

Evolution of the Z-Score in Size-Reduced Bicuspid Homografts

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Background and aim of the study: Human homografts are frequently used to establish an anatomic continuity between the right ventricular outflow tract (RVOT) and the pulmonary artery. Their limited availability, especially in small sizes, has encouraged the use of alternative strategies, such as size-reduced bicuspid homografts. The study aim was to analyze the follow up of patients who had received a standard tricuspid or size-reduced bicuspid homograft in the RVOT position, and to investigate modifications of the patients' Z-scores over the years. **Methods:** A consecutive series of 107 patients aged ≤ 16 years, who underwent RVOT repair between 1989 and 2010 to treat tetralogy of Fallot (ToF), was retrospectively reviewed. Of these patients, 17 received a size-reduced bicuspid pulmonary homograft, while 90 received a standard tricuspid homograft. The mean follow up periods were 10.5 years (range: 0.02-21.4 years) for the whole study population, and 11.8 years and 3.4 years, respectively, for the tricuspid and size-reduced bicuspid

homograft groups.

Results: Freedom from mortality at 10 years was $95 \pm 3\%$. During the observation period, 27 patients (31%) in the tricuspid homograft group and two (12%) in the size-reduced bicuspid group presented with graft failure. According to the multivariable analysis, the only independent predictor of graft failure was patient age (hazards ratio 0.86). The 17 patients who had received a size-reduced bicuspid homograft were then age-matched to an equal-sized population of tricuspid homograft patients. A comparative analysis of the time-weighted average of the Z-scores for these tricuspid and size-reduced bicuspid homograft subgroups during the follow up period failed to identify any statistical difference ($p = 0.5$).

Conclusion: In terms of Z-score evolution, size-reduced bicuspid homografts offer results which are comparable to those achieved with tricuspid homografts.

The Journal of Heart Valve Disease 2012;21:521-526

Human homografts are frequently used to establish an anatomical continuity between the right ventricular outflow tract (RVOT) and the pulmonary artery. However, their limited availability - especially in small sizes - has encouraged the use of alternative strategies, such as size-reduced bicuspid homografts or xenografts. The downsizing procedure of the homograft, as described in 1994 by Michler et al. (1), consists of the excision of one leaflet, thereby allowing a reduction of about one-third of the homograft diameter.

The aim of the present study was to analyze the follow up of patients who had received a standard tricuspid or size-reduced bicuspid homograft in the RVOT position, and to investigate the modification of the Z-score over the subsequent years. Only those patients who had undergone repair of the tetralogy of Fallot (ToF) were included in the study.

Clinical material and methods

Patients

A consecutive series of 107 patients aged ≤ 16 years who had undergone RVOT repair between 1989 and 2010 because of ToF were retrospectively reviewed. Of these patients, 17 had received a size-reduced bicuspid

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pulmonary homograft, and 90 had received either a standard tricuspid aortic (n = 17) or pulmonary (n = 73) homograft.

The baseline characteristics of the sample populations are summarized in Table I. The patients in the size-reduced bicuspid homograft group were generally younger, had a smaller body surface area (BSA) and Z-score value, and also received a smaller graft compared to those in the tricuspid homograft group.

Definitions

Graft failure was defined as a need for surgical repair, replacement, or percutaneous intervention of the graft. Excluded from the graft failure definition were percutaneous interventions that were required because of peripheral pulmonary artery stenosis.

The most frequent indication of graft surgery or percutaneous interventions was the presence of severe stenosis (instantaneous peak gradient ≥ 50 mmHg) or severe regurgitation (grade 3 on a scale of 1 to 4), associated with at least one of the following: a reduction in exercise tolerance; dilatation of the right ventricle; presence of tricuspid insufficiency; or presence of arrhythmias. The second indication was a diagnosis of endocarditis.

The patient's BSA was computed according to the DuBois formula (2), while the Z-score was calculated as the number of standard deviation units of difference between the observed diameter of the homograft and the predicted diameter of the pulmonary valve of the patients (3). Predicted pulmonary valve diameters were obtained from published data (3).

Grafts

The homografts utilized were cryopreserved valve conduits that had been processed by the European Homograft Bank (EHB, Brussels, Belgium). No ABO blood group or gender matching was conducted, and homograft preparation was carried out as described previously (4).

Surgical approach

The RVOT surgery in this cohort of patients with ToF consisted of a primary repair (in 60% of cases), with homograft implantation or initial Sano shunt and secondary homograft implantation in case of pulmonary atresia and/or branch pulmonary artery atresia (40% of cases).

The size-reduced bicuspid homografts were obtained from a downsizing procedure carried out on the tricuspid pulmonary homografts. This was achieved by making a longitudinal incision of the homograft wall through the middle portion of one of the three leaflets, after which the homograft was opened and spread onto a flat surface. Two additional parallel incisions were then made in order to remove two longitudinal strips of the wall, each of which contained a half-leaflet; the remaining tissue was then wrapped around a Hegar dilator. A continuous 6-0 Prolene suture was used to approximate the two lateral margins and to restore the cylindrical shape of the homograft. Valve competence was tested in the operating room by using a saline test. The downsizing procedure achieved a mean decrease of the homograft diameter by 35%.

Graft implantations were made while the patient was supported by cardiopulmonary bypass and moderate hypothermia or normothermia. The surgical procedures were carried out either under cardioplegic heart arrest (n = 87) or fibrillating heart (n = 20). The conduits were cut as short as possible, and the distal anastomosis was performed using 4-0 or 5-0 continuous Prolene sutures. If necessary, the incision to the left or right pulmonary artery was extended to the correct fitting of the interposed graft. The proximal anastomosis was performed using a 4-0 suture at the level of the crista supraventricularis; the anastomosis to the right ventricle was sometimes enlarged with a right ventricular outflow hood of xenopericardium.

Table I: Baseline characteristics of the sample population.

Parameter	Total population (n = 107)	Tricuspid homograft group (n = 90)	Bicuspid homograft group (n = 17)	Standardized difference of the mean (%)
Age (years)*	7.8 ± 4.8	8.7 ± 4.6	2.7 ± 2.4	+163
BSA (m ²)*	0.9 ± 0.4	1.0 ± 0.4	0.5 ± 0.1	+171
Female gender	49 (46)	37 (41)	12 (71)	
Cross-clamp time (min)*	63.2 ± 26.2	61.4 ± 25.2	83.3 ± 30.2	-78
Graft size (mm)*	20.3 ± 3.5	21.1 ± 3.3	16.3 ± 1.7	+182
Z-score*	1.2 ± 1.0	1.1 ± 0.9	1.7 ± 1.2	-56

Values are mean ± SD.

Values in parentheses are percentages.

BSA: Body surface area.

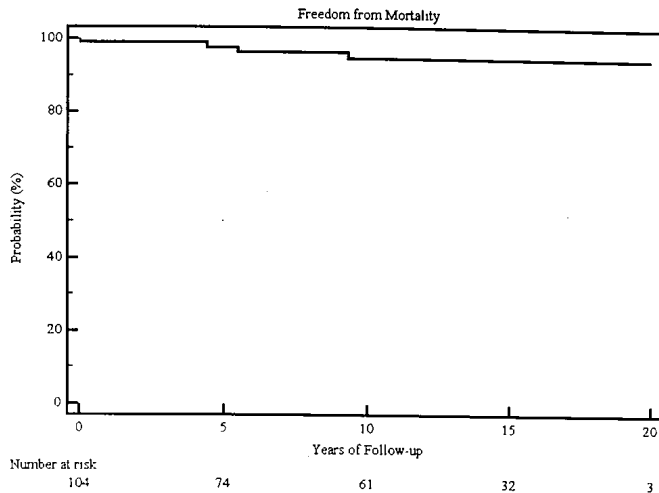


Figure 1: Kaplan-Meier freedom from mortality (30-day death is included).

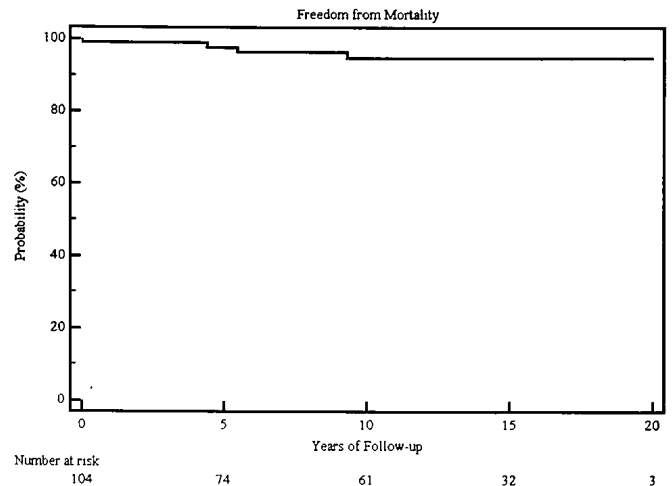


Figure 2: Kaplan-Meier freedom from graft failure.

Follow up

None of the patients received any anti-aggregation or anti-coagulation therapy, and all were followed up by echocardiography at six-month intervals. The mean follow up period of the whole sample population was 10.5 years (range: 0.02 to 21.4 years), while the mean follow up periods of the tricuspid and size-reduced bicuspid homograft groups were 11.8 years (range: 0.01 to 21.4 years) and 3.4 years (range: 0.02 to 16.4 years), respectively. Three patients of the tricuspid homograft group were lost to follow up, which was 97% complete.

Data analysis

Continuous variables were expressed as mean \pm SD, while dichotomous categorical variables were indicated as percentages (absolute frequency).

Unadjusted mid-term rates of freedom from graft failure were calculated using the Kaplan-Meier method. All operative data listed in Table I were studied as independent variables by univariable Cox regression analysis to identify factors predictive of graft failure. The variables associated to the event with a p-value ≤ 0.20 in the bi-variable Cox regression analysis were then entered together into a backward logistic Cox regression multivariable model with 'graft failure' as the dependent variable. From this model, the independent predictors of graft failure of the whole sample population were obtained.

An age-matching procedure was carried out in order to obtain two homogeneous groups of patients. This consisted of a nearest-neighbor 1:1 matching within a caliper width of 0.1 between the bicuspidalized and the tricuspid groups. To assess the balance in terms of covariate distributions between the two groups, before and after matching, the standardized difference, which is not influenced by the sample size (5), was obtained.

The standardized difference was the mean difference computed as a percentage of the average standard deviation (6,7).

The time-weighted average method was used to compare the Z-score evolution in the two matched groups (8). Thus, the area under the curve (AUC) of the Z-score values for each patient was computed. To simplify the computation, the baseline value was assumed to be zero; the AUC of each patient was then divided by the total time interval (the time of the last observation minus the time of the first observation). The time-weighted average of the Z-score in all patients was then obtained. The Mann-Whitney test was used to compare the time-weighted average of the Z-score of the two matched groups.

All statistical analyses were performed using MedCalc for Windows (version 9.3.7.0; MedCalc Software, Mariakerke, Belgium).

Results

Mortality

Mortality events were registered only in the tricuspid homograft group. One patient (1%) died during the first postoperative month as the result of a severe thromboembolic event.

Three other patients died during the remaining follow up. The first death occurred at 4.4 years after surgery, and was caused by severe right heart failure. The second death was registered after 5.5 years, and attributed to pneumonia. The third death occurred at 9.3 years, and was caused by myocardial infarction due to left coronary artery spasm during right pulmonary artery percutaneous stenting. The overall survival of the sample population, including the only early death, using the Kaplan-Meier method, is shown graphically in Figure 1. Freedom from mortality at one,

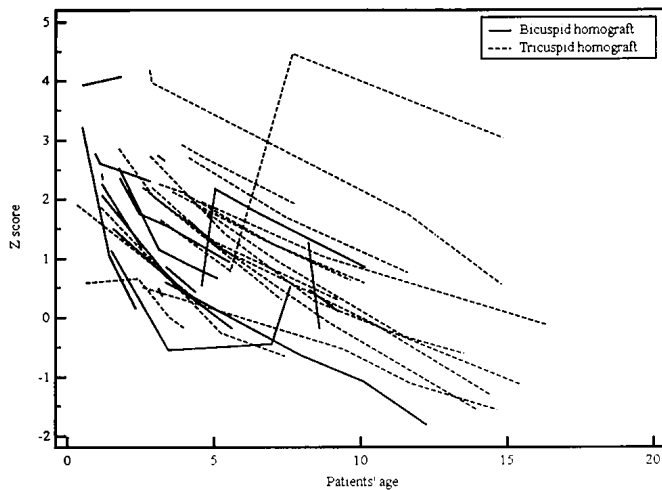


Figure 3: Modifications of the Z-score over the years. Each line represents a single patient, and is constituted by measurements of the Z-score (vertical axis) at different ages (horizontal axis). Patients with a longer follow up received more measurements and show longer Z-score lines. The mean Z-score of the 34 matched patients tended to decrease as the patients aged because, in most of the cases, the diameter of the homograft remained constant while the patients' BSA increased. Four patients (three solid lines, one dotted line) showed an increment of the Z-score: in these patients a dilatation of the homograft was documented.

five, and 10 years was $99 \pm 1\%$, $98 \pm 2\%$, and $95 \pm 3\%$, respectively.

During the observation period (mean 11.8 years), 27 patients (31%) of the tricuspid homograft group presented with graft failure. The causes of such failure were pulmonary valve stenosis ($n = 16$), supra-avalvular stenosis ($n = 4$), stenosis of the distal anastomosis ($n = 4$), endocarditis ($n = 1$), subvalvular stenosis ($n = 1$), and pulmonary regurgitation ($n = 1$). In four patients with pulmonary valve stenosis, death was associated with severe pulmonary valve regurgitation.

Treatment was administered percutaneously in

17 patients; this consisted of balloon dilatation of the stenotic segment of the homograft in 11 cases, and Melody valve implantation in six cases. Surgical treatment consisting of graft replacement was preferred in 10 patients.

During a shorter observation period (mean 3.4 years), two patients in the size-reduced bicuspid homograft group (12%) presented with graft failure; the cause was supra-avalvular stenosis in one case and valvular stenosis in the other case. Treatment included percutaneous balloon dilatation and graft replacement, respectively.

Freedom from graft failure of the whole sample population at one, five, and 10 years was $97 \pm 2\%$, $88 \pm 3\%$, and $71 \pm 5\%$, respectively (Fig. 2). Freedom from graft failure of the size-reduced bicuspid homograft and tricuspid homograft groups at three years was similar, at $93 \pm 7\%$ and $92 \pm 3\%$, respectively.

Predictive analysis

According to the multivariable analysis, the only independent predictor of graft failure was patient age (hazards ratio 0.86; 95% CI 0.78-0.94; $p = 0.02$). In particular, the younger the patient at the time of operation, the higher the risk of graft failure. Hence, the implantation of a size-reduced bicuspid homograft was not a risk factor for graft failure.

As second step of the analysis, 17 patients who had received a size-reduced bicuspid homograft were age-matched to an equal-sized population of patients in the tricuspid homograft group. The characteristics of these 34 matched patients are listed in Table II.

In both groups, the modifications of the Z-score over time were computed (see Fig. 3). In most patients of both groups the Z-score was between 0 and +2, and decreased progressively over the years. This event was related mathematically to the increment in the BSA, although the homograft diameter was unchanged during the same period. There were some exceptions to

Table II: Baseline characteristics of the two age-matched groups.

Parameter	Age-matched tricuspid homograft group (n = 17)	Bicuspid homograft group (n = 17)	Standardized difference of the mean (%)
Age (years)	2.7 ± 1.3	2.7 ± 2.4	0
BSA (m^2)	0.2 ± 0.2	0.5 ± 0.1	-189
Female gender	7 (41)	12 (71)	
Cross-clamp time (min)	73.7 ± 23.6	83.3 ± 30.2	-35
Graft size (mm)	18.6 ± 3.5	16.3 ± 1.7	+83
Z-score	2.0 ± 0.6	1.7 ± 1.2	+31

Values are mean \pm SD.

Values in parentheses are percentages.

BSA: Body surface area.

this, however. During the observation period (mean 3.4 ± 4.1 years), three patients (18%) in the size-reduced bicuspid homograft group presented with homograft dilatation (reflected by an ascending Z-score segment in Fig. 3). In these patients, increments in homograft diameter of 25%, 31%, and 40%, respectively, were documented. Two of these patients with homograft dilatation presented with graft failure (the causes were described previously).

During a longer observation period (mean 11.7 ± 3.8 years), only one patient (6%) in the tricuspid group presented with homograft dilatation; in this case the homograft diameter increment was 82%. Nine patients (52%) of the group presented with graft failure, the causes of which were pulmonary valvular stenosis ($n = 7$), pulmonary valvular regurgitation ($n = 1$), and supralvalvular stenosis ($n = 1$). Until recently, the patient with a dilated homograft had shown no signs of graft dysfunction. A comparative analysis of the time-weighted average of the Z-score of the tricuspid and size-reduced bicuspid homograft group failed to show any statistical difference ($p = 0.5$).

Discussion

The limited availability of homografts of small sizes has motivated the development of different strategies for reconstruction of the RVOT among the pediatric population. Of these procedures, two in particular have grown in popularity: xenografts, which are available also in small sizes; and size-reduced bicuspid homografts. The potential of the most widely used xenografts to reconstruct the RVOT has been explored, often with contradictory results (9-11). An alternative solution would be to use a size-reduced bicuspid homograft, whereby the homograft diameter can in fact be reduced by about one-third.

An understanding of the hemodynamics of a congenitally bicuspid aortic valve (CBAV) can be useful when predicting the functionality of a size-reduced bicuspid homograft in the pulmonary position. For example, when Robicsek et al. (12) studied human aortic CBAVs in vitro the roots were distally cannulated and pressurized to 80 mmHg.

On video imaging at 500 frames per second, it was evident that a bicuspid valve does not fully open, but rather shows an elliptical shape of the orifice. In particular, during systole the two leaflets are partially opened, curving upwards and circumferentially. The fold line between the portion of leaflets that opens, and that which remains parallel to the valvular plane, is subject to the systolic flow. This opening characteristic can configure a stenotic valve, and is different from the hemodynamics of a tricuspid valve where, during systole, all of the leaflets are fully extended and parallel to the blood flow. Thus, it has been suggested that

the stress overload of a CBAV can predispose to fibrosis and calcification and, therefore, to its structural degeneration. In contrast, the size-reduced bicuspid homograft in the RVOT is subject to lower pressures, and therefore may perform hemodynamically better than a CBAV.

Reports of the use of size-reduced bicuspid homograft are few and difficult to interpret, because of the limited sample populations. For example, Koirala et al. (13) reported the details of 21 children who had received a size-reduced bicuspid homograft in the RVOT position because of pulmonary atresia (PA; $n = 10$), truncus arteriosus ($n = 3$), ToF/double outlet right ventricle ($n = 3$), transposition of the great arteries (TGA; $n = 2$), aortic atresia ($n = 1$) and aortic valve disease ($n = 2$). In these children, freedom from interventional cardiac catheterization or surgical replacement of the conduit was 47% at five years.

Subsequently, McMullan et al. (14) analyzed a group of 14 size-reduced bicuspid homografts implanted in the RVOT position in patients with truncus arteriosus communis. Freedom from graft failure (severe conduit stenosis, moderate or greater regurgitation) at three years was 56%. Likewise, Bové et al. (15) described 36 patients who had received size-reduced bicuspid homografts in the RVOT, and compared these with a similar group of 41 children who had received the Contegra graft. Echocardiography at discharge showed a competent valve function in 27 (75%) of the bicuspidalized group, compared to 23 (59%) of the Contegra group. More recently, Yang et al. (16) analyzed the results of an implantation of size-reduced bicuspid homografts in 45 children in whom the diagnoses were ToF ($n = 19$), PA ($n = 11$), truncus arteriosus ($n = 7$), and TGA ($n = 8$). Freedom from graft dysfunction was 53% at five years.

In the present study, in order to select a more homogeneous population, only patients with ToF were included. Yet, despite this strict selection criterion addressing only a limited sample population for analysis, there were important differences in terms of covariate distributions between the two patient groups. Those patients in the size-reduced bicuspid homograft group were younger and received smaller homografts than those of the tricuspid group. These differences reflected the poor availability of small-sized homografts. During the observation period, only two patients with size-reduced bicuspid homografts required surgical or percutaneous intervention on the graft. Hence, freedom from graft failure of the size-reduced bicuspid homograft group was 93%.

According to the multivariable analysis, the only independent predictor of graft failure was patient age (HR 0.86) and, indeed, such a relationship between age and the risk of graft failure has been previously

documented (17). This relation can in fact be interpreted as a consequence of the graft-patient mismatch that tends to occur much earlier in very young patients, who constitute the subgroup with the highest risk of graft failure. The analysis of an age-matched sample population showed a progressive decrease in the Z-score over the years in most patients and in both groups, with three cases and one case of homograft dilatation being documented in the size-reduced bicuspid homograft and tricuspid group, respectively. In the remaining patients, the Z-score remained mostly at between 0 and +2.

As the Z-score is a dynamic parameter, its time-weighted average was computed for all patients and used to compare its evolution between the two groups. Accordingly, no statistical difference was identified in terms of Z score evolution between the two matched groups of patients.

Study limitations

The primary limitations of the study were its retrospective nature, the limited sizes of the populations analyzed, and the differences in terms of follow up periods of the two groups.

In conclusion, in terms of Z-score evolution, size-reduced bicuspid homografts offer results that are comparable to those achieved with tricuspid homografts in the treatment of ToF.

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Acknowledgement

We would like to thank the European Homograft Bank (EHB) for allowing us to use the EHB data registry.