Long-term morphological changes in a cryopreserved pulmonary valve homograft

Adriana Luk BSc¹, Jagdish Butany MBBS MS FRCPC^{1,2}, Sarah A Erlich BSc¹,
Jessica Henry BA¹, Tirone E David MD FRCSC³

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Pulmonary homografts (PHs) are frequently used to replace the native pulmonary valve in the Ross procedure, and in the reconstruction of the right ventricular outflow tract.

The case of a 25-year-old man whose PH was replaced 12 years after undergoing the Ross procedure is reported. The clinical cause of the PH failure was stenosis. Morphological studies showed cusp tissue degeneration with tears and calcification, as well as pannus growth on the flow and nonflow surfaces of the cusps and the pulmonary artery graft. The durability of this PH was likely due to a combination of low pressure on the right side of the heart and the patient's age at surgery.

Key Words: *Congenital heart disease; Cryopreserved pulmonary homograft; Ross procedure*

The first valved homograft was implanted by Ross and Somerville in 1966 (1), and since then, it has been the mainstay for right ventricular outflow tract (RVOT) reconstruction in cases of congenital anomalies and in the Ross procedure. In the latter case, the PH is inserted in the pulmonic position and the native pulmonary valve is used to replace the diseased aortic valve. Postoperatively, these patients have good to excellent long-term results; the patients are typically close to full-grown adults at the time of the procedure (2).

CASE PRESENTATION

A 25-year-old man was admitted for treatment of an aortic root aneurysm with severe aortic insufficiency after the Ross procedure 12 years earlier. The pulmonary homograft was stenotic. He was apparently asymptomatic, was not taking any medications and had recently quit smoking. Perioperative transesophageal echocardiography demonstrated a slightly dilated left ventricle with decreased systolic function (ejection fraction 35% to 45%), dilated aortic root measuring 6.3 cm in diameter and severe aortic regurgitation. There was moderate pulmonic stenosis, with a peak gradient of 10 mmHg and moderate pulmonic regurgitation. A patent foramen ovale was also found. The patient underwent an aortic valve-sparing operation with preservation of the pulmonary autograft valve, replacement of the stenotic pulmonary homograft (PH) with another 30 mm PH and primary closure of the atrial septal defect. Nine days postoperatively, his two-dimensional echocardiogram showed trace aortic regurgitation and a normally

Des modifications morphologiques à long terme de l'homogreffe d'une valvule pulmonaire cryoconservée

Les homogreffes pulmonaires (HP) sont souvent utilisées pour remplacer la valvule pulmonaire native pendant l'intervention de Ross et pour reconstruire l'entraînement de la chambre de chasse du ventricule droit.

On rend compte du cas d'un homme de 25 ans dont l'HP a été remplacée 12 ans après une intervention de Ross. La défaillance de l'HP était causée par une sténose. Des études morphologiques ont révélé une dégénérescence des tissus valvulaires accompagnée de déchirures et de calcifications, ainsi qu'une excroissance du pannus sur les surfaces de débit et de non-débit des valvules et de la greffe de l'artère pulmonaire. La durabilité de cette HP est probablement imputable à l'association d'une faible tension du côté droit du cœur et de l'âge du patient au moment de l'opération.

functioning PH. He was discharged home 13 days later and returned to his native country, Italy.

PATHOLOGY

The excised PH conduit had a length of 5.7 cm and a maximum outer diameter of 3.6 cm. The pulmonary artery (PA) wall thickness ranged from 0.5 mm to 1.0 mm, with few visible adhesions. All three homograft cusps showed structural changes, with significant loss of cuspal tissue. Only one cusp appeared relatively intact, but it was short (0.5 mm) compared with the normal length of 1.5 cm to 1.6 cm. The second cusp was largely absent and the residual tissue showed pannus originating from the suture line and apparent loss at the distal end. The third cusp was only partially seen; the rest of it appeared to have been lost and torn, and had prolapsed (Figure 1A). The base of this cusp showed significant fibrosis and calcification. The PA showed aneurysmal dilation (Figure 1B), with a circumference of over 7.5 cm. Histologically, the RVOT tissues, cusps and the PA showed pannus that covered the flow and nonflow surfaces of the cusps. There was no recognizable RVOT myocardium, and this subvalvular region showed fibrosis and elastosis. The cusps showed tissue degeneration and tears. In addition, the bases of the cusps showed calcification, cartilaginous metaplasia and areas of ossification with marrow spaces (Figures 2A and 2B). The graft PA showed thinning of its wall, total loss of the native smooth muscle cells, increased fibrosis and some 'collapse' of elastic plates, as well as calcification within the homograft wall (Figure 2B). There was no evidence of inflammation in any of the

¹Department of Pathology, Toronto General Hospital/University Health Network; ²Faculty of Medicine University of Toronto; ³Department of Surgery, Division of Cardiac Surgery, Toronto General Hospital/University Health Network, Toronto, Ontario

Correspondence: Dr Jagdish Butany, Department of Pathology, 11th floor, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5C 2C4. Telephone 416-340-3008, fax 416-340-4213, e-mail jagdish.butany@uhn.on.ca

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Figure 1) The excised homograft. **A** The homograft shows three cusps (arrowheads). One of these cusps (arrows) was torn and had prolapsed. **B** The homograft shows aneurysmal dilation (arrows) with a large ridge of calcification (asterisk)

examined tissues, nor was there any evidence of damage to the elastic tissue in the arterial media.

DISCUSSION

In this PH, excised 12 years following the Ross procedure, there was significant loss of cusp tissue due to primary tissue degeneration and increase in thickness due to pannus growth. The PA showed changes in its thickness and aneurysmal dilation. The presence of pannus and calcification of the cusps explained the moderate degree of stenosis, and the loss of cusp tissue and aneurysmal dilation of the PA explained the moderate degree of incompetence of the PH. There was no significant inflammatory cell infiltrate in or around the PH tissues, as reported to be found in stentless porcine bioprosthesis (3), and in cryopreserved allografts (4). Vogt et al (4) reported evidence of cellular rejection in right-sided cryopreserved allografts from children two to 16 years of age explanted two weeks to seven years after implantation, and none in left-sided homografts found in their adult population. Our patient, who had undergone implantation at the age of 13 years, had no evidence of graft rejection; this finding was surprising, but it may be age-dependent and idiosyncratic, because cellular rejection may occur in certain individuals of younger age groups.

There are few reports in the literature that discuss the long-term morphological changes in explanted PHs in post-Ross procedure

Figure 2) Histological images of the homograft. **A** Transverse section of the pulmonary artery (PA) and cusp leaflet (C). The flow surface of the leaflet is covered with a layer of pannus along its entire length (arrowheads). There is extensive calcification at the tip of the leaflet and at the base of the cusp (asterisks). At the base of the cusp, there is ossification and cartilaginous metaplasia (O) (Movat pentachrome stain, original magnification $\times 2.5$). **B** Cross-section through the PA and a second cusp leaflet (C). The flow surface of the leaflet is covered with a layer of thick pannus across its entire length. The pannus continues along the pulmonary homograft wall (arrowheads). Note the extensive calcification along the PA homograft (asterisk) (Movat pentachrome stain, original magnification $\times 1.6$)

patients. Data from Tweddell et al (5) suggest that homograft replacement in a child who has had a previous RVOT reconstruction would likely be necessary 10 years after initial surgery. In their patient cohort, only one of 42 patients required surgery for replacement, 13 years postimplantation. The mean follow-up for these patients was 3.6 years, and it is possible that PH failure would not have been seen in patients in this short period of time after the index operation. Along with this case, Forbess et al (2) reported two patients older than 10 years of age ($n=48$) who required homograft replacement due to obstruction. Their data suggested that patients with homografts implanted at an age older than 10 years have optimal survival (94%) at five years. Both studies suggest that younger patients receiving smaller implants would eventually outgrow their PH and require replacement during periods of rapid growth, eventually leading to PH failure. None of these studies described the

explanted, cryopreserved PH valve's morphology to explain the basis of PH failure.

Hazekamp et al (6) followed 53 pediatric (mean age of 9.7 years) Ross procedure patients. Of this group, eight required reoperation, but only two patients had their PH replaced for obstruction. Unlike our case, these two patients had their reoperations at five and eight years following the Ross procedure, which were performed at one month and 4.8 years of age, respectively. The reasons for early failure were similar to those already mentioned.

Only one previous case, reported by Butany et al (7), described valve morphology after explantation. Similar to our case, the patient was older than 10 years of age at index surgery and required PH replacement nine years later. Microscopically, pannus was found on the homograft and on the flow and nonflow surfaces of the cusps, with evidence of calcification, ossification and thrombus; however, the cuspal tissue had remained intact, and the cusps were not significantly sclerosed or shortened as was seen in the present case. The reported reason for the PH failure was pannus

growth onto the cusps, which leads to restricted cusp movement and cellular proliferation at the distal end of the PA (also pannus), which at both sites leads to functional stenosis of the PH. No comment was made about the presence or absence of an inflammatory infiltrate.

CONCLUSION

Twelve years after implantation, this asymptomatic 25-year-old man underwent replacement of his PH, which showed significant cuspal tissue loss and pannus growth onto the cusps, as well as calcification and ossification at the bases of the cusps. These would have contributed to its stenosis, incompetence and eventual failure, necessitating surgical explantation. This PH was replaced while right and left ventricular function were still good. It is hoped that the new implanted cryopreserved PH will last for several more years, giving this young man many more productive years of life. Inflammation or cellular infiltration does not seem to play any significant roles in PH failure.

REFERENCES

1. Ross DN, Somerville J. Correction of pulmonary atresia with a homograft aortic valve. *Lancet* 1966;2:1446-7.
2. Forbess JM, Shah AS, St Louis JD, Jagers JJ, Ungerleider RM. Cryopreserved homografts in the pulmonary position: Determinants of durability. *Ann Thorac Surg* 2001;71:54-60.
3. Butany J, Zhou T, Leong S, et al. Inflammation and infection in nine surgically explanted stentless bioprosthetic heart valves. *Cardiovasc Pathol* 2007. (In press)
4. Vogt PR, Stallmach T, Niederhauser U, et al. Explanted cryopreserved allografts: A morphological and immunohistochemical comparison between arterial allografts and allograft heart valves from infants and adults. *Eur J Cardiothorac Surg* 1999;15:639-45.
5. Tweddell JS, Pelech AN, Frommelt PC, et al. Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. *Circulation* 2000;102(Suppl 3):III130-5.
6. Hazekamp MG, Grotenhuis HB, Schoof PH, Rijlaarsdam ME, Ottenkamp J, Dion RA. Results of the Ross operation in a pediatric population. *Eur J Cardiothorac Surg* 2005;27:975-9.
7. Butany J, Ahluwalia MS, Nair V, David TE. Cryopreserved pulmonary homograft: Postimplant changes. *Cardiovasc Pathol* 2004;13:59-61.