | 0.98 | 2.29 |
| Propensity score | 0.82 | 0.83 | 0.17 | 4.07 |
| Type of prosthesis (mechanical) | <0.001 | 0.09 | 0.05 | 0.19 |
| Year of operation | <0.001 | 0.86 | 0.82 | 0.91 |

AVR = aortic valve replacement; MVP = mitral valve repair; DVR = double valve replacement.

## Comment

For surgery in patients with double valve disease, the choice of MVP versus MVR remains controversial. Our retrospective study of more than 22 years indicated both MVP and MVR combined with AVR provided excellent long-term survival (> 85% at 10 years after surgery in both groups). This was favorably compared with other reports [8–11], probably due to younger population (mean age, 54 years) and smaller number of patients in NYHA class III/IV (46%) in our study.

Freedom from thromboembolic event was similar between the DVR and the AVR + MVP group up to 15 years after surgery. Moreover, freedom from other morbidities, including major bleeding (98% ± 1% in the DVR group vs 99% ± 1% in the AVR + MVP group at 15 years) or prosthetic valve endocarditis (93% ± 3% in the DVR group vs 97% ± 3% in the AVR + MVP group at 15 years) was also similar between the groups. These results indicated that both DVR and AVR + MVP provided excellent survival and low morbidity up to 15 years after surgery

In sharp contrast, regarding reoperation, a significantly higher incidence was observed in the AVR + MVP group as compared with the DVR group. This was probably related to the fact that two-thirds of patients with AVR + MVP received bioprosthetic valves even in younger populations; of those, 57% had the first-generation Ionescu-Shiley valve [12]. Early structural deterioration of this valve was the primary cause of reoperation for the AVR + MVP group. On the other hand, double valve surgery using mechanical valve in both groups provided better results without structural deterioration, which resulted in no reoperation (Fig 2).

In the AVR + MVP group, the patients with rheumatic heart disease had higher risk for reoperation as compared with those with nonrheumatic heart disease. Because the majority of patients with rheumatic heart disease had some component of mitral stenosis, decision to perform the MVP versus MVR is difficult [13]. In this series, open mitral commissurotomy was commonly performed for the patients with mitral stenosis; most of these patients eventually required mitral valve replacement. Thus, our results indicated that double valve replacement might be a best option for patients with rheumatic heart disease [14].

For risk factor analysis of mortality and freedom from reoperation, we have used a multivariable model with the incorporation of propensity score. This will minimize

the biases in the observational study and have demonstrated that the choice of MVR or MVP does not significantly affect patient long-term survival up to 20 years (Table 5). Instead, history of myocardial infarction and preoperative NYHA class IV were the strong predictors for early and late death after surgery for double valve disease.

Moreover, multivariable risk analysis using propensity score revealed that only bioprosthesis and early year of operation were the significant predictors for reoperation. There was certainly a logistic concern that year of operation was a risk simply because cases in recent years did not have enough follow-up time. However, if we analyze the data in patients before 1995, year of operation was still the strong predictor for reoperation (data not shown). Advanced myocardial protection and improved operative technique as well as well understanding of pathophysiology of the valves may contribute to these improvements.

The major limitation of our study is that it was not randomized, and there were significant differences between the baseline characteristics of patients in the DVR group and the AVR + MVP group. The decision for MVP versus MVR reflected the surgeons' experience. To minimize the effect of these biases, propensity score was incorporated into the multivariate analysis. Another limitation includes inability to assess precise valve function by echocardiography because late follow-up echocardiography was available in only 60% of the patients, and this was not incorporated in the current study. Instead, assessment of durability of valves was based on either survival or free from reoperation. Further prospective study is certainly warranted to elucidate the precise difference of durability of valves in the two cohorts.

In conclusion, although both DVR and AVR + MVP resulted in good survival, DVR with mechanical valves should be the procedure of choice for the majority of patients, because of higher freedom from valve failure and similar rate of thromboembolic complications as compared with AVR + MVP. MVP should not be performed in patients with rheumatic disease because of the high incidence of late failures.

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## Appendix

*Variables Studied in Multivariable Analysis of Risk Factors for Survival and Reoperation**

*Demography*
Age (years) at operation, gender

*Cardiac Comorbidity*
NYHA functional class, history of myocardial infarction, transient ischemic attack, chronic heart failure, rheumatic fever, preoperative atrial fibrillation

*Operative Procedures and Time*
Year of operation, surgical method of AVR with MVP, or double valve replacement, concomitant Maze procedure, cardiopulmonary bypass time, and aortic cross-clamp time.

*All variables are dichotomous (yes/no), unless indicated to be continuous or ordinal.

## DISCUSSION

DR LISHAN AKLOG (Boston, MA): That was an excellent presentation. I just had a question; maybe I missed it, but I did not see where you specified what the severity of mitral regurgitation was in these patients preoperatively and, more specifically, what the functional classification was. And related to that, what was the technique of mitral repair? Did everybody just receive an annuloplasty alone or were there other concomitant techniques that were used in the mitral repair patients?

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2003;75:28–34

DR HAMAMOTO: Preoperatively echocardiography was performed and severity of mitral valve dysfunction was almost the same between the AVR plus MVP group and double valve replacement group. In the case of aortic valve replacement, it was mechanical valve plus mitral valve repair group; the severity of mitral valve dysfunction was a little bit milder than the aortic valve replacement with bioprosthetic mitral valve repair.

DR AKLOG: How severe was it? Did these patients have moderate MR, was it mild MR, and what was the severity, on average, even if it was the same between the two groups?

DR HAMAMOTO: In the AVR + MVP group, the severity of mitral valve dysfunction was moderate to severe. Similar results were found with the DVR group; especially in the AVR with mechanical valve plus mitral valve plasty group, they had mild to moderate regurgitation.

DR AKLOG: What was the technique of repair? Was it annuloplasty alone?

DR HAMAMOTO: The technique of mitral valve repair is commissurotomy in 40%, Kay procedure was in about 40%, and annuloplasty about 20%, and these techniques were combined, two or three techniques were combined.

DR AKLOG: Were you able to correlate the durability with the specific technique? You said only 20% got an annuloplasty ring. Was there a correlation between the technique of repair? The ones that failed, were they less likely to have had an annuloplasty ring?

DR BANDO: Dr Aklog, let me answer the question for you. I am a co-author of this paper. The patients with rheumatic heart disease and significant mitral stenosis were the majority of patients. That is why we used commissurotomy in the patients. But for the majority of the patients with pure mitral regurgitation, we do use the ring as well as the posterior leaflet repair.

DR BELHAM AKPINAR (Istanbul, Turkey): As far as I understood, you stopped giving anticoagulation after some time in both groups, more commonly in the group that you had repair of the mitral valve. Is that true, you do not give any anticoagulation after some time? You stop giving anticoagulation?

DR HAMAMOTO: In both groups just after the operation anticoagulation was started by warfarin, but after 3 months the bioprosthetic valve replacement plus mitral valve plasty group had no anticoagulation, no antiplatelet drugs.

DR JONATHAN HAMMOND (Hartford, CT): In the mitral valve repair group that was reoperated upon, maybe you said this in your presentation, but I did not catch it, which valve or valves were being redone?

DR HAMAMOTO: Aortic valve replacement with the mitral valve repair group had a higher incidence of reoperation.

DR HAMMOND: In other words, the mitral repair was durable. It was the aortic valve that had to be redone?

DR HAMAMOTO: In almost all cases the repair of the mitral valve is replacement with bioprosthetic mitral valve repair.

# 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/(m$^2$/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.[1,2] 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.[3] 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.[2,4–8] Further, recent investigations have suggested that BAV is associated with accelerated degeneration of the aortic media.[9,10] 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.[11–14]

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[7,15–18] 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.

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This study was supported in part by the Research Grant for Cardiovascular Diseases from Ministry of Health, Labor and Welfare of Japan. This study was presented at the 75th Annual Scientific Sessions of the American Heart Association, Chicago, IL, November, 2002.



*Circulation* is available at http://www.circulationaha.org DOI: 10.1161/01.cir.0000087449.03964.fb

**Characteristics of Patients**

| | BAV-OP | BAV-NOP | TAV-OP | P |
|---|---|---|---|---|
| Age, years | 50±14 | 44±11 | 52±13 | ns |
| Follow-up period, years | 8.7±5.1 | 8.0±4.4 | 10.6±4.4 | ns |
| Sex, % men | 7/13 (54%) | 16/18 (89%) | 7/14 (50%) | <0.05* |
| AR dominant | 8/13 (62%) | 11/18 (61%) | 7/14 (50%) | ns |
| AS dominant | 5/13 (39%) | 7/18 (39%) | 7/14 (50%) | ns |
| FS, % | 35.6±6.3 | 37.9±8.0 | 32.6±6.8 | ns |
| SBP (baseline), mm Hg | 125±20 | 137±24 | 132±16 | ns |
| DBP (baseline), mm Hg | 71±10 | 74±14 | 72±16 | ns |
| SBP (follow-up), mm Hg | 135±14 | 129±16 | 132±11 | ns |
| DBP (follow-up), mm Hg | 81±10 | 73±11 | 75±10 | ns |
| BSA, $m^2$ | 1.57±0.21 | 1.74±0.11 | 1.53±0.18 | <0.01* |

AR, aortic regurgitation; AS, aortic stenosis; FS, left ventricular fractional shortening; SBP, systolic blood pressure; DBP, diastolic blood pressure; BSA, body surface area; BAV-OP, patients with bicuspid aortic valve; BAV-NOP, patients without bicuspid aortic valve; TAV-NOP, patients with tricuspid aortic valve.

*BAV-OP versus TAV-OP and BAV-OP versus BAV-NOP.

# 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[19] 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-NOP 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.[8,9,13,15,20] 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/($m^2$/year); $P$=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/($m^2$/year) at the sinuses of Valsalva, 0.10±0.06 versus 0.08±0.06 mm/($m^2$/year) at the sinotubular junction, 0.18±0.08 versus 0.09±0.09 mm/($m^2$/year) 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

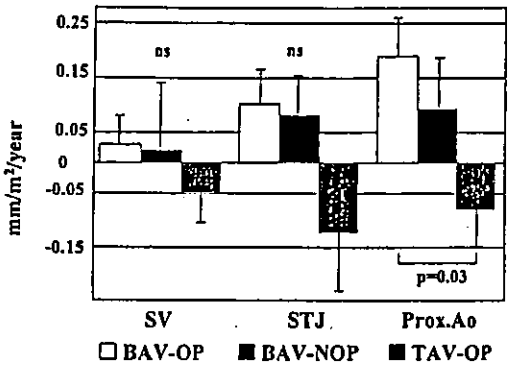


**Figure 1.** Annual dilation rate in each group. SV=sinuses of Valsalva; STJ=sinotubular junction; Prox. Ao=proximal aorta 1 cm above the sinotubular junction. The dilation rate of the BAV-OP patients tended to be faster than that of TAV-OP patients

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 ($P<0.05$).

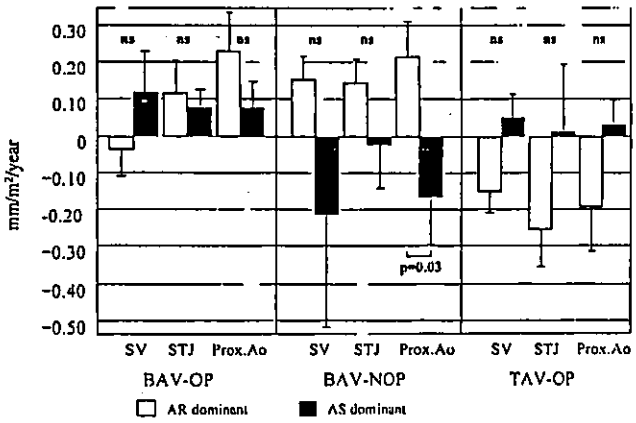


**Figure 2.** Effect of aortic stenosis or aortic regurgitation on aortic dilation. In the patients with BAV, AR dominant group showed more progressive dilation compared with AS dominant group. In the patients with TAV, the presence of AR or AS before AVR had little effect on the progression. Abbreviations are as in Figure 1.

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 ($y=-1.45+0.30\times DBP+0.55\times FS$, $r=0.74$, $P<0.05$). 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 metallproteinases (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[10] 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.[21–25] 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.

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# 8. 本邦における心臓移植と問題点

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**key words**　heart transplantation, left ventricular assist system (LVAS), bicaval anastomosis, immunosuppression, brain death

## 動　向

1997年10月の脳死臓器移植法の発効から5年が経過し，予定より2年遅れてやっと国会や厚生労働省において法律や施行ガイドラインの「見直し」検討に入ったが，その成果はいまだみえていない．この間，施行された心臓移植手術は2002年10月の時点で14例と著しく少ない状況が続いている．この少ない提供状況は待機患者の死亡率の増加，補助人工心臓（LVAS）の必要度の著しい増加，長期化する待機への病院側対応の困難性の増加，渡航移植の希望者の増加など多くの問題を提示しており，さらに"3年後"の「法」の見直し時期の大幅な遅延が加わって社会問題を生じていると考える．改善への取り組みを強く希望するところである．一方，わずか14例のわが国での心臓移植であるが，その成績は良好であり，「高度先進医療」の承認も得られ，医学，医療的な面では初期の目的と期待を達成できたものと考える[1]．国立循環器病センターで移植を施行し，看護した7例を中心に日本の心臓移植の現状を報告し，またわが国で現在直面している困難な問題について世界の状況と対比して述べたい．

## A. 心臓移植適応

日本循環器学会心臓移植適応検討小委員会の1997年4月1日より2002年6月20日までの報告を表1に示す．心臓移植適応と判定されたものは検討症例228例中186例（82%）であった．このうち日本臓器移植ネットワーク（NW）に登録されたものは15歳以上113名，15歳未満3名で，前者113名のうち待機中死亡34名（30%），移植11名（10%）で現在（2002年6月30日）登録中は62名である．15歳未満は3名で，うち移植2名，死亡1名であった．NW登録者116名中，移植できた者13例（11%）に対し，死亡35名（30%）と3倍弱であった．この間，海外で移植を受けた者は22名と国内での移植例よりずっと多いという皮肉な現実もある．この現状を年間2,000～2,500例の心臓移植が行われている米国の状況と比較することは容易でないが，対象疾患では日本では全例が心筋症であり，米国ではその比率は冠動脈疾患と半々の状況である．移植を受けたものをみると，日本ではすべてがstatus Iで米国ではstatus Iは62%である．