Early Degeneration of Porcine Xenograft Valves in Pediatric Patients Who Have Undergone Apico-Aortic Bypass

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The glutaraldehyde-preserved stented porcine xenograft valve has been durable in adult patients with a low incidence of valve-related complications. In children, however, early degeneration and calcification of this valve is now being reported. The etiology of the early degeneration is still unclear but may be related to calcium metabolism, tissue fatigue, and host rejection. During the last 5 years at the Texas Heart Institute, 21 patients under 23 years of age underwent implantation of an apico-aortic conduit containing a porcine xenograft valve for treatment of severe forms of left ventricular outflow tract obstruction. Because of early failure, the valve was replaced in two patients (11.5%) within 3 years of implantation. Although early degeneration of the porcine valve might occur in some children, it may still be the preferred valve to use in young patients because anticoagulation is not required with its use.

DEGENERATION and calcification of the glutaraldehyde-preserved stented porcine xenograft valve are uncommon complications after implantation in adult patients; however, several reports have indicated a more frequent occurrence in young patients.[1-4] The reason remains unclear.

During the last 5 years, we have implanted apico-aortic conduits containing porcine bioprostheses in 21 patients under the age of 23 years for surgical treatment of severe left ventricular outflow tract obstruction. Early degeneration and calcification of the conduit valve occurred in two patients who required conduit valve replacement.

Case Reports

Case 1

A 17-year-old boy who had undergone valve-conduit surgery 2 years earlier was admitted for reevaluation because of recurring episodes of dyspnea and chest pain. He had had repair of coarctation of the aorta at the age of 10 weeks. At age 5, he was noted to have re-stenosis of the coarctation as well as aortic stenosis. He underwent a second repair of the coarctation and, one year later, an aortic valvotomy. At age 11, he developed congestive heart failure secondary to aortic insufficiency and underwent aortic valve replacement with a No. 17 Björk-Shiley prosthesis.

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Four years later, he began to develop dyspnea on exertion and mild chest pain. Chest roentgenography showed marked cardiomegaly. Electrocardiography disclosed left ventricular hypertrophy. Cardiac catheterization showed severe aortic stenosis with a 90 mm Hg gradient across the prosthetic aortic valve.

In 1977, when the boy was 15, a conduit containing a 20 mm porcine valve was inserted from the left ventricular apex to the supraceliac abdominal aorta. There was no pressure gradient after insertion of the conduit, and he resumed normal activities.

During a follow-up visit one year later, a faint diastolic murmur was heard over the area of the conduit valve, but the patient was asymptomatic. Two years after the valve-conduit had been implanted, the patient again developed dyspnea on exertion and mild pain in the left upper quadrant of the abdomen. A Grade 4/6 diastolic murmur was heard over the area of the conduit valve. Chest roentgenography disclosed severe cardiomegaly with increased pulmonary venous markings. Electrocardiography showed left ventricular hypertrophy and first degree atrioventricular block. The results of cardiac catheterization are shown in Table I. A left ventriculogram and thoracic aortogram disclosed a dilated, but normally contracting left ventricle and severe insufficiency of the conduit valve (Fig. 1).

Operation was performed through an upper abdominal approach without cardiopulmonary bypass. The porcine valve and the adjacent Dacron tube graft were replaced with a No. 21 St. Jude prosthetic valve. The porcine valve was severely deformed with calcified leaflets (Fig. 2). Cultures of the blood and valve cusps were negative for bacterial growth. On the eighth day after operation, the patient was discharged on a regimen of digoxin, aspirin and dipyridamole. Five months after operation, he was again an active teenager, and his most recent chest roentgenogram showed normal cardiac size.

Case 2

A 9-year-old boy was readmitted to this institution 3 years after implantation of a valved conduit. He had had valvular aortic stenosis at the age of 2 years. Cardiac catheterization at that time showed a 40 mm Hg gradient across the aortic valve and normal end-diastolic pressures. He was discharged with follow-up recommended.

Two years later he was readmitted to the hospital for evaluation. A Grade 4/6 systolic ejection murmur was heard over the aortic area. A chest roentgenogram showed severe cardiomegaly, and an electrocardiogram showed left ventricular hypertrophy with strain and ST segment depression. Repeat cardiac catheterization revealed a 100 mm Hg gradient across the aortic valve with a hypoplastic aortic annulus. In 1976, when the child was 6 years of age, he underwent insertion of a conduit containing a No. 17

TABLE I. Preoperative Cardiac Catheterization Data in Cases 1 and 2 (Pressures recorded in mm Hg)

Site	Case 1	Case 2
Right atrium	a = 5, v = 5 (4)	a = 5, v = 4 (2)
Left atrium	a = 42, v = 36 (38)	a = 16, v = 21 (13)
Pulmonary artery	60/38 (42)	24/10 (17)
Pulmonary artery wedge	(24)	(13)
Right ventricle	60/0 (5)	36/0 (3)
Left ventricle	130/0 (40)	240/0 (16)
Conduit P*	105/0 (40)	195/15
Conduit D**	95/55 (75)	160/35

*Conduit P = pressure in conduit proximal to porcine valve.
**Conduit D = pressure in conduit distal to porcine valve.

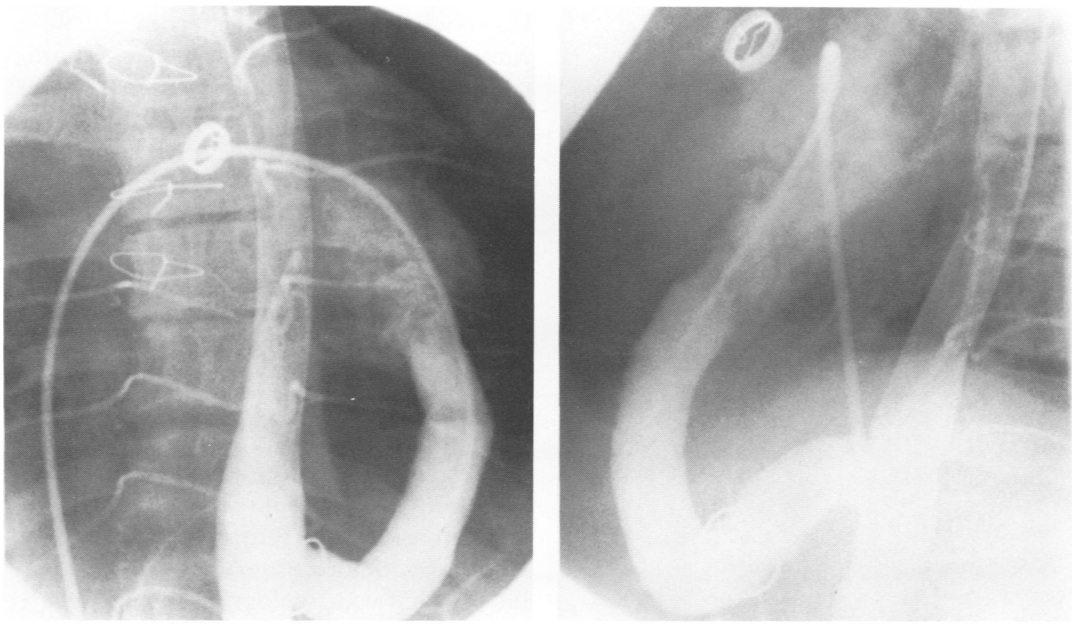

Fig. 1 (Case 1) Midthoracic aortogram recorded in diastole with a catheter passed transseptally from the left ventricle through the conduit to the midthoracic aorta. Note severe regurgitation of contrast medium from the descending aorta into the left ventricle by way of the incompetent conduit valve.
A = anteroposterior view
B = lateral view

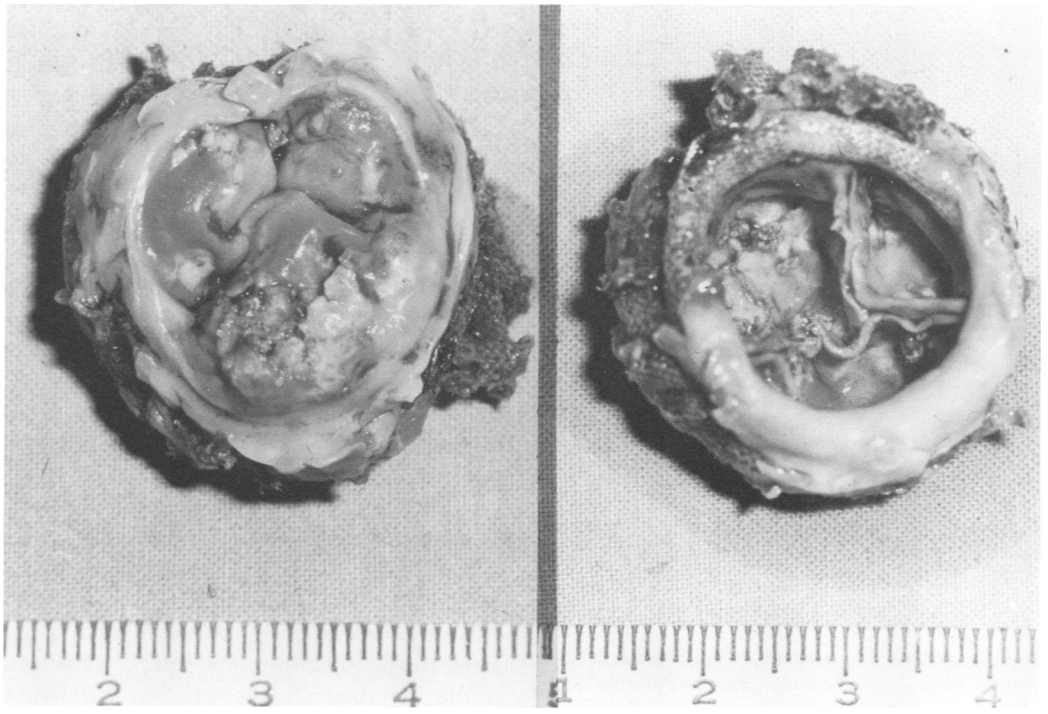

Fig. 2 Porcine valve removed from Case 1. Note the extensive calcification along the leaflets and at the commissures.

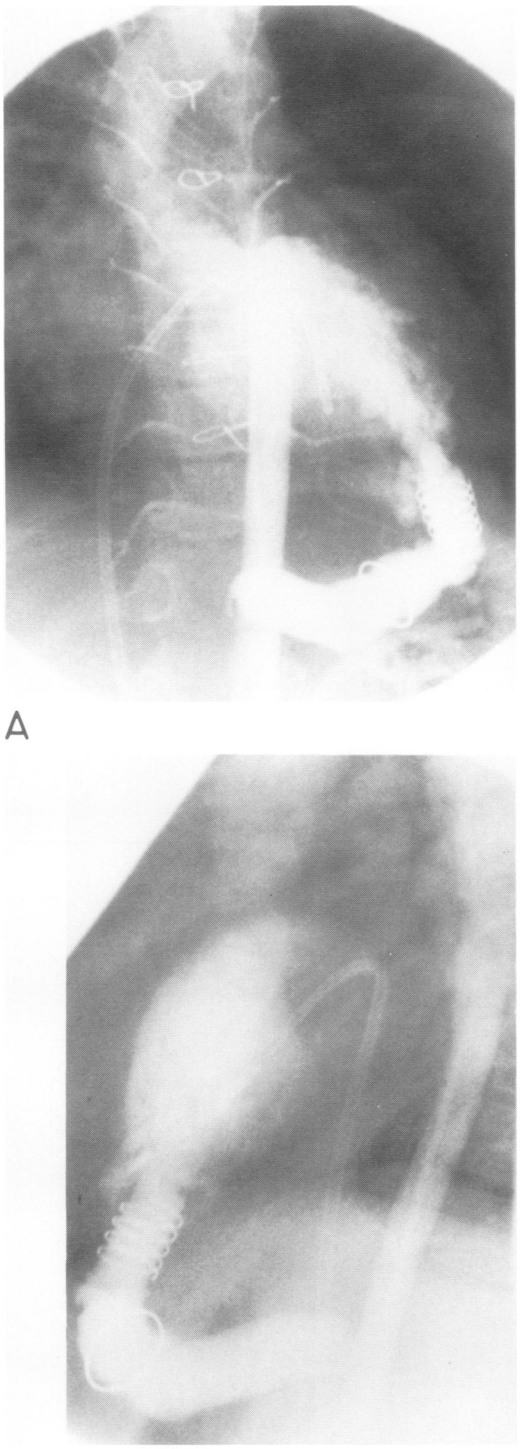

Fig. 3 (Case 2) Retrograde midthoracic aortogram recorded in diastole showing gross regurgitation of contrast medium across the incompetent conduit valve into the left ventricle.
A = anteroposterior view
B = lateral view

Hancock porcine valve from the left ventricular apex to the supraceliac abdominal aorta. On follow-up examination one year later, he had a faint systolic murmur over the conduit valve. His chest roentgenogram was normal, and there were no further ST segment changes on the electrocardiogram.

At the age of 9, three years after implantation of the valved conduit, the patient was readmitted because of a Grade 4/6 diastolic murmur heard over the conduit valve. He had no chest pain or dyspnea on exertion. Chest roentgenography then showed cardiomegaly with increased pulmonary venous congestion; electrocardiography disclosed left ventricular hypertrophy. Cardiac catheterization was repeated (Table I). A left ventriculogram showed severe outflow tract obstruction, through both the natural aortic and conduit valves. In addition, severe conduit valve insufficiency was noted (Fig. 3).

Reoperation was performed under temporary cardiopulmonary bypass. The stenotic aortic valve was bicuspid and mildly calcified, and a valvotomy was performed. The porcine conduit valve was calcified and deformed (Fig. 4) and was replaced with a No. 16 St. Jude prosthetic valve. On the eleventh day after operation, the patient was discharged on a regimen of aspirin and dipyridamole.

Discussion

The glutaraldehyde-preserved porcine xenograft valve has undergone extensive clinical use during the past 8 years and, in many centers, it is the preferred valve for use in adults. It has good hemodynamic characteristics, a low rate of thromboembolism without the use of anticoagulants, a low rate of endocarditis, and has been proven durable in adults for up to 8 years.

Severe forms of left ventricular outflow tract obstruction have been relieved by a valved conduit from the left ventricular apex to the abdominal aorta.[5-11] This technique has been effective, particularly in children with severe valvular or supravalvular aortic stenosis when a small or

hypoplastic aortic annulus precludes satisfactory valvotomy or valve replacement. The use of the glutaraldehyde-preserved porcine xenograft valve in the conduit in children has the advantage of not requiring anticoagulation while still maintaining a low rate of thromboembolism. Avoiding anticoagulation is a desirable characteristic in this group of patients because they are particularly active and often subjected to trauma.

Reports of early failure and calcification of porcine xenograft valves in children are beginning to appear in the literature. Forfar et al[12] described a 12-year-old patient whose Carpentier-Edwards prosthetic mitral valve showed severe microscopic calcification within 3 weeks of implantation. Thandroyen et al[4] operated on four children aged 13 to 15 years, in whom Hancock mitral valve bioprostheses calcified and failed within 17 to 25 months after implantation. Geha et al[1] reported seven cases of xenograft valve failures (three aortic, two mitral, and two conduit) within 4 years of implantation in patients less than 17 years of age.

Since 1975, we have used an apico-aortic conduit containing a porcine xenograft valve in 31 patients who had severe forms of left ventricular outflow tract obstruction. Twenty-one patients were under 23 years of age when the porcine valved conduits were implanted; and two patients of this group (11.5%) subsequently had the valves replaced because of degeneration and calcification—one after 24 months and the other after 36 months.

There were similar pathological changes in the conduit valves removed from both patients. Both valves had gross and microscopic calcification along the free edges of the leaflets and at the commissural attachments (Figs. 2 and 4). There was almost total dehiscence in one of the leaflets of the valve removed in Case 2 (Fig. 4). Shown on microscopic examination of the leaflets were areas of collagen degeneration with surrounding areas of calcification and only minimal inflammatory cell infiltrate.

The etiology of the accelerated degeneration and calcification of porcine xenograft valves in children is multifactoral. However, it appears that collagen degeneration, from whatever cause, is the initiating event that subsequently leads to calcification and valve dysfunction. Three possible causes of degeneration have been suggested: (1) early tissue fatigue; (2) increased calcium

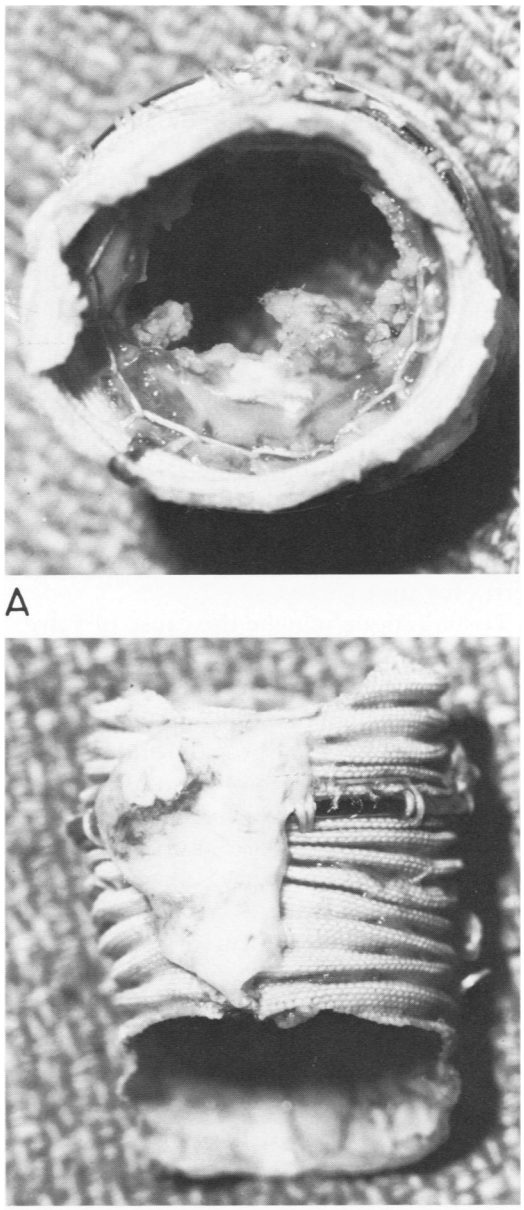

Fig. 4 Section of conduit and porcine valve removed from Case 2 shows (A) severe calcification of the valve along with degeneration of the leaflets, and (B) near total dehiscence of one of the leaflets.

turnover in children, resulting in leaflet calcification and valve dysfunction; and (3) host rejection of the valve.

Tissue fatigue and subsequent valve dysfunction frequently were observed with the earlier formaldehyde-preserved heterograft valve, which discouraged its use clinically. Carpentier[13] introduced glutaraldehyde as a preserving agent in 1968 and showed that the valves so preserved were far more desirable than those preserved in formalin. The increased durability resulted from multiple and irreversible cross-linkages between collagen molecules created during the tanning process. The glutaraldehyde-preserved valve subsequently gained widespread clinical acceptance, and its durability was proved in several large series for up to 8 years.[14-16]

Tissue fatigue may be the cause of valve failure in some of the young patients who have been reported recently. Although glutaraldehyde enhances collagen stabilization in the tissue valves, it does not render them totally nonbiodegradable. Some of the early degenerated valves removed from patients, including the two cases presented here, have shown primary collagen degeneration in the leaflets. Carpentier,[13] who suggested the mechanism of tissue valve destruction 13 years ago, believed that the rate of collagen denaturation would determine the durability of the tissue valve. The small sized valves used in children, which result in increased pressure gradients and stress on the leaflets, may also enhance early tissue fatigue.

It is known that calcium turnover is high in children who maintain a positive calcium balance.[17] Soft tissue calcifications have been observed in patients who are undergoing dialysis for chronic renal failure and in patients with bone tumors,[18] all of whom have an abnormal calcium metabolism. Our two reported patients had normal serum calcium levels, as has been the case in previous reports; however, the fact that accelerated degeneration and calcification of these valves occurs in this subset of patients with a high calcium turnover suggests that calcium metabolism may play a role in the pathogenesis.

Rejection of the tissue valve by the host also may play a role in the degeneration. Although histological studies in our two cases did not reveal an abundance of inflammatory cells in the destroyed valves, Spray and Roberts[19] found inflammatory cells present in 70% of 44 bioprosthetic studies after valve failure. They also reported that the greatest inflammatory reaction was seen in a valve implanted for only 14 days in a patient who had previously had a bioprosthesis implanted, suggesting that host sensitization to bioprosthetic antigens had occurred after destruction of the first bioprosthesis.

The ideal prosthetic cardiac valve has yet to be developed. The glutaraldehyde-preserved porcine heterograft valve has been durable, with a low rate of valve-related complications in the adult for periods up to 8 years, and probably is the valve of choice in this group of patients. In children, the durability has been less successful, and more reports of early valve failure probably can be expected. However, the low rate of thromboembolism and the added feature of unnecessary anticoagulation may make the glutaraldehyde-preserved bioprosthesis the preferred valve, even in children, until a better substitute can be developed.

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