Homograft survival after tetralogy of Fallot repair: determinants of accelerated homograft degeneration

Els Troost, Bart Meyns, Willem Daenen, Frans Van de Werf, Marc Gewillig, Kristien Van Deyk, Philip Moons, and Werner Budts

Aims Homografts are frequently implanted in patients with tetralogy of Fallot (TOF). However, the lifespan of homografts is shorter than that of graft recipients, thus making surgical re-intervention unavoidable. Therefore, to determine variables that could influence their survival, we retrospectively studied the survival pattern of homografts used to treat TOF.

Methods and results Sixty-eight TOF patients, >14 years of age (mean age: 34 ± 11; 71% male), were selected from our database of congenital cardiology cases. These patients underwent their first homograft implantation at a median age of 24 years (range: 14–49). The primary endpoint, homograft failure, was defined as homograft replacement or percutaneous balloon dilatation when the echocardiographic gradient reached more than 50 mmHg. Kaplan–Meier analysis revealed that the mean event-free survival time of first homografts was 14.6 years (CI, 12.9–16.2 years). The median increase in the homograft gradient was 1.1 mmHg/year (range: 0.0–22.1) for a median follow-up time of 8.4 years (range: 1.3–17.9). Stepwise regression analysis identified the homograft gradient at 1 month after surgery to be the strongest predictor of homograft degeneration (R² = 0.23, β = 0.26, P = 0.001). Immunological variables, gender, and post-operative inflammatory indicators were unrelated to the degree of homograft gradient increase. Finally, patient age at the time of first homograft implantation and previous palliative surgery was significantly associated with the gradient at 1 month (Spearman’s rho = −0.41 and −0.29, respectively; P = 0.004 and 0.048, respectively).

Conclusion Homograft survival in patients with TOF repair is quite good. However, some patients develop accelerated homograft degeneration. We found that the gradient of the homograft 1 month after surgery is most indicative of accelerated homograft degeneration. We hypothesize that mechanical, not immunological, factors play an important role in homograft degeneration.

Introduction

Since Ross and Sommervile first reported the use of valved homografts in the reconstruction of the right ventricular outflow tract (RVOT) in 1966, the use of both aortic and pulmonary homografts to treat all kinds of right-sided congenital heart defects has become widespread. Throughout the 1980s, cryopreserved homografts became the conduit of choice for this type of procedure, because of its excellent haemodynamic profile, ease of handling and suturing, improved haemostasis and resistance to infection. The superior haemodynamic profile of cryopreserved homografts also precludes the post-operative use of anticoagulation treatments, thus making them a very attractive application, especially in children and young patients. Indeed, several studies have demonstrated that these procedures promote both optimal patient survival as well as superior event-free survival rates.

The longevity of homografts depends greatly on different risk factors such as patient’s age, complexity of the underlying congenital disease, type of homograft (e.g. aortic homografts have worse outcomes), and heterotopic position of the homograft implant. A possible immunological basis for biodegeneration of homografts is still debated and is yet to be clearly proved.

Patients with Tetralogy of Fallot (TOF) commonly receive homograft implants, since a tendency exists towards correcting this disease while patients are still young. However, the lifespan of homografts is much shorter than that of the patients receiving them, thereby making surgical re-intervention unavoidable. It remains debatable whether current data on homograft function in general can be applied to both young and adult patients with TOF. Moreover, some typical features of congenital lesions,
such as right ventricular dilatation and/or dysfunction and associated lesions on peripheral pulmonary branches, seem to influence homograft outcome.7

Taken together, these issues prompted us to study the survival pattern of homografts used to treat TOF, with a goal of identifying variables that could influence their survival.

Methods

Patient selection

From our database of patients with congenital heart disease, we selected all TOF patients >14 years of age who had undergone at least one homograft implantation in anatomic position between 1987 and 2005. Clinical follow-up data were provided by paediatric (patients <16 years) and adult congenital cardiologists (patients >16 years) at our hospital. The review protocol was approved by the institutional Ethics Committee.

Review of patient files

Files of all study patients were available for tabulating demographic variables, peri-operative characteristics related to the initial homograft implantation (e.g. indication for homograft implantation, inflammatory response, clamp time, homograft characteristics); standard echocardiographic follow-up data; and the reason for homograft failure at late follow-up.

To better understand the inflammatory response after homograft implantation, we reviewed carefully the peri-operative characteristics of each patient. Since these data covered a period of more than 15 years, our initial, but rudimentary, attempt to determine inflammatory reactions involved tabulating the duration and degree of elevated post-operative body temperature and eventually included noting the patients’ erythrocyte sedimentation rate (ESR), as an indirect marker of inflammation. Later, we opted to use C-reactive protein levels rather than ESR values as an inflammation marker, because at the time C-reactive protein seemed to be a more reliable measure for inflammation. However, during the course of our study, the accepted normal CRP and ESR reference ranges had changed, so that neither was suitable to use as a tool for evaluating the post-operative inflammatory response.

We also characterized the homografts processed by the European Homograft Bank (EHB, Brussels, Belgium). These EHB homografts were sterile, cryopreserved aortic and pulmonary valve conduits. These grafts were derived from three types of donors: recipients of cardiac transplantations, multi-organ donors with non-transplantable hearts, and non-beating heart cadavers with a warm ischaemia time of <6 h. The size of the homografts was chosen based on the diameter of the RVOT; no attempt had been made for matching ABO blood group or gender.

Homograft characteristics at late follow-up

Homograft failure was the primary endpoint and was defined as homograft dilatation or homograft replacement (which occurred if the homograft gradient was >50 mmHg). The decision to dilate or replace a homograft depended on its functioning level as well as on patients’ symptoms and clinical condition, both of which were mainly affected by progressive pressure overload of the right ventricle. To the best of our knowledge, no patient with a homograft gradient of greater than 50 mmHg has been managed conservatively.

In addition, we estimated the rate of homograft degeneration for each homograft by calculating the yearly increase in peak instantaneous gradient over the RVOT:

\[
\text{maximal gradient at end of follow-up} = \text{homograft gradient at 1 month follow-up period under study}
\]

Statistical analysis

Data were tested for symmetry. When symmetry was detected, the results were reported as means ± standard deviations. When symmetry was absent, data were reported as medians and ranges (minimum and maximum). Proportions were expressed as percentages.

Kaplan-Meier event-free survival curves were plotted for the primary endpoint. Follow-up times of patients who died during the follow-up were censored only when death occurred before one of the study endpoints was reached. Two in-hospital deaths were immediately censored.

Cox regression analysis was done to identify predictors of homograft failure. We first performed a univariate Cox regression analysis after controlling for the proportional hazard assumption. The following were included separately as independent variables in the univariate analysis: gender; number of previous interventions; age at first homograft implantation; type of graft; clamp time; age of donor; size of homograft; maximal post-operative body temperature; number of days with temperature >38°C; use of antibiotics; use of aspirin or non-steroidal antiflogistics; matching ABO; matching rhesus (Rh) factor; and homograft gradient at 1 month. The dependent variable was defined as homograft dilatation or homograft replacement. As a second step, we performed a backward multivariate Cox regression analysis using clamp time, patient age at first homograft, and homograft gradient at 1 month, all of which were independent variables found to have a \( P < 0.30 \) in the univariate analysis. Probability of F-to-enter was ≤0.50; probability of F-to-remove was ≥1.00.

Linear regression analysis was done to identify predictors of the rate of homograft degeneration. We first performed a univariate regression analysis after verifying normal P–P plots of regression-standardized residuals. The variables included in the analysis were the same as in the Cox regression analysis. As a second step, we performed a backward multivariate linear regression analysis using the following variables: number of previous interventions; maximal post-operative temperature; number of days with temperature >38°C; and homograft gradient at 1 month. These variables were found to have a \( P < 0.30 \) in the univariate analysis. Probability of F-to-enter was ≤0.50; probability of F-to-remove was ≥1.00.

Spearman rho correlations between variables and a Mann–Whitney U test were performed where applicable. Statistical significance level was set to \( P < 0.05 \). All tests were two-sided. Statistical analyses were carried out with SPSS 11.5 for Windows.

Results

Patient characteristics

Sixty-eight patients were selected from the database of congenital heart disease cases. Their characteristics are summarized in Table 1. Thirty-two of these patients first underwent a shunt procedure before undergoing repair without a homograft. Only two patients underwent primary repair with immediate implantation of a homograft.

Peri-operative characteristics

The peri-operative characteristics of each patient at the time of their first homograft implantation are listed in Table 2. As noted above, two patients received their first homograft immediately after repair. In more than 90% of the patients, the first homograft was implanted to treat severe pulmonary valve regurgitation, which developed as a result of the use of a transannular patch during the first repair procedure. In the remaining patients, residual stenosis was the indication for homograft implantation.
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>48/20</td>
</tr>
<tr>
<td>Previous interventions, n</td>
<td>66</td>
</tr>
<tr>
<td>Repair after shunt procedures</td>
<td>32</td>
</tr>
<tr>
<td>Modified Blalock-Taussig shunt</td>
<td>21</td>
</tr>
<tr>
<td>Potts anastomosis</td>
<td>3</td>
</tr>
<tr>
<td>Waterston shunt</td>
<td>8</td>
</tr>
<tr>
<td>Infundibulectomy/Hancock/transannular patch</td>
<td>4/4/24</td>
</tr>
<tr>
<td>Immediate repair without shunt</td>
<td>34</td>
</tr>
<tr>
<td>Infundibulectomy</td>
<td>5</td>
</tr>
<tr>
<td>Hancock/other xenograft</td>
<td>4</td>
</tr>
<tr>
<td>Transannular patch</td>
<td>25</td>
</tr>
<tr>
<td>Patient age at analysis, years (mean ± SD)</td>
<td>34 ± 11</td>
</tr>
</tbody>
</table>

Table 2 Peri-operative characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Perioperative characteristics of patients (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related variables</td>
<td></td>
</tr>
<tr>
<td>Median age at first homograft, years (range)</td>
<td>24 (14–49)</td>
</tr>
<tr>
<td>Median clamp time, min (range)</td>
<td>45 (0–165)</td>
</tr>
<tr>
<td>Homograft-related variables</td>
<td></td>
</tr>
<tr>
<td>Median size mm (range)</td>
<td>24 (18–29)</td>
</tr>
<tr>
<td>Type, n</td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>65</td>
</tr>
<tr>
<td>Age of donor (mean ± SD), years</td>
<td>40.3 ± 11.9</td>
</tr>
<tr>
<td>Immunological-related variables</td>
<td></td>
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<tr>
<td>ABO compatibility, n</td>
<td></td>
</tr>
<tr>
<td>Match</td>
<td>16</td>
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<tr>
<td>Mismatch</td>
<td>40</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
</tr>
<tr>
<td>Rhesus factor, n</td>
<td></td>
</tr>
<tr>
<td>Match</td>
<td>45</td>
</tr>
<tr>
<td>Mismatch</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>11</td>
</tr>
<tr>
<td>Maximum post-operative temperature (mean ± SD), °C</td>
<td>37.8 ± 0.5</td>
</tr>
<tr>
<td>Number of days with temperature &gt;38 °C, days</td>
<td>0 (0–14)</td>
</tr>
<tr>
<td>Use of antibiotics, n (yes/no/unknown)</td>
<td>13/44/11</td>
</tr>
<tr>
<td>Use of anti-inflammatory drugs, n (yes/no/unknown)</td>
<td>12/43/11</td>
</tr>
</tbody>
</table>

Patient outcome

The overall mortality during the median follow-up period of 8.4 years (range: 1.3–17.9) was 8.8% (6/68). The in-hospital mortality for all patients who underwent an RVOT reconstruction with a homograft was 2.9% (2/68). Late mortality occurred because of heart failure (n = 1) or sudden cardiac death attributed to malignant ventricular arrhythmias (n = 3).

During the follow-up period, three patients required cardiac transplantation because of end-stage right ventricular dysfunction. The mean homograft survival time after the first homograft implantation was 16.7 years (CI, 15.5–17.7 years).

Homograft failure

We defined homograft failure as homograft dilatation or homograft replacement following a failed balloon dilatation. The mean event-free survival time of the first homograft was 14.6 years (95% CI, 12.9–16.2) (Figure 1). Five homografts required explantation and replacement with a second homograft, because the patients developed endocarditis (n = 2) or stenosis of the pulmonary conduit and unacceptable pressure overload of the right ventricle (n = 3). In five patients, a balloon dilatation was carried out because of valvular (n = 2) or supravalvular (n = 3) stenosis; none of these patients received surgical re-intervention during the follow-up period. Since all patients with a peak-to-peak gradient of greater than 50 mmHg expressed symptoms in daily life, none of these patients were managed conservatively. No severe pulmonary regurgitation was detected. A small number of homografts displayed moderate pulmonary insufficiency, mainly secondary to a more distal stenosis. Re-interventions for pulmonary valve regurgitation were not required.

The median increase in homograft gradient was 1.1 mmHg/year (range: 0.0–22.1) over the 8.4 year median follow-up time. Follow-up events are summarized in Table 3.

Predictors of homograft failure and rate of homograft degeneration

We performed a univariate Cox regression analysis, designating patient-, homograft-, and immunology-related variables (Table 2) as the independent variables, and homograft failure as the dependent variable. None of the independent variables were statistically reliable predictors of homograft failure. Next, we performed backward multivariate Cox regression analysis of patient-, homograft-, and immunology-independent variables that reached $P < 0.30$ in the univariate Cox regression analysis. This analysis identified clamp time and homograft gradient at 1 month to be predictors of homograft failure (HR, 1.03; 95% CI, 1.00–1.06; and HR, 1.14; 95% CI, 1.03–1.27, respectively).

Both univariate and multivariate linear stepwise regression analyses using patient-, homograft-, and immunology-related variables as independent variables and homograft degeneration rate as the dependent variable identified the homograft gradient at 1 month to be prognostic for homograft degeneration rate [i.e. homograft degeneration rate $= (1.49 + 0.26 \times \text{gradient at 1 month; } R^2 = 0.23, \beta = 0.26, P = 0.001] (Figure 2).

Finally, patient’s age during his/her first homograft implant and patient’s previous palliative surgery history were significantly associated with the homograft gradient at 1 month (Spearman’s rho $= −0.41$ and $−0.29$, respectively; $P = 0.004$ and 0.048, respectively). A Mann–Whitney U test confirmed that the median homograft gradient at 1 month was significantly higher in patients that received no...
Discussion

The main finding of our study is that the homograft gradient 1 month after implantation in TOF patients reliably predicted homograft degeneration rate ($R^2 = 0.23$, $\beta = 0.26$, $P = 0.001$). We found no relationship between immunological- and homograft-related variables and homograft degeneration. However, the homograft gradient at 1 month was associated with the patient’s age at the time of his/her first homograft implant and previous palliative surgery history (Spearman’s rho = −0.41 and −0.29, respectively; $P = 0.004$ and 0.048, respectively).

Since the 1980s saw an increasing use of homografts, several studies have reported excellent patient survival rates of more than 90% 5 years after implantation as well as optimal homograft survival, free of homograft failure, of 60% to more than 90% 5 years after implantation. These homograft survival rates are far more favourable than those reported with porcine xenografts. In a retrospective study of 505 patients (174 xenografts and 331 allografts), Homann et al. documented a homograft failure rate of up to 70% 10 years after xenograft implantation compared with 30% for allografts. In our series of cases, we observed a homograft failure rate of 25% at 10 years, which is consistent with the published data.

Nevertheless, several groups have described accelerated homograft degeneration, especially in young patients. The longevity of homografts seems to be adversely affected by different risk factors, such as patient’s age at the time of his/her first homograft implantation (grafts of younger recipients have shorter lifespans); smaller homograft size (which is merely a reflection of the patient’s age); complexity of the underlying disease; homograft type (worse outcomes are associated with aortic homografts); and heterotopic position of the graft. Most of these risk factors seem to be attributed to mechanical factors.

In addition, homografts used in Ross operations also fare better than those used in non-Ross operations. These observations suggest that the associated lesions of right-sided congenital heart defects, patient age at implantation, and homograft size influence the survival of homografts. Indeed, Oosterhof et al. demonstrated that in TOF patients, residual lesions occurring during the first year after pulmonary valve replacement have an impact on event-free homograft survival. They stated that severe pulmonary regurgitation before surgery was related to early homograft dysfunction; we could not identify whether this also occurred in our study cases. We did find, however, that homograft gradient values measured 1 month after surgery predicted the homograft degeneration rates of grafts in subpulmonary positions. Moreover, including covariates in the analysis revealed that the patient’s age at the time of homograft implantation and previous palliative surgeries were significantly associated with the gradient at 1 month.
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younger the patient at the time of homograft implantation and the fewer previous palliative surgeries the patient had had, the higher the gradient at 1 month. These associations agree with the previously mentioned mechanical explanation. In contrast to patients who do not undergo palliative surgery, patients who undergo palliative surgery (shunt procedures) usually have a better-developed pulmonary artery tree, which in turn is related to a better match between the homograft and native pulmonary vessels. We also previously showed that a homograft implanted in an extra-anatomical position accelerates homograft degeneration, probably due to mechanical factors such as tension and kinking of the homograft. This finding has also been subscribed by other groups.

An immunological basis for homograft degeneration has been alluded to by several authors, although definitive pathological evidence is still lacking. Legare et al. showed in a rat model with syngeneic and allogeneic aortic valve implants that graft cryopreservation itself leads to cellular injury and results in reduced endothelial cell viability. This structural damage seems to be induced by two processes: (1) an early infiltration of myeloid mononuclear cells, regardless of allostimulation; and (2) a concomitant immune activation accompanied by infiltration of alloreactive T-cells. In their homograft explant study, Koolbergen et al. also observed an early loss of cellular elements and tissue architecture, which was most pronounced during the first year after implantation. Moreover, the homograft adopted a nearly acellular appearance after 1 year, at which time valve tissue cellularity consisted mainly of ingrown host cells with a substantial portion of inflammatory cells. Therefore, the overall acceptable clinical performance of cryopreserved homografts must be mainly a result of the preservation of the collagenous skeleton and components of the extracellular matrix. Koolbergen et al. concluded that, after immune-mediated injury, the reduced cell numbers they observed were probably mediated by apoptosis rather than necrosis, since the influx of macrophages and T-cells was not accompanied by deposition of IgG or C3 complement. These findings were also corroborated by other explant studies in humans.

Several authors have tried to determine whether HLA incompatibility relates to homograft failure. In 96 homografts implanted in the RVOT, Baskett et al. documented that younger patient age, use of an aortic homograft, and short preservation time were associated with a higher risk of re-operation. In 47 of these patients, a complete HLA mismatching or HLA-mismatching implants. The existing literature, however, remains contradictory: Three studies failed to show a significant effect of HLA mismatch or humoral response on homograft survival and/or failure. In addition, older patients are thought to exhibit weaker immune responses. Indeed, younger patient age is a known independent risk factor for homograft survival. Since being of young age is associated with having a more active immune system, homograft degeneration in young patients should not only be a reflection of somatic outgrowth. In our study, although we could not confirm that immune reactions took place immediately after homograft implantation, we did observe that younger ages were significantly associated with higher homograft gradients at 1 month.

Others have attempted to determine whether ABO mismatching can approximate the presence of an immune reaction and homograft failure. In a study comprising a limited group of 59 patients, 85% of which received aortic valve homografts, Christenson et al. found that ABO incompatibility accelerated homograft degeneration. These findings, however, could not be corroborated by studies of larger patient populations, as reported by Meyns et al. and Jashari et al.

We also examined ABO and Rh factor matching and mismatching but did not find a relationship between ABO/Rh factor donor/recipient compatibility and homograft failure or homograft degeneration rate. One possible explanation for this finding is that almost all of our patients received pulmonary valve homografts, which might induce different immune responses compared with those induced by aortic valve homografts.

Regardless of the underlying mechanism of homograft degeneration, current clinical practice must consider that all homograft patients will require re-intervention at some point. Thus, cardiac specialists must be prepared to effectively deal with these re-interventions. Retrospective analysis of different groups indicates that a second homograft implantation can be successfully performed with low morbidity and mortality outcome and with a graft survival time comparable with that of the patient’s first homograft. Stark et al., however, reported a worse outcome for re-operations, attributing this finding mainly to technical (mechanical) reasons, as suggested in this paper.

Our study had several limitations. First, a selection bias undoubtedly existed. The patients were selected from a single-centre database, which could influence the study results. Secondly, the number of patients was limited, which could lead to low statistical power, especially for the Cox regression analysis. Another limitation is that our study included patients of only 14 years of age and older. One might argue that we should have also included patients younger than 14 years, but the literature has already shown that homograft failure cannot be mainly explained by somatic outgrowth. Thirdly, we used linear regression analysis to assess causal relationships between various peri-operative variables, which can be a potential source of bias, since this type of analysis can be influenced by one or two outliers. Subjecting all data to linear regression analysis resulted in the following: $R^2 = 0.23$, $\beta = 0.26$, $P = 0.001$. Deleting the highest value (22 mmHg/year) resulted in $R^2 = 0.30$, $\beta = 0.20$, $P = 0.0001$, whereas deleting the two highest values (22 and 14 mmHg/year) resulted in $R^2 = 0.05$, $\beta = 0.07$, $P = 0.13$. Fourthly, we assumed that homografts degenerated in a
linear fashion. To the best of our knowledge, no data are currently available in the literature that either confirm or refute this assumption. Finally, because of our study’s retrospective design, we had to deal with missing data, especially those concerning immunological parameters. We addressed this limitation by tracing each patient’s body temperature profile during the first week after homograft implantation and by determining ABO and Rh factor compatibility between grafts and recipients. Although these are rudimentary parameters, they gave us a rough indication of post-operative inflammation in our patients.

Conclusion

We found that the rate of homograft degeneration was influenced by the homograft gradient measured 1 month after repair surgery. This gradient was higher in patients who underwent no previous palliative shunting and in whom the homograft was implanted at a younger age. We hypothesize that mechanical factors might play an important role in homograft degeneration. Moreover, because the patient population we studied was relatively older, we believe that immunological factors may play a less obvious role in homograft degeneration. If this is indeed the case, then the possibility of replacing a homograft with another (pulmonary valve) homograft would remain, only if mechanical stress factors could be excluded. Larger prospective trials will be necessary to elucidate these remaining issues.

Conflict of interest: none declared.

References


