Factors Affecting Longevity of Homograft Valves Used in Right Ventricular Outflow Tract Reconstruction for Congenital Heart Disease

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Background—Few studies have explored the long-term function of cryopreserved homograft valves used for reconstruction of the right ventricular tract (RVOT) in patients with congenital heart disease.

Methods and Results—Among 205 patients receiving cryopreserved homografts for reconstruction of the RVOT between November 1985 and April 1999, the outcome of 220 homografts in 183 operative survivors was analyzed. There were 150 pulmonary and 70 aortic homografts used. Median age at implantation was 4.4 years (mean 6.9 ± 7.6 years, range 3 days to 48 years). End points included (1) patient survival, (2) homograft failure (valve explant or late death), and (3) homograft dysfunction (homograft insufficiency or homograft stenosis). Survival was 88% at 10 years. Freedom from homograft failure was 74 ± 6% at 5 years and 54 ± 7% at 10 years. Univariable analysis identified younger age, longer donor warm ischemic time, valve Z value < 2, and previous procedure as risk factors for homograft failure and dysfunction. Aortic homograft type and extracardiac operative technique predicted homograft valve failure but not dysfunction. For patients ≤ 1 year of age, valve type did not predict failure or dysfunction. Multivariable analysis identified younger age and longer donor warm ischemic time as risk factors for homograft failure and dysfunction, whereas, Z value < 2 and aortic valve type predicted homograft valve failure.

Conclusions—Homograft valves used for RVOT reconstruction provide effective intermediate palliation with excellent late survival. Factors that adversely affect graft longevity include younger age, longer donor warm ischemic time, smaller homograft size, use of aortic homograft in the older patient, and extracardiac operative technique.

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Key Words: valves ¡ heart defect, congenital ¡ surgery

Valved conduits are commonly used in cardiac reconstruction for lesions in which there is hypoplasia of the right ventricular outflow tract (RVOT) or pulmonary arteries and/or in which the postoperative right heart pressures may be elevated, such as tricuspid arteriosus and pulmonary atresia with ventricular septal defect.1-5 Valved conduits are also used for management of right ventricular failure caused by pulmonary insufficiency and ventricular arrhythmias after initial nonvalved repair.6-8 Valved homografts, initially introduced in 1966 by Ross and Somerville,2 have become the most commonly used valved conduit for reconstruction of the RVOT.2,9-12 Among the advantages of homografts are the technical ease of implantation and improved hemostasis.12-14 Early results with cryopreserved homografts for reconstruction of the RVOT in congenital heart disease have been good, but there are few studies reporting late outcomes. The purpose of this study was to evaluate factors affecting the durability of homografts used in the reconstruction of the RVOT in congenital heart disease.

Methods

From November 1985 through April 30, 1999, 205 patients with congenital heart disease underwent RVOT reconstruction, with a total of 242 cryopreserved homograft valves at Children’s Hospital of Wisconsin, Milwaukee. There were 22 (11%) early deaths in the group (within 30 days of operation or same hospitalization). The purpose of this study was to determine factors affecting the durability of homografts used in RVOT reconstruction; therefore, perioperative deaths not attributable to homograft failure or dysfunction were excluded from risk factor analysis. The remaining 183 patients who received a total of 220 homograft valves during this time period constitute the population for this review and analysis. Of these 183 patients, 178 underwent initial homograft placement at the Children’s Hospital of Wisconsin and an additional 5 were seen for homograft replacement after initial homograft placement at another hospital. Medical records and clinic charts were reviewed for all
TABLE 1. Diagnostic Categories of RVOT Homograft Recipients, Previous Procedures, and Initial and Replacement Homograft Operative Characteristics

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Previous Nonhomograft Procedure, Palliative/Corrective</th>
<th>Initial Homograft</th>
<th>Age at Initial Homograft, y*</th>
<th>Homograft Replacement, n</th>
<th>Age at Replacement, y*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF/DOVR, PS</td>
<td>24% (n=13)/73% (n=40)</td>
<td>55</td>
<td>11.2</td>
<td>2</td>
<td>8.7</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>14% (n=4)/18% (n=5)</td>
<td>28</td>
<td>0.23</td>
<td>22</td>
<td>4.2</td>
</tr>
<tr>
<td>TGA, VSD, PS/L-TGA</td>
<td>73% (n=19)/19% (n=5)</td>
<td>26</td>
<td>2.9</td>
<td>4</td>
<td>5.0</td>
</tr>
<tr>
<td>Pulmonary atresia, VSD</td>
<td>64% (n=25)/21% (n=8)</td>
<td>39</td>
<td>2.5</td>
<td>8</td>
<td>4.2</td>
</tr>
<tr>
<td>Pulmonary atresia, IVS</td>
<td>14% (n=1)/86% (n=6)</td>
<td>7</td>
<td>7.9</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>TOF, APVS</td>
<td>9% (n=1)/18% (n=2)</td>
<td>11</td>
<td>1.4</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>AS/AI (Ross procedure)</td>
<td>0% (n=0)/58% (n=7)</td>
<td>12</td>
<td>12.4</td>
<td>0</td>
<td>--/--</td>
</tr>
<tr>
<td>Total</td>
<td>35% (n=63)/41% (n=73)</td>
<td>178</td>
<td>4.4</td>
<td>42</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* Values are median (range).

Tof indicates tetralogy of Fallot; DOVR, double-outlet right ventricle; PS, pulmonary stenosis; TGA, transposition of the great vessels; VSD, ventricular septal defect; IVS, intact ventricular septum; APVS, absent pulmonary valve syndrome; AS, aortic stenosis; AI, aortic insufficiency; and L, left.

Implant techniques varied, based on the recipient’s anatomy, and were categorized into 3 groups. For extracardiac placement, the posterior one third of the homograft annulus was sutured directly to the superior edge of a ventriculotomy in the pulmonary ventricle. A hood was used to complete the connection to the right ventricle. A variety of materials were used for the hood including the attached anterior mitral leaflet of an aortic homograft, an additional piece of homograft, pericardium, or synthetic material, such as Dacron (Du Pont Co) or Gore-Tex (W.L. Gore and Associates). In situ placement described operations in which the homograft annulus was sutured to the infundibular septum, placing the homograft within the RVOT in a near anatomic position. When necessary, completion of the in situ implantation also involved placement of a hood. Finally, valve replacement was used to describe procedures in which a subsequent homograft was being placed in a patient who had previously undergone homograft RVOT reconstruction by either the in situ or extracardiac technique. Table 2 summarizes the operative techniques and homograft type by primary diagnostic category.

Homograft failure was defined as explant of the valve for any reason or late death (occurring >30 days after surgery) as the result of any cause. Homograft dysfunction was defined as any one of the following: moderate or severe stenosis or insufficiency as well as explant or late death. Homograft insufficiency was defined echocardiographically as moderate when there was a broad regurgitant jet of less than the annulus width associated with diastolic color Doppler flow reversal from the distal main pulmonary artery. A regurgitant jet that encompassed the entire annulus width associated with diastolic flow reversal in the branch pulmonary arteries was graded as severe. Homograft stenosis was defined as a transvalvular peak instantaneous pressure gradient >40 mm Hg. The follow-up echo in which the patient first met one or both of these dysfunction criteria was recorded as the duration of functional valve life.

Descriptive data are presented as mean values±1 SD. For continuous variables, ANOVA techniques were used to analyze between-group differences; χ² was used for categoric variables. Survival curves for freedom from valve failure and valve dysfunction were obtained by use of the Kaplan-Meier method, and comparisons were performed with the log-rank test. To evaluate the impact of younger age on homograft durability, age was entered into multivariable analysis as both a continuous variable and dichotomized into 2 categories: ≤1 year and >1 year. Additional survival analyses for the separate end points of homograft failure or dysfunction were performed by means of a Cox proportional hazards, multiple regression model. The selection of independent variables for the model was based on statistical significance in univariable testing. A value of P<0.05 was considered significant. All analyses were performed with SPSS® Version 9.0 software (SPSS Inc).
Results

There were 22 early deaths among 205 patients undergoing placement of a homograft in the RVOT. There were 6 late deaths. Two patients died of complications of bacterial endocarditis and 1 patient died from cardiogenic shock and congestive heart failure 2 months after repair of truncus arteriosus. These 3 deaths are considered to be valve related. The remaining 3 late deaths were not related to the homograft valve. One late death occurred as a consequence of mitral stenosis and insufficiency after a Ross-Konno procedure for aortic stenosis. One patient with tetralogy of Fallot and absent pulmonary valve syndrome with severe bronchomalacia died of pulmonary complications. One patient died of pneumonia after aspiration. For the entire group of 205 valve recipients, late survival was 88% at 10 years (Figure 1).

Mean age at implantation was 6.9 ± 7.6 years, with a median age of 4.4 years and a range of 3 days to 48 years. There were 44 (24%) patients ≤ 12 months of age. Earliest conduit replacement was performed 10 days after initial homograft placement, as part of a revision of pulmonary artery reconstruction in a patient with pulmonary atresia/ventricular septal defect and major aortopulmonary collaterals. One conduit is in place 13 years after implantation. There have been 42 valves explanted. In this group, 32 patients have undergone 1 homograft replacement, and of these 32 patients, 5 patients have undergone a second homograft replacement. Five patients had their homograft explanted and replaced with an RVOT outflow patch or other nonhomograft valved conduit. Among late survivors, 135 (74%) patients have their original homograft in place and 98 (54%) have valves that are free from dysfunction. Freedom from homograft failure was 95 ± 2% at 1 year, 74 ± 4% at 5 years, and 54 ± 7% at 10 years (Figure 2). Freedom from dysfunction was 84 ± 3% at 1 year, 47 ± 5% at 5 years, and 22 ± 5% at 10 years.

The results of the univariable and multivariable analyses are summarized in Table 3. Univariable analysis identified younger age (Figure 3), longer warm ischemic time (Figure 4), implanted valve *Z* value, and previous operative procedure as predictive of homograft failure and dysfunction. The use of an aortic homograft (Figure 6) and extracardiac operative technique were predictive of homograft failure but not dysfunction. Duration of cryopreservation, date of operation, homograft replacement, and sex were not significant. To further delineate the impact of valve size on homograft failure, *Z* values were determined at the time of homograft implantation and last follow-up. Failed homografts had smaller *Z* values compared with functioning homografts.
homografts at the time of surgery (1.1±1.0 versus 1.9±1.4, P=0.001) and at the time of last follow-up (0.77±1.5 versus −0.3±1.4, P<0.001). To rule out the possibility of different growth rates between patients who received small and large homografts, we also determined the net change in Z value from implantation to last follow-up. There was no difference in the net change in Z value between the failure and nonfailure groups (−1.2±1.3 versus −1.4±1.1, P=NS) or between the dysfunction and no dysfunction groups (−1.4±1.2 versus −1.1±1.3, P=NS).

Multivariable analysis identified younger age, longer warm ischemic time, and Z value <2 as independent risk factors for homograft failure and dysfunction. The use of an aortic homograft was identified as an independent risk factor for failure but not dysfunction, whereas extracardiac operative technique was identified as an independent risk factor for dysfunction but not failure. Multivariable analysis did not identify previous procedure as a risk factor for either failure or dysfunction. The multivariable analysis reported in Table 3 was performed with age as a continuous variable. Multivariable analysis was also performed with age used as a dichotomous variable, ≤1 year, and >1 year. Although for patients >1 year of age, the use of an aortic homograft still predicted homograft failure; for patients ≤1 year, homograft type did not have an impact on failure or dysfunction.

**Discussion**

Homografts were the initial valved conduit used for reconstruction of the RVOT; however, early preservation techniques involving antibiotic preservation were associated with early valve failure. Porcine heterografts mounted in Dacron conduits became available in a variety of sizes and were widely used for complex reconstructions. Heterografts, however, were more difficult to implant. In particular, they did not conform to the anatomy as easily as homografts, and hemostasis was more difficult to achieve. Furthermore, the porcine conduits became calcified rapidly, and the Dacron graft developed a pseudointimal peel that could result in stenosis of small-diameter conduits. The development of cryopreservation techniques combined with improved availability has resulted in the widespread use of homografts for reconstruction of the RVOT in congenital heart disease. Although early results with homograft reconstruction of the RVOT have been good, relatively few data are available on the mid- and long-term results. The purpose of this study was to determine the mid-term result of homograft reconstruction of the RVOT and to identify risk factors for homograft failure and dysfunction.

This series of patients includes a broad spectrum of congenital heart defects involving hypoplasia or atresia of the

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**TABLE 3. Risk Factors for Homograft Failure (Explantation or Late Death) and Dysfunction (Explantation, Late Death, Moderate or Severe Stenosis or Insufficiency): Results of Univariable and Multivariable Analysis**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Univariable Analysis, P</th>
<th>Multivariable Analysis, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Failure</td>
<td>Dysfunction</td>
</tr>
<tr>
<td>Younger age</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Longer warm ischemic time</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Z value &lt; 2</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic homograft</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Extracardiac placement</td>
<td>0.004</td>
<td>NS</td>
</tr>
<tr>
<td>Previous procedure</td>
<td>&lt;0.001</td>
<td>0.017</td>
</tr>
<tr>
<td>Longer duration of cryopreservation</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Homograft valve replacement</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Date of operation</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
pulmonary valve and RVOT. For the period of time included in this review, only 6% of patients had RVOT homografts placed as part of surgery for aortic stenosis or insufficiency. Therefore, this study is representative of the outcomes that can be expected for homograft reconstruction of the RVOT in congenital heart disease. Our data are consistent with the overall results of other contemporary series reviewing the outcome of homograft reconstruction of the RVOT. Gradual deterioration over time can be expected for homograft reconstruction of the RVOT in congenital heart disease. Our data are consistent with the overall results of other contemporary series reviewing the outcome of homograft reconstruction of the RVOT. Gradual deterioration over time can be expected for homograft valves.9–12 The 14-year period of this study spanned significant changes in the timing of surgery, role of palliative procedures, and improvements in perioperative management.

To remove confounding variables caused by operative mortality and isolate those factors affecting durability of the homografts themselves, we analyzed risk factors for freedom from failure and dysfunction among operative survivors only. Freedom from failure was 74% at 5 years and freedom from dysfunction was 47% at 5 years (Figure 2). These data would suggest that valve dysfunction is likely to occur by 10 years and that homograft replacement may be required in many patients having a homograft placed in the RVOT during childhood. However, late survival is excellent, with only 6 late deaths among 183 patients (Figure 1).

Younger age was identified as a risk factor for homograft failure and dysfunction (Figure 3). Primary repairs in the newborn period or infancy were frequent in this series (n=44) and included 28 patients undergoing repair of truncus arteriosus. Limitations of the size of homografts that can be implanted in neonates, infants, and small children will predictably result in the need for homograft replacement as the child grows.9,10,12 The data support the concept of outgrowth as a mode of failure of the homograft. Z values were used to normalize homograft size to the patients’ body surface area. Multivariable analysis identified smaller Z value at implantation (<2) as a risk factor for homograft failure (Figure 5). To further explore the role of growth as a factor in homograft failure, the Z value of patients at the time of homograft implantation was compared between the failure and nonfailure groups. The Z value at implantation was significantly higher among patients whose homografts had not failed: 1.9±1.4, compared with 1.1±1.0 for failed homografts (P<0.001). The Z value at last follow-up, determined by normalizing the homograft size (assuming no change in valve diameter since implantation) to the patient’s size at last follow-up, was also evaluated. Again, homografts that had not failed had a significantly higher Z value, 0.77±1.5, compared with failed homografts, −0.3±1.4 (P<0.001). The net change in Z value from implantation to last follow-up was not significantly different in either comparison (failure versus nonfailure, dysfunction versus no dysfunction) identifying similar growth in all patients. These data suggest that whenever possible, larger homografts should be used.

The use of aortic homografts was associated with more rapid homograft failure and was significant in the multivariable analysis (Figure 6). To more completely evaluate the interaction of age and homograft type, the impact of homograft type (aortic versus pulmonary) on freedom from failure and dysfunction was evaluated in patients >1 and <1 year of age. In patients <1 year of age, homograft type alone was not predictive of homograft failure. These findings are consistent with data reported by Perron and associates17 that in small patients, size and outgrowth overwhelm homograft type as a predictor of failure. This suggests that aortic homografts can be used for complex reconstruction in newborns and infants without the need for earlier reoperation.
Given the relative shortage of small pulmonary homografts, the determination that aortic homografts can be used in infants and neonates without compromising long-term results may allow better utilization of the available homograft supply.

Recent reports suggest that the durability of homografts has decreased in the current era. Niwaya et al. noted that homograft replacement was associated with a higher risk of failure than the original homograft. Possible explanations for this observation include a broadening of the indications for homograft placement including younger patients with more complex lesions as well as a decreased threshold for replacement of a dysfunctional homograft. Another possible explanation for these observations is a change in the homograft donor supply. In this study, increased duration of warm ischemic time was identified as a risk factor for homograft failure (Figure 4). The overall pressure on the scarce resource of heart donors for transplantation and homograft valves may have resulted in a broadening of donor criteria for homografts. In particular, given the increase in pediatric heart transplantation, homografts are more commonly obtained from asystolic donors. Homografts with longer donor warm ischemic time may have more injury, resulting in an exaggerated reparative and immune response in the host that results in more rapid dysfunction and failure. The overall increase in the warm ischemic time among more recently procured homografts may result in decreased performance compared with historic controls.

Limitations of This Study
This is a retrospective analysis of patients with diverse anatomy operated on over a 14-year period. Undoubtedly, indications for homograft use, timing of surgery, and indications for homograft replacement changed during this time period. Variables analyzed such as homograft type were determined by surgeon preference and graft availability and were not randomized or standardized. It is possible, because of the relations between variables, such as operative technique and diagnosis, that the influence of some factors have been underestimated and others have been given more importance. Only operative survivors were analyzed to remove the influence of perioperative factors on long-term outcome. Nevertheless, this series looks at factors affecting the durability of homografts in a large number of patients undergoing RVOT reconstruction for congenital heart disease. The long-term outcome of cryopreserved homografts is not completely established, and therefore the contribution of these data is important. Continued follow-up studies will be necessary to identify risk factors for homograft failure.

Conclusions
Among 183 patients undergoing reconstruction of the RVOT with cryopreserved homografts, durability of the homografts was adversely affected by younger age, longer donor warm ischemic time, smaller homograft size at implantation, the use of aortic homografts in older patients, and extracardiac operative technique. Outgrowth of the homograft valves appears to be an important cause of homograft failure. Despite a gradual deterioration, homograft function over time and patient survival were excellent.

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References
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