Increased pulmonary flow velocities in oversized homografts in patients after the Ross procedure

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Abstract

Objective: Between September 1991 and July 1996, 60 patients (mean age 29.8 ± 9 years; range 5–57) underwent aortic root replacement with pulmonary autograft, a viable biologic and nondegenerating substitute. The pulmonary root was replaced with cryopreserved homografts from cardiac transplant recipients. The aim of this study was to evaluate differences in early valve function of viable and cryopreserved allografts. Methods: All patients had Doppler echocardiographic examinations preoperatively, at discharge from hospital and 54 patients at 1 year follow-up. We measured aortic and pulmonary peak flow velocities with continuous and pulsed-wave Doppler, and graded aortic and pulmonary insufficiency (AI, PI) with color Doppler flow (grade 0–IV). Intraoperatively, the diameters of the pulmonary root and the pulmonary homograft were measured with standard valve probes and matched to body surface area. Results: Pulmonary peak flow velocity (PV max) increased significantly from preoperative 0.87 ± 0.11 m/s to 1.30 ± 0.34 m/s postoperatively (P < 0.001). The implanted homografts (mean 25.9 ± 2.4 mm) were larger than their native pulmonary diameter (mean 23.3 ± 1.8 mm) in all patients. Homograft size matched for body surface area (BSA) did not correlate with increased PV max. There was a significant increase of PV max at follow-up (FU) since discharge, also (1.83 ± 0.53 m/s; P < 0.001). Pulsed-wave Doppler demonstrates that increase of PV max is located directly at the homograft leaflets and not at the anastomoses. Aortic peak flow velocities (AV max) were normal postoperatively and at FU (post 1.35 ± 0.35 m/s; FU 1.17 ± 0.27 m/s). There was no significant change in AI or PI since discharge (AI FU 0.8 ± 0.4; PI FU 0.7 ± 0.5). Eight patients with fever and symptoms diagnosed as post-pericardiotomy syndrome had significantly higher PV max at FU (PV max = 2.41 ± 0.40 m/s; P < 0.02). Conclusions: The Ross procedure leads to normal AV max but significant increase of PV max even in oversized cryopreserved homografts immediately after surgery. Further increase of PV max without changes in AV max in the first year demonstrates that changes in flow velocities are valve related and not due to increase in cardiac output. Further investigations will be necessary to determine whether this observation is due to valve rejection or early leaflet degeneration and treatment with immunosuppressive therapy is warranted. © 1997 Elsevier Science B.V.

Keywords: Cryopreserved homograft; Immunosuppression; Pulmonary autograft; Pulmonary flow velocity

1. Introduction

Pulmonary autograft is used in an increasing number of patients for aortic valve replacement because it is the only technique for implantation of a vital and nondegenerating valve substitute with hemodynamic performance similar to that of native aortic valves [1–3]. Freedom from thromboembolic events, evidence of growth in children and long-term results with a free-
dom from valve-related complications of 70% at 20 years make the pulmonary autograft, especially in young patients, one of the best solutions for aortic valve replacement [2,4,5].

Because of the reported viability of cryopreserved allografts, mostly cryopreserved pulmonary homografts from cardiac transplant recipients are chosen for reconstruction of the right ventricular outflow tract [6,7]. Cryopreservation does not alter antigenicity of aortic allografts and the immunologic response may influence early and late valve function more than previously thought [8–10].

The aim of our study was to compare early valve function of the viable pulmonary autograft and the cryopreserved homograft in patients after the Ross procedure.

2. Patients and methods

Since 1991, 60 patients with a mean age of 29.8 ± 9 years (range 5–57 years) underwent pulmonary autograft valve replacement with their native pulmonary valve. Fourteen patients were younger than 18 years; there were 50 male and 10 female patients. In the first two patients, we used the subcoronary implantation technique, but all remaining 58 patients underwent aortic root replacement with direct implantation of the coronary arteries. All patients received cryopreserved pulmonary homografts from cardiac transplant recipients, mostly from our own homograft bank, for reconstruction of their right ventricular outflow tract. Only four homografts came from other institutions. The pulmonary valves were taken from donors younger than 55 years, prepared within 24 h and sterilized in a mixed antibiotic solution (vancomycin, cefoxitin, metronidazol, polymyxin B) for 24 h. They were then incubated in dimethyl sulfoxide (DMSO) as antioxidation in the vapor phase of a liquid nitrogen container at −174°C. No blood group or HLA matching was done. We use as an operative technique three running sutures for proximal and one running suture for the distal homograft anastomosis. The mean aortic cross-clamp time was 118 ± 23 min, mean extracorporal circulation time 165.4 ± 35 min. Additional surgery was performed in four patients (mitral valve reconstruction in two, VSD closure and abnormal pulmonary vein inflow in two other patients). In 70% of the patients (n = 42), the pathology was isolated aortic regurgitation.

Preoperatively, the mean New York Heart Association (NYHA) class was 2.8 ± 0.4. In asymptomatic patients, we try to operate before irreversible ventricular dilatation or reduced ventricular function will occur.

Transthoracic echocardiography was performed preoperatively for evaluation for valve repair (n = 60), at discharge from hospital (n = 59) and at 1 year follow-up (n = 54). Intraoperatively, the operative results were proven with transesophageal echocardiography. We used Hewlett Packard Sonos 1500 and 2500 machines with 2.2/2.5 MHz transthoracic and 5 MHz transesophageal probes. During each echocardiographic examination, aortic and pulmonary insufficiency (AI, PI) were graded with color Doppler flow from the width and length of the regurgitant jet into the left or right ventricular outflow tract and ventricles (grade 0–IV). The maximum aortic and pulmonary flow velocities (AVmax, PVmax) were measured with continuous wave Doppler (normal: AVmax = 1.0–1.8 m/s; PVmax = 0.6–0.9 m/s). Pulsed-wave Doppler was used for localization of the gradient drop at the right ventricular outflow tract and the pulmonary homograft to determine the origin of increased flow velocity whether it came from the anastomosis or the homograft leaflets. All echocardiographic measurements were averaged from three cardiac cycles. Intraoperatively, the diameters of pulmonary autografts and homografts were measured with standard valve probes and matched to body surface area.

Data are presented as mean ± S.D. Changes in echocardiographic measurements from pre- to postoperatively and at follow-up were analyzed by the paired t-test. P-values of less than 0.05 were considered significant.

3. Results

One patient died because of sudden cardiac death on the 5th postoperative day (perioperative mortality = 1.7%). At the beginning of our series, two patients were reoperated because of residual aortic regurgitation within the first year. In both patients, leaflet perforation of the pulmonary autograft could be reconstructed with a glutaraldehyde-fixed pericardial patch. One patient established moderate pulmonary regurgitation with homograft endocarditis 5 months postoperatively and was treated medically. He was excluded from pulmonary flow velocity measurements at follow-up. All patients were in NYHA class I, except for one patient with moderate AI at follow-up and the patient after homograft endocarditis, who were in NYHA class II.

Aortic regurgitation decreased significantly from preoperative 3.1 ± 0.5 to 0.4 ± 0.3 postoperatively (P < 0.001; n = 59). Two patients established moderate AI at follow-up but there was no significant increase from discharge to follow-up (mean AI FU = 0.8 ± 0.4; NS). All patients had normal aortic peak flow velocities and gradients (G) at discharge and at follow-up (mean AVmax Postoperatively, 1.35 ± 0.35 m/s; AG, 72.9 ± 0.5 mmHg; FU, 1.17 ± 0.27 m/s; AG, 5.4 ± 0.3 mmHg).
Mean pulmonary peak flow velocity increased significantly from preoperative $0.87 \pm 0.11 \text{ m/s}$ (range: 0.66–1.03 m/s) to $1.30 \pm 0.30 \text{ m/s}$ (range: 1.05–2.25 m/s) postoperatively ($P < 0.001$, $n = 59$). No patient had normal pulmonary flow velocity at discharge. There was a significant increase from postoperatively to 1 year follow-up, also (mean $\text{PV}_{\text{max}}$, $1.83 \pm 0.53 \text{ m/s}$; $\text{PG}$, $14.0 \pm 1.1 \text{ mmHg}$; range, 1.23–3.01 m/s; $P < 0.001$, $n = 54$). There was no significant change in pulmonary insufficiency (PI) from discharge ($\text{PI} = 0.5 \pm 0.4$) to follow-up ($\text{PI} = 0.7 \pm 0.5$).

Intraoperatively, the pulmonary diameters were measured (mean $23.3 \pm 1.8 \text{ mm}$; range 17–29 mm). All native pulmonary roots were smaller than the implanted pulmonary homografts (mean $25.9 \pm 2.4 \text{ mm}$; range 21–31 mm). There was no correlation between homograft size matched for body surface area and increased pulmonary flow velocities (see Fig. 1).

Moving the sample volume of the Doppler beam from the right ventricular outflow tract through the homograft leaflets to the pulmonary artery, pulsed-wave Doppler showed that the increase of pulmonary flow velocity is located at the homograft leaflets and not at the anastomosis in all patients.

Eight patients developed fever and symptoms of chest and/or pleuritic pain, malaise and weakness within the first postoperative month, but none had signs of infection (negative blood cultures, no homograft regurgitation or vegetations). These symptoms were diagnosed as post-pericardiotomy syndrome. Interestingly, those patients had significantly higher pulmonary flow velocities at follow-up (mean $\text{PV}_{\text{max}}$, $2.41 \pm 0.40 \text{ m/s}$; $\text{PG}$, $23.2 \pm 2.3 \text{ mmHg}$; range, 1.97–3.01; $P < 0.02$; $n = 8$) (see Fig. 2).

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Discharge</th>
<th>Follow-up</th>
</tr>
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<td>$1.35 \pm 0.35$</td>
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<td>$5.4 \pm 0.5$</td>
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<td>$0.4 \pm 0.3$</td>
<td>$0.8 \pm 0.2$</td>
</tr>
<tr>
<td>$\text{PV}_{\text{max}}$</td>
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<td>$1.3 \pm 0.34$</td>
<td>$1.83 \pm 0.53$</td>
</tr>
<tr>
<td>$\text{PG}$</td>
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<td>$6.8 \pm 0.5$</td>
<td>$14.0 \pm 1.1$</td>
</tr>
<tr>
<td>$\text{PI}$</td>
<td>$0.5 \pm 0.3$</td>
<td>$0.5 \pm 0.4$</td>
<td>$0.7 \pm 0.5$</td>
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Fig. 2. Flow velocities, pressure drops and regurgitation fraction preoperatively, at discharge and at follow-up ($\text{AV}_{\text{max}}$, peak aortic flow velocity (m/s); $\text{AG}$, aortic peak gradient; $\text{PV}_{\text{max}}$, pulmonary peak flow velocity; $\text{PG}$, peak gradient (mmHg); $\text{PI}$, pulmonary incompetence).

### 4. Conclusions

Patients after aortic valve replacement with pulmonary autograft received their living pulmonary valve as a nondegenerating substitute with a reported durability of more than 90% freedom from valve-related complications at 10 years and 70% after 20 years [5,11,12]. This type of valve replacement is the only substitute with hemodynamic performances that are similar to native aortic valves [3,15] and makes the Ross procedure the operation of choice in young patients with aortic valve disease [2,3,12]. In our series, all patients had normal aortic flow velocities at discharge and at follow-up, with a very low incidence of residual regurgitation. Only two patients during our learning curve with this complex operation had to be reoperated in the first year. No reoperation occurred in the last 5 years.

The need for reconstruction of the right ventricular outflow tract makes this operation for a double valve replacement with cross-clamp times of about 2 h [16]. However, with the routine use of retrograde blood cardioplegia, we demonstrate that operative mortality of 1.7% is acceptable for such perfect hemodynamic results in mostly active and young patients. For reconstruction of the right ventricular outflow tract, mostly cryopreserved homografts are used because of its reported viability. However, longer durability is discussed controversially [12,15]. At long term follow-up, homograft stenosis due to leaflet degeneration is the main cause of reoperation [7] and oversizing could be one option for longer valve survival.

Echocardiography is today the gold standard in the follow-up program in patients after cardiac valve replacement [13,14,17]. Especially with modern Doppler technologies, changes in blood flow velocities due to valvular dysfunction after aortic valve replacement can be observed very early before symptoms occur, and timing of optimal treatment is possible. In patients after the autograft procedure, most interest is directed to-
ward the aortic position, but in the long-term follow-up, the pulmonary homograft might be the major cause of reoperations [7].

We observed a significant increase in pulmonary flow velocities from the preoperative to the postoperative stage, and from discharge to 1 year follow-up. There was no change in aortic flow velocities in the same time, demonstrating that there was no change in cardiac output. Flow velocities at semilunar valves are dependent on the blood volume and orifice area. Increase of cardiac output accelerates both aortic and pulmonary flow velocities. The observation of isolated increase of pulmonary flow velocity demonstrates that the pulmonary homograft valve area is smaller than the native pulmonary valve of the patient even in these oversized homografts. We compared intraoperatively measured homograft size matched to body surface area with measurements of the patients native pulmonary valve. There was no correlation with increased pulmonary flow velocities. Pulsed-wave Doppler demonstrates that the gradient is located directly at the homograft leaflets and not at the anastomosis. We conclude that increased flow velocities are valve related and stiffness of the homograft leaflets or the homograft wall, even in cryopreserved homografts, decreases valve opening. Eight patients with fever and symptoms diagnosed as post-pericardiotomy syndrome had significantly higher flow velocities at their homografts after 1 year, but none of these patients had signs of infection. The one excluded patient, after homograft endocarditis, established moderate homograft insufficiency with normal pulmonary flow velocity. We conclude that some immunologic response after allograft implantation leads to infiltration or edema of the homograft leaflets and may affect valvular function. We know from other studies that cryopreservation does not alter antigenic expression of aortic allografts. In addition, with in situ hybridization, living donor fibroblasts could be isolated years after implantation of cryopreserved allografts [9]. Short-course cyclosporin A immunosuppressive therapy lead to better allograft valve survival in rats [19]. Most of our patients are in NYHA class I and only echocardiography shows impaired homograft function. Mid-term and long-term follow-up will show if early increase of pulmonary flow velocities is correlated with allograft long-term durability. Patients with any symptoms of immunologic response should be treated very carefully and short-course immunosuppressive therapy should be discussed to increase homograft survival in the pulmonary position [10,18,19].

References

Appendix A. Conference discussion

Dr Z. Al-Halees (Riyadh, Saudi Arabia): I thank the authors for bringing to our attention a forgotten problem after the Ross procedure. We also encountered similar findings in the pulmonary homograft in the pulmonary position after the Ross procedure but with some differences. Since we started doing the Ross procedure in 1990—we now have about 130 Ross procedures—we have complete echocardiographic data on at least 116 of these patients. These studies are done right after the operation, every 6 months and yearly thereafter. We found that there is increased velocity in the pulmonary homograft in the pulmonary position immediately after operation and the gradient continues to increase up to about 1.5 years later and then for some unknown reason stabilizes afterwards. If we take a velocity of 2 m/s, then almost 70% of the patients would have that. However, about 14% of the patients will have a maximum velocity above 3 m/s, which means a gradient of more than 50 mmHg. Some of these gradients develop as early as 6 months. In our series, one patient needed reoperation because he was symptomatic and with a gradient of more than 100 mmHg. Two other patients had their right ventricular outflow tract augmented during reoperation on the aortic valve for one and the tricuspid valve for the other. In our series, we found that the gradient could be either at the proximal anastomosis, at the annulus level, or distally. Actually, some of those homografts had become almost like a tube of calcium. So, like you, we believe that there could be some immunologic phenomenon and the role of immunosuppression under these circumstances, of course, remains to be explored. I congratulate the authors for the excellent presentation and I believe that all surgeons and cardiologists should be aware of this potential problem after the Ross procedure. Thank you.

Dr Moidl: Thank you very much for your comment. We never saw these high velocities in aortic homografts in the aortic position, but we think that the left ventricle has much more power to open up the valve than the right ventricle. In the pulmonary position, you see the changes in velocities much earlier, before the patient establishes symptoms. We will see what happens to the patients with the highest flow velocities soon after the operation at follow-up.

Dr G. Pettersson (Copenhagen, Denmark): Could I ask you a question about technical details? How much do you trim the autograft? How do you orient the autograft? What about the importance of homograft length?

Dr Moidl: We performed, for example, the distal anastomosis the same length as in the cardiac transplantation procedure. We never had a problem of the anastomosis in more than 600 transplantations.