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Donald J. Magilligan Jr.

Joseph W. Lewis Jr.

J. Lancelot Lester III

Paul D. Stein

Mohsin Alam

See next page for additional authors

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Natural History of the Porcine Bioprosthetic Heart Valve

Donald J. Magilligan, Jr, MD,* Joseph W. Lewis, Jr, MD,* J. Lancelot Lester, III, MD,* Paul D. Stein, MD, Mohsin Alam, MD,** Jeffrey B. Lakier, MD,** Julio C. Davila, MD,* and David W. Smith, MPH, PhD*****

The porcine bioprosthesis has been the prosthetic valve of choice at Henry Ford Hospital since October 1971. By 1979, 23 cases of degeneration had been seen, and the rate seven years after implantation was 16%. Now, with a ten-year follow-up, there are 41 degenerated valves. After seven years, the percent free of degeneration is 88% (SE of 2% [standard error]); at eight years, 82% (SE of 2.9%); at nine years, 80% (SE of 3.4%); and at ten years, the percent free of degeneration is 69% (SE of 6.5%). There was no difference in degeneration between men and women, between aortic or mitral position, or between the valves which were or were not rinsed in antibiotics. The incidence of degeneration was significantly greater in patients under 35 years of age. Contrary to our expectations, the number of valves removed for degeneration has not increased linearly, although the number at risk has continued to rise. In 1977, we removed four valves for degeneration; in 1978, eight valves; in 1979, 11 valves; in 1980, five valves; and in 1981, ten valves. The duration of implantation for degenerated valves has increased from 56 months (SD [standard deviation] of 11 months) in 1977-78 to 77 months (SD of 19 months) in 1981. Analysis of cohorts from 1972, 1973, 1974, all now followed for seven years, reveals that at seven years the percent free of degeneration for 1972 is 88% (SE of 4.4%); for 1973, 83% (SE of 4.8%); and for 1974, 95% (SE of 2.6%). Although a difference is suggested, it is not yet statistically significant ($p = .48$) due to the small number of valves degenerating. The incidence of porcine bioprosthetic degeneration appears to be decreasing, possibly because valves manufactured later in the series are more durable.

In the search for an ideal tissue heart valve prosthesis, the porcine aortic bioprosthesis was a natural progression from the aortic allografts. Allografts, using tissue from the same species, were used enthusiastically, as first reported by Duran in 1962 (1), because they improved the hemodynamics and decreased thrombogenicity when compared to mechanical protheses. Problems of availability, sterility, and durability next led to the use of strut-mounted fascia lata valves (2). At a workshop on tissue heart valves in 1969, allogeneic fascia lata valves seemed to have the greatest promise, while xenogenic valves, using tissue from different species, were relegated to a minor position (3). However, the poor durability and high infection rate of the fascia lata valves (4) led to the use of xenogenic valves. The aortic valve of the pig and calf seemed to be the best choices based on the relative vascularity and similarity of their physical properties to those of human valves (3). O'Brien (5) showed that these valves were satisfactory for clinical use. The one drawback of the porcine aortic valve is that its right coronary leaflet contains an inflexible septal shelf of myocardium that reduces the active orifice area and introduces variability in its performance as a bioprosthesis (6).

Originally, xenogenic valves were treated with mercurial salts to sterilize them and destroy their antigenicity. However, these valves failed in a short time because of collagen degeneration and inflammatory cell infiltration

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*Department of Surgery, Division of Thoracic Surgery, Henry Ford Hospital
**Department of Internal Medicine, Division of Cardiovascular Medicine, Henry Ford Hospital
***Statistical Research Laboratory, University of Michigan, Ann Arbor, MI
Address reprint requests to Dr. Magilligan, Jr, Department of Surgery, Division of Thoracic Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202

(7). O'Brien (8) and Ionescu (9) proposed using formalin-treated valves, but these valves deteriorated rapidly due to a reversible binding of formalin with valve protein, which led to a reversal of collagen cross-linking in vivo. The resultant loss of fixation led to mechanical failure of the disrupted collagen and an immunologic reaction with the unbound, antigenically active proteins (10). Glutaraldehyde, used as a tanning agent by the shoe industry because it produces stable collagen cross-linking while maintaining flexibility, was used by Carpentier (3). Although the initial results reported in 1969 were favorable, it was not until an oxidizing step with methylperiodate was eliminated that buffered glutaraldehyde, in its present concentrations, could be used to preserve collagen both in vivo and in vitro (11).

Valves were treated in buffered glutaraldehyde and then mounted on dacron or teflon-covered stents using the two-suture line technique that Barrat-Boyes developed for aortic allografts (12). Reis' introduction of the flexible stent (13) was an important step since it markedly decreased mechanical stress on the tissue and resulted in less fatigue. Consequently, by 1970, a porcine bioprosthetic valve was being produced that was sterile and readily available in all sizes. This prosthesis had low antigenicity and projected durability greater than either allografts or formalin-treated valves.

The porcine xenograft bioprosthesis has been the prosthetic valve of choice at Henry Ford Hospital since October 1971. The valve has performed well hemodynamically and has a low incidence of thromboembolism. As with all tissue valves, the main concern is its durability. The following is a report on the natural history of the porcine bioprosthesis, with a maximum follow-up of ten years, four months.

Materials and Methods

All patients who have had a porcine bioprosthetic valve inserted are followed by yearly visit or letter as close as possible to the anniversary of implantation. All patients were accounted for in 1981; follow-up was 100%.

Spontaneous degeneration of the porcine bioprosthesis is indicated clinically by valve incompetence or stenosis and confirmed by degeneration of changes on gross or histological examination of the explanted valve. Degeneration was not judged to be spontaneous in the presence of clinical, bacteriological, or histological evidence of endocarditis.

Actuarial curves for valve survival without degeneration were constructed according to the method of Berkson and Gage (14). Confidence limits were determined as described by Irwin (15). Groups were compared by the chi-square test with matrix inversion (16).

Results

Forty-one instances of spontaneous valve degeneration have occurred in a follow-up period of up to 124 months. Sixteen patients have been followed longer than ten years. The survival of valves without degeneration, calculated according to the life table method (14), is plotted in Fig. 1. The earliest degenerated valve occurred at 14 months, the next at 40 months. The percent valve survival without degeneration was as follows: at five years, 96% (SE of 1.0%); at six years, 93% (SE of 1.5%); at seven years, 88% (SE of 2.0%); at eight years, 82% (SE of 2.9%); at nine years, 80% (SE of 3.4%); and at ten years, 69% (SE of 6.5%).

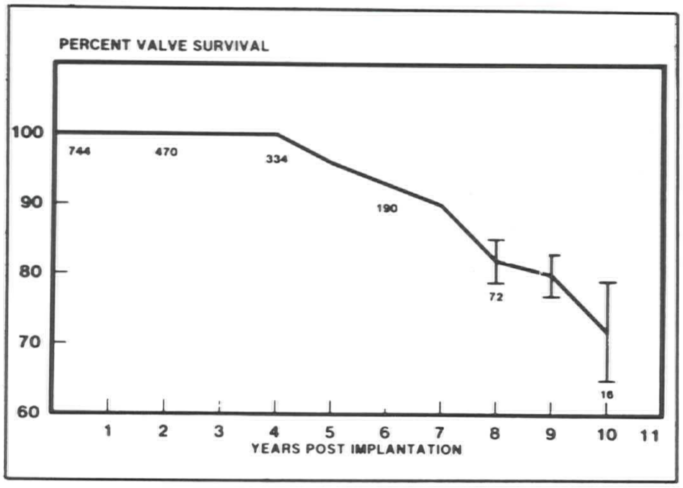

Fig. 1

Survival of valves without degeneration with longest follow-up at 10 years.

There was no significant difference (p = 0.30) between male patients (362 valves) and female patients (382 valves). There were 284 aortic, 427 mitral, and 33 tricuspid valves at risk. Valve survival without degeneration indicated no significant difference (p = 0.77) between aortic and mitral valves.

Survival without degeneration was compared for five age groups: up to 20 years, 21 to 25 years, 26 to 30 years, 31 to 35 years, and older than 35 years. Degeneration was shown to be similar for all age groups under 35 years. However, the difference between those under 35 and those over 35 was significant (p = .005), as shown in Fig. 2.

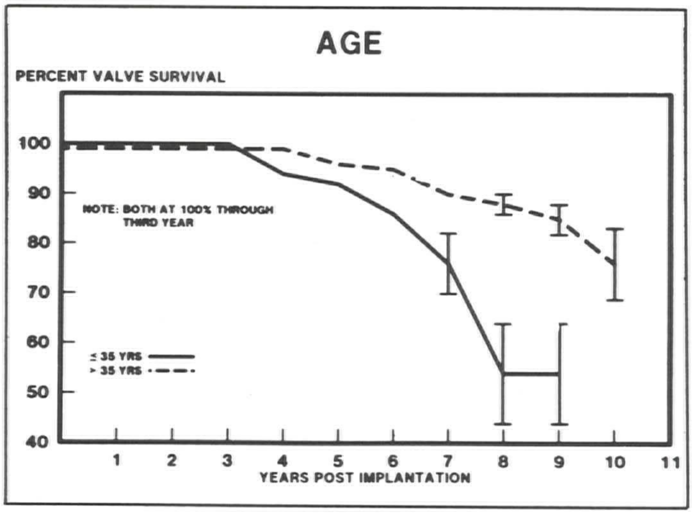

Fig. 2

Survival of valves without degeneration for those patients under 35 and those over 35 years of age. The difference was significant (p=.005).

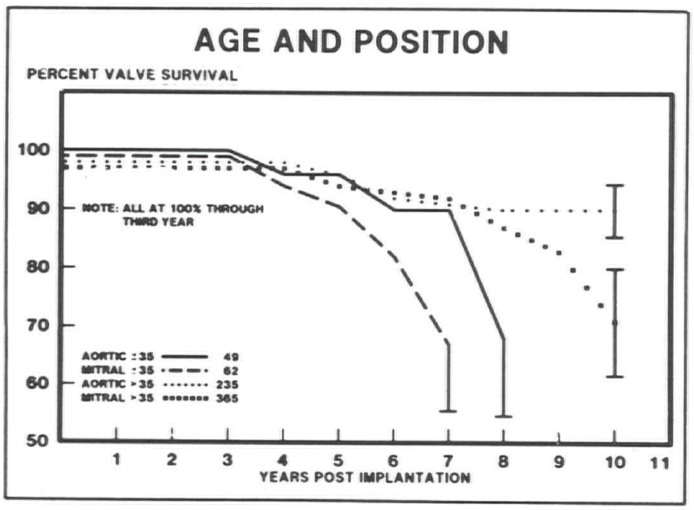

Fig. 3

Survival of valves without degeneration for patients under 35 and over 35 years of age and for position. For both aortic and mitral positions, patients under 35 years old had a poorer response than patients over 35 years old.

There was no significant difference (p=0.69) when valve position was analyzed by sex of the patient. However, when valve position and the age groups under 35 and over 35 years were analyzed, those over 35 (Fig. 3) had a significantly greater degeneration free percentage for both aortic and mitral positions (p = 0.03).

Before October 1974, the porcine bioprosthetic valves were immersed in a solution containing 1 gm neomycin and 10,000 units of bacitracin in 100 ml of saline, as outlined in the manufacturer's instructions (17). These instructions were revised in October 1974, with the warning that neomycin and bacitracin "will cause a chemical change tending to make the leaflets stiff" (8). Subsequently, in our institution, valves were rinsed only in lactate Ringer's solution. To determine whether antibiotic rinsing might play a part in degeneration, we compared the survival of valves implanted before October 15, 1974 ("early") to that of valves implanted subsequently that had not undergone antibiotic rinsing ("late"). At six years, the survival for early valves was 93% (SE of 1.9%) and for late valves it was 94% (SE of 2.5%) (p=0.83).

In 1980, we reported eight years of experience with porcine bioprosthetic valves (19). During the previous year, 11 valves had been removed for degeneration, and we expected the number of valves requiring removal for degeneration to increase linearly with the increasing number of valves at risk and increasing length of implantation. However, as seen in Fig. 4, this has not been the case. In 1977, four valves were removed for spontaneous degeneration, eight in 1978, 11 in 1979; in 1980 only five valves were removed for degeneration, in 1981, ten, and thus far in 1982, only two. The total number of valves at risk has increased each year; and in October 1981, there were 557. Similarly, the duration of implantation until degeneration has lengthened. Whereas in 1977 and 1978 it was 56 months (SD of 11.8 months), the time increased in 1979 (71 months, SD of 14.4 months), 1980 (79 months, SD of 15.7 months), 1981 (77 months, SD of 19 months), and in 1982 (113 months, SD of 1.4 months). Thus, degeneration is occurring less frequently than was predicted in 1980.

To evaluate further this evidence that valves implanted early in the series behaved differently from those implanted later, we analyzed valve cohorts by year of

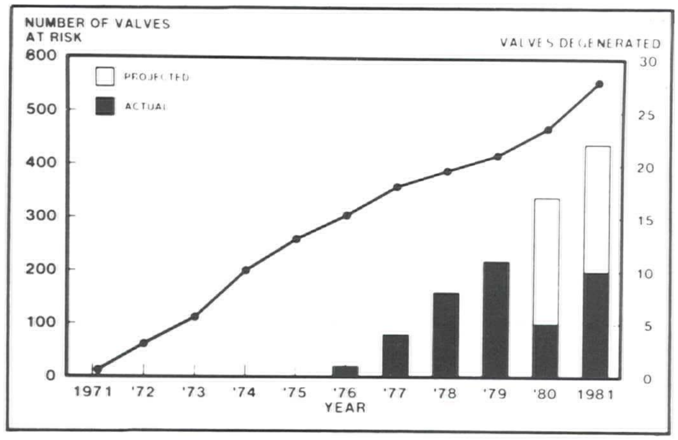

Fig. 4

Degenerated Valves Removed: 1971-1981.

implantation. Excluding 1971 when only 15 porcine valves were inserted (none of which degenerated), three cohorts with at least seven years' follow-up are available for analysis. At seven years, the percentage of valves free of degeneration is as follows: 1972, 88% (SE of 4.4%); 1973, 83% (SE of 4.8%); 1974, 95% (SE of 2.6%). Although the difference between these three cohorts is not statistically significant due to the small numbers of degenerated valves, the evidence suggests that valves implanted in 1974 are more durable than those implanted in 1972 and 1973 (Fig. 5). However, this is true only if the cohorts in the three years are equally matched for age, which is the one risk factor for degeneration. The mean age for the three years was similar (1972, 47.4 years, SD of 13.7 years; 1973, 47.3 years, SD of 13.9 years; 1974, 46.5 years, SD of 13.1 years), but the distribution among patients 35 years and younger was dissimilar. In 1972, 15 of 73 (20%) were 35 years and younger; in 1973, 15 of 78 (19%); and in 1974, 5 of 80 (8%). This difference is important if the patients with degenerated valves in 1972 and 1973 were 35 years or younger. Of the 13 degenerated valves in the 1972 cohort, 9 (69%) were in patients under 35 years; in 1973, 4 of 14 (29%); and in 1974, 2 of 4 (50%). The difference in the rate of degeneration between the 1972 and the 1974 cohort may be due to the larger number of younger patients in the 1972 group. However, this does not explain why the 1973 group has a greater incidence of degeneration than the 1974 group, since most degenerated valves occurred in patients over 35 years old. Incidence of degeneration in 1982 is less than predicted in 1980. Only further follow-up will show if this trend is real and give clues to the reasons.

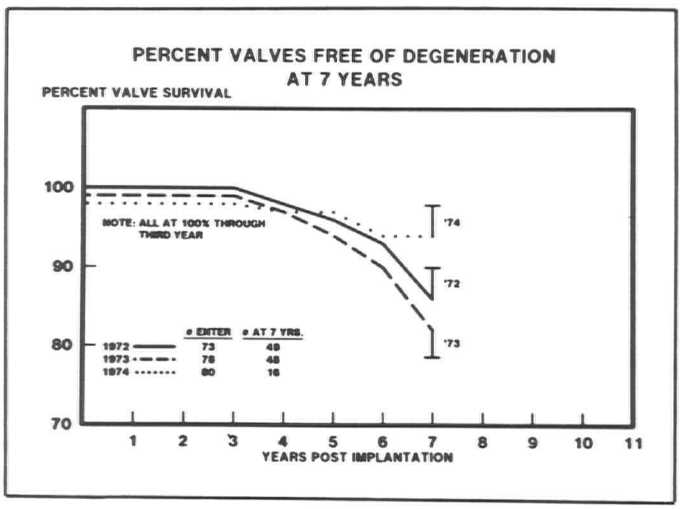

Fig. 5

Survival of valves without degeneration for the cohorts from 1972, 1973, 1974, all of which have had at least seven years' follow-up.

Discussion

The limitation of a tissue valve is its durability. Tissue failure has led to the abandonment of homografts (20), fascia lata valves (2), and xenografts fixed with mercurials and formalin (7,10). The first xenobioprostheses treated with the buffered glutaraldehyde were inserted in 1969 (21), and more time is required to evaluate Carpentier's prediction of 80% tissue survival for ten years (22).

The glutaraldehyde-treated procine bioprosthesis has been subjected in vitro to durability evaluation by accelerated fatigue testing. Although these tests show tears near the commissures (23,24) and collagen disruption due to compression force at the base of the leaflet (25), it is difficult to apply the results to clinical situations. The mode of failure may be similar to that seen clinically, but it is difficult to predict whether the failure will occur after two (23) or 12 (25) years. We agree with Rainer that in vitro studies do not allow us to predict the fate of the tissue valves in a clinical setting (26). A number of reports describe the spontaneous degeneration or primary tissue failure of porcine bioprosthetic valves (26-35).

Gross and microscopic pathology of valves that have undergone spontaneous degeneration ranges from simple tears at the commissures (36) and isolated cusp perforation (37) to variable degrees of surface and full thickness calcification (28, 31-35). Histology of the porcine bioprosthesis has been extensively studied before implantation and at various periods after it has been removed (38). Before implantation, but after processing, endothelium and acid mucopolysaccharides are lost. Less than two months after implantation there is insudation of plasma proteins, formation of a surface layer of fibrin, and deposition of macrophages, giant cells, and platelets. Late changes consist of progressive disruption of collagen, erosion of valve surfaces, formation of platelet aggregates, and accumulation of lipid. Progressive breakdown of collagen ultimately leads to tissue failure (38-40). However, this report of collagen breakdown has not been confirmed by others (41) and is not consistent with the persistent satisfactory functioning of the valve which occurs in most patients for up to nine years. An immunologic reaction has not been shown to be associated with degeneration like that which occurs with formalin-treated porcine bioprostheses (10).

Overall valve survival without degeneration (Fig. 1) at six, seven, and eight years has improved since our 1980 report (19). As more valves have been evaluated, the standard errors have become smaller. The leading edge of a clinical life table does not provide an accurate interpretation of events, since the large standard errors make this information unreliable (42). We expect our nine-year data (SE of 3.4%) to be fairly accurate, but the ten-year data with 16 patients (SE of 6.5%) may overestimate the incidence of degeneration.

As in 1980, we found no significant difference in the incidence of degeneration between men and women, between the aortic or mitral position, or between valves rinsed in antibiotic solution or not so treated.

The incidence of degeneration is greater in younger patients. Although our calculations suggest that the age dividing line for durability might be 20 years, this could not be shown statistically. As in the 1980 report, statistically significant differences occurred between patients under 35 years old and those over 35 years old ($p = .005$). If the dividing age is falling, statistical significance requires study of a larger number of young patients.

In 1980, response to our report of 23 cases of valve degeneration (19) varied from disbelief at the low incidence to the prediction that primary valve failure would inevitably occur within ten years for all glutaraldehyde-treated bioprostheses. As the experience increases in all large series, the incidence of degeneration in the past two years has been less than predicted in 1980. To explain this decrease, we find only that the 1974 cohort of valves had a seven-year survival of 95% compared to 88% and 83% for 1972 and 1973, respectively. Increased experience suggests that valves produced in 1974 were more durable than those of 1972 and 1973.

The fact remains that in 1982 we are removing far fewer porcine bioprosthetic valves for degeneration than was predicted in early 1980.

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