Intermediate Term Results of Isolated Mitral Valve Replacement with Glutaraldehyde-Preserved Porcine Xenograft Valve: Clinical and Hemodynamic Comparison between Hancock Valve and Angell-Shiley Valve

YUZURU KAGAWA, KOICHI TABAYASHI, YASUYUKI SUZUKI, TAKASHI ITO, NAOSHI SAT0 and TOGO HORIUCHI

Department of Thoracic and Cardiovascular Surgery, Tohoku University School of Medicine, Sendai 980

KAGAWA, Y., TABAYASHI, K., SUZUKI, Y., ITO, T., SAT0, N. and HORIUCHI, T. Intermediate Term Results of Isolated Mitral Valve Replacement with Glutaraldehyde-Preserved Porcine Xenograft Valve: Clinical and Hemodynamic Comparison between Hancock Valve and Angell—Shiley Valve. Tohoku J. exp. Med., 1986, 150 (1), 37–50 —— Clinical and hemodynamic assessments were carried out for 30 cases, who underwent isolated mitral valve replacement with glutaraldehyde-preserved porcine xenograft valve. The cases were divided into two groups, according to the types of prostheses. Group H comprised 23 cases with Hancock 342 valve and group AS, 7 cases with Angell-Shiley valve. Mean (s.d.) follow-up periods were 4.0±0.7 in group H and 4.6±0.6 years in group AS. Incidence of valvular malfunction was 3.3 in group H and 9.3% per patient-year in group AS. Cumulative survival and event-free rates were calculated by actuarial method, which revealed 91 and 83% in group H and 70 and 71% in group AS at 6 years after operation. Hemodynamic assessments were carried out in 20 cases, in which complete data at rest and during exercise were obtained. Valvular function deteriorated during exercise in both groups. Parameters showing valvular function in group AS were worse than those in group H. It is concluded from this study that (1) intermediate late results are satisfactory in group H, (2) incidence of valvular malfunction is high in children and in group AS, (3) thromboembolisms are seen even in cases with recourse to anticoagulant, (4) xenograft valves are stenotic especially in high flow state and (5) valvular function of AS valve is inferior to H valve. —— mitral valve replacement; porcine xenograft valve; survival rate; event-free rate; valvular function

Several types of glutaraldehyde preserved porcine xenograft valves have been widely used in the field of cardiac valvular surgery since early 1970’s in anticipation for excellent antithrombogenicity even without recourse to anticoagulants. Hydrodynamic function, durability and compatibility to the human body are supposed to differ from the types of prostheses, because the method for prepara-
tion of porcine valve and material and structure of the stent are different respectively (Carpentier et al. 1974; Angell et al. 1977; Chaitman et al. 1979; Rossister et al. 1980). Though durability of porcine xenograft valve is not known entirely, there were many reports regarding the good valvular functions in the adults, as the intermediate results were obtained (Hannah and Reis 1976; Cévesc et al. 1977; Lurie et al. 1977; Angell et al. 1979; Cohn et al. 1979). On the contrary, high incidence of calcification of xenograft valves, especially in children (Kutsche et al. 1979; Silver et al. 1980; Thandroyen et al. 1980; Wada et al. 1980; Kagawa et al. 1982, 1984) and valvular malfunction due to primary tissue failure in adults (McIntosh et al. 1975; Brown et al. 1978; Grehl et al. 1981; Kagawa et al. 1984) were also reported. Furthermore, slight suspicions for antithrombogencity, which was regarded as the biggest advantage of porcine xenograft valves were also incurred (Stinson et al. 1974; Jamieson et al. 1981). The purpose of this paper is to arouse the problems regarding the porcine xenograft valves through the analyses of intermediate late results and complications of the cases who underwent mitral valve replacement (MVR) with porcine xenograft valves and evaluation of the prosthetic valvular function in the intermediate late postoperative stage.

**MATERIAL AND METHODS**

Among 282 cases who underwent isolated MVR during the period from 1964 to 1985, two types of porcine xenograft valve, that is Hancock (H) model 342 valve and Angell-Shiley (AS) valve, were used for 33 consecutive cases during the limited period of 4 years since 1976. Of the 33, 3 cases who died of postoperative complications such as rupture of the left ventricle or acute renal failure were excluded from this study. Thirty cases comprised 16 males and 14 females and the age at operation ranged from 3 years to 58 years with an average of 35.4±15.4 years. There were 4 cases, who were less than 15 years of age.

The cases were divided into two groups according to the types of prostheses. Group H comprised 12 males and 11 females and the age ranged from 3 years to 58 years with an average of 38±15.5 (s.D.) years. Group AS comprised 3 males and 4 females and the age ranged from 8 years to 55 years with an average of 35.4±16.7 years.

Main pathological changes of mitral valve in group H were mitral stenosis (MS) in 8 and mitral regurgitation (MR) in 15 cases and those in group AS were MS in 5 and MR in 2 cases. As to the preoperative clinical symptoms, there were 5 cases in group H and 3 cases in group AS, who were in class IV according to the New York Heart Association (NYHA) classification, 6 cases in group H and 3 cases in group AS, whose cardiothoracic ratio exceeding 70%, 18 cases in group H and 4 cases in group AS, who were associated with atrial fibrillation and 3 cases in group H and one case in group AS, who had major thromboembolic episodes. The size of the prostheses were smaller than 25 mm in 3, 27 mm in 6 and 29 to 31 mm in 21 cases. Postoperative anticoagulation therapy was used in a same criteria as for the mechanical valves for 19 cases in group H and 4 cases in group AS, who had one or more conditions such as atrial fibrillation, embolic episodes, left atrial thrombi or enlarged left atrium.

Follow-up results were analyzed using actuarial method (Anderson et al. 1974). Postoperative deaths were restricted only for the cases who died of prosthesis related complications, such as heart failure resulted from prosthesis malfunction, severe low cardiac output syndrome immediately after replacement of malfunctioning prosthesis and complication of anticoagulant therapy. Postoperative complications were restricted only for major
Porcine Xenograft Valve

thromboembolism with sequelae, valvular malfunction confirmed by cardiac catheterization and bleeding related to anticoagulation therapy.

Hemodynamic assessments for evaluation of valvular function were carried out by means of cardiac catheterization. Complete hemodynamic data both at rest and during exercise using a bicycle ergometer were obtained in 14 cases of group H and 6 cases of group AS. Mean intervals between MVR and cardiac catheterization were 2 years and 5 months in group H and 2 years and 7 months in group AS. Cardiac index (CI), pulmonary arterial systolic pressure (PAP), pulmonary arterial wedge pressure (PAWP), diastolic pressure gradient across the prosthesis (ΔP), effective orifice area (EOA) calculated from Gorlin's formula and performance index (PI) (Gabby et al. 1978); that is EOA/mounting area (MTG-A) of prosthesis were calculated. PAWP was measured using Courand or Barman catheter inserted into pulmonary artery. Left ventricular enddiastolic pressure was measured at the point 0.04 sec after Q wave of ECG, and mean value of 5 or more measurements was used when associated with atrial fibrillation. Cardiac output was measured by means of thermodilution method using a Swan-Ganz catheter introduced into pulmonary artery. Mean value of 3 measurements both at rest and during exercise was used.

Statistical significance between the valvular functions at rest and during exercise in same group or between groups H and AS was tested by paired t-test and significance was taken as p < 0.05. The data were presented in terms of mean ± s.e., unless otherwise stated.

Hemodynamic changes on the passage of time were analyzed to elucidate the progress of prosthesis malfunction in cases who underwent replacement of original prosthesis or died of prosthesis related complication.

RESULTS

Follow-up periods ranged from 3 years 2 months to 6 years with an average of 4.0±0.7 years in group H and from 3 years 5 months to 6 years with an average of 4.6±0.6 years in group AS. Cumulative survival rate 6 years after operation was 91% in group H and 70% in group AS. Proportion of survivals decreased gradually after the lapse of 4 years (Fig. 1). Causes of 4 deaths were prosthesis malfunction caused by calcification seen in 3 children and bleeding related to anticoagulation therapy in one case. Physical activity of 26 survivors according to NYHA classification was grade I in 21 cases, grade II in 3 cases and grade III in 2 cases. The reason for poor physical activity of these 2 cases, who were still in grade III was prosthesis malfunction and sequelae of cerebral embolism in each one case. Cumulative event-free rates 6 years after operation were 83% in group H and 71% in group AS (Fig. 2). Postoperative complications consisted of prosthesis malfunction caused either by calcification, stiffening or rupture of porcine valve in 6, cerebral embolism in 2 and bleeding in one case. Incidence of prosthesis malfunction was 4.8%/pt-y in group H and 9.3%/pt-y in group AS. The incidence was as high as 17.9%/pt-y (10.8%/pt-y in group H and 26.7%/pt-y in group AS) in children, but that in adults was no more than 2.8%/pt-y (2.4%/pt-y in group H and 4.1%/pt-y in group AS) (Fig. 3). The incidence of thromboembolism was 1.6%/pt-y as a whole, 2.2%/pt-y in group H and nil in group AS.

Cardiac catheterization data are summarized as mean ± s.d. (Table 1, Fig. 4).
There were significant elevation of CI, PAWP, PAP and $\Delta p$ during exercise when compared to those at rest, in the both groups. There was no significant difference in CI both at rest and during exercise between groups H and AS. But PAWP, PAP, $\Delta p$ of group AS showed significantly higher values both at rest and during exercise than those of group H. As to the mean value of $\Delta p$ and EOA of groups H and AS, investigated according to the size of prostheses, there were no differences in size 27 mm, but in 29 and 31 mm prostheses, group H showed better results than group AS (Fig. 5). PI was obtained putting MTG-A’s on abscissa.
Porcine Xenograft Valve

Fig. 3. Incidence of prosthesis malfunction.
H, Hancock; AS, Angell-Shiley.

Fig. 4. Heart catheterization data.
Closed circle, group H (n=14); open circle, group AS (n=6); R, at rest; E, during exercise. Values are Means±s.d.; *, <0.05; **, <0.01.

Table 1. Heart catheterization data

<table>
<thead>
<tr>
<th></th>
<th>Hancock (n=14)</th>
<th>Angell-Shiley (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At rest</td>
<td>During exercise</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.63±1.10</td>
<td>5.50±1.42</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>13.12±6.67</td>
<td>27.6±7.13</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>32.70±11.50</td>
<td>57.35±13.03</td>
</tr>
<tr>
<td>Δp (mmHg)</td>
<td>7.96±5.36</td>
<td>19.32±8.49</td>
</tr>
<tr>
<td>PI</td>
<td>0.39±0.15</td>
<td>0.29±0.15</td>
</tr>
</tbody>
</table>

CI, cardiac index; PAWP, pulmonary arterial wedge pressure; PAP, pulmonary arterial systolic pressure; Δp, pressure gradient across the mitral prostheses; PI, performance index. Values are expressed in terms of mean±s.d.
and EOA's at rest and during exercise on ordinate. PI's at rest were from 0.25 to 0.78 in group H and from 0.09 to 0.38 in group AS (Fig. 6A). Four cases, whose PI's were less than 0.25, were all associated with severe heart failure. PI's during exercise were smaller than those at rest in 15 cases, and less than 0.25 in 10 cases (Fig. 6B). Mean values of PI's at rest and during exercise were 0.39±0.15 and 0.27±0.15 in group H and 0.18±0.11 and 0.17±0.11 in group AS. But there were no statistical differences between PI's at rest and during exercise within the same group or those of groups H and AS (Fig. 7).

Fig. 8 shows the changes of hemodynamics in early postoperative and in the late stage of the cases who underwent replacement of malfunctioning prostheses or died of congestive heart failure resulted from malfunction of prosthesis. Although CI, Δp, EOA and PI were satisfactory and improvement of clinical symptoms were remarkable immediately after initial MVR, hemodynamics and clinical symptoms deteriorated in the late stage. CI's decreased in all except for one case associated with MR due to rupture of porcine xenograft valve. Δp's which were 1 to 7 mmHg in early stage increased to 14 to 18 mmHg. EOA narrowed to 0.34 to 0.37 cm² except for one case. PI's were less than 0.25 in all cases. Gross findings of extirpated prostheses were calcification in 3 and rupture of the right coronary cusp of the porcine valve in one case.

**DISCUSSION**

Since the clinical application of prosthetic heart valves, improvement in
surgical treatment for valvular disease has become remarkable. The functions of prosthetic heart valves showed notable progress recently, through many improvement in design and material, but there still remain postoperative complications related to prostheses. Of these, thromboembolisms have been one of the most serious complications and strongly influenced on the results of valve replacement. To solve this problem, prosthetic valves with high antithrombogenicity were eagerly anticipated. Xenograft prosthetic valve, which is quite different from mechanical valve in material and shape, have been widely used since the beginning of 1970's as the ideal substitute for human valve, from the advantage that the incidence of early postoperative thromboembolism is low (Stinson et al. 1974; Hannah and Reis 1976; Cevesc et al. 1977; Lurie et al. 1977; Cohn et al. 1979; Jamieson et al. 1981), therefore postoperative anticoagulation therapy, which is sometimes troublesome to the patients especially to children, is unnecessary.
According to several reports (Davila et al. 1978; Angell et al. 1979; Cohn et al. 1979; Borkon et al. 1981a), thromboembolism-free rates of H or AS valves in mitral position were reported as 83 to 94%. As against, those in mechanical valve of new design were 85 to 91% in Björk-Shiley (BS) valve (Tandon et al. 1978;
Karp et al. 1981) and 95% in Saint Jude Medical valve (Nicoloff et al. 1981). Although it would be controvertible to compare the thromboembolism-free retes of xenograft and mechanical valves in a same standard, because all cases with mechanical valves are under recourse to anticoagulant, these results suggest that the antithrombogenicity of xenograft valve are not absolutely superior to that of mechanical valves.

In our series, anticoagulation therapy was indicated according to the criteria stated previously. Consequently 77% of the cases were regarded as the candidates for anticoagulation therapy, thus the biggest advantage that patients bearing xenograft valve are freed from the hazards of postoperative anticoagulation therapy, was markedly spoiled. Incidence of thromboembolism of 44 cases who underwent MVR with BS valve in our institute during the almost same period as xenograft valve was 1.9%/pt-y (Kagawa et al. 1981). Furthermore, the fact that thromboembolisms were seen in cases with recourse to anticoagulant would suggests that xenograft valves are not superior to mechanical valves in antithrombogenicity.

As to the durability of xenograft valves, there were many reports regarding satisfactory follow-up results of MVR with xenograft valves (Hannah and Reis 1976; Cévesc et al. 1977; Lurie et al. 1977; Cohn et al. 1979). There were some interrogations however that the incidence of xenograft malfunction increases abruptly after the lapse of 5 to 6 years postoperatively (Oyer et al. 1980). In our series, xenograft malfunction occured after lapse of 4 years. Most characteristic findings were high incidence in AS valve and extremely high incidence in children.

It was reported clinically and experimentally, that xenograft valvular functions are not satisfactory even at rest or low flow state and this tendency increases during exercise, i.e. in high flow state (Horowitz et al. 1974; Aaslid et al. 1975; Roberts 1976; Borkon et al. 1981b; Delcan et al. 1982). In our series, both H and AS valves were stenotic even at rest and this tendency increased significantly during exercise. Significantly higher values of PAWP, PAP and Δp both at rest and during exercise of group AS than those of group H suggest that valvular function of AS valve is inferior to H valve, because there was no significant difference between CI's of both groups. The reason for difference in valvular function and incidence of prosthesis malfunction in a late stage would be attributable to the different treatment of porcine tissue of the both valves. The objectives of the treatment of porcine xenograft with glutaraldehyde are to sterilize, to eliminate antigenicity and to form irreversible cross links between the amino group of collagen and glutaraldehyde for prevention of collagen denaturation (Carpentier et al. 1969). Concentration of glutaraldehyde used in H valve is 0.2% and 0.5% in AS valve (Lefrak and Starr 1979). Although details of treatment of the porcine valve were not clearly reported from Hancock and Shiley laboratories, higher concentration of glutaraldehyde presumably produce
more stiff leaflet, thus higher resistance to the blood stream of AS valve. Angell (Angell et al. 1977) attributed prosthesis dehiscence caused by glutaraldehyde and noted problem is virtually eliminated by using standarized glutaraldehyde solution to avoid excessive polymer formation and strict adherence to the rinsing protocol.

Up to the present time, many indices have been used for evaluation of valvular function (Fletcher et al. 1974; Aaslid et al. 1975; Gabbay et al. 1978). For mechanical valves, discharge coefficient (Cd) (Gabbay et al. 1978) have been used \[Cd = \frac{EOA}{\text{actual orifice area (AOA)}}\]. In xenograft valves, opening angles of each leaflets are not equal and orifice of the valve does not form true circle, so that it is difficult to calculate AOA by actual measurement as applied for mechanical valve. PI, which may be construed as performance of xenograft valve, i.e. how efficiently xenograft valve uses AOA of human valve, was adopted in this study. PI's of H valve were from 0.40 to 0.43, when calculated from EOA obtained by in vitro study, reported from Hancock laboratory and PI value of 0.4 was aimed as a standard for the both H and AS valves. PI's at rest were less than 0.4 in 71% of group H and in all cases of group AS. PI's during exercise were less than 0.4 in 95% and less than 0.25 in 50% of all cases. Mean values of PI's were higher in group H than in group AS both at rest and during exercise. Although PI does not indicate valvular function directly, because EOA, which is a basis for calculation of PI, is influenced by many factors of cardiac functions, such as CI, heart rate and left ventricular endodiastolic pressure, PI could be regarded as one of the most effective indices regardless of the size of prosthesis. All cases whose PI's were less than 0.25 were severely symptomatic. PI of less than 0.25 means the 75% stenosis of the original valvular area of the human body. The fact that 50% of all cases showed PI's less than 0.25 during exercise suggests poor valvular function in high flow state.

During the follow-up period, 3 cases of re-MVR and one death resulted from prosthesis malfunction were experienced. In all cases, valvular functions, which were satisfactory in early postoperative stage deteriorated in late stage. From this fact, meticulous follow-up should be emphasized for the cases bearing xenograft valves, considering sudden increase in number of prosthesis malfunction after lapse of 4 to 6 years.

As stated afore, there have been many problems in clinical application of porcine valves. To improve hemodynamics and durability of the porcine valve, modification in design and tissue preparation have been done. Porcine xenograft valves of new-generation, such as Carpentier-Edwards supra-annular valve (Carpentier et al. 1982; Jamieson et al. 1986) and Hancock II valve (Wright et al. 1982) were developed for these purpose. A pressurelized system was utilized to hold the porcine leaflets in their normal configuration during tanning process with glutaraldehyde for porcine xenograft valves of first-generation, such as H and AS valves. The importance of low-pressure fixation was reported by Broom in 1978.
Porcine Xenograft Valve

(Broom 1978). Low-pressure fixation with glutaraldehyde keeps structure of collagen and elastic fibers normal, thus eliminates fatigue induced destruction of valvular structure. Carpentier fixed valve tissue with glutaraldehyde at 4 mmHg and Hancock laboratory changed preservation of Hancock II valve for these aimes. Flexibility of the stent is also important factor (Reis et al. 1971). Materials of the stent was also changed from polypropylene to Derline (ultrahigh molecular weight polyethylene) to reduce fatigue stress of leaflets (Carpentier et al. 1982; Wright et al. 1982). Calcification of the xenograft valve, especially in children has been a major problem (Kutsche et al. 1979; Silver et al. 1980; Thandroyen et al. 1980; Wada et al. 1980; Kagawa et al. 1982, 1984). The result of calcium mitigation with use of surfactant in animal experiments was reported by Arbustini (Arbustini et al. 1984), which revealed decrease in calcification of porcine valve implanted in the tricuspid position of a sheep. Although precise mechanism of calcium mitigation of surfactant is not known yet, it is presumed that penetration of lipid and phospholipid into valve tissue, which is the initial process of calcification, is inhibited by hydrophilic part of surfactant. Preliminary calcium mitigation treatment has been used for the new-generation valves, in anticipation for prevention of calcification (Jamieson et al. 1986). Hemodynamic study has shown superior characteristics of these new-generation valves (Cosgrove et al. 1985). It would be necessary yet to follow these patients with the new-generation porcine xenograft valves for a longer period, to confirm valvular function and clinical results in a late postoperative stage.

References


Porcine Xenograft Valve


