Autograft or allograft aortic valve replacement in young adult patients with congenital aortic valve disease

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Aims

We analysed the outcome of young adults with congenital aortic valve disease who underwent allograft or autograft aortic valve or root replacement in our institution and evaluated whether there is a preference for either valve substitute.

Methods and results

Between 1987 and 2007, 169 consecutive patients with congenital aortic valve disease aged 16–55, participating in our ongoing prospective follow-up study, underwent 63 autograft and 106 allograft aortic valve replacements (AVRs). Mean age was 35 years (SD 10.8), 71% were males. Aetiology was 71% bicuspid valve, 14% other congenital, and 15% BV endocarditis. Twenty-two percent underwent previous cardiac surgery; 11% had an ascending aorta aneurysm. Two patients died in hospital. During follow-up six more patients died and 45 patients required valve-related re-operations. Thirteen-year survival was 97% for autograft and 93% for allograft recipients, 13 year freedom from valve-related re-operation was 63% for autograft and 69% for allograft patients.

Conclusion

In patients with congenital aortic valve disease, autograft and allograft AVR show comparable satisfactory early and long-term results, with the increasing re-operation risk in the second decade after operation remaining a major concern.

Keywords

Aortic valve replacement • Congenital aortic valve disease • Young adults • Prosthetic valve selection
• Autograft • Allograft

Introduction

Prosthetic valve selection for patients who require aortic valve replacement (AVR) remains a delicate and complicated topic of discussion, as evidenced by the major criteria for aortic valve selection in ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease.1 For young adult patients with a congenital aortic valve stenosis this is particularly true. The guidelines state that ‘although the Ross operation, homograft, heterograft, and valve repair each appear to offer an attractive alternative to a mechanical valve for those with a relative contraindication to warfarin for anticoagulation (e.g. athletes or women desiring pregnancy), in the absence of long-term results, it is not believed that the indications for surgery with the Ross operation, heterograft, or homograft differ from those for mechanical valve replacement at this time’.1

In our own institution, we started using autografts and allografts for AVR in the late 80s, assuming that their durability would be better compared with bioprostheses, their haemodynamic profile superior to mechanical prostheses and bioprostheses, and because they offer (in particular young adult) patients the option of an active life without the limitations of anticoagulation that would be required after implantation of a mechanical prosthesis. We systematically and carefully followed patients over time2–4

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and are now able to make present reliable observations on valve performance and patient outcome well into the second decade after operation.

The aim of this study is to analyse the clinical results of aortic valve and root replacement with autografts vs. allografts in young adult patients with congenital aortic valve disease that are participating in our centre’s prospective cohort study and assess whether there is a preference for one of these valve substitutes in this particular patient population.

**Methods**

**Patients**

Between April 1987 and January 2007, 499 consecutive patients underwent autograft or allograft aortic valve or root replacement at Erasmus University Medical Center Rotterdam. All patients who receive an autograft or allograft in aortic position in our centre are followed prospectively at yearly intervals. Completeness of follow-up is currently 98%.<sup>2–4</sup> Institutional Review Board approval was obtained for this prospective follow-up study; the Institutional Review Board waived informed consent.

We performed in this prospective cohort of 499 patients a retrospective analysis of those patients with congenital aortic valve disease, no previous AVR, and an age at operation between 16 and 55 years. Congenital aortic valve disease was defined as: bicuspid aortic valve or discrete subaortic obstruction, resulting in subvalvular or valvular aortic stenosis, aortic regurgitation or a prolapse of one of the aortic cusps into a ventricular septal defect causing aortic regurgitation. The enrolment was based on the presence of congenital aortic valve disease, either determined on pre-operative echocardiography or based on the abnormalities seen at operation.

The total number of excluded patients was 330, of these patients, 70 patients were younger than 16 years of age and 106 patients were older than 55 years. These patients were excluded because they did not fit the age criteria. Furthermore, 154 patients were between 16 and 55 years of age, but were excluded because these patients required surgery for another aetiology than congenital aortic valve disease. Other aetiologies were rheumatic disease ($n = 21$), endocarditis ($n = 44$), senile degeneration of a tricuspid valve ($n = 20$), aneurysm ($n = 15$), dissection ($n = 13$), and re-operation ($n = 41$). This selection resulted in 169 patients: 63 autograft patients and 106 allograft patients. Pre-operative patient characteristics are displayed in Table 1. Overall mean patient age was 35.0 years (SD 10, range 16–55 years).

**Operation**

Root replacement was performed as a freestanding root with re-implantation of the coronary arteries in 61 autograft patients and 66 allograft patients. In two autograft patients an inclusion cylinder aortic root replacement was done<sup>6</sup> and 40 allograft patients underwent subcoronary allograft implantation<sup>6</sup>. The autograft or allograft root was placed in the left ventricular outflow tract (LVOT) and anulus with a short rim of right ventricular muscle, which was kept to a minimum and no measures were taken to reinforce the aortic root or sinotubular junction. Either continuous or interrupted sutures were used for the proximal anastomosis, depending on the surgeon’s preference. Initially in this series, the autograft was placed on the anulus, in more recent years particular attention is paid to place the autograft inside the anulus. During the autograft procedure, reconstruction of the right ventricular outflow tract (RVOT) was done using an allograft. Details on these allografts are displayed in Table 2. Surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. Crystalloid cardioplegia and topical cooling were used for myocardial protection.

**Follow-up**

All patients who receive an autograft or allograft at Erasmus MC are followed prospectively by annual telephone interviews and through visits to their cardiologist. Echocardiographic follow-up is obtained at 6 months post-operative, 1 year post-operative, and thereafter biennially by means of serial standardized echocardiography.<sup>2–4</sup> Valve-related complications were defined according to the 1996 guidelines for reporting morbidity and mortality after cardiac valvular operations.<sup>7</sup> The mode of autograft and allograft failure was determined at time of re-operation or death.

The study database was frozen for analysis on 1 April 2007. Follow-up was 96.5% complete.<sup>8</sup> Overall median follow-up duration was 10.1 years (interquartile range 6.9 years), with total follow-up of 1743 patient years, for autograft patient mean follow-up was 10.3 years (SD 3.8, range 0–18.4 years) with 650 patient years and for allograft patients mean follow-up was 10.3 years (SD 4.9, range 0.1–19.8 years) with 1093 patient years.

**Statistical methods**

Continuous data are presented as mean ± 1 standard deviation, and compared with the unpaired $t$-test or the Mann–Whitney U-test. Categorical data are presented as proportions, and compared with the Fisher’s exact test or the $\chi^2$ test. To account for the inflation of the experiment wise Type I error due to multiple testing, we used the Bonferroni post-hoc test in case of comparison of more than two categories.

Univariable logistic regression was used to assess differences in patient and procedural characteristics between autograft and allograft procedures. Univariable logistic regression was used to determine factors associated with the different valve substitute groups. The following factors were analysed: age at operation (continuous variable expressed in years), sex, previous surgery on the LVOT, New York Heart Association Class (defined as I, II, III and IV), pre-operative creatinine level (micromoles/L), pre-operative ventilation support, abnormal cardiac rhythm pre-operative (other pre-operative rhythm than sinus rhythm), left ventricular function (defined qualitatively as good or impaired on either angiography or echocardiography), active endocarditis (operated on before completing a standard course of antibiotics), and pre-operative haemodynamic diagnosis.

Cumulative survival and freedom from re-operation or re-intervention were analysed using the Kaplan–Meier method. Survival curves were compared using the Log-rank test. Univariable Cox regression was used for analysis of time-related events. The following factors were analysed as potential risk factors for re-operation for structural failure:

Patient age, gender, previous cardiac surgery, endocarditis as the aetiology for operation and allograft characteristics (as mentioned in Table 2).

Age-matched survival in the general population was calculated using the Dutch population life tables. A $P$-value of $\leq 0.05$ was considered statistically significant. All testing was performed two-sided. For all analyses SPSS 12.0 for Windows statistical software (SPSS, Chicago, Ill) was used.

Using Egret, the incidence of structural valve deterioration requiring re-operation was described by a Weibull curve, which is a generalization...
of the exponential distribution that accommodates a changing risk over time.9,10

**Results**

**Valve selection**

Patients who received an autograft were younger at the time of operation (OR 1.09, 95% CI 1.06–1.14; P < 0.001), were more often females (OR 3.2, 95% CI 1.6–6.5; P = 0.001), had more previous surgery on the LVOT (OR 4.0, 95% CI 1.5–10.7; P = 0.005), more commonly underwent elective surgery (OR 2.6, 95% CI 1.01–6.6; P = 0.05), and had a good pre-operative left ventricular function (OR 100 (63) 97 (103) 0.18). Creatinin [μmol/L; (SD; range)] 72 (16; 38–121) 92 (36; 39–371) <0.001

Systolic LVF (1 missing)

| Good, % (n) | 91 (57) | 78 (83) | 0.04 |
| Impaired, % (n) | 9 (5) | 22 (23) | 0.02 |

NYHA class

| I/III, % (n) | 90 (57) | 77 (83) | 0.04 |
| IV, % (n) | 20 (13) | 30 (32) | 0.18 |

Type operation

| Emergency, % (n) | 4 (4) | 4 (4) | 0.12 |
| Urgent, % (n) | 10 (6) | 18 (19) | 0.14 |
| Elective, % (n) | 90 (57) | 77 (83) | 0.04 |
| Ventilatory support, % (n) | 2 (2) | 2 (2) | 0.27 |

LVF, left ventricular function measured by angiography or 2D-echocardiography; NYHA class, New York Heart Association classification.

Two allograft patients received a pulmonary allograft in the aortic position (Table 2). One of the patients required a re-operation within 2 weeks after initial implantation of the pulmonary allograft and received a new aortic allograft. Six years after this allograft implantation this patient required another re-operation and received a mechanical prosthesis. This patient is alive today. The other pulmonary allograft patients required a re-operation 6 years after allograft implantation. Unfortunately, this patient died 3 years after the re-operation due to an intracerebral bleeding.

**Early morbidity and mortality**

Peri-operative details are displayed in Table 3. Two patients, both autograft recipients, died in hospital (3.2%). One patient died during a long and complicated autograft procedure due to low output failure (see details in what follows). The other autograft patient died on the 13th post-operative day due to mediastinitis and sepsis.
Five patients, two autograft patients and three allograft patients (all root replacements), required coronary artery bypass grafting due to procedural complications. Furthermore, 11 autograft patients required a rethoracotomy for persistent bleeding. Circulatory arrest was employed in four allograft root replacement patients because additional replacement of the ascending aorta...
with a vascular prosthesis was required, and in one autograft patient because the ascending aorta perforated during sternotomy.

**Follow-up and survival**

During follow-up six more patients died (3.6%), all allograft recipients [linearized occurrence rate (LOR) 0.55%/patient year]. Causes of death were: stroke (n = 1), sudden unexplained death (n = 5), and non-valve related death (n = 1).

Overall cumulative survival was 94.6 ± 2.1 at 13 years, for autograft recipients 96.8 ± 2.2% and 92.7% ± 3.3% for allograft recipients (p = 0.45). Figure 1 shows overall survival for autograft and allograft recipients compared with 35 year old males in the general Dutch population.

**Re-operation**

During follow-up there were 45 valve-related re-operations: 37 for structural valve deterioration, seven for non-structural valve deterioration, one for recurrent endocarditis.

Sixteen autograft recipients (LOR 2.5%/patient year) and 21 allograft recipients (LOR 1.9%/patient year) required re-operation for structural valve deterioration. Structural valve deterioration in autografts was caused by progressive dilatation of the neo-aortic root and subsequent aortic regurgitation, while in allografts it was characterized by degeneration and calcification. In four of the 10 autograft re-operations a degenerated pulmonary allograft was concomitantly replaced with another cryopreserved pulmonary allograft. One autograft patient underwent an isolated pulmonary allograft replacement with a vascular prosthesis.

The seven re-operations for non-structural valve failure or technical valve failure occurred all in allografts that were implanted using the subcoronary technique (LOR 0.64%/patient year). The re-operation for recurrent endocarditis was in a patient with a subcoronary allograft (LOR 0.09%/patient year). See Table 4 for details on re-operations.

There was no re-operative mortality. One autograft patient who received a mechanical valve conduit had a major stroke in the immediate post-operative period.

**Other valve-related events**

In the autograft patient group, one patient had a recurrent episode of endocarditis (0.15%/patient year), and one patient had a pulmonary embolism (0.15%/patient year). In the allograft patient group, one patient had a recurrent episode of endocarditis (0.09%/patient year) and two allograft patients had a TIA (LOR 0.18%/patient year). Figure 4 shows the freedom from any valve-related event. Overall freedom from any valve-related event at 13 years was 59.1 ± 5.5%, for autograft patients 59.2 ± 9.5% and for allograft patients 59.0 ± 6.8% (P = 0.62).

### Table 4 Details on re-operations

<table>
<thead>
<tr>
<th></th>
<th>Autograft (n = 16)</th>
<th>Allograft (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause for aortic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>valve re-operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural failure, n</td>
<td>16</td>
<td>21</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-structural valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deterioration, n</td>
<td>—</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>Endocarditis, n</td>
<td>—</td>
<td>1</td>
<td>0.45</td>
</tr>
<tr>
<td>Valve substitute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inserted at</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>re-operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prosthesis, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bentall procedure, n</td>
<td>13</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Autograft, n</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Allograft, n</td>
<td>2</td>
<td>3*</td>
<td>0.83</td>
</tr>
<tr>
<td>Stentless bioprosthesis, n</td>
<td>1</td>
<td>1</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Subcoronary allografts.

Overall freedom from aortic valve re-operation was 94.5 ± 1.8% at 5 years and 61.4 ± 5.5% at 13 years. For autograft patients freedom from aortic valve re-operation was 100% at 5 years and 63.4 ± 9.6% at 13 years, for allograft patients 91.2 ± 2.8% at 5 years and 59.8 ± 6.8% at 13 years (P = 0.48). See also Figure 2. Freedom from aortic valve re-operation for structural valve deterioration for all valves was 98.8 ± 0.9% at 5 years and 67.2 ± 5.2% at 13 years, for autograft patients 100% at 5 years and 63.4 ± 9.6% at 13 years and for allograft patients 98.0 ± 1.4% at 5 years and 68.8 ± 6.3% at 13 years (P = 0.44). No factors were found to be associated with an increased risk on re-operation for structural failure in both the allograft and autograft group. Figure 3 shows the observed freedom from re-operation from structural valve deterioration and the corresponding Weibull functions representing the increasing hazard with time of structural valve deterioration for both allografts and autografts.
Table 5 shows aortic regurgitation for both allograft and autograft patients, pulmonary regurgitation for autograft patients at echocardiography and NYHA class at last follow-up. Echocardiographic measurements of patients who underwent re-operation or died during follow-up were excluded. Autograft patients had a larger aortic annulus at last follow-up compared with allograft patients \( (P_{0.001}) \) and no differences were observed in functional exercise capacity.

**Discussion**

Our study shows satisfactory results on early and long-term survival for both the autograft and the allograft in patients with congenital aortic valve disease. On the other hand, it also shows that durability of both procedures is limited and the majority of patients will require a re-operation later in life.

**Early morbidity and mortality**

AVR with an autograft or allograft is a complex operation illustrated by the long cardiopulmonary bypass and cross-clamp times. Still, this can safely be performed evidenced by the low hospital mortality of 3% for autograft patients and no hospital mortality for allograft patients.

**Survival**

No differences were observed in late survival between both valve substitutes and late survival was comparable with that of the general age-matched Dutch population. Allograft patients more often underwent AVR for endocarditis on the aortic valve or

**Table 5 Echocardiographic and functional outcome at last follow-up visit**

<table>
<thead>
<tr>
<th></th>
<th>Autograft</th>
<th>Allograft</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>n = 42</td>
<td>n = 72</td>
<td></td>
</tr>
<tr>
<td>Grade 0–0.5+, %</td>
<td>21 (9)</td>
<td>28 (20)</td>
<td>0.44</td>
</tr>
<tr>
<td>Grade 1+, %</td>
<td>41 (17)</td>
<td>39 (28)</td>
<td>0.90</td>
</tr>
<tr>
<td>Grade 2+, %</td>
<td>26 (11)</td>
<td>29 (21)</td>
<td>0.71</td>
</tr>
<tr>
<td>Grade 3+, %</td>
<td>10 (4)</td>
<td>4 (3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Grade 4+, %</td>
<td>2 (1)</td>
<td>—</td>
<td>0.19</td>
</tr>
<tr>
<td>PR</td>
<td>n = 44</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Grade 0–0.5+, %</td>
<td>86 (38)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grade 1+, %</td>
<td>12 (5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grade 2+, %</td>
<td>2 (1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grade 3+, %</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grade 4+, %</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diameter aortic annulus (mm)</td>
<td>n = 38</td>
<td>n = 65</td>
<td></td>
</tr>
<tr>
<td>&lt;30, %</td>
<td>13 (5)</td>
<td>20 (13)</td>
<td>0.38</td>
</tr>
<tr>
<td>30–&lt;40, %</td>
<td>41 (16)</td>
<td>74 (48)</td>
<td>0.001</td>
</tr>
<tr>
<td>40–&lt;50, %</td>
<td>41 (16)</td>
<td>6 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50, %</td>
<td>5 (2)</td>
<td>—</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean diameter aortic annulus [mm, (range)]</td>
<td>37 (26–52)</td>
<td>33 (21–44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NYHA class</td>
<td>n = 45</td>
<td>n = 73</td>
<td>0.18</td>
</tr>
<tr>
<td>I/II, %</td>
<td>98 (44)</td>
<td>92 (67)</td>
<td></td>
</tr>
<tr>
<td>III/V, %</td>
<td>2 (1)</td>
<td>8 (6)</td>
<td></td>
</tr>
</tbody>
</table>

AR, aortic regurgitation; PR, pulmonary regurgitation.
valve prosthesis, a factor that may have affected long-term survival. However, only one of the six late deaths was in a patient with endocarditis aetiology, and all other late deaths were in patients who did not have a previous AVR for endocarditis. On the other hand, a survival difference between the autograft and allograft in favour of the autograft is observed in a randomized controlled study of Aklog et al., although survival differences between the two valve substitutes were not significant. When comparing patient survival after AVR with an autograft or allograft to the patient survival of other valve substitutes available in patients under 55 years of age, long-term survival rates for autograft and allograft patients are better than other valve substitutes in this patient population. Whether this is due to patient selection or the haemodynamic superiority of human tissue valves is a question that requires further exploration.

Re-operation

Although freedom from re-operation for any cause was comparable for both the allograft and autograft, causes for re-operation differed considerably between the valve types. Indications for re-operation for autograft patients were endocarditis, perivalvular leakage, and structural failure. Structural allograft failure was characterized by degeneration and calcification, an observation that is confirmed by several other institutions.

Indication for autograft patients to return for re-operation was solely structural failure. The autograft failed due to progressive dilatation of the neo-aortic root with subsequent aortic regurgitation. No age-dependency was observed for autograft structural valve failure in this study. In the present study, the autograft roots were placed in the LVOT and annulus with a short rim of right ventricular muscle, which was kept to a minimum and no measures were taken to reinforce the aortic root or sinotubular junction. Minimization of the length of the autograft root may result in less dilatation and may produce better durability. Furthermore, reinforcement of the aortic root or sinotubular junction may enhance durability as well.

The majority of our study patients have a bicuspid valve, the most common congenital valvular abnormality, which comprises 1% of the general population. It remains debatable if presence of a bicuspid valve is a risk factor for re-operation after the pulmonary autograft procedure. A bicuspid valve is reported to be associated with a high incidence of aortic root dilatation due to aortic wall abnormalities. Moreover, Schoof et al. observed in a recent autograft explant study that there was no association between bicuspid valve disease and histological changes in explanted pulmonary autografts.

The necessity for re-operation will increase for both valves in the second decade after operation and this increase seems larger for autograft patients. This trend is already to some extent seen in Figure 3 and is also reported in other series. Structural failure is the main disadvantage of allografts and autografts compared with mechanical prostheses, which have an unlimited durability. Comparing allografts with stented biological prostheses a comparable age-dependent structural failure rate is observed in adult patients, which is not observed in adult autograft patients. This suggests an advantage of the autograft in younger patients and of a biological prosthesis or allograft in older patients. However, Svensson et al. provided an overview of different surgical strategies in young adult patients and compared the available valve substitutes. They concluded that the structural failure rate of biological valves is much higher and of mechanical prostheses much lower in young adults compared with the allograft or autograft and would therefore be not a good solution in young adults. Yet, the main disadvantage of the mechanical prostheses remains the anticoagulation use and the related complications, such as bleeding events and higher thrombo-embolic event rates.

Although the CPB times for re-operation on a pulmonary autograft are observed to be longer, yet not significant, re-operation on a calcified allograft takes a lot more effort than on a dilated pulmonary autograft. The dilated autograft root allows the surgeon a clear view of the insufficient autograft and its dilated annulus, on which an anastomosis is easier to perform. The calcified aortic allograft on the other hand is rigid causing a smaller operation field.

Valve-related events

Occurrence rates of valve-related events other than re-operations are low in our study population. Concha et al. compared the pulmonary autograft to the mechanical prosthesis regarding early and long-term results and observed no other valve-related events than pulmonary stenosis in the pulmonary autograft group compared with major bleeding, thrombo-embolic complications related to coumarin, and prosthetic valve endocarditis in mechanical prosthesis group. Other reports comparing the allograft to the mechanical prosthesis show similar results, suggesting that these human tissue valves provide a superior valve substitute in this regard compared with mechanical prostheses.

Conclusions

In young adult patients with congenital aortic valve disease, our study shows that both the allograft and autograft are valve substitutes with satisfactory results regarding early and long-term patient survival, with late survival even comparable with the general age-matched population. These patients comprise a young patient population with little co-morbidity, who have an active lifestyle with a long life-expectancy and in whom preferably anticoagulation treatment should be avoided. However, the major limitation of human tissue valves is the increasing high incidence of re-operations for structural valve deterioration in the second decade after operation.

Conflict of interest: none declared.

References


