A morphologic study of Carpentier-Edwards pericardial xenografts in the mitral position exhibiting primary tissue failure in adults in comparison with Ionescu-Shiley pericardial xenografts

Hirohisa Machida, MD^{a,d}
Hatsue Ishibashi-Ueda, MD^b
Kiyoharu Nakano, MD^c
Yoshikado Sasako, MD^a
Junjiro Kobayashi, MD^a
Ko Bando, MD^a
Kenji Minatoya, MD^a
Hiroji Imamura, MD^d
Soichiro Kitamura, MD^a

Objective: We sought to investigate the durability and mechanism of the Carpentier-Edwards pericardial xenograft in the mitral position in comparison with that of the Ionescu-Shiley pericardial xenograft.

Methods: A total of 284 patients who received the Ionescu-Shiley pericardial xenograft in the mitral position between 1980 and 1984 and 84 patients who received the Carpentier-Edwards pericardial xenograft in the mitral position between 1984 and 1999 were included in the study. The freedom from reoperation rates for both graft types were determined. For morphologic study, the pathologic findings of 23 valves of 123 explanted Ionescu-Shiley pericardial xenografts with structural valve deterioration, nonstructural valve deterioration, or both were determined and compared with those of 20 explanted Carpentier-Edwards pericardial xenografts with structural valve deterioration, nonstructural valve deterioration, or both. Each pathologic finding was graded and assigned a score. Both types were matched for age at reoperation (50-75 years) and duration of valve function (8-11 years).

Results: Freedom from reoperation caused by structural valve deterioration, nonstructural valve deterioration, or both was significantly better for Carpentier-Edwards pericardial xenografts than for Ionescu-Shiley pericardial xenografts at 8 years after the operation (Carpentier-Edwards pericardial xenografts: 91.3% vs Ionescu-Shiley pericardial xenografts: 71.9%, $P = .0061$), but it was similar for both types at 12 years (Carpentier-Edwards pericardial xenografts: 43.6% vs Ionescu-Shiley pericardial xenografts: 43.6%, $P = .2865$). No severe leaflet tears were seen among Carpentier-Edwards pericardial xenografts. The mean area percentage of tissue overgrowth was 15.3% in Carpentier-Edwards pericardial xenografts and 3.4% in Ionescu-Shiley pericardial xenografts ($P = .0001$). The mean calcification area percentage was 13.6% in Carpentier-Edwards pericardial xenografts and 31.5% in Ionescu-Shiley pericardial xenografts ($P = .0001$).

From the Departments of Cardiovascular Surgery^a and Pathology,^b National Cardiovascular Center, Osaka, Japan; Department of Cardiovascular Surgery,^c Kanto Medical Center, NTT EC, Tokyo, Japan; and Department of Thoracic and Cardiovascular Surgery,^d Kansai Medical University, Osaka, Japan.

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Address for reprints: Hirohisa Machida, MD, Department of Cardiovascular Surgery, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565, Japan (E-mail: hmachida@d2.dion.ne.jp).

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Conclusions: Tissue overgrowth on the atrial surface, ventricular surface, or both was the cause of structural valve deterioration, nonstructural valve deterioration, or both of Carpentier-Edwards pericardial xenografts in adults. This was different from Ionescu-Shiley pericardial xenograft failure, which resulted from severe calcification and leaflet tears. Organized thrombi on cusps, in addition to valve design, may have contributed to such tissue overgrowth on Carpentier-Edwards pericardial xenografts.

The first generation of pericardial valves, the Ionescu-Shiley pericardial xenograft (ISPX; Shiley Laboratories, Irvine, Calif), was the first choice among bioprostheses for valve replacement at the National Cardiovascular Center, Osaka, Japan, between 1980 and 1984. However, it has been withdrawn from clinical use because of the observed high rate of valve insufficiency characterized by calcification and leaflet tears.¹⁻⁴ The Carpentier-Edwards pericardial xenograft (CEPX; Baxter Healthcare Corp, Santa Ana, Calif), the second generation of pericardial valves, which was designed to provide a superior hemodynamic performance and better durability than its predecessors, has been used in our institute since 1984. The intermediate follow-up period of CEPXs has shown low rates of valve-related events, especially valve deterioration after leaflet tears.^{5,6} However, its durability in the mitral position has been of considerable concern for cardiologists. According to the results of operations performed at our institute, it was reported that up to 4 years after valve replacement, the incidence of bioprosthetic valve failure was lower for CEPXs compared with for ISPXs.^{7,8} Recently, however, after more than 10 years of experience with CEPXs, the number of patients undergoing a second valve replacement because of prosthetic valve failure has been increasing in our institute.

The purpose of this study was to investigate the durability and the mechanism of primary failure of CEPXs at a single institute, with emphasis on the pathologic findings of explanted valves in comparison with ISPXs.

Patients and Methods

At our institute, between 1980 and 1984, 284 patients received ISPX valves in the mitral position (ISPX group), and since 1984, 84 patients received CEPX valves (CEPX group) in the mitral position. The patient population of the ISPX group consisted of 117 (41.2%) men and 167 (58.8%) women, with an age range of 18 to 73 years (mean, 50.0 years); the CEPX group consisted of 32 (38.1%) men and 52 (61.9%) women, with an age range of 18 to 80 years (mean, 57.5 years) (Table 1). In the CEPX group 73.1% and 24.3% of patients were shown to have chronic atrial fibrillation and sinus rhythm, respectively. In the ISPX group 81.6% and 18.0% of patients were shown to have chronic atrial fibrillation and sinus rhythm, respectively.

Patients were operated on through a median sternotomy with

standard cardiopulmonary bypass, hemodilution, and moderate hypothermia. Myocardial protection was obtained with crystalloid or blood cardioplegia and topical cooling. Bioprosthetic valves were implanted in the para-annular position by using an everting mattress suture technique with pledgets.

Postoperative warfarin anticoagulation was initiated as soon as oral administration became possible and was continued for as long as 3 months. Patients with atrial fibrillation, however, were maintained on warfarin therapy for longer durations; the treatment was sometimes modified according to the cardiologist's decision. Finally, 53.4% and 68.4% of the patients with atrial fibrillation were maintained on warfarin therapy for longer durations in the CEPX group and the ISPX group, respectively. An adequate anticoagulation state was that in which the prothrombin time ranged from 25% to 45%, which was equivalent to 2.9 to 1.8 times the control prothrombin time international normalized ratio.

At present, 123 patients with ISPXs and 25 patients with CEPXs underwent a second mitral valve replacement because of structural valve deterioration (SVD), nonstructural valve dysfunction (NSVD), or both. The average functioning duration of prostheses was 9.3 ± 1.7 years (range, 7.5-12.2 years) in the CEPX group and 7.9 ± 3.2 years (range, 0.5-18.2 years) in the ISPX group. The mean age of patients at reoperation was 61.0 ± 10.5 years (range, 30-77 years) in the CEPX group and 57.1 ± 9.6 years (range, 26-78 years) in the ISPX group. Twenty-three ISPXs with a functioning duration of 8.0 to 11.0 years in patients between 41 and 65 years of age were selected (mean age at explantation, 62.8 years; average functioning duration, 9.4 years) to match the average functioning duration of prostheses and patient age of both groups. ISPX valves that were not available for re-examination and 4 CEPX valves from patients with infective endocarditis were excluded from the morphologic and histopathologic evaluation. Eventually, 23 valves of 123 explanted ISPXs and 20 valves of 25 explanted CEPXs were examined for macroscopic and microscopic study. This selection was done before histologic analysis was started. The size of each explanted valve was larger than 25 mm in diameter.

Clinical and operative data were obtained from medical records of the patients. The "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations" were used for definition of valve-related complications.⁹ Because most explanted valves had mingled degenerative change (eg, both moderate calcification and massive pannus formation), the differences between SVD and NSVD were not very clear, particularly with regard to pathologic investigation. Therefore in this study we used the terms SVD and NSVD. Prosthetic valve failure caused by endocarditis or thrombus formation was excluded from this definition.

The following macroscopic changes of the bioprostheses were assessed and classified into 4 grades (grades 0-3) as follows: (1)

TABLE 1. Patient characteristics

Variable	Carpentier-Edwards pericardial valve						Ionescu-Shiley valve					
	Valve implanted		Valve explanted				Valve implanted		Valve explanted			
	Total	M/F	Total	M/F	Study cases	M/F	Total	M/F	Total	M/F	Study cases	M/F
No. of patients	84	32/52	25	6/19	20	5/15	284	117/167	123	42/81	23	5/18
Age at implant (y)												
Mean	57.5		51.1		51.3		50.0		49.2		52.6	
Range	18-80		23-68		23-68		18-73		18-68		45-63	
Duration of implant (y)			9.3		10.1				7.9		9.4	
Range (y)			7.5-12.2		7.5-12.2				0.5-18.2		8.0-10.8	
Mean age at explant (y)			61.0		61.3				57.1		62.8	
Range (y)			30-77		30-77				26-78		54-73	
Causes of reoperation												
Stenosis					4						4	
Regurgitation					6						10	
Stenosis and regurgitation					10						9	

the degree of cusp miscoaptation, representing the severity of opening and closing disturbance; (2) leaflet tears; (3) fibrous tissue overgrowth from the valve ring (ie, pannus formation on the atrial surface, the ventricular surface, or both of the valve cusps); and (4) the degree of thrombus formation. Each pathologic finding was individually evaluated and graded according to the following criteria: (1) grade 0, no macroscopically detected pathologic changes, no leaflet tears, and no tissue overgrowth; (2) grade 1 (mild changes), single and small leaflet tear and small tissue overgrowth; (3) grade 2 (moderate changes), single but large leaflet tear or multiple small tears and fibrous tissue overgrowth from the ring reaching the middle of the cusp; and (4) grade 3 (severe changes), more than 2 large leaflet tears and fibrous tissue overgrowth spread over most of the cusp.

For histopathologic analysis of the removed bioprostheses, specimens were fixed in 10% buffered formalin, and the cusps were cut from the suture ring to the tip at midcusp region. Then thin 3- to 4- μ m paraffin sections were stained with hematoxylin and eosin, Masson's trichrome, elastic van Gieson, and von Kossa stains. Stained specimens were measured by using a computer morphologic analyzing system (Nikon Cosmo Zone II, Tokyo, Japan) to determine the areas of calcification and overgrowing fibrous tissue and their percentage to the whole surface area of the cusp. These parameters were measured in every slice of the cusps for all patients. Also, the maximal thickness of each cusp was measured by using the ocular micrometer of the microscope. All histopathologic findings were evaluated by one experienced pathologist.

Data are reported as means $\pm$ SD. The nonparametric freedom from SVD, NSVD, or both curve was plotted according to the Kaplan-Meier method. Univariate comparison of SVD-free ratio, NSVD-free ratio, or both was made with the log-rank test. The Student *t* test (for discrete variables) and the χ^2 test (for continuous variables) were used for intergroup comparison of pathologic findings. Multivariate analysis was made with stepwise discriminant analysis to evaluate the histopathologic changes of explanted bioprostheses. Parameters for multivariate analysis included patient age and sex, implanted duration, and pathologic grading of each valve.

Results

The rate of freedom from reoperation caused by SVD, NSVD, or both is demonstrated in Figure 1. The freedom from reoperation rate at 8 years after the operation was significantly better in the CEPX group compared with that in the ISPX group (CEPX group: 91.3% vs ISPX group: 71.9%; $P = .0061$, log-rank test). However, in the CEPX group reoperation caused by SVD, NSVD, or both increased with time, and the 2 actuarial curves crossed at 11 to 12 years after the operation; the rate of freedom from reoperation caused by SVD, NSVD, or both was similar for both groups at 12 years (CEPX group: 43.6% vs ISPX group: 43.6%; $P = .2865$, log-rank test). Perivalvular leakage was evaluated in all patients in the postoperative periods. The incidence of perivalvular leakage that necessitated a second mitral valve replacement was 0% (0/84) in the CEPX group and 1.4% (4/284) in the ISPX group.

The macroscopic findings of the CEPXs (Figure 2, *top left*) were as follows: (1) miscoaptation of the cusp closure lines; (2) tissue overgrowth on the atrial aspect, ventricular aspect, or both of the valve; and (3) absence of significant leaflet tears. The macroscopic findings of the ISPXs (Figure 2, *bottom left*) included the following: (1) nodular intrinsic calcification of the cusps; (2) leaflet tears starting from the stent posts; and (3) noticeable rigidity of the cusps. According to the above-mentioned grading system, grade 2 and 3 leaflet tears were seen in 10 (43.5%) of the 23 patients with ISPXs. On the other hand, no leaflet tears (grade 0) were detected in 14 (70.0%) and grade 1 leaflet tears were seen in only 6 (30.0%) of the 20 patients with CEPXs; grade 2 or 3 leaflet tears were not found in the CEPX group ($P = .002$). In about half of the CEPXs, grade 2 or 3 tissue overgrowth was seen on the atrial aspect, the ventricular aspect, or both. On the other hand, at ISPXs, tissue overgrowth was less than grade 2 (atrial: $P = .0001$, ventricular: $P = .001$).

Figure 1. Actuarial curve of freedom from reoperation caused by SVD, NSVD, or both.

TABLE 2. Pathologic grading of explanted CEPX and ISPX

	Carpentier-Edwards valve (n = 20)				Ionescu-Shiley valve (n = 23)				P value
	0+	1+	2+	3+	0+	1+	2+	3+	
Leaflet tear	14 (70%)	6 (30%)	0 (0%)	0 (0%)	4 (17%)	9 (70%)	9 (39%)	1 (4%)	.002*
Tissue overgrowth on atrial aspect	4 (20%)	7 (35%)	6 (30%)	3 (15%)	12 (52%)	11 (48%)	0 (0%)	0 (0%)	.0001*
Tissue overgrowth on ventricular aspect	8 (40%)	4 (20%)	5 (25%)	3 (15%)	20 (87%)	3 (13%)	0 (0%)	0 (0%)	.001*
Thrombus in atrial aspect	3 (15%)	8 (40%)	4 (20%)	5 (25%)	8 (35%)	13 (57%)	1 (4%)	1 (4%)	.014*
Calcification	1 (5%)	9 (45%)	7 (35%)	3 (15%)	2 (9%)	7 (30%)	1 (4%)	13 (57%)	.001*
Collagen bundle separation	0 (0%)	3 (15%)	13 (65%)	4 (20%)	0 (0%)	4 (17%)	13 (57%)	6 (26%)	.738
Cholesterol deposition	5 (25%)	8 (40%)	7 (35%)	0 (0%)	3 (13%)	11 (48%)	5 (22%)	4 (17%)	.312
Serum insudation	0 (0%)	11 (55%)	8 (40%)	1 (5%)	0 (0%)	10 (43%)	11 (48%)	2 (9%)	.727

* $P < .05$.

The incidence of large thrombi tended to increase among CEPXs ($P = .014$) (Table 2).

Histologic examination of ISPXs showed separation of collagen bundles, cholesterol crystal deposition, and destructive calcification of the cusps (Figure 2, *bottom right*). Examination of CEPXs revealed fibrous tissue overgrowth on the atrial aspect, the ventricular aspect, or both; serous insudation of the separated collagen bundles; and band-like or fine granular intrinsic calcification (Figure 2, *top right*). Tissue overgrowth was more frequent in CEPXs, and its area percentage to the whole cusp area was much wider than that seen in ISPXs (CEPX: $15.3\% \pm 12.3\%$ vs ISPX: $3.4\% \pm 6.5\%$, $P = .0001$). Calcification areas were significantly larger among ISPXs compared with among CEPXs (CEPX: $13.6\% \pm 11.6\%$ vs ISPX: $31.5\% \pm 10.6\%$, $P = .0001$). The mean cusp thickness of ISPXs was larger than that of CEPXs (CEPX: $1029.4 \pm 4.2 \mu\text{m}$ vs ISPX: $1509.1 \pm 193.1 \mu\text{m}$, $P = .012$) (Table 3). Cusp thickening might be attributed to intrinsic calcification and serum insudation. According to the

data from Baxter Co, the cusp thickness of a nonimplanted new valve ranges from 500 to 600 μm , and therefore both CEPXs and ISPXs were 2 or 3 times thicker than nonimplanted valves. The degeneration of cusp collagen bundles and cholesterol and serum insudation were not significantly predominant in either type (Table 2).

Multivariate analysis showed that leaflet tears ($P = .005$), calcification ($P = .035$), and tissue overgrowth on the atrial aspect, the ventricular aspect, or both ($P = .013$ and $P = .0001$, respectively) were significant. Tissue overgrowth on the ventricular aspect and leaflet tears were the most important factors in prognosis of durability of CEPXs and ISPXs, respectively (Table 4).

Discussion

The present study showed the following: (1) the rate of freedom from reoperation caused by SVD, NSVD, or both was similar at 12 years after the operation in both the CEPX and ISPX groups; (2) no significant leaflet tears were found

Figure 2. *Top left*, CEPX explanted 11 years after implantation is viewed from the ventricular aspect. Sugar coat-like tissue overgrowth that induced valve insufficiency is seen. *Top right*, Microscopic findings of CEPX cusp showing thick and dense fibrous tissue on the ventricular surface. (Hematoxylin and eosin stain, original magnification 40 $\times$.) *Bottom left*, ISPX explanted 10 years after implantation is viewed from the ventricular aspect. Large leaflet tear running toward the cusp-base and granular calcification on the cusp are observed. *Bottom right*, Microscopic findings of ISPX cusp demonstrating nodular calcification that destroyed the collagen bundles and caused increasing thickness of the cusp. (Masson trichrome stain, original magnification 40 $\times$.)

among CEPXs; (3) incidence of calcification among CEPXs was lower compared with that of ISPXs; (4) massive tissue overgrowth on the atrial aspect, the ventricular aspect, or both of valves was seen among CEPXs; (5) the incidence of tissue degeneration of CEPXs (ie, collagen bundle separation, cholesterol deposition, or serous insudation) was similar to that of ISPXs; and (6) according to the results of multivariate analysis, SVD, NSVD, or both of CEPXs caused by severe tissue overgrowth was the main cause of reoperation after 10 years. Organized thrombi on the cusp surfaces might have contributed to such tissue overgrowth.

The CEPX valve was designed with an original leaflet clamping, which eliminated retention suture and risk of abrasion. The preparatory treatment of the pericardium was performed with 0.25% to 0.6% buffered glutaraldehyde. Because of these characteristics, CEPX bioprostheses showed satisfactory intermediate results in both the aortic and mitral positions, as reported previously.^{5,6,10,11} However, our data suggested that despite the durability of this valve in the mitral position at up to 8 years of follow-up, the rate of SVD, NSVD, or both beyond this time was significant. Despite the absence of significant leaflet tears in

TABLE 3. Microscopic comparison of explanted CEPX versus ISPX

	Carpentier-Edwards valve (n = 20)	Ionescu-Shiley valve (n = 23)	P value
Tissue overgrowth area/whole cusp area (%)	15.3 ± 12.3	3.4 ± 6.5	.0001
Calcification area/whole cusp area (%)	13.6 ± 11.6	31.5 ± 10.6	.0001
Maximum cuspal thickness (μm)	1029.4 ± 4.2	1509.1 ± 193.1	.0001

CEPXs, reoperation caused by SVD, NSVD, or both has increased significantly.

ISPXs, the first generation of pericardial valves, have been withdrawn from clinical use because of the associated high rate of insufficiency. The mode of deterioration was largely documented: valve design failure, tissue preparation failure, or both was the main cause rather than pericardium failure.^{3,4,12-14} Prosthetic ISPX valve failure in long-term implantation has been well described by Schoen and coworkers.² They have reported that the characteristics of SVD, NSVD, or both of ISPXs were intrinsic cuspal calcification and design-related leaflet tears or commissural perforations. Leaflet tears of ISPXs were usually caused by abrasions or fatigue of the tissue at the stent posts. Calcium deposition on bioprosthesis was dependent on patient factors, such as age, renal function, and calcium intake.¹⁵ It was hypothesized that calcification of bioprosthetic tissue was due to inability of the devitalized cells to maintain a low intracellular content of free calcium in the presence of high extracellular calcium¹⁶; this was compatible with our results. On the contrary, when compared with ISPXs, severe cuspal tears and perforation were not seen and the degree of calcification was milder in CEPXs. This might be attributable to the improvement of heteropericardium fixation and the design of the cuspal structure of CEPX valves.

We reported previously that tissue overgrowth, so-called pannus formation, on the cusps of CEPX in the tricuspid position made the cusps shrink and caused regurgitation.¹⁷ This tissue overgrowth might have been related to the anatomic and hemodynamic characteristics of the right ventricle. Because the right ventricle has a wedge-shaped configuration, prosthetic cusps adjacent to the sewing cuff might easily touch the remnant of the native valve and its subvalvular component, resulting in thrombus formation and tissue overgrowth. In this study the average patient age and the duration of valve implantation were similar between the CEPX and ISPX groups. The severity of tissue overgrowth from the sewing ring and struts was significantly higher for CEPXs than for ISPXs. Severe tissue overgrowth may have caused miscoaptation of the cusp closure line and increased its rigidity, resulting in mitral regurgitation or

TABLE 4. Multivariate analysis by stepwise discriminant analysis

	Wilks lambda	F value	P value
Leaflet tear	0.545	18.171	.005
Calcification	0.446	14.505	.035
Tissue overgrowth on atrial aspect	0.446	16.163	.013
Tissue overgrowth on ventricular aspect	0.757	18.792	.0001

stenosis regurgitation, which are defined as nonstructural dysfunctions.⁹ Thrombi formed on the fibrous tissue were also recognized. A few months after the operation, fibrin thrombi appeared on the sewing ring and cuspal leaflet. Organization of the fibrin thrombi results in proliferation of fibrous tissue. Thereafter, endothelialization should be continued. On the other hand, tissue overgrowth, accompanied by endothelialization, is often observed in the sewing cuff of any bioprosthesis and mechanical valves. CEPXs, which have improved characteristics, also have another feature in their design. The continuity of CEPX between sewing ring and cuspal leaflet was notably smooth compared with that of ISPXs. Therefore we speculate that the fibrous tissue with endothelialization around the prosthetic valve might have grown over a subtle gap between the sewing ring and cuspal leaflets onto the prosthetic cusps adjacent to this sewing ring, resulting in fibrous thrombus formation and tissue overgrowth. We think that tissue overgrowth onto the cuspal leaflet might be peculiar to CEPXs, and the shape of CEPXs will probably be related to tissue overgrowth. In addition, the styles of the sewing rings are markedly different among CEPXs and ISPXs. The ISPX valve used Dacron velour, whereas the CEPX valve used Teflon nonvelour. This difference might be the main reason that there were differences in tissue overgrowth and valve failure.

Other pathologic findings, cholesterol deposition, and degeneration of collagen bundles of the xenograft should be chronologic changes; the extent of these changes was not significantly different between CEPXs and ISPXs.

The influence of patient age on the incidence of primary tissue failure is well known.¹⁸ Neville and colleagues¹⁹ reported that 12-year actuarial freedom from structural deterioration was 52% in patients under 60 years of age and 100% in patients over 60 years of age. Our data demonstrated that the rate of freedom from reoperation caused by SVD, NSVD, or both was worse at 12 years after the operation. According to the current strategy for mitral valve replacement with a bioprosthesis, the majority of the candidates were patients older than 60 years. This study, including relatively younger patients, might underestimate the durability of the CEPX. Use of the CEPX for elderly patients will produce better durability, as reported previously by Neville and colleagues.¹⁹ At present, we mainly use bioprostheses for elderly patients.

The absence of severe leaflet tears in CEPXs was a significant advantage because acute regurgitation of the valve causing acute cardiac failure has been avoided. The CEPX structure, which followed the concept of near-anatomic configuration of central flow trileaflet prostheses, still has another structural limitation (ie, tissue overgrowth other than chronologic degeneration of the cusp). We believe that more modification of valve structure would be required for better durability.

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