

Calcification of glutaraldehyde-fixed porcine xenograft

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Rose, A. G., Forman, R., and Bowen, R. M. (1978). *Thorax*, 33, 111-114. **Calcification of glutaraldehyde-fixed porcine xenograft.** The clinical and light and electron microscopic findings are reported in a 14-year-old patient who died 12 months after mitral valve replacement with a Hancock prosthesis. Severe cusp calcification had led to immobilisation of the valve and stenosis. Calcification involved the substance of the valve cusps. The cause of the calcification in this patient is unknown.

Several reports suggest that the glutaraldehyde-treated, flexible, stent-mounted porcine xenograft has a greater durability than formalin-fixed grafts (Carpentier *et al.*, 1974; Pipkin *et al.*, 1976; Hannah and Reis, 1976). As a result such prostheses are being widely used. In our institution a total of 126 glutaraldehyde-treated porcine xenografts have been inserted over the past 24 months (68 Hancock and 58 Carpentier-Edwards prostheses). Ten out of the 126 patients have come to necropsy (8 Hancock and 2 Carpentier-Edwards prostheses). In nine out of the 10 patients the postoperative survival period ranged from 0-4 weeks, thus preventing assessment of durability. The tenth patient, who survived 12 months after mitral valve replacement with a Hancock prosthesis, forms the substance of this report. He died because of malfunction of the graft due to severe calcification and immobilisation of the prosthetic cusps.

Case report

At the age of 10 years the patient had acute rheumatic carditis and evidence of mitral valve disease. He subsequently developed class 3 symptoms of effort intolerance with signs of severe mitral incompetence, pulmonary hypertension, and tricuspid incompetence confirmed at cardiac catheterisation. In November 1975, when aged 14 years, the mitral valve was replaced with a 29 mm Hancock porcine heterograft, and a tricuspid annuloplasty was performed. Before insertion the prosthesis was removed from its glutaraldehyde bathing solution and washed three times in normal saline for nine minutes.

After operation the patient became asymptomatic and received only oral penicillin. Ejection systolic and short mid-diastolic murmurs were always audible over the mitral area. One year after operation the patient was readmitted with dyspnoea and recurrent haemoptyses of two weeks' duration. He had a sinus tachycardia and mitral mid-diastolic and systolic murmurs. His antistreptolysin O titre, sedimentation rate, and serum calcium were normal. He died of sudden cardiac arrest 48 hours after admission to hospital.

CARDIAC PATHOLOGY

The Hancock prosthesis (Fig. 1) was securely inserted, and the sewing ring was covered by host tissue. The cusps showed no sign of laceration or

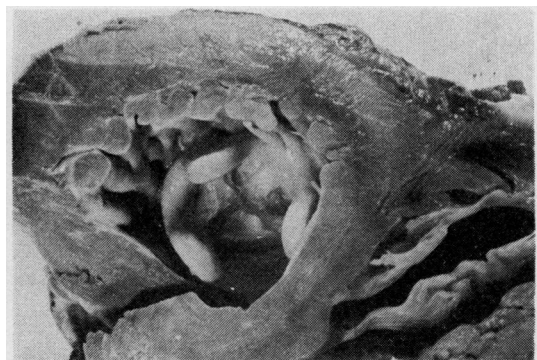


Fig. 1 The calcified Hancock mitral xenograft is viewed in situ from its ventricular aspect. The calcification spares the free margins of the xenograft cusps. The tricuspid valve is visible to the right.

shortening, and the valve appeared competent. However, the xenograft was functionally stenotic owing to diffuse, severe calcification of all three cusps. Scanty antemortem thrombi (platelets and fibrin) were present on the concave aspect of the cusps. Calcification imparted a brittle, eggshell-like consistency to the cusps and immobilised most portions of the three cusps in the closed position. A small thrombus was present in the dilated left atrium close to, but separate from, the site of insertion of the prosthesis. The calcification did not extend to the free margins of the cusps.

Microscopic examination of the xenograft (Fig. 2) revealed extensive calcification within the substance of each cusp. The calcific deposits occupied the site of the cusp fibrosa and extended into the arterialis and ventricularis portions of each cusp. The calcification did not appear to have originated within surface thrombi. The scanty thrombi present on the concave aspect of the cusps were devoid of calcification. Within the cusps were a few poorly preserved fibrocytes, and an occasional monocyte was present on their surfaces. The fibrosa was discernible as a distinct layer only near the non-calcified free margin of each cusp.

Electron microscopy of a sample from the non-calcified free margin of one cusp revealed the presence of ample collagen (Fig. 3). The collagen fibrils appeared generally well preserved. Foci of collagen fibril loss were however present, and amorphous, finely granular material was seen in

such areas. A few elongated connective tissue cells were observed within the cusps. Nuclear outlines were fairly well delineated, but cytoplasmic detail was mainly lost.

Discussion

The glutaraldehyde-preserved porcine xenograft valve is being widely used, and present assessment of its prolonged durability appears favourable (Carpentier *et al.*, 1974; Pipkin *et al.*, 1976; Hannah and Reis, 1976). Few patients have been followed up for more than five years at the present time. While calcification of fresh aortic homograft valves may be a significant problem (Smith, 1967; Davies *et al.*, 1968), this was not encountered with formalin-treated xenografts (Ionescu *et al.*, 1968; Rose, 1972). Roberts (1976), quoting Hancock (in a personal communication), states that, at least up to five years, calcific deposits in the Hancock prosthetic valve cusps have been infrequent and minimal. Carpentier *et al.* (1974) detected calcification and perforation of a glutaraldehyde-fixed xenograft one year after operation. The xenograft had been implanted in a tubed conduit for the treatment of pulmonary atresia. The same authors noted calcification histologically in four of their xenograft valves, particularly at the base of the cusps.

The severe calcification in our patient's xenograft one year after implantation is very disturbing. The overall late incidence of this serious

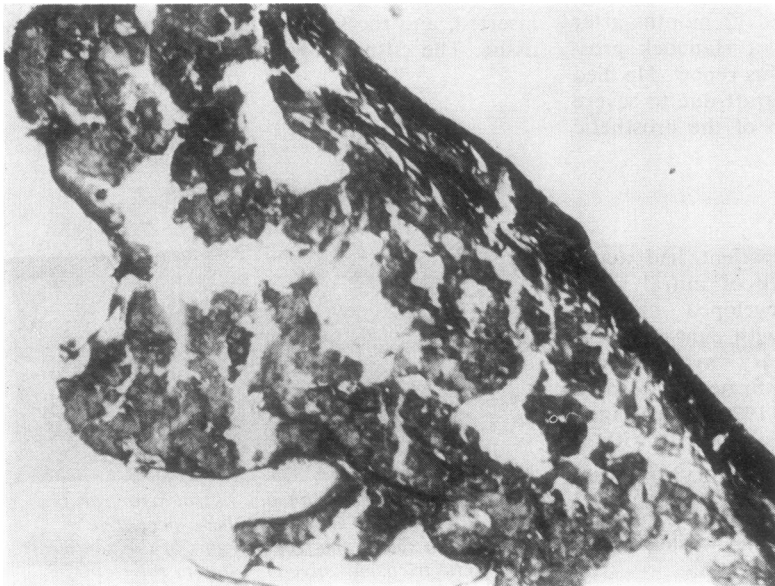


Fig. 2 A portion of the xenograft cusp. The cusp is extensively calcified, and sectioning has caused fragmentation of the brittle calcified tissue (Haematoxylin and eosin $\times 150$).



Fig. 3 Electron micrograph of portion of free margin of one of the xenograft cusps shows moderately well preserved collagen fibrils and a portion of a connective tissue cell (centre). Collagen fibrils vanish into amorphous, finely granular debris (top left and bottom right), probably indicative of collagen degeneration $\times 7135$.

complication is unknown. The reason for the calcification in our patient is not clear. No disease associated with hypercalcaemia was present. The calcification appeared to be dystrophic in nature and involved the collagen substance of the cusps rather than resulting from organisation of surface thrombi.

References

- Carpentier, A., Deloche, A., Relland, J., Fabiani, J. N., Forman, J., Camilleri, J. P., Soyer, R., Dubost, C., and Malm, J. R. (1974). Six-year follow-up of glutaraldehyde-preserved heterografts. With particular reference to treatment of congenital valve malformations. *Journal of Thoracic and Cardiovascular Surgery*, **68**, 771-782.
- Davies, H., Missen, G. A. K., Blandford, G., Roberts, C. I., Lessof, M. H., and Ross, D. N. (1968). Homograft replacement of the aortic valve. A clinical and pathologic study. *American Journal of Cardiology*, **22**, 195-217.
- Hannah, H., and Reis, R. L. (1976). Current status of porcine heterograft prostheses. A 5-year appraisal. *Circulation*, **54**, Supplement III, 27-31.
- Ionescu, M. I., Wooler, G. H., Whitaker, W., Smith, D. R., Taylor, S. H., and Hargreaves, D. H. (1968). Heart valve replacement with reinforced aortic heterografts. Technique and results. *Journal of Thoracic and Cardiovascular Surgery*, **56**, 333-350.
- Pipkin, R. D., Buch, W. S., and Fogarty, T. J. (1976). Evaluation of aortic valve replacement with a porcine xenograft without long-term anticoagulation. *Journal of Thoracic and Cardiovascular Surgery*, **71**, 179-186.
- Roberts, W. C. (1976). Choosing a substitute cardiac valve: 'type, size, surgeon. *American Journal of Cardiology*, **38**, 633-644.
- Rose, A. G. (1972). Pathology of the formalin-treated heterograft porcine aortic valve in the mitral position. *Thorax*, **27**, 401-409.
- Smith, J. C. (1967). The pathology of human aortic valve homografts. *Thorax*, **22**, 114-138.

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