Durability of down-sized homografts for the reconstruction of the right ventricular outflow tract

Julie Cleuziou, Keti Vitanova, Jelena Kasnar-Samprec, Jürgen Hörer, Rüdiger Lange and Christian Schreiber

Department of Cardiovascular Surgery, German Heart Centre Munich, Technische Universität München, Munich, Germany

OBJECTIVES: Small-sized homografts are rare but may be required for the reconstruction of the right ventricular outflow tract (RVOT). Down-sizing adult-sized homografts can be an option to overcome the shortage of availability.

METHODS: Since 1994, we have been down-sizing adult-sized homografts by excising one cusp. The aim of the study was to analyse the durability of down-sized homografts and compare it with small-sized homografts in a paediatric population. All patients below a body weight of 14 kg were included in the study. The end-point of the study was homograft failure.

RESULTS: A total of 152 patients met the inclusion criteria of the study, of which 82 patients (54%) received a down-sized homograft. The median age was 17.1 (0.3–64.8) months and the mean weight 8.4 ± 3.4 kg. Fifty-eight patients (38%) were under 1 year and 10 (6.5%) under 1 month of age at the time of homograft implantation. The mean homograft size of the whole study population was 14.7 ± 2.5 mm and the mean z-score was 1.6 ± 0.9. The median follow-up time was 10 (0.03–19.7) years. Early mortality after homograft implantation was 5% (n = 8), 4 of these patients had received a down-sized homograft. The study population comprised early survivors, that is, 144 patients. During follow-up, a total of 46 homografts failed, 23 in each group, after a mean time of 5.7 ± 4.2 years. Freedom from homograft failure was 94.6 ± 2.6, 87.2 ± 4 and 68.6 ± 6.6% for down-sized homografts and 95.2 ± 2.7, 78.7 ± 5.5 and 61 ± 7% for small-sized homografts at 1, 5 and 10 years, respectively (P = 0.3). Risk factors for homograft failure in the multivariable analysis were a homograft z-score of <1 and age below 1 year at the time of implantation (P = 0.02).

CONCLUSION: Down-sized homografts demonstrated a durability similar to that of small-sized homografts. Therefore, down-sizing adult-sized homografts by creating a bicuspid valve to fit into the corresponding RVOT in children with congenital heart defects is an excellent method to overcome the shortage of small-sized homografts.

Keywords: Congenital heart disease • Right ventricular outflow tract • Homograft

INTRODUCTION

There is an ongoing search for the ideal conduit for replacing the right ventricular outflow tract (RVOT) in patients with congenital heart disease. The ideal conduit should have excellent haemodynamic characteristics, growth potential, a low predisposition for infections and should be non-thrombogenic. As the ideal conduit does not yet exist, numerous investigations are focusing on detailed analyses of currently available conduits [1–5]. These reports include patients of all ages but do not specifically consider the subgroup of young children. However, especially young children require multiple repeated surgeries because of the inevitable degeneration of biological conduits [2, 6–8]. Homografts provide the best option for the reconstruction of the RVOT, achieving almost ideal characteristics with low thrombogenicity, excellent haemodynamics and good durability [8, 9]. However, homografts are difficult to obtain, especially in small sizes. To overcome the shortage of small-sized homografts, Michler et al. [10] have suggested down-sizing adult-sized homografts to fit into the RVOT of infants. Since then, some encouraging results of this method have been published [11–13]. However, these reports are based on small patient cohorts and long-term data are lacking.

The aim of our study was to analyse the durability of down-sized homografts in a paediatric population requiring reconstruction of the RVOT.

METHODS

Patient population

Institutional Review Board approval was obtained to conduct this retrospective follow-up study. All patients who received a
homograft for reconstruction of the RVOT were identified from the institutional database. All homografts originated from our own bank and were cryopreserved. Down-sized homografts were used at our institution from 1994 onwards and were exclusively implanted in patients with a body weight of less than 14 kg. Therefore, our study included all patients with a body weight of 14 kg or less, receiving a homograft in the RVOT since 1994. The decision on whether a patient would receive a down-sized homograft or a small-sized homograft was dependent on the availability of grafts. The end-point of the study was defined as ‘homograft failure for any reason’. Indications for homograft failure included at least a moderate stenosis or a moderate insufficiency or endocarditis. All patients reaching the end-point of the study had a replacement of the homograft.

Operative data

Surgery was performed through a midline sternotomy, cardiopulmonary bypass and after cooling to a core temperature of 32°C. Depending on the type of operation performed, previous shunts were taken down and the repair of the underlying heart defect was completed. For down-sizing the homograft, a longitudinal incision was first made into one of the commissures next to the leaflet to be resected. Then, one leaflet was excised and finally the homograft was reconstructed with a running 5/0 polypropylene suture (Fig. 1). The homograft was shortened distally to position the valve close to the pulmonary bifurcation, minimizing the risk of sternal compression. At the proximal end, homografts were extended either with a polytetrafluoroethylene (PTFE) tube graft or with a Dacron patch. No routine postoperative anticoagulation was initiated. The homograft diameters were converted into z-scores according to the nomograms published by Zilberman et al. [14].

Follow-up

All patients were seen routinely at our outpatient clinic or by referring paediatric cardiologists. All medical reports including operative notes were reviewed. Follow-up time was calculated by deducting the last follow-up date from the operating date. On echocardiography, a homograft stenosis was graded moderate if the peak velocity was 3–4 m/s and the peak gradient 36–64 mmHg [15]. Homograft insufficiency was graded by mapping the dimensions of the insufficiency jet with a colour flow Doppler echocardiography, according to the guidelines for echocardiography [15]. If a moderate stenosis or insufficiency was present, the diagnosis was verified by angiography.

Statistical analysis

Statistical analysis was performed using the SPSS 21.0 software (SPSS, Inc., Chicago, IL, USA). Frequency data are given as absolute numbers and percentages. Comparisons for categorical variables were calculated with the two-tailed χ² test. Continuous data are given as medians with ranges or as means with standard deviation. Comparisons for continuous variables were calculated with the t-test for independent samples. The Kaplan–Meier method was used to estimate the freedom from events. The time of homograft implantation was defined as time point zero. Differences between groups were calculated with the log-rank test. Risk factors for homograft failure were analysed with a linear univariable and multivariable Cox regression model. For all tests, a P ≤ 0.05 was considered significant. All variables with a P-value of ≤ 0.1 in the univariable analysis were entered into the multivariable model.

RESULTS

Patients

Between 1994 and 2013, a total of 152 patients met the inclusion criteria of the study. Fifty-eight patients (38%) were under 1 year and 10 (6.5%) under 1 month of age at the time of homograft implantation. In 35 patients (23%) of the whole study group (20 patients with a down-sized homograft), the homograft implanted had a z-score below 1. A down-sized homograft was implanted in 82 patients (54%). The adult-sized homografts were reduced in size to a mean of 67 ± 5% of their original size. There was no difference in age, weight, homograft size, z-score and diagnosis between patients who received a down-sized homograft and patients who received a small-sized homograft. Patients’ characteristics are depicted in Table 1.

Prior to homograft implantation, 74% of the patients had undergone a previous operation, 55 patients (49%) had had a palliative procedure and 53 patients (47%) a repair of the underlying heart disease. Of 21 patients undergoing a repair of a common arterial trunk (CAT), 15 obtained a small-sized homograft compared with 6 with a down-sized homograft (P = 0.02). A majority of the down-sized homografts (73%) were from the pulmonary origin, compared with 43% of the small-sized homografts (P < 0.001). Down-sized homografts were extended with a PTFE tube graft in 63%, compared with 41% of the small-sized homografts (P = 0.009). Other operative characteristics were evenly distributed between the groups (Table 1).

Survival

Early mortality after homograft implantation was 5% (n = 8). Three patients died following CAT repair from low cardiac output. Two patients following a tetralogy of Fallot repair died from severe right ventricular dysfunction. One neonate died after a Ross operation on ECMO from severe mitral valve regurgitation due to a

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Figure 1: Down-sized homograft with a bicuspid valve.
dysplastic mitral valve. One patient with a complex double outlet right ventricle died from heart failure and one patient with pulmonary atresia, ventricular septal defect and MAPCA died intraoperatively from persistent high pulmonary vascular resistance.

Seven patients (5%) died late after homograft implantation at a median time of 10 months (3 months–11 years). The homograft function was good in all patients and death was unrelated to the homograft. Causes of death were chronic cardiac failure (n = 3), seizure (n = 1), myocardial infarction after transcatheter pulmonary valve implantation (n = 1) and unknown in 2 patients. Long-term survival was 92 ± 3 and 91 ± 3% after 1 year, 92 ± 3 and 90 ± 4% after 5 years, 91 ± 3 and 90 ± 4% after 10 years for patients with a down-sized and small-sized homograft, respectively (P = 0.9, Fig. 2).

### Homograft failure

The analysis for homograft failure comprised early survivors, that is, 144 patients. During the follow-up, a total of 46 homografts were explanted, 23 in each group, after a mean time of 5.7 ± 4.2 years. One patient underwent a transcatheter valve implantation. Freedom from homograft failure for patients with a down-sized and small-sized homograft was 94.6 ± 2.6 and 95.2 ± 2.7% at 1 year, 87.2 ± 4 and 78.7 ± 5.5% at 5 years and 68.6 ± 6.6 and 61 ± 7% at 10 years, respectively (P = 0.3, Fig. 3). Indications for homograft exchange were a stenosis in 56% (n = 26) and a combined stenosis with insufficiency in 26% (n = 12). From the 12 homografts with a combined stenosis and insufficiency, the majority (n = 10) were small-sized homografts (P = 0.01). Other reasons were an isolated insufficiency in 6 and an endocarditis in 2 patients. The mean z-score at the time of homograft failure was −0.98 ± 1.5 for down-sized homografts and −0.98 ± 1.6 for small-sized homografts (P = 0.9).

### Risk factors for homograft failure

CAT repair and a homograft extension with a PTFE graft emerged as risk factors for homograft failure in the univariable analysis. A homograft z-score of <1 and an age below 1 year at the time of implantation were independent risk factors for homograft failure.

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**Table 1:** Demographic and operative data of 152 patients undergoing homograft implantation for replacement of the right ventricular outflow tract

<table>
<thead>
<tr>
<th>Variable</th>
<th>Down-sized HG (n = 82)</th>
<th>Small-sized HG (n = 70)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>17.7 (0.3–64.8)</td>
<td>16.2 (0.4–45.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>9.0 (2.9–14)</td>
<td>8.4 (2.0–13.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Conduit size (mm)</td>
<td>14.8 ± 1.5</td>
<td>14.6 ± 3.3</td>
<td>0.6</td>
</tr>
<tr>
<td>z-Score</td>
<td>1.5 ± 0.8</td>
<td>1.6 ± 1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Previous operation, n (%)</td>
<td>65 (79)</td>
<td>47 (67)</td>
<td>0.07</td>
</tr>
<tr>
<td>Rastelli operation, n (%)</td>
<td>16 (19)</td>
<td>8 (11)</td>
<td>0.2</td>
</tr>
<tr>
<td>TOF/PA + VSD repair, n (%)</td>
<td>23 (28)</td>
<td>15 (21)</td>
<td>0.4</td>
</tr>
<tr>
<td>Ross operation, n (%)</td>
<td>4 (5)</td>
<td>6 (8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Conduit reoperation, n (%)</td>
<td>20 (24)</td>
<td>13 (18)</td>
<td>0.4</td>
</tr>
<tr>
<td>CAT repair, n (%)</td>
<td>6 (7)</td>
<td>15 (21)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>13 (16)</td>
<td>13 (18)</td>
<td>0.3</td>
</tr>
<tr>
<td>Pulmonary homograft, n (%)</td>
<td>60 (73)</td>
<td>30 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extension with PTFE, n (%)</td>
<td>52 (63)</td>
<td>29 (41)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

HG: homograft; CAT: common arterial trunk; TOF: tetralogy of Fallot; PA: pulmonary atresia; VSD: ventricular septal defect; PTFE: polytetrafluoroethylene.

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**Figure 2:** Survival for 152 patients after reconstruction of the RVOT, stratified by patients with small-sized homograft and patients with down-sized homograft. RVOT: right ventricular outflow tract.

**Figure 3:** Freedom from homograft failure in 144 patients, stratified by patients with small-sized homograft and patients with down-sized homograft.
homografts are competent and exhibit low pressure gradients [16].

Although we did not examine the haemodynamic function of the homografts have been described in different studies [11, 12]. Despite this, homograft failure of only 47% [11, 12]. In both publications, there were no differences in durability between small-sized and down-sized homografts described a 5-year freedom from homograft failure [11, 12]. In one study, we could demonstrate that a z-score of at least 1, without oversizing more. Especially in down-sized homografts, the size of the original homograft should be big enough.

Homograft durability is limited and the search for a long-lasting conduit is ongoing. Different mechanisms leading to homograft degeneration are discussed. Outgrowth can be a problem in a paediatric population, especially in fast growing newborns and infants [2, 7]. However, defining outgrowth is not obvious. One possible method is to measure the z-score at the time of conduit explantation [7]. The z-score determines if a conduit has become too small for the body surface area. In our study, the mean z-score at the time of homograft failure was approximately –1. Remarkably, the z-scores were not different between down-sized homografts and small-sized homografts. If outgrowth was the sole reason for homograft failure, the solution could be to implant oversized homografts as suggested by Forbes et al. [17]. However, reports looking at oversized conduits showed no influence on durability [19] and a higher annual increase in regurgitation [20]. Still, we could demonstrate that a z-score of less than 1 is associated with a reduced durability. Therefore, we recommend using homografts of a z-score of at least 1, without oversizing more. Especially in down-sized homografts, the size of the original homograft should be big enough.

Homografts from aortic origin have also been associated with a shorter durability than pulmonary homografts [6, 17]. The reason for this finding has been attributed to a higher tendency of calcification of aortic homografts [21]. In the present investigation, we could not confirm this finding. We did not find that the aortic origin of the homograft was a risk factor for homograft failure.

Independent of the good results with down-sized homografts, due to a constant lack of homografts, down-sizing can only be a valuable method if homografts are available. Always accessible alternative conduits are bovine jugular vein conduits and porcine-valved conduits. A recent prospective multicentre study including only patients with truncus arteriosus repair demonstrated that there is no difference in conduit performance between bovine jugular vein conduits and pulmonary homografts [3]. Our results showed that there was no difference in performance and durability between bovine jugular vein conduits and porcine-valved conduits [18].

### DISCUSSION

Our study shows that risk factors for homograft failure are an age of below 1 year and the use of homografts with a z-score of less than 1. However, there is no significant difference in durability between down-sized homografts and small-sized homografts in young children up to a median follow-up time of 10 years. On the basis of these findings, we state that down-sizing is a valid method to overcome the shortage of small-sized homografts yielding equal long-term results.

The feasibility and standard use of down-sized cryopreserved homografts have been described in different studies [11–13]. Although we did not examine the haemodynamic function of the down-sized homografts, others have shown that down-sized homografts are competent and exhibit low pressure gradients [16].

The largest clinical study on down-sized homografts published so far comprised 45 patients [13]. However, the average mean follow-up time of all studies was only 5 years [11, 12]. In the present cohort, we included 82 patients with a down-sized homograft and the median follow-up time was 10 years.

The time from implantation to failure of all homografts in our study was 5.7 ± 4.2 years and the freedom from homograft failure at 5 years was 83%, regardless of down-sizing. In a study by Yang et al. who looked exclusively at down-sized homografts in 45 young patients, the freedom from homograft failure at 5 years was 89% and thus, matched our results [13]. In contrast, other publications, comparing cryopreserved small-sized homografts with down-sized homografts described a 5-year freedom from homograft failure of only 47% [11, 12]. In both publications, there were no differences in durability between small-sized and down-sized homografts. However, in these studies, only patients following CAT repair and patients of younger age were examined. Both parameters have been shown to decrease the durability of homografts [6, 13, 17, 18] and could have influenced the homograft durability.

In our patient population, we found age below 1 year to be an independent risk factor for homograft failure. This subgroup of patients remains a challenge for the attending surgeons and choosing the right conduit is difficult. In a recent study, we could demonstrate that the durability of conduits in young children is independent of the type of conduit [18].

**DISCUSSION**

Our study shows that down-sizing adult-sized homografts to fit into the RVOT of young children is a suitable method to overcome the shortage of small-sized homografts. Furthermore, the durability of these down-sized homografts shows no statistical difference

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**Table 2:** Risk factors for homograft failure in 144 patients (early survivors) following homograft implantation for replacement of the right ventricular outflow tract

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Age &lt;1 year</td>
<td>2.2 1.2–4</td>
<td>3.2 1.6–6.2</td>
</tr>
<tr>
<td>Z-score &lt;1</td>
<td>1.8 0.9–3.3</td>
<td>2.7 1.4–5.3</td>
</tr>
<tr>
<td>CAT repair</td>
<td>2 1.4–3</td>
<td>0.05</td>
</tr>
<tr>
<td>Extension with PTFE</td>
<td>0.5 0.3–1</td>
<td>0.04</td>
</tr>
<tr>
<td>Down-sized homograft</td>
<td>0.7 0.4–1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Aortic homograft</td>
<td>1.4 0.8–2.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**P-values:**

- **Age <1 year:** 0.01
- **Z-score <1:** 0.07
- **CAT repair:** 0.05
- **Extension with PTFE:** 0.04
- **Down-sized homograft:** 0.3
- **Aortic homograft:** 0.4

**P-values for multivariable analysis:**

- **Age <1 year:** 0.001
- **Z-score <1:** 0.004

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CAT: common arterial trunk; CI: confidence interval; HR: hazard ratio; PTFE: polytetrafluoroethylene.

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in the multivariable analysis. Down-sized homografts and aortic origin of the homograft were not associated with a higher failure rate (Table 2).

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Homograft durability is limited and the search for a long-lasting conduit is ongoing. Different mechanisms leading to homograft degeneration are discussed. Outgrowth can be a problem in a paediatric population, especially in fast growing newborns and infants [2, 7]. However, defining outgrowth is not obvious. One possible method is to measure the z-score at the time of conduit explantation [7]. The z-score determines if a conduit has become too small for the body surface area. In our study, the mean z-score at the time of homograft failure was approximately –1. Remarkably, the z-scores were not different between down-sized homografts and small-sized homografts. If outgrowth was the sole reason for homograft failure, the solution could be to implant oversized homografts as suggested by Forbes et al. [17]. However, reports looking at oversized conduits showed no influence on durability [19] and a higher annual increase in regurgitation [20]. Still, we could demonstrate that a z-score of less than 1 is associated with a reduced durability. Therefore, we recommend using homografts of a z-score of at least 1, without oversizing more. Especially in down-sized homografts, the size of the original homograft should be big enough.

Homografts from aortic origin have also been associated with a shorter durability than pulmonary homografts [6, 17]. The reason for this finding has been attributed to a higher tendency of calcification of aortic homografts [21]. In the present investigation, we could not confirm this finding. We did not find that the aortic origin of the homograft was a risk factor for homograft failure.

Independent of the good results with down-sized homografts, due to a constant lack of homografts, down-sizing can only be a valuable method if homografts are available. Always accessible alternative conduits are bovine jugular vein conduits and porcine-valved conduits. A recent prospective multicentre study including only patients with truncus arteriosus repair demonstrated that there is no difference in conduit performance between bovine jugular vein conduits and pulmonary homografts [3]. Our results showed that there was no difference in performance and durability between bovine jugular vein conduits and porcine-valved conduits [18].

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**CONCLUSION**

Our study shows that down-sizing adult-sized homografts to fit into the RVOT of young children is a suitable method to overcome the shortage of small-sized homografts. Furthermore, the durability of these down-sized homografts shows no statistical difference.
compared with small-sized homografts. We recommend to calculate the z-score before implanting homografts and to aim for a z-score of at least 1, without oversizing more.

**STUDY LIMITATIONS**

This is a retrospective study over a long period of time. The absence of a prospective and randomized character of the study meant that a selection bias of patients could not be ruled out. Changes in surgical and postoperative management might have influenced the results. We linked homograft durability with homograft exchange, assuming that a homograft had failed if there had been an indication for an exchange. However, homograft failure is an ongoing process and patients might be asymptomatic for a long time. The decision on when to proceed with homograft exchange might have been biased by different opinions of the attending physicians and even the care-givers of the patients.

**Conflict of interest:** none declared.

**REFERENCES**


