Porcine Xenograft Valves
Long-term (60-89-month) Follow-up

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SUMMARY An analysis of 211 patients who had porcine xenograft valve replacements at Henry Ford Hospital between October 1971 and March 1974, was accomplished, with 100% follow-up. The follow-up period extended from 60-89 months after implantation. One hundred sixty-seven patients with 192 valves survived the perioperative period and were subjected to life table analysis. Hemodynamically significant porcine xenograft degeneration that required reoperation occurred in 18 patients, two of whom had infective endocarditis. Only four valves failed within 48 months of surgery. Ten of 42 (23.8%) patients with isolated aortic valve replacement and eight of 102 patients (7.8%) patients with isolated mitral valve replacement required reoperation ($p < 0.01$). In patients under 25 years of age, six of nine surviving patients had repeat operations. Our data indicate that porcine xenograft degeneration is related to the duration of implantation and the age of the patient at the time implantation was performed. In addition, porcine xenograft valves in the aortic position are more likely to degenerate than are those in the mitral position.

THE GLUTERALDEHYDE-prepared porcine xenograft is one of the most encouraging valve substitutes available. The initial highly satisfactory results reported with this prosthesis have resulted in its use for replacement of diseased aortic, mitral and tricuspid valves.$^{1-4}$ Although the porcine xenograft valve has good hemodynamic features and a low thromboembolic rate,$^{1, 2, 5, 4}$ it has the same potential for late degeneration as other bioprosthetic valves.$^{6}$ Recent reports have suggested a low incidence of degeneration in adult patients$^{7}$ and a higher rate in children.$^{8}$ We recently described the echocardiographic characteristics of degenerated porcine xenografts.$^9$ Because of these observations we analyzed the first 211 patients in whom a gluteraldehyde porcine xenograft was implanted at this institution. This enabled us to obtain a minimum 5-year follow-up in order to assess the long-term durability of the valve.

Methods

Two hundred eleven patients received 252 porcine valve xenografts between October 1971 and March 1974. All deaths during the initial hospitalization and up to 1 month postoperatively were considered perioperative deaths, and accounted for 44 patients. There were 167 surviving patients with 192 valves 1 month after surgery. Information on all these was obtained regarding cardiac status, hospital admissions after valve replacement, evidence of thromboembolic episodes and current medication. A further 42 patients died during the follow-up period, leaving 125 patients alive at the end of the study (March 1979). Of these, 112 patients were evaluated at Henry Ford Hospital during a closing period (January through March 1979). The remaining 13 patients were unable to return for follow-up examination, but 12 were contacted by telephone and one by letter. If any symptoms were reported the patient's physician was contacted.

Xenograft valve failure was diagnosed if there was disruption or distortion of the valve mechanism resulting in a hemodynamic lesion necessitating xenograft replacement. All patients included under this definition of xenograft dysfunction thus had the valves replaced.

In this paper we assess the long-term durability of the porcine xenograft. Hence, the 1-month mortality or perioperative mortality is not included in long-term survival statistics. Several reports$^{6, 4}$ and our current experience indicate that there is no difference in perioperative mortality when using xenografts compared with other valve prostheses. Patients who developed infective endocarditis and died during the course of therapy and in whom the cause of death was not due primarily to valve failure are not included in the definition of valve dysfunction. Also, patients who died without a necropsy being performed are not included as valve failures. Both of these groups are included in the overall mortality. Systemic thromboembolism was diagnosed if a persistent neurologic deficit occurred postoperatively or if absent or diminished peripheral pulses were noted. Bland systemic emboli to other viscera were not noted in this series.

Patients with large left atria and those with atrial fibrillation were anticoagulated and were maintained indefinitely on warfarin unless bleeding complications occurred.

Statistical analysis comparing the rate of reoperation in the mitral and aortic groups was done using the chi-square method for cumulative actuarial analysis, based on a generalized Kruskal-Wallis test.$^{10}$ Statistical analysis comparing valve degeneration between the younger patients (younger than 25 years) and older patients (older than 25 years) was done using standard chi-square testing.

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Results

There were 192 porcine xenograft valve insertions in the 167 patients who survived longer than 1 month. One hundred two patients had mitral valve replacements, 42 aortic, 13 mitral and aortic, eight mitral and tricuspid and two mitral, aortic and tricuspid. Thus, 125 mitral, 57 aortic and 10 tricuspid xenograft valves were followed long-term. The age range of the patients was 8–77 years (mean age 50 years). Nine patients were under 25 years. One hundred seventeen patients were female. At the end of the follow-up period, 84 patients with mitral, 27 with aortic, eight with aortic and mitral, one with mitral, aortic and tricuspid and five with mitral and tricuspid xenografts (total 125 patients) were alive.

Actuarial survival curves for the group as a whole and for subsets of valve replacements are shown in figures 1–3. Figure 1 shows overall mortality for the 167 patients alive 1 month after surgery. A progressive and almost linear mortality is seen, with an 89-month cumulative survival of 72%. The timing of patients requiring reoperation as a result of valve failure is shown in figure 2. The cumulative valve failure rate at 48 months was only 4%; however, in the next 30 months this figure almost tripled, with an additional 11% valve failures.

During the period of follow-up, 18 of the 167 had reoperation for replacement of the porcine xenograft valve (fig. 2, table 1). In 15, this was necessary because of spontaneous dysfunction of the xenograft. There was no evidence of infective endocarditis either before surgery or on histologic examination of the removed valve. Two patients had had preoperative evidence of infective endocarditis (one aortic and one mitral) and one patient had a thickened aortic porcine valve replaced at a second operation to repair paravalvar leaks. The aortic valve was replaced in 10 of the 18 patients and the mitral valve in the remaining eight. Ten of the 42 patients (23.8%) with isolated aortic and eight of the 102 patients (7.8%) with isolated mitral porcine xenografts required reoperation. Using the life-table curves at 89 months (fig. 3), the difference between the cumulative reoperation rates for mitral

![Figure 1. Actuarial survival curve for all patients starting at 1 month after valve replacement. A 72% survival appears at 89 months.](attachment:figure1.png)

![Figure 2. Time of reoperation for valve failure starting 1 month after first valve replacement. The cumulative valve failure rate was 4% at 48 months and 15% at 89 months. Note that the valve failure rate almost tripled from 48 to 89 months.](attachment:figure2.png)
(0.88 ± 0.04 (SEM)) and aortic (0.61 ± 0.10) porcine xenografts is statistically significant (p < 0.01).

In the nine patients younger than 25 years of age in whom the initial porcine xenograft valve implantation was carried out, six required reoperation, five of whom showed spontaneous degeneration (55.5%), compared with 12 of 158 patients over the age of 25, 11 of whom showed spontaneous valve degeneration (7%) (p < 0.01). Four of the patients younger than 25 years had mitral xenograft valve dysfunction and in the remaining two, the aortic xenograft required replacement (table 1). Figures 4 and 5 demonstrate examples of spontaneous valve degeneration. Severe calcific degeneration of an aortic valve xenograft (patient 16) (table 1) is shown in figure 4, and a tear in a mitral xenograft at a commissure with involvement of two leaflets (patient 14) (table 1) in figure 5.

Culture-proved infective endocarditis occurred in five patients, two of whom presented as valve failures. The latter two patients required valve replacement.

![Plot of cumulative proportion of reoperation](image)

**Figure 3.** The disparity in failure rates for aortic vs mitral valve xenografts starting at 1 month after first valve replacement. Note that the incidence of valve failure in the aortic position (23.8%) was significantly higher than in the mitral position (7.8%) (p < 0.002). MVR = mitral valve replacement; AVR = aortic valve replacement.

### Table 1. Clinical Description of Patients Requiring Reoperation

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age (years)/Sex</th>
<th>Valve site</th>
<th>Duration (months)</th>
<th>Valve description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15/M</td>
<td>Aortic</td>
<td>17</td>
<td>Valve dehiscence around 1/3 circumference with ruptured leaflet attachment</td>
</tr>
<tr>
<td>2</td>
<td>25/M</td>
<td>Aortic</td>
<td>25</td>
<td>Thickened valve leaflets found at reoperation for paravalvar leak</td>
</tr>
<tr>
<td>3</td>
<td>61/M</td>
<td>Aortic</td>
<td>39</td>
<td>One cusp torn at attachment, second cusp perforated</td>
</tr>
<tr>
<td>4</td>
<td>33/F</td>
<td>Aortic</td>
<td>44</td>
<td>Infective endocarditis; multiple sterile vegetations with tear in one leaflet</td>
</tr>
<tr>
<td>5</td>
<td>35/M</td>
<td>Aortic</td>
<td>48</td>
<td>Torn leaflet with gross calcification of valve</td>
</tr>
<tr>
<td>6</td>
<td>46/F</td>
<td>Mitral</td>
<td>52</td>
<td>Degenerated valve; torn leaflet</td>
</tr>
<tr>
<td>7</td>
<td>21/M</td>
<td>Mitral</td>
<td>54</td>
<td>Drug addict; preoperative <em>strep. fecalis</em> endocarditis, valve destroyed; no active infection at surgery</td>
</tr>
<tr>
<td>8</td>
<td>55/F</td>
<td>Mitral</td>
<td>57</td>
<td>Diffuse calcification of all three cusps; edges of leaflets destroyed</td>
</tr>
<tr>
<td>9</td>
<td>49/M</td>
<td>Aortic</td>
<td>61</td>
<td>Valve calcified and fibrosed</td>
</tr>
<tr>
<td>10</td>
<td>58/F</td>
<td>Mitral</td>
<td>61</td>
<td>Focal calcification of leaflets with thickening of edges; two leaflets torn</td>
</tr>
<tr>
<td>11</td>
<td>16/M</td>
<td>Mitral</td>
<td>63</td>
<td>Widely incompetent, calcified valve</td>
</tr>
<tr>
<td>12</td>
<td>70/F</td>
<td>Mitral</td>
<td>68</td>
<td>Calcified, rigid valve, leaking</td>
</tr>
<tr>
<td>13</td>
<td>20/F</td>
<td>Mitral</td>
<td>69</td>
<td>Severely calcified, leaking valve</td>
</tr>
<tr>
<td>14</td>
<td>21/M</td>
<td>Mitral</td>
<td>69</td>
<td>Two leaflets torn at commissure</td>
</tr>
<tr>
<td>15</td>
<td>60/M</td>
<td>Aortic</td>
<td>71</td>
<td>Leaflets thin, torn along commissural supports and frayed along coapting margins</td>
</tr>
<tr>
<td>16</td>
<td>33/M</td>
<td>Aortic</td>
<td>72</td>
<td>Aortic valve calcified, stenosed and incompetent</td>
</tr>
<tr>
<td>17</td>
<td>69/M</td>
<td>Aortic</td>
<td>73</td>
<td>One cusp frayed with tear in area of attachment to sewing ring</td>
</tr>
<tr>
<td>18</td>
<td>63/M</td>
<td>Mitral</td>
<td>76</td>
<td>Torn leaflets</td>
</tr>
</tbody>
</table>
after treatment of the endocarditis. The remaining three patients died while under treatment for infective endocarditis and one of these had necropsy evidence of aortic and mitral porcine xenograft stenosis. The other two patients had only slightly thickened valves with small vegetations at necropsy. One died after a cerebral embolus and the other after a coronary artery embolus. Three further patients who died during the follow-up period had necropsies performed. In all three instances the valve was reported to be macroscopically normal.

Twenty of our patients (9.5%) experienced systemic thromboembolic events (table 2). Fourteen of these had mitral valve replacements (12 mitral and two aortic and mitral). All but one had atrial fibrillation. Systemic emboli occurred in six patients who had isolated aortic valve replacement, two of whom had chronic atrial fibrillation. Five of the thromboembolic events in patients who had a mitral valve inserted occurred within the first month, and one of these patients died. Thromboembolic events were directly responsible for the death of the patient in six other instances (three mitral valve, two aortic valve and one mitral and aortic valve). Three other patients died 8 months, 6 years and 5 years after a cerebrovascular accident that left them partially disabled.

All 112 patients examined from January 1979 to March 1979 had improved symptomatically compared with their preoperative New York Heart Association classification.

Discussion

There is little doubt that prosthetic heart valve replacement has resulted in symptomatic improvement of survivors and an increased overall survival of patients with valvular heart disease. However, the diversity and number of available valve prostheses bears witness to our failure to achieve a satisfactory valve substitute. In 1969, Carpentier and his associates started using gluteraldehyde-prepared porcine xenografts, with encouraging results. Since the Hancock porcine xenograft became readily available in 1971, it has been used extensively and most of the reports reveal a low incidence of valve failure.

In our series, 167 patients with 192 valves survived the perioperative period. Forty-two patients died during the subsequent follow-up period. Six of these died secondary to known valve failure. In 12 other patients, valvular degeneration occurred and required valve replacement. In our series only four of the 18 documented valve failures occurred within 48 months of insertion and one of these was associated with infective endocarditis. The incidence of valve degeneration increased significantly 4 years after operation (fig. 2). Failure occurred in 7.8% of the mitral xenograft valves and in 23.8% of the aortic valve replacements. This rate of valve failure may represent an optimistic

| Table 2. Incidence of Thromboembolism in 211 Patients After Xenograft Valve Replacement |
|----------------------------------------|--------|---------|----------|--------|
| Valve                   | Early  | Late    | Total    | %      |
| Mitral                  | 4      | 8       | 12/118   | 10.2   |
| Aortic                  | 1      | 5       | 6/55     | 10.9   |
| Mitral and aortic       | 1      | 1       | 2/21     | 9.5    |
| Total                   | 6      | 14      | 20/211   | 9.5    |

Early is less than 1 month after replacement; late is more than 1 month after replacement.
view, because a proportion of the patients who died postoperatively with evidence of congestive heart failure and in whom a necropsy was not performed may have had undiagnosed valve degeneration. The incidence of valve dysfunction in other reported series is difficult to ascertain because of relatively abbreviated periods of follow-up. In a recent series reported by Cohn et al., 7 323 patients were reported, with a mean follow-up of 33 months. Only 58 patients in the series were followed for longer than 48 months and 29 were followed for more than 60 months, the latter comparable to our series. Nevertheless, seven patients developed valve dysfunction. Although the authors did not discuss the duration of implantation of the dysfunctioning valves, the incidence of dysfunction after 48 months is likely to be considerably higher than the reported incidence of 1.4% for the total group (seven of 323). Particularly noteworthy in our series is the finding that six of nine patients younger than age 25 years who survived the perioperative period had the xenograft replaced for valve-related problems. This high incidence of valve failure in younger patients has also been noted by Kutsche et al., 8 who reported xenograft valve dysfunction in three of nine patients younger than age 15 years, occurring at 3.3, 3.6 and 4.8 years after implantation. The cause for the poor prognosis of the valve in this age group is not apparent. However, these data support our own observations and emphasize that when studying the long-term viability of biologic prostheses, where aging is an essential factor, short-term studies are of little value.

The gross pathology of the dysfunctioning porcine xenograft valves in our patients ranged from simple perforation of a cusp and tearing of a cusp from its commissural support to marked calcification and cusp degeneration. Several reports have now described the light microscopic and structural changes occurring in gluteraldehyde-prepared porcine valves. Light microscopy demonstrates early fibrin deposition 20-22 with a later tendency to histiocyte and giant cell accumulation. 2, 20, 22 Calcification of porcine xenografts in several patients with chronic renal failure suggested that these patients may be more susceptible to degenerative changes. 23, 24 None of our patients had chronic renal failure or abnormalities of calcium metabolism. Ultrastructural analysis of fresh unimplanted valves, valves removed less than 2 months after insertion and valves removed 2-76 months after insertion suggest progressive disruption of collagen fibers. All valves inserted at Henry Ford Hospital up to October 1974 were inserted after rinsing with neomycin and bacitracin. This practice, initiated on the advice of Hancock laboratories (Davila JC: personal communication) was discontinued after a warning from them that antibiotic rinsing may affect leaflet flexibility. Whether the antibiotic treatment contributed to valve dysfunction in our patients is debatable. Many of the surviving patients with similarly prepared xenografts have normally functioning valves both clinically and echocardiographically. Furthermore, degenerative changes similar to those reported in this study have been observed by others, apparently without antibiotic pretreatment. 2, 20-24

In our series there is a statistically significant higher failure rate for aortic valves than for mitral valves, 23.8% vs 7.8% (p < 0.01). This may relate to different hemodynamic stresses imposed by the relatively poor hydraulic function of the xenograft valve in the aortic compared with the mitral position. 19 Apart from earlier degeneration of the xenograft valve in patients 25 years or younger, there has been no correlation of valve failure with sex, race, blood pressure or renal status. Although thrombosis of porcine xenografts has been reported, 20-24 this complication did not occur in our series.

Infective endocarditis is an important complication of prosthetic valve replacement. 25-28 Some reports have suggested that endocarditis occurring on heterograft valves is more easily treated than on other prosthetic valves. 27, 28 Ferrans and co-workers have pointed out several important differences between porcine valve heterografts and other valve prostheses. Particularly with heterografts, the prosthetic material itself is infected, with possible resultant destruction. Thus, although antibiotic therapy should be initiated in all instances, valve replacement should be performed if progressive hemodynamic dysfunction occurs.

A low incidence of thromboembolism was initially reported in patients with porcine xenograft valve replacements. 5, 20-30-32 The 9.5% incidence of thromboembolic events occurring in our patients is, however, not surprising, considering that 48% of the patients had atrial fibrillation associated with left atrial enlargement preoperatively. Early thromboembolism occurs possibly secondary to preexisting atrial thrombi. In patients with atrial fibrillation and large left atria secondary to mitral valve dysfunction, continued stasis after valve replacement is likely, and may be aggravated by left ventricular dysfunction, an occasional occurrence in the group. 44 We recommend long-term anticoagulation after xenograft valve replacement in patients with atrial fibrillation, large left atria and residual left ventricular dysfunction.

In summary, after insertion, porcine xenograft valve failures increase in frequency 48 months after replacement. The incidence of valve failures is high in young persons. The failure rate for the aortic xenograft is significantly higher than for the mitral xenograft. Thromboembolism still occurs, but appears to be primarily related to persistent atrial fibrillation. We recommend long-term anticoagulation in all patients with atrial fibrillation or large left atria. Despite these limitations of the gluteraldehyde-preserved porcine xenograft, it is probably the best available valve prosthesis, particularly for the mitral position.

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