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Instantaneous Risk of Events Following Aortic Valve Replacement with Pericardial Valves

A Ten-Year Experience

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Actuarial curves and linearized rates of occurrence are statistical functions that traditionally have been used to evaluate freedom from, or incidence of, valve-related events that occur as a result of aortic valve replacement (AVR); however, the instantaneous risk of an event can be more precisely pinpointed by the use of a time-related hazard function. This function was used to analyze 240 cases involving patients who underwent AVR with the Ionescu-Shiley bovine pericardial valve. Follow-up was for 10 years. The period from 60 to 70 months after implantation was apparently critical, since specific and cumulative events (intrinsic tissue failure, thromboembolism, prosthetic valve endocarditis, cumulated events, and death due to valve-related events) peaked during this period. We suspect important degenerative bioprosthetic changes take place during this period and are the cause, in part, for this pattern. In an effort to reduce the incidence of thromboembolism, close observation, and probably antiplatelet drug administration, should be initiated 60 months after implantation of this valve. ***(Texas Heart Institute Journal 1988;15:31-34)***

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Conflicting reports have appeared in the literature regarding the behavior of the Ionescu-Shiley bovine pericardial valve (ISPV). Some investigators have discontinued its use, while others have continued to implant this valve.[1-3] The advantages of the ISPV have been defined as low thromboembolic rate and excellent hemodynamics, even with small valve sizes; thus its preferred use is in the older patient who has a small aortic anulus.[4-6] Valve durability and intrinsic failure have been issues of intense debate.[1-3]

Indispensable requisites for a thorough assessment of a given valve substitute have been 1) a time-frame longer than 8 years, 2) completeness of follow-up, and 3) stringent analysis of valve-related events. Traditionally, conclusions regarding valve-related events and valve durability have been drawn from linearized rates of, or actuarial freedom from, occurrence—or from both. However, these results are not always indicative of actual valve performance. To better assess the behavior of this bioprosthesis, a homogenous group of patients who underwent aortic valve replacement (AVR) with the standard ISPV was analyzed with a time-related hazard function in order to ascertain the instantaneous risk of occurrence of a given event. This function depicts the conditional occurrence rate, i.e., the probability of occurrence of a given event within a very small time-frame. In practice, the hazard function is estimated as the proportion of events occurring within an interval of time during the aging process.[7]

Patients and Methods

Demography

From February 1977 to December 1983, 240 patients underwent AVR with the standard Ionescu-Shiley bovine pericardial bioprosthesis. The group consisted of 147 males and 93 females (ratio, 1.6 to 1.0). Ages of patients ranged from 17 to 86 years (mean, 62.5 years). At the time of operation, 164 patients

(68.3%) fell into NYHA Classes III or IV. One hundred ten patients (45.8%) also underwent a concomitant procedure: Of these, 67 underwent surgery for ischemic heart disease; 33 underwent multivalvular surgeries, with or without surgeries for ischemic heart disease; and 10 underwent miscellaneous surgeries.

Hospital Mortality

Sixteen patients (6.7%) died during their initial hospitalization. No deaths were valve-related. Of the 130 patients who underwent isolated AVR, 6 (4.6%) died in hospital. There was no statistically demonstrable difference in hospital mortality between patients who underwent isolated AVR and those who underwent AVR together with a concomitant procedure.

Follow-up

The status of all 224 patients discharged from the hospital was ascertained by questionnaire and computer analysis thereof. The questionnaire was completed by a cardiologist or cardiac surgeon, or both, after examination of the patient; alternatively, it was completed by telephone interview with the patient, or with the patient and referring physician. The cumulative total of follow-up patient-years was 1001.9 (mean, 53.7 ± 1.7 months). No patient was lost to follow-up, so mortality amd other variables were not affected by incomplete follow-up.

Statistical Methods

Analysis of patient- and valve-related events was achieved by the application of a time-related hazard function to ascertain the instantaneous risk of a given valve- or patient-related event,[7] and by calculation of the linearized rate of occurrence (percentage per patient-year) and determination of actuarial freedom from an event.[8] Analysis of survival data and time-related events was done actuarially, using the Kaplan-Meier estimate.[7] The proportion and degree of uncertainty in each actuarial analysis is expressed by the 70% confidence limit (CL), corresponding to one standard error. Kaplan-Meier estimates were also used to generate the nonparametric estimate for instantaneous risk (hazard function) of a given event.[7] Possible differences in survival and percentage of freedom from an event in two groups were tested using logrank statistics.[7] A $p \leq .05$ was considered statistically significant. Valve-related events considered were thromboembolism (TE), infective endocarditis (IE) whether it compromised valve function (PVE) or not, intrinsic tissue failure (ITF), anticoagulant-related hemorrhage (ARH), accumulated valve-related events (AVRE), death because of valve-related events (DVRE), death and reoperation because of valve-related events (D&RVRE), and total late patient mortality (LM).

Results

Late Mortality

Late death occurred in 49 patients (21.9%), or 4.9%/patient-year. Thirty of these late deaths (13.4%), or 3%/patient-year, were cardiac related. Of these 30, 6 (2.7%) were valve related (70% CL = 1.6% to 4.3%), or 0.6%/patient-year. Of these 6, 5 (2.2%) were because of PVE, or 0.4%/patient-year, and 1 (0.4%) was because of ITF, or 0.09%/patient-year).[9] The instantaneous risk of late mortality peaked between 60 and 80 months after operation.

Patient Survival

At 8.7 years, 56.1 ± 5.8% of the 240 patients had survived *and* retained their original prostheses. Actuarial late survival of patients who had undergone isolated AVR (65.1 ± 8.5%) was significantly better than in those cases where a concomitant procedure had been performed (46.8 ± 8.3%) ($p < .001$).

Valve-Related Events

Infective endocarditis. Nineteen (7.9%) of the 240 patients, or 1.9%/patient-year, experienced IE. Eleven patients (57.9%) survived (70% CL = 43.5% to 71.3%). Ten episodes (52.6%) of compromised bioprosthetic function occurred (70% CL = 38.4% to 66.5%, or 1.0%/ patient-year). Actuarial probability of freedom from all IE was 84.5 ± 5.0% at 8.7 years, while that of PVE was 89.2 ± 4.0%. The instantaneous risk of PVE peaked from 60 to 70 months after operation, while IE that did not compromise valve function appeared as an earlier and constant lower risk (Table I).

Intrinsic tissue failure. Adopting Borkon's definition of ITF,[10] 17 valves failed (7.6%) because of this event (70% CL = 5.8% to 9.9%), or 1.7%/patient-year). Failures occurred from 32 to 91 months after implantation in patients who were ages 23 to 77 years (mean, 54.6 years) at the time of implantation. Ten were male, and seven were female. Calcification of the bioprosthesis was the main cause of tissue failure in 15 instances, one of which contributed directly to the death of the patient;[9] in 5 of these instances, there was also rupture of 1 or more leaflets. In addition, 1 tear and 1 perforation occurred in the absence of calcification. Typical pathological changes have been described in detail.[11,12] Actuarial freedom from ITF was 78.1 ± 6.8% at 8.7 years. The peak instantaneous risk of ITF occurred from 60 to 90 months after implantation (Fig. 1). Intrinsic tissue failure did not affect patient survival. Conversely, actuarial patient survival of those experiencing ITF was 87.5 ± 8.6% at 8.7 years, compared with 55.2 ± 6% for those who did not ($p = .002$).

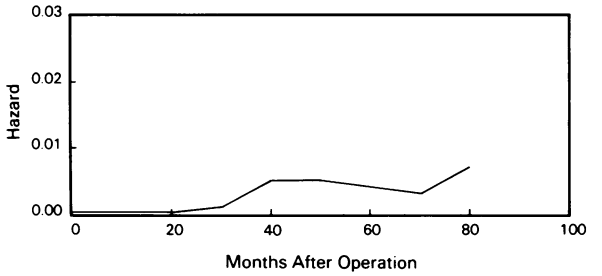

Fig. 1 *Hazard function for intrinsic valve failure.*

Thromboembolism. This was defined as all new focal neurological deficits, either transient or permanent, as well as any clinically detectable noncerebral emboli.[13] Patients with isolated AVR had not been routinely placed on anticoagulant prophylaxis; those having had multivalve surgery received long-term sodium dicumarol therapy. Recognized anticoagulant-related hemorrhage did not occur.[13]

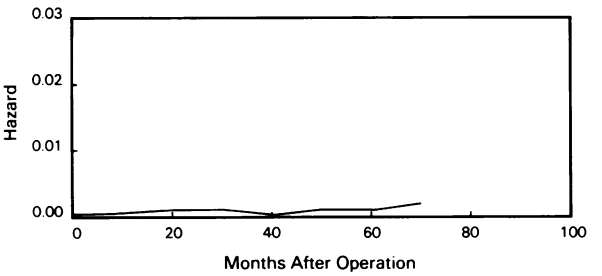

Fig. 2 *Hazard function for thromboembolism.*

Nine patients (3.8%) experienced peripheral thromboembolism, or 0.9%/patient-year. All episodes were nonfatal. Of these events, one calcified, partially thrombosed, failing ISPV gave off transient renal emboli. There was no significant difference in occurrence of peripheral thromboembolism between those patients who underwent isolated AVR and those who underwent concomitant procedures

Fig. 3 *Hazard function for cumulative valve-related events (intrinsic valve failure, thromboembolism, infective endocarditis affecting valve).*

(p = ns). Actuarial probability of freedom from TE at 8.7 years was 91.6 ± 3.2%. After an initial low time-related hazard function, the peak instantaneous risk of TE occurred 60 to 70 months after operation (Fig. 2) (Table I).

Cumulative Valve-Related Events. Thirty-six valve-related events (15% of the 240 patients) occurred within the time-frame of this analysis, at a linearized rate of 3.6 events per 100 patient-years. Actuarial freedom from AVRE was 63.2 ± 7.6%. Six deaths (2.7%) occurred as a consequence, or 0.6%/patient-year, and actuarial freedom from DVRE at 8.7 years

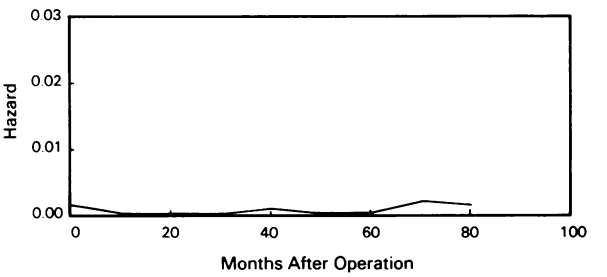

Fig. 4 *Hazard function for death because of cumulative valve-related events.*

was 95.3 ± 2.5%. The peak instantaneous risk of AVRE occurred from 60 to 70 months after operation (Fig. 3); that of DVRE occurred from 70 to 80 months after operation (Fig. 4). Correspondingly, the instantaneous risk of death or reoperation because of a valve-related event, or both, occurred from 70 to 80 months after operation (Fig. 5) (Table I).

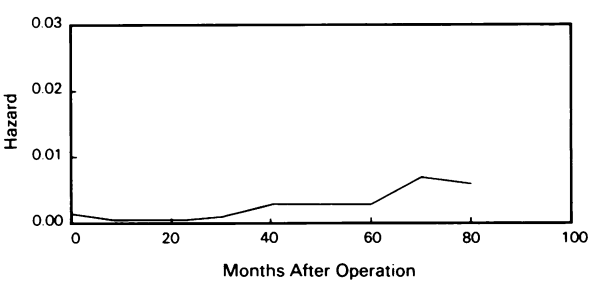

Fig. 5 *Hazard function for death and/or reoperation because of cumulative valve-related events.*

Discussion

This analysis disclosed that a hazard function at 60 to 70 months post-implantation had a significant exponential increase for all analyzed events. Based on these results, we suspect degenerative leaflet changes have taken place and are responsible, at least in part, for the incremental incidence of all events at this time.

TABLE I. Occurrence of Events

Event	Linearized Rate (%)/pt-yr	Actuarial Freedom (%) at 8.7 yrs	Peak Hazard Function (months)
ITF	1.7	78.1 ± 6.8	60-90
TE	0.9	91.6 ± 3.2	60-70
PVE	1.0	89.2 ± 4.4	60-70
AVRE	3.8	63.2 ± 7.6	60-70
DVRE	0.6	95.3 ± 2.5	70-80
D&RVRE	2.7	70.4 ± 7	70-80

ITF = intrinsic tissue failure; TE = thromboembolism; PVE = pericardial valve endocarditis; AVRE = accumulated valve-related events; DVRE = death because of valve-related events; D&RVRE = death and reoperation because of valve-related events

On the basis of these data and personal experiences, we recommend close observation of similar groups of patients and perhaps, in appropriate cases, the initiation of antiplatelet drug prophylaxis 60 months after valve implantation, in an effort to decrease the incidence of thromboembolism and other events.

The appearance of a new murmur 60 to 70 months after implantation warrants full hemodynamic investigation; if a malfunction is discovered, even on a moderate scale, elective bioprosthetic replacement should be considered.[3]

The use of a time-related hazard function is helpful in pinpointing the instantaneous risk of a valve-related event. It is recommended as an additional analytical tool for evaluating valve performance.

References

1. Ionescu MI, Tandon AP, Silverton NP, Chidambaram M, Smith DR. Long-term durability of the pericardial valve. In Bodnar E, Yacoub M (eds): *Biologic and Bioprosthetic Valves. Proceedings of the Third Internation symposium.* Yorke Medical Books, 1986; pp 165-176.
2. Gabbay S, Bortollotti U, Wasserman F, Trindel N, Factor SM, Frater RWM. Long-term follow-up of the Ionescu-Shiley mitral pericardial xenograft. J Cardiovasc Thorac Surg 1984; 88:758.
3. Duncan JM, Cooley DA, Reul GJ, Ott DA, Livesay JJ, Frazier OH, Walker WE. Experience with the St. Jude Medical Valve and the Ionescu-Shiley bovine pericardial valve at the Texas Heart Institute. In Matloff JM (ed): *Cardiac Valve Replacement. Current Status.* Boston, Martinus Nijoff Publishing, 1985; pp 233-245.
4. Gonzalez-Lavin L, Chi S, Blair TC, Jung JY, Fabaz AG, McFadden PM, Lewis B. Five year experience with the Ionescu-Shiley bovine pericardial valve (ISPX) in the aortic position. Ann Thorac Surg 1983; 36:270.
5. Garcia-Bengochea JB, Alvarez JR, de la Pena MG. Long-term clinical results with the Ionescu-Shiley pericardial xenograft valve. In Bodnar E, Yacoub M (eds): *Biologic and Bioprosthetic Valves. Proceedings of the Third International Symposium.* Yorke Medical Books, 1986; pp 205-213.
6. Bove EL, Helak JW, Potts JL, Marvasti MA, Eich RH, Parker FB Jr. Postoperative hemodynamic evaluation of the Ionescu-Shiley prosthesis in the small aortic root. In *Proceedings of the Cardiac Prostheses Symposium.* Pebble Beach, CA, Shiley Inc., 1982; pp 187-192.
7. Lee LT. *Statistical Methods for Survival Data Analysis.* Belmont, CA, Lifetime Learning Publications, 1980.
8. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1985; 53:457.
9. Johnson D, Gonzalez-Lavin L. Myocardial infarction secondary to calcific embolization: An unusual complication of xenobioprosthetic degeneration. Ann Thorac Surg 1986;42:102.
10. Borkon AM, McIntosh CL, VonRueden TJ, Morrow AG. Mitral valve replacement with the Hancock bioprosthesis: Five to ten year follow-up. Ann Thorac Surg 1981;32:127.
11. Johnson DE, Billingham ME, Gonzalez-Lavin L. Pathologic changes in dysfunctional Ionescu-Shiley bovine pericardial heterograft valves. In *Cardiac Prostheses Symposium III.* Irvine, CA, Shiley Inc., 1987; pp 135-145.
12. Schoen FJ, Fernandez J, Gonzalez-Lavin L, Cernaianu A. Causes of failure and pathologic findings in surgically removed Ionescu-Shiley bovine pericardial heart valve bioprostheses. Circulation 1987; 76:618.
13. Gonzalez-Lavin L, Tandon AP, Chi S, Blair TC, McFadden PM, Lewis B, Daughters G, Ionescu MI. Risk of thromboembolism and hemorrhage following mitral valve replacement. A comparative analysis between porcine xenograft and Ionescu-Shiley bovine pericardial valves. J Thorac Cardiovasc Surg 1984; 87:340.