SURGERY FOR ACQUIRED HEART DISEASE

THE CARPENTIER-EDWARDS PERICARDIAL AORTIC VALVE

Ten-year results

To evaluate the function of the Carpentier-Edwards pericardial valve in the aortic position, we analyzed the results of 310 aortic valve replacements performed between 1982 and 1985. Mean age was 64.2 ± 10.8 years (range 22 to 95 years); 190 patients (61.3%) were male patients. There were 18 hospital deaths (5.8%), and none were valve related. Follow-up of the 292 survivors was 100% complete at a mean of 7.8 ± 2.9 years; 2290 patient-years of follow-up were available for analysis. There were 133 late deaths (45.5%). Actuarial survivals at 5 and 10 years were 82.5% and 45.9%, respectively. The 10-year actuarial freedom from events was $88.7\% \pm 2.1\%$ for thromboembolism, $90.9\% \pm 1.8\%$ for hemorrhage, $94.3\% \pm 1.6\%$ for endocarditis, and $91.2\% \pm 2.6\%$ for structural deterioration. The 153 hospital survivors 65 years of age or older had an extremely low incidence of structural valve deterioration, with only four explants and 95.5% actuarial freedom from explantation at 10 years, and a linearized rate of 0.3 ± 0.2 per patient-year compared with 88.6% and 0.7 ± 0.2 for patients younger than 65 years of age. Twelve valves were explanted for structural deterioration. Of these, 11 (93%) had leaflet calcification causing stenosis and one had a wear-related leaflet tear. The Carpentier-Edwards pericardial valve has a low incidence of valve-related complications. The freedom from structural valve deterioration is low at 10 years, particularly in patients 65 years of age and older. (J THORAC CARDIOVASC SURG 1995;110:651-62)

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Twenty years of experience with porcine bioprosthetic valves in the aortic position has shown a low incidence of thromboembolic complications,^{1,2} restrictive hemodynamics in small sizes,³⁻⁶ and an incidence of structural deterioration of 20% at 10 years.⁷ This rate of structural

valve deterioration is exactly what Carpentier, the originator of the glutaraldehyde fixation process, had predicted.⁸ This limited durability has been the major factor restricting the use of porcine valves. In 1971 Ionescu introduced valves constructed of bovine pericardium.⁹ This valve and other pericardial valves had excellent hemodynamics but an unacceptably high rate of structural deterioration, which resulted in many interested observers condemning pericardium as a material for valve construction.¹⁰⁻¹²

The Carpentier-Edwards pericardial valve (Baxter Healthcare Corp., Edwards Division, Santa Ana, Calif.) introduced in 1980 was the result of major design alterations. In vitro testing raised expectations for excellent hemodynamics and vastly improved durability.¹³ The hemodynamic advantage of

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Fig. 1. Actuarial survival for patients discharged from the hospital was 46% at 10 years. Bars represent 1 standard error.

Table I. Surgical procedure (*n* = 310)

Procedure	<i>n</i>	%
Isolated AVR	135	43.5
AVR and CABG	127	41.0
AVR and other valve	37	11.9
AVR and other	11	3.6

CABG, Coronary artery bypass grafts.

this valve over porcine valves has been confirmed clinically.¹⁴ A few clinical reports with limited follow-up have shown excellent results and have hinted at an excellent freedom from structural valve deterioration.¹⁵⁻¹⁷ Widespread use is dependent on reports of valve durability at 10 years and beyond.

Patients and methods

Between June 1982 and July 1985, 310 patients had Carpentier-Edwards pericardial valves (model 2700) inserted in the aortic position. Mean age was 64.2 ± 10.8 years (range 21 to 95 years); 142 patients (45.8%) were less than 65 years of age, and 190 (61.3%) were male; 203 patients (66%) were in New York Heart Association functional class III or IV; 102 patients (33%) were in functional class II; 40 patients (12.9%) underwent reoperations. Indications for aortic valve replacement (AVR) were aortic stenosis in 93 patients (30%), aortic insufficiency in 40 (13%), mixed lesions in 154 (50%), and failed prosthesis in 23 (7%). Significant coronary artery disease was present in 130 patients (41.4%), and 64 patients (20.7%) had other coexisting valvular disease. Valve sizes

Table II. Late events (*n* = 100)

	No.
Thromboembolism	36
Endocarditis	19
Anticoagulant-related hemorrhage	24
Valve explantation	21

implanted were as follows: 19 mm in 64 patients (20.6%), 21 mm in 99 patients (31.9%), 23 mm in 93 (30.0%), and 25 mm in 54 (17.4%). The surgical procedures are listed in Table I.

Follow-up information was obtained during outpatient clinic appointments or documented by telephone interviews made between 6 and 12 months during the first postoperative year and annually thereafter. Follow-up of 292 hospital survivors was 100% complete at a mean of 7.8 ± 2.9 years with 2290 patient-years of follow-up available for analyses. Follow-up of 138 late survivors was 100% complete at a mean of 9.9 ± 0.9 years; 1362 patient-years were available for analysis.

Patients routinely received warfarin sodium (Coumadin) for 12 weeks after the operation. The continuation of warfarin beyond this time period, usually for patients in atrial fibrillation, was at the discretion of individual cardiologists. Ninety percent of patients were discharged receiving anticoagulant therapy. At recent follow-up, 75 of 138 patients (54.3%) continued to receive anticoagulation therapy.

Statistical analyses. The guidelines for reporting morbidity and mortality after cardiac valvular operations¹⁸ were used in this report. Death and event-free survival estimates were calculated by the method of Kaplan and

Fig. 2. Actuarial freedom from thromboembolism was 89% at 10 years. The hazard function curves suggest higher early risk. Bars represent 1 standard error.

Meier.¹⁹ Cox's²⁰ proportional hazards models were used to assess the relationship between various factors and event-free survival. In all cases, *p* values less than 0.05 were considered significant. Linearized rates for late events represent the number of events per 100 patient-years. Semi-parametric hazard curves were generated by modeling the hazard function as a quadratic function of time with the use of a logistic regression model.

Freedom from structural valve deterioration curves were assessed with the use of the method of Grunkemeier and associates²¹ (Appendix). Rather than using actuarial risk, which reflects valve life as though patients were immortal, Grunkemeier's "actual risk" adjusts the curves for the fact that many patients will die of other causes before structural valve deterioration. According to this

methodology, patients who die without ever having structural valve deterioration are treated as patients who will never have structural valve deterioration rather than patients who might have had structural valve deterioration had they lived. Parametric Weibull models and nonparametric Kaplan-Meier models were evaluated, and the Weibull distribution was determined to fit the data well.

Results

There were 18 hospital deaths (5.8%). None were valve related. There were 133 late deaths (46%), of which 91 (68%) were cardiac related. Late deaths were cardiac related in 91 patients and noncardiac

Fig. 3. Actuarial freedom from endocarditis was 94% at 10 years. The hazard function curves suggest a constant risk. Bars represent 1 standard error.

in 42 patients. Actuarial survival rates at 5 and 10 years were $82.5\% \pm 2.2\%$ and $45.9\% \pm 3.2\%$, respectively (Fig. 1). At recent follow-up, 113 patients (82%) were in New York Heart Association functional class I, 20 patients (15%) were in functional class II, and five (3%) were in class III or IV. In the 292 hospital survivors, there were 100 late events (Table II). Ten-year actuarial freedom from thromboembolism was $88.7\% \pm 2.1\%$ (Fig. 2). Thirteen patients had 19 episodes of endocarditis, and the actuarial freedom from endocarditis was $94.3\% \pm 1.6\%$ at 10 years (Fig. 3). There were 24 episodes of significant anticoagulation-related hemorrhage resulting in a 10-year actuarial freedom of

$90.9\% \pm 1.8\%$ (Fig. 4). The annualized rate for these complications is found in Table III.

Twenty-one valves were explanted. Three valves were removed for endocarditis, and six were removed prophylactically at the time of mitral valve surgery. Twelve valves were explanted for structural deterioration. Of these, 11 had leaflet calcification, and one had a wear-related tear. Mean interval from implantation to explantation date for structural deterioration was 8.16 ± 1.7 years (range 4.5 to 10 years). Actuarial freedom from explantation for structural deterioration at 10 years was $91.2\% \pm 2.7\%$ (Fig. 5). Actual freedom from structural valve deterioration was 96% (Fig. 6). Actual freedom

Fig. 4. Actuarial freedom from anticoagulant related hemorrhage was 91% at 10 years. The hazard function curve suggests a higher early risk. Bars represent 1 standard error.

from structural valve deterioration at 10 years was 97% for patients 65 years of age or older and 94% for patients less than 65 years of age (Fig. 7). Although age less than 65 years was a univariately significant predictor for explantation for all causes ($p = 0.0002$), it was not found to be a significant predictor for explantation caused by structural deterioration ($p = 0.452$).

Event-free survival at 5 and 10 years was $69.9\% \pm 2.7\%$ and $37.2\% \pm 3.1\%$, respectively (Fig. 8). Multivariate analyses identified age of 65 years or older ($p = 0.0002$) and coronary artery disease ($p = 0.0001$) as significant risk factors.

Table III. Annualized rates

Thromboembolism	1.6 ± 0.3
Hemorrhagic complications (anticoagulant-related)	1.0 ± 0.2
Endocarditis	0.8 ± 0.3
Structural deterioration	0.5 ± 0.1
All four events	3.9 ± 0.5

Values are mean percentage per patient-year $\pm$ standard error.

The freedom from all events was $85.8\% \pm 2.2\%$ and $68.5\% \pm 3.5\%$ at 5 and 10 years, respectively (Fig. 9). Multivariate analysis identified concomitant valve surgery as the sole predictor of late events

Fig. 5. Actuarial freedom from structural valve deterioration was 91% at 10 years. The hazard function curve suggests a slowly rising incidence over time. Bars represent 1 standard error.

($p < 0.002$). The freedom from events was $72\% \pm 4\%$ at 10 years for patients with only aortic valve disease and $56\% \pm 7\%$ for patients with other valve disease, including concomitant coronary artery disease ($p = 0.002$) (Fig. 10). Analyses of patients who underwent isolated AVR, AVR and other valve procedures, and AVR and coronary artery bypass grafting showed an actuarial survival of $53.8\% \pm 4.7\%$ for those undergoing isolated AVR, $38.7\% \pm 5.3\%$ for patients who had an additional valve procedure, and $34.7\% \pm 9.2\%$ if concomitant coronary artery bypass grafting was performed (Fig. 11). Actuarial freedom from late events for these three groups of patients is $73.7\% \pm 4.6\%$, $68.1\% \pm 6.7\%$, and $46.2\% \pm 9.7\%$, respectively (Fig. 12).

Discussion

The introduction of valves constructed of pericardium by Ionescu and associates⁹ in 1971 offered an alternative to glutaraldehyde-treated porcine valves. Flow studies showed superior hemodynamic characteristics,^{22, 23} and durability testing predicted limited durability of the valve and mode of failure.^{24, 25} These predictions were confirmed in clinical experience.¹⁰⁻¹² The Ionescu-Shiley valve (Shiley, Inc., Irvine, Calif.) had excellent hemodynamics²²; however, structural deterioration appeared within 2 to 6 years.^{11, 26-30} Pericardial valves constructed in a similar fashion produced hemodynamic and durability results paralleling those of the Ionescu-Shiley valve.^{11, 31} These results raised doubts in the surgical

Fig. 6. Although the actuarial freedom from structural valve deterioration was 91% at 10 years, the actual risk of structural valve deterioration was 96%.

Fig. 7. The actual risk of structural valve deterioration at 10 years was 97% and 94% for patients ≥ 65 and < 65 years of age, respectively.

community as to the appropriateness of glutaraldehyde-treated bovine pericardium for valve construction.

The Carpentier-Edwards pericardial valve resulted from significant design modifications.¹⁶ The most important difference between the Carpentier-Edwards and other pericardial valves is that the two pieces of pericardium of adjacent cusps pass be-

tween the two arms of the stent rather than over the stent. Additionally, it has a flexible stent and the shape of the pericardial cusps are the result of finite element analysis. The cusps are matched for thickness and treated with surfactant to retard calcification.

In vitro hemodynamic data obtained by Gabbay and Frater¹³ suggested that this valve had excellent hemodynamics. These findings were confirmed by

Fig. 8. The actuarial event free survival was 37% at 10 years. Bars represent 1 standard error.

Fig. 9. The actuarial freedom from valve related complications was 69% at 10 years. Bars represent 1 standard error.

clinical evaluations comparing the hemodynamic performance of the standard and SupraAnnular Carpentier-Edwards porcine valves with the Carpentier-Edwards pericardial valve.¹⁴ The latter was superior in providing adequate hemodynamics—even in the 19 mm size. Pelletier¹⁷ and Frater¹⁶ and their associates reported similar findings using echocardiographic data.

In vitro wear-testing of Carpentier-Edwards pericardial valves by Gabbay and Frater¹³ raised expectations for improved durability when compared with results from porcine or other valves constructed of bovine pericardium. Three clinical reports show structural deterioration data for this valve. Pelletier and associates¹⁷ reported a 5-year freedom from primary tissue failure of 100% in 181 valves. Perier

Fig. 10. The actuarial freedom from valve related complications was significantly lower in patients who had associated valve procedures ($p = 0.002$). Bars represent 1 standard error.

Fig. 11. The actuarial survival at 10 years for isolated AVR, AVR and other valve procedures, and AVR and coronary artery bypass grafting were 54%, 39%, and 35%, respectively. Bars represent 1 standard error.

and associates¹⁵ found a 100% freedom from structural valve deterioration at 9 years in 124 patients. Frater and associates¹⁶ reported a freedom from structural valve deterioration of 97.2% at 7 years in 719 patients. Eight of 15 valve replacements were for structural valve deterioration as a result of stenosis. This report extends the follow-up to 10 years, and freedom from structural valve deterioration remains superb at 94%. It is noteworthy that all

structural valve deteriorations previously reported were a result of calcification.¹⁶ We recognized a leaflet tear in a valve removed from a patient 8 years after implantation. This extremely low incidence of leaflet tears is unquestionably a result of design improvements.

Recent large series³²⁻³⁶ (Table IV) evaluating porcine valves report widely differing percentages for 10-year freedom from structural valve deteriora-

Fig. 12. The actuarial freedom from events at 10 years for isolated AVR, AVR and other valve procedures, and AVR and coronary artery bypass grafting was 74%, 68%, and 46%, respectively. Bars represent 1 standard error.

Table IV. Porcine valves: 10-year freedom from structural valve deterioration

Principal investigator	n	Freedom from structural valve deterioration
Jones (1990) ³²	522	79%
Magilligan (1990) ³³	492	76%
Jamieson (1988) ³⁴	572	83%
Burdon (1992) ³⁵	857	85%
Akins (1990) ³⁶	429	91%

tion ranging from 76% to 91%. Three of these series^{32, 33, 35} report on the Hancock porcine valve. Ten-year and 15-year freedoms from structural valve deterioration were 76% to 86% and 37% to 63%, respectively. The two remaining series^{34, 36} studied Carpentier-Edwards porcine valves and reported 10-year freedom from structural valve deterioration of 83% and 91%. The average 10-year freedom from structural valve deterioration is 83%.

Because structural deterioration has been the Achilles heel of all previous biologic valves, a significant improvement in valve durability has major implications for surgeons and patients undertaking valve replacement. It has long been recognized that porcine valves do not have the same failure rate in all patients.^{37, 38} Magilligan and associates³³ were the first to point out the high incidence of structural valve deterioration in young patients. Jamieson and associates³⁴ stratified patients according to age, pointing out that freedom from structural valve

deterioration improves with advancing age. They further observed that structural valve deterioration occurred more frequently in the mitral position. Most recently, Jones and associates³² focused our attention on age as a factor in the decision-making process, and in subsequent publications³⁹ noted the important implications of concomitant coronary artery disease affecting the choice of valves.

These findings prompted Starr and Grunke-meier⁴⁰ to evaluate the methods of analysis of structural valve deterioration. They pointed out that actuarial analyses may not be the most appropriate method for presenting data on structural valve deterioration for clinical decision making. Actuarial studies are designed to evaluate survival probabilities. They have also been applied to the evaluation of nonfatal events. Actuarial curves censor death and thus provide an estimate of the probability of structural valve deterioration if all patients survived until their valves failed. This method is useful in comparing valves, but it is less applicable to the decision making when patients die. Clearly, actuarial analysis overestimates that structural valve deterioration rate, and this error is magnified with increasing age. The actual risk of a nonfatal event has more clinical relevance because it describes percentage of patients with structural valve deterioration, given the fact that death does intervene.

In an attempt to guide the patient's and surgeon's

decision regarding the most appropriate valve choice, we have adopted the actual risk of structural valve deterioration from Grunkemeier and associates²¹ and compared it with the actuarial risk of structural deterioration. The comparison of the two makes it apparent that the actuarial risk of structural valve deterioration appears to be higher than the actual risk of structural valve deterioration. It is apparent that a risk of structural valve deterioration in patients 65 years of age and older is extremely low. This statistical method seems to be the more appropriate way of evaluating biologic valves, particularly in older patients.

The superior hemodynamics and the low incidence of structural valve deterioration of the Carpentier-Edwards valve have made it our biologic valve of choice. Its excellent results in patients 65 years of age and older has proven its efficacy in this age group. These findings have important implications for younger patients whose life expectancy is limited because of concomitant disease. As the follow-up study achieves 15 years, it may be possible to extend present age limitations where the Carpentier-Edwards pericardial valve is used.

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Appendix

The SAS module, PROC LIFEREG (SAS Institute, Inc., Cary, N.C.), was used to estimate a time to death distribution and a time to failure distribution. Both of the distributions were fit from the Weibull family as suggested by Grunkemeier. This analysis is achieved in PROC LIFEREG by using the "/dist = weibull" option. That part of the process does not require extensive knowledge of the SAS programming language. The difficulty in applying this methodology is in the translation and reparametrization of the SAS program output.

Let $S_{\text{surv}}(t)$ denote the survival function and $f_{\text{svd}}(t)$ denote the failure time distribution in the notation used by Grunkemeier. The SAS output provides a mean parameter and a scale parameter for each weibull distribution (μ , and σ). This notation is not the standard notation for a Weibull distribution, so new parameters (γ and α) were computed as $\gamma = 1/\sigma$ and $\alpha = \exp\{-\mu/\sigma\}$, with $\exp\{x\}$ denoting e^x . Now, $S_{\text{surv}}(t) = \exp\{-\alpha t^\gamma\}$, where $\alpha = \exp\{-\mu_{\text{surv}}/\sigma_{\text{surv}}\}$ and $\gamma = 1/\sigma_{\text{surv}}$. And $f_{\text{svd}} = \alpha \gamma t^{(\gamma-1)} \exp\{-\alpha t^\gamma\}$, where $\alpha = \exp\{-\mu_{\text{svd}}/\sigma_{\text{svd}}\}$ and $\gamma = 1/\sigma_{\text{svd}}$.

The "actual" failure time distribution can now be computed with Grunkemeier's formula, $\int_{t=0}^T S_{\text{surv}}(t) f_{\text{svd}}(t) dt$. Numeric integration was used to compute this integral for each particular value of T .