Abstract

Objective: We aimed to evaluate the adaptive growth and remodeling behavior of the transplanted heart in pediatric heart-transplant recipients by comparing donor body surface area (BSA) and cardiac dimensions during transplantation with the corresponding parameters of the recipient over a period of time. Methods: A retrospective review of medical and echocardiographic records of 167 children (8.65 ± 5.98, median 9; range 0–17 years) who underwent orthotopic heart transplantation between 1987 and March 2010 was done. Results: In the first 30 days post-transplantation, right- and left-ventricular end-diastolic diameters, volumes, and myocardial mass were found to be significantly increased (z score 3.96, p < 0.000) in relation to the recipients’ BSA. Within the first year of post-transplantation, there was a significant reduction in the right-ventricular diameter (z score, −1.0 to +1.6, p = 0.000), left-ventricular diameter (z score −1.0 to +1.9, p = 0.000), right-ventricular end-diastolic volume (z score −1.3 to +1.9, p = 0.000) and left-ventricular mass (z score, −1.4 to +1.7, p = 0.000) and left-ventricular mass (z score, −1.4 to +1.8, p = 0.000). During subsequent follow-up periods of 2–5 and 6–10 years, the aforementioned cardiac dimensions and volumes increased appropriately in accordance to the BSA (p = 0.000). In all the cardiac dimensions and volumes measured, donor–recipient mismatch did not influence the continuous growth of the measured parameters, which was in accordance to the recipients’ BSA over time. Kaplan–Meier survival analysis showed a survival rate of 61.7% at 10 years. There is no statistically significant difference in survival rate among patients with varying donor–recipient weight ratios and donor–recipient BSA ratios (p = 0.53). Conclusions: This study demonstrates that the transplanted heart undergoes remodeling processes and grows adaptively, in accordance to the BSA, over a period of time.

Keywords: Pediatric heart transplantation; Cardiac dimensions; Ventricular remodeling

1. Introduction

Heart transplantation is now widely accepted as a standard treatment modality for infants and children with end-stage cardiomyopathy or non-correctable congenital heart disease [1–3]. Several previous investigations [4–8] in recent years have focused on the long-term function of the transplanted heart. However, there is a paucity of information available regarding the growth and development of transplanted heart in infants and children, as much as data addressing heart remodeling following transplantation. Previous studies [7–9] demonstrated that following pediatric cardiac transplantation, cardiac chamber growth is normal over the long term, but few literatures focused on ventricular growth in children after cardiac transplantation, and the pattern of changes in cardiac dimensions after transplantation has remained unclear. This issue is especially important as elucidation of changes in ventricular dimensions and volumes during this period would improve our understanding of the process of adaptation of the donor heart to the recipients’ circulation, especially following donor–recipient size disparity transplantation. Presently, there are no long-term studies made available regarding the morphologic adaptation and ventricular geometry remodeling of the transplanted heart in accordance with the growth of the child over time.

We therefore aimed to evaluate the adaptive growth and remodeling pattern of the transplanted heart after orthotopic heart transplantation in infants and children by comparing donor body surface area (BSA) and cardiac dimensions during transplantation to the corresponding parameters of the recipient over a period of time.

2. Patients and methods

The Institutional Review Board approved this retrospective study and waived the need for patient consent.
2.1. Patients

The patient population for this study consisted of 167 patients, who underwent orthotopic heart transplantation at the German Heart Institute Berlin from 1987 to 2010. Heart transplantation was performed for dilated cardiomyopathy \((n = 118)\), restrictive cardiomyopathy \((n = 14)\), congenital heart disease \((n = 30)\), acute rejection \((n = 2)\) and chronic heart rejection \((n = 3)\). Medical records of patients were reviewed for age, gender, weight, height, BSA, and indications for transplantation. The donor’s age, height, and weight at the time of transplantation were likewise reviewed. The study patients were classified based on their donor-to-recipient weight ratio and donor-to-recipient BSA ratio.

2.2. Immunosuppression protocol

Our triple drug immunosuppressive therapy has evolved through the years of experience. It consists of an induction therapy designed to reduce the incidence of early rejection and is given 6 h post-heart transplantation with intravenous antithymocyte globulin 1.5 mg kg\(^{-1}\) on the first 3 days accompanying intravenous prednisolone at 2.5—5 mg kg\(^{-1}\) day\(^{-1}\). Thereafter, steroids are tapered at 2 mg kg\(^{-1}\) day\(^{-1}\) orally. Cyclosporine is started immediately preoperatively at 6 mg kg\(^{-1}\) orally and is continued at 2 mg kg\(^{-1}\) intravenously or 6 mg kg\(^{-1}\) orally to target a trough level of 250 ng ml\(^{-1}\). Mycophenolate mofetil (MMF) is started preoperatively at 1000 mg orally and is continued at 1000 mg twice daily, either orally or intravenously. This triple therapy with cyclosporine/MMF/stereoids is alternatively applied with Everolimus \((2 \times 0.75 \text{ mg orally daily, target trough levels } 3–8 \text{ ng ml}^{-1})\) instead of MMF, if there are no contraindications to Everolimus.

2.3. Follow-up

Follow-up data were provided by both the Department of Congenital Heart Disease/Pediatric Cardiology and the Department of Clinical Studies, Deutsches Herzzentrum Berlin and by written correspondence from the referring physicians. No patients were lost to follow-up. All patients operated on from 1987 to 2010 had complete follow-up with series of echocardiograms. It is our institutional policy that each transplanted patient undergoes echocardiographic examination on a weekly basis from the first week post-transplant until 24 weeks post-transplant. Thereafter, an echocardiographic follow-up protocol consisting of set time points, such as monthly for the next 6 months, bimonthly within the next year, quarterly for the next 4 years, then every 4 months for the next 5 years, and semi-annually or as often as clinically indicated afterward, are followed. The mean duration of follow-up was 13 ± 0.8 (range 5 months to 22 years) years, providing a total of 1157.79 patient years.

2.4. Echocardiographic evaluation of cardiac dimensions, mass and volume

Echocardiographic reports were reviewed in detail to determine the change in cardiac dimensions, mass and volume over the follow-up period. Initial echocardiographic evaluations were done 30 days after cardiac transplantation, and final evaluations at 10–15 years after transplantation. Each echocardiogram included an evaluation of cardiac anatomy and ventricular function and dimensions, by two-dimensional imaging with pulsed- and color Doppler mapping.

2.5. Measurements

Right and left ventricles were imaged from the parasternal and subxiphoid long- and short axis, as well as apical four-chamber view. The following measures were obtained. End-diastolic diameter was measured in the antero-posterior plane as the maximal diastolic diameter between the septal to posterior wall endocardium at the level of the papillary muscle tips. Posterior wall thickness was measured in diastole between the papillary muscles at the level of the papillary muscle tips. Ventricular length was measured in diastole (the video frame showing maximal dimension) from the midpoint of the mitral valve annulus to the apical endocardium. Ventricular volume was calculated using the biplane area—length method \([10,11]\): Volume = \(5/6 \times L \times A\), where \(L\) is the left-ventricular (LV) length measured from the midpoint of the mitral valve annulus to the apical endocardium, and \(A\) is the planimetered LV short axis cross-sectional area. Volume was measured in systole (minimal dimension) and diastole (maximal dimension). In addition to planimetry, for verification purposes, the ventricular end-diastolic volume was also calculated using the cube function formula. This function assumes that the ventricle is a prolate ellipsoid of regular configuration with a long-to-short axis length ratio of 2:1. The formula used for calculation of left-ventricular end-diastolic volume (LVEDV) is: \(LVEDV = \frac{1}{3} \pi LVIDd^3\) [3]. Ventricular mass was calculated as: \(\text{Ventricular mass} = 1.04(\text{IVSd} - \text{LVIdd} - \text{LVPWtd})\) [3], where \(\text{IVSd} = \text{interventricular septal thickness in diastole, LVIdd} = \text{LV end-diastolic minor axis dimension, and LVPWtd} = \text{LV posterior wall thickness in diastole}\). To adjust for age-, body-size-, and growth-related changes in ventricular dimensions, linear measurements were indexed to the square root of BSA \((\text{BSA}^{1/2})\), and volumetric and mass measurements were indexed to \(\text{BSA}^{1.5}\) [12].

2.6. Statistical analysis

All data were analyzed with Statistical Package for Social Sciences (SPSS) 16.0 software program (SPSS, Chicago, IL, USA) for Windows. Demographic variables are expressed as mean ± SD, mean ± standard error of the mean (SEM) as well as range, as appropriate. Univariate comparisons of mean ventricular diameter, volume, and mass, and mean changes indexed to the donor’s BSA with those indexed to the recipients’ BSA at selected time post-transplant intervals (30 days, 1 year, 2—5 years, 6—10 years) were compared using Student’s t-test. The significance of difference between serial measurements was analyzed with a univariate model of analysis of variance (ANOVA) followed by the Fisher protected least significant difference post hoc analysis. Correlations and linear regression analyses with the least-squares method were used to evaluate the relation between the donor—recipient weight and donor—recipient BSA ratios.
To facilitate comparison between cardiac dimensions, z values were computed as follows: z score 0 (measured value – mean value of normal controls)/SD of normal controls. For all tests, a p value ≤ 0.05 was considered significant. Comparison of survival rates was performed by the log-rank test. Cumulative survival was analyzed according to Kaplan–Meier estimates with 95% confidence interval (CI).

2.7. Definition of normal growth

Normal growth was defined as a lack of z-score change between early and late follow-up. Failure of growth of any dimension would be detected as a statistically significant decline in z score. To verify that our method of stratifying data from the normal patient population did not itself introduce errors, the raw data were reanalyzed from one measurement, the VEDD, using a second statistical method to determine z-score divisions (the loecs fit), and found no effect on our analysis of z-score changes.

3. Results

3.1. Patient profile

The demographic profile of infants and children who underwent orthotopic cardiac transplantation is shown in Table 1. The mean age at transplantation was 8.65 ± 5.9 years (range 2 months to 17.9 years). Mean donor age was 14.9 ± 8.1 years (range 1 month to 60 years). Mean donor-to-recipient weight ratio is 1.5 and mean donor-to-recipient BSA ratio is 1.6. Age at follow-up is a mean of 15.58 ± 8.49 years (range 2 months to 33.86 years).

3.2. Linear growth

Linear growth was normal in our patients. Five patients were three standard deviations below normal at early follow-up, but were close to the normal range at late follow-up. These patients included three infants, who have shown delayed linear growth while still receiving steroids, and two children on high-dose immunosuppressants because of rejection episodes. In these patients with poor linear growth, cardiac chamber growth occurred and was appropriate for BSA. Over time, the mean change in BSA was 0.24 ± 0.03 m² (range 0.12–0.50 m²). By expressing cardiac growth as a function of BSA, we were able to compensate for those transplant patients who have shown delayed linear growth.

3.3. Donor–recipient sizes

Because a mismatch in size between the donor and recipient could result in early alterations in the perceived cardiac growth rate, we compared donor and recipient size by a paired Student’s t-test and found no significant differences among those with a donor–recipient weight ratio of <0.8, 0.8–1.2, and >1.2 and a donor–recipient BSA ratio of <1.0, 1.0, and >1.0 (p = 0.80, 0.44, 0.48, respectively) (Table 2). In all the cardiac dimensions and volumes measured, donor–recipient mismatch did not influence the continuous growth of the measured parameters, according to the recipients’ BSA over time.

3.4. Echocardiographic data: Cardiac dimensions

Changes in ventricular diameter, volume, and mass following transplantation for all patients are detailed in Tables 2 and 3.

3.5. Thirty days post-transplantation

Patients had initially higher right-ventricular (RV) end-diastolic diameters (mean 22.86 ± 13.7, range 8–47 cm/m² BSA) and LV (mean 34.33 ± 20.4, range 15–68, cm/m² BSA) end-diastolic diameters, RV (mean 132.29 ± 81, range 119–290, ml/m² BSA) and LV (mean 120.77 ± 72, range 80–278, ml/m² BSA) end-diastolic volumes, and RV (mean 26.99 ± 14.5, range 3–53, g/m³ BSA) and LV (mean 83.85 ± 47.3, range 10–198, g/m³ BSA) mass in the first 30 days post-heart transplantation (Table 2).

3.6. 1-Year post-transplantation

Comparing the obtained values during the first 30 days of transplantation, there was a significant decrease (p = 0.00, Table 2) in RV (mean 14.19 ± 13.3, range 10–39, cm/m² BSA) and LV (mean 20.22 ± 19.9, range 13–59, cm/m² BSA) end-diastolic diameters, RV (mean 101.07 ± 74.4, range 90–250, ml/m² BSA) and LV (mean 92.51 ± 71, range 90–240, m² BSA) end-diastolic volumes, and RV (mean 26.99 ± 14.5, range 3–53, g/m³ BSA) and LV (83.85 ± 47.3, range 10–198, g/m³ BSA).

Table 1. Demographic profile of heart-transplant children.

<table>
<thead>
<tr>
<th>Demography</th>
<th>Recipient</th>
<th>Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (M/F)</td>
<td>167 (93/74)</td>
<td>167 (91/76)</td>
</tr>
<tr>
<td>Age at heart transplantation (mean ± SD, years)</td>
<td>8.65 ± 5.98 (range 1 month to 17.9 years)</td>
<td>14.93 ± 8.11 years (range 1 month to 60 years)</td>
</tr>
<tr>
<td>Age at follow-up (mean ± SD, years)</td>
<td>15.58 ± 8.49 (range 2 months to 33.9 years)</td>
<td>14.93 ± 8.11 years (range 1 month to 60 years)</td>
</tr>
<tr>
<td>Mean weight at transplantation (mean ± SD, kg)</td>
<td>31.85 ± 19.4 (median 28.5, range 3.5–67)</td>
<td>48.73 ± 22.9 (median 32, range 4–90)</td>
</tr>
<tr>
<td>Mean height at transplantation (mean ± SD, cm)</td>
<td>125.43 ± 38.4 (median 134, range 50–177)</td>
<td>141.09 ± 38.2 (median 38, range 74–190)</td>
</tr>
<tr>
<td>Mean body surface area at transplantation (mean ± SD, m²)</td>
<td>1.03 ± 0.49 (median 1.02, range 0.2–1.8)</td>
<td>1.64 ± 0.52 (median 1.45, range 0.2–2.2)</td>
</tr>
</tbody>
</table>
Table 2. Echocardiographic data on ventricular diameter, volume and mass during different follow-up periods.

<table>
<thead>
<tr>
<th>Follow-up, post-transplantation (time point)</th>
<th>0.9—2.0</th>
<th>1.2 to +2.3</th>
<th>1.0 to +1.9</th>
<th>0.9—2.0</th>
<th>1.8 to +2.3</th>
<th>1.2 to +2.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>1.9 to +1.8</td>
<td>1.9 to +1.8</td>
<td>1.9 to +1.8</td>
<td>1.9 to +1.8</td>
<td>1.9 to +1.8</td>
<td>1.9 to +1.8</td>
</tr>
<tr>
<td>1 year</td>
<td>2.3 to +2.4</td>
<td>2.3 to +2.4</td>
<td>2.3 to +2.4</td>
<td>2.3 to +2.4</td>
<td>2.3 to +2.4</td>
<td>2.3 to +2.4</td>
</tr>
<tr>
<td>2—5 years</td>
<td>3.0 to +3.3</td>
<td>3.0 to +3.3</td>
<td>3.0 to +3.3</td>
<td>3.0 to +3.3</td>
<td>3.0 to +3.3</td>
<td>3.0 to +3.3</td>
</tr>
<tr>
<td>6—10 years</td>
<td>4.0 to +4.7</td>
<td>4.0 to +4.7</td>
<td>4.0 to +4.7</td>
<td>4.0 to +4.7</td>
<td>4.0 to +4.7</td>
<td>4.0 to +4.7</td>
</tr>
</tbody>
</table>

3.7. 2—5 Years post-transplantation

The ventricular end-diastolic diameters (RV mean 21.4 ± 11.6, range 12—41, cm/m² BSA and LV mean 20.75 ± 20.4, range 13—60, cm/m² BSA), the ventricular end-diastolic volumes (RV mean 109.72 ± 80.7, range 101—265, ml/m² BSA and LV mean 101.3 ± 99, range 94—251, ml/m² BSA), and ventricular mass (RV mean 44.31 ± 39, range 6—55, g/m² BSA and LV mean 77.24 ± 38.1, range 9—160, g/m² BSA) increased accordingly 2—5 years post-heart transplantation. Comparing these to those values obtained during the first year post-transplantation, these were significant increases (p < 0.00) as well as when compared with those values obtained 30 days after transplantation (Tables 2 and 3).

3.8. 6—10 Years post-transplantation

The ventricular end-diastolic diameters (RV mean 22.19 ± 11, range 15—42, cm/m² BSA and LV mean 27.95 ± 19.9, range 19—59, cm/m² BSA), the ventricular end-diastolic volumes (RV mean 106.54 ± 85.6, range 103—278, ml/m² BSA and LV mean 118.54 ± 80.0, range 110—263, ml/m² BSA), and ventricular mass (RV mean 65.26 ± 36, range 10—75, g/m² BSA and LV mean 84.89 ± 38.2, range 15—75, g/m² BSA) increased proportionally 6—10 years post-heart transplantation. Aside from the LEDV and left-ventricular myocardial mass, whose difference from the

<table>
<thead>
<tr>
<th>Paired sample tests</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-ventricular end-diastolic dimension (cm/m² BSA)</td>
<td>1 versus 2</td>
<td>5.352</td>
<td>6.576—10.648</td>
</tr>
<tr>
<td>1 versus 3</td>
<td>3.258</td>
<td>6.02—2.473</td>
<td>0.00</td>
</tr>
<tr>
<td>1 versus 4</td>
<td>0.560</td>
<td>0.46 to 1.331</td>
<td>0.57</td>
</tr>
<tr>
<td>Right-ventricular end-diastolic volume (ml/m² BSA)</td>
<td>1 versus 2</td>
<td>6.335</td>
<td>21.796—41.537</td>
</tr>
<tr>
<td>1 versus 3</td>
<td>4.638</td>
<td>14.979—37.222</td>
<td>0.00</td>
</tr>
<tr>
<td>1 versus 4</td>
<td>2.984</td>
<td>7.871—39.063</td>
<td>0.00</td>
</tr>
<tr>
<td>Right-ventricular myocardial mass (g/m² BSA)</td>
<td>1 versus 2</td>
<td>6.565</td>
<td>2.441—4.990</td>
</tr>
<tr>
<td>1 versus 3</td>
<td>6.389</td>
<td>5.595 to 2.295</td>
<td>0.00</td>
</tr>
<tr>
<td>1 versus 4</td>
<td>14.547</td>
<td>−13.53 to 10.29</td>
<td>0.00</td>
</tr>
<tr>
<td>Left-ventricular end-diastolic dimension (cm/m² BSA)</td>
<td>1 versus 2</td>
<td>8.957</td>
<td>10.912—17.083</td>
</tr>
<tr>
<td>1 versus 3</td>
<td>8.581</td>
<td>11.275—18.02</td>
<td>0.00</td>
</tr>
<tr>
<td>1 versus 4</td>
<td>8.156</td>
<td>12.18—20.08</td>
<td>0.00</td>
</tr>
<tr>
<td>Left-ventricular end-diastolic volume (ml/m² BSA)</td>
<td>1 versus 2</td>
<td>5.839</td>
<td>19.073—38.564</td>
</tr>
<tr>
<td>1 versus 3</td>
<td>4.094</td>
<td>11.93—34.19</td>
<td>0.00</td>
</tr>
<tr>
<td>1 versus 4</td>
<td>2.594</td>
<td>4.541—34.073</td>
<td>0.11</td>
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<tr>
<td>Left-ventricular myocardial mass (g/m² BSA)</td>
<td>1 versus 2</td>
<td>7.311</td>
<td>10.369—18.059</td>
</tr>
<tr>
<td>1 versus 3</td>
<td>3.429</td>
<td>2.880—10.736</td>
<td>0.00</td>
</tr>
<tr>
<td>1 versus 4</td>
<td>2.71</td>
<td>4.713—10.736</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table 3. Multivariate analysis of ventricular diameter, volume and mass during different follow-up periods.

Postoperative follow-up: 1 = 30 days; 2 = 1 year; 3 = 2—5 years; and 4 = 6—10 years.
Fig. 1. A. Right-ventricular end-diastolic diameter (RVEDD). B. Left-ventricular end-diastolic diameter (LVEDD). C. Right-ventricular end-diastolic volume (RVEDV). D. Left-ventricular end-diastolic diameter (LVEDV). E. Right-ventricular (RV) myocardial mass. F. Ventricular myocardial mass, over time.
The mean duration of follow-up was $13 \pm 0.8$ (range 3 months to 22 years) years, providing a total of 1157.79 patient years. Cumulative survival rate at 10 and 15 years is 61.7% and 42.8 ± 8% (Fig. 2(A)). When the survival rate is stratified based on donor–recipient weight ratio, survival rate is $90.1 \pm 6.1\%$, $81.6 \pm 8.3\%$, and $73.4 \pm 10.8\%$ at 30 days, 1, and 5 years, respectively, for a donor–to–recipient weight ratio of $<0.8$; in patients with a donor–recipient weight ratio of $0.8–1.2$, the survival rate is $89.7 \pm 3.4\%$, $81.8 \pm 4.4\%$, $73.2 \pm 5.2\%$, $62.9 \pm 6.2\%$, and $45.9 \pm 8.7\%$, at 30 days, 1, 5, 10, and 15 years, respectively; in patients with a donor–recipient weight ratio of $>1.2$, the survival rate is $91.0 \pm 3.5\%$, $87.9 \pm 4.0\%$, $82.7 \pm 4.8\%$, and $56.1 \pm 2.8\%$ at 30 days, 1, 5, and 10 years, respectively (Fig. 2(B)). When the survival rate is stratified based on donor–recipient BSA ratio, the survival rate is $91.2 \pm 6.3\%$, $82.2 \pm 5.1\%$, $77.4 \pm 5.8\%$, and $63.0 \pm 7.5\%$ at 30 days, 1, 5, and 10 years, respectively, for a donor-to-recipient BSA ratio of $<1.0$; in patients with a donor–recipient BSA ratio of 1.0, the survival rate is $81.3 \pm 9.8\%$ and $67.7 \pm 11.9\%$, at both 30 days and 1 year and at both 5 and 10 years, respectively; in patients with a donor–recipient weight ratio of $>1.0$, the survival rate is $90.4 \pm 3.0\%$, $86.9 \pm 3.6\%$, $78.8 \pm 4.3\%$, $58.0 \pm 6.4\%$, and $46.3 \pm 7.4\%$ at 30 days, 1, 5, 10, and 20 years, respectively (Fig. 2(C)).

There is no statistically significant difference in survival rates among patients with different donor–recipient weight ratios obtained 30 days post-transplantation was not statistically significant ($p = 0.11$ and 0.78, respectively), all parameters attained statistically significant difference when compared with values measured 1 year ($p = 0.00$) and 2–5 years ($p = 0.00$) after transplantation (Tables 2 and 3).

All calculated z scores 2–5 years and 6–10 years post-transplantation were normal when indexed to BSA (Table 2). Ventricular end-systolic and end-diastolic diameters fell between the 5th and 95th percentiles, and all patients have demonstrated normal chamber growth. Although cardiac mass is linearly related to BSA, cardiac dimensions increase as an exponential function of BSA.

The cardiac dimensions and volumes measured are demonstrated in Fig. 1(A)–(F). As BSA increased, there is an associated rise in cardiac dimensions and volume. The mean ventricular diameters and myocardial mass, which was $85.6 \pm 16.8\%$ of that predicted normal for BSA after the first year and $96.4 \pm 7.5\%$ of that predicted normal after 5 years, suggests growth and adaptation of cardiac dimensions and volumes appropriate for body growth.

All recipients experienced normal volume growth commensurate with BSA growth to maintain a ratio of ventricular volume predicted for BSA of $>90\%$. The ventricular mass increased in accordance with the increase in end-diastolic volume.

In the present study, we avoided the problems inherent in a linear index by expressing all cardiac dimensions as a nonlinear function of BSA.

### 3.9. Follow-up and survival

The mean duration of follow-up was $13 \pm 0.8$ (range 3 months to 22 years) years, providing a total of 1157.79 patient years. Cumulative survival rate at 10 and 15 years is 61.7% and 42.8 ± 8% (Fig. 2(A)). When the survival rate is stratified based on donor–recipient weight ratio, survival rate is $90.1 \pm 6.1\%$, $81.6 \pm 8.3\%$, and $73.4 \pm 10.8\%$ at 30 days, 1, and 5 years, respectively, for a donor–to–recipient weight ratio of $<0.8$; in patients with a donor–recipient weight ratio of $0.8–1.2$, the survival rate is $89.7 \pm 3.4\%$, $81.8 \pm 4.4\%$, $73.2 \pm 5.2\%$, $62.9 \pm 6.2\%$, and $45.9 \pm 8.7\%$, at 30 days, 1, 5, 10, and 15 years, respectively; in patients with a donor–recipient weight ratio of $>1.2$, the survival rate is $91.0 \pm 3.5\%$, $87.9 \pm 4.0\%$, $82.7 \pm 4.8\%$, and $56.1 \pm 2.8\%$ at 30 days, 1, 5, and 10 years, respectively (Fig. 2(B)). When the survival rate is stratified based on donor–recipient BSA ratio, the survival rate is $91.2 \pm 6.3\%$, $82.2 \pm 5.1\%$, $77.4 \pm 5.8\%$, and $63.0 \pm 7.5\%$ at 30 days, 1, 5, and 10 years, respectively, for a donor-to-recipient BSA ratio of $<1.0$; in patients with a donor–recipient BSA ratio of 1.0, the survival rate is $81.3 \pm 9.8\%$ and $67.7 \pm 11.9\%$, at both 30 days and 1 year and at both 5 and 10 years, respectively; in patients with a donor–recipient weight ratio of $>1.0$, the survival rate is $90.4 \pm 3.0\%$, $86.9 \pm 3.6\%$, $78.8 \pm 4.3\%$, $58.0 \pm 6.4\%$, and $46.3 \pm 7.4\%$ at 30 days, 1, 5, 10, and 20 years, respectively (Fig. 2(C)).
ratio and in patients with different donor—recipient BSA ratios ($p = 0.53$).

4. Discussion

The questions of whether a transplanted heart in a newborn grows to adult size along with the child, and whether the dimensional growth of the organ allows adequate function over time, have been largely answered in this investigation. The other question that awaits to be answered is what could be the mechanisms involved in adaptation of a transplanted heart to its new environment. This is the issue that we are focusing on in ongoing investigations.

In this study, it was shown that cardiac dimensions and volumes increased in size appropriate to age and BSA of the recipient over time, regardless of donor-to-recipient size mismatch. Over time, the transplanted heart, even a large donor heart, adapts to its new environment accordingly and grows along with somatic development of the patient.

Our results elucidate adaptation of the transplanted ventricle to the recipient circulation in the first months following transplantation in infants and children. The transplanted heart has adapted to the functional demands of the recipient circulation over time. A large donor organ would be expected to exhibit regression of ventricular mass with time as an adaptive phenomenon. This phenomenon may represent the effect of intrinsic of time-dependent factors that regulate cardiac growth [13]. These factors are unrelated to the functional demands of the heart and may involve genetic programming as well as humoral growth factors. It is conceivable that unidentified humoral trophic factors may persist in the recipient circulation for a period after transplantation, regardless of the size of the transplanted organ. This could lead to continued growth of ventricular myocardium in the early post-transplant period, manifesting as the early increase in ventricular mass and volume that we observed regardless of donor-to-recipient weight ratio or donor-to-recipient BSA ratio. Over time post-transplantation, the effect of these intrinsic factors may be overridden by the effect of load-dependent adaptation of the heart.

Whether our findings represent cardiac growth or physiological adaptation of a small heart to increased cardiac output requirements is an interesting and provocative issue. Cardiac growth is a physiological adaptation in normal population. But, how about a transplanted heart, which is chronically denervated and subject to constant immunological barrage? Does it grow or just adapt? Cardiac growth is modulated by intrinsic factors, which include the ability of myocytes to undergo hyperplasia and be influenced by humoral growth substances, as well as by extrinsic factors related to the cardiac response to hemodynamics. With a transplanted heart, could it be different, especially with the effects of chronic denervation, high catecholamine levels, and constant immunological bombardment? Could it be a form of physiological adaptation, which means that the heart increases in dimensions in response to the hemodynamic demands of the growing body, or in response to functional load placed on the heart? Cardiac growth occurs even in the presence of delayed linear growth. In our study, we have proven it is cardiac growth because we have indexed the dimensions to the BSA, and we have even proven that the transplanted heart in a donor-to-recipient BSA ratio of $> 1$ decreased in dimensions 30 days after transplantation. In this case, we call it precisely 'physiological adaptation', as the hemodynamic demands of the small growing body are less. Furthermore, echocardiographic data have shown increased dimensions with body growth, indicating that the transplanted hearts have adapted to functional load as body mass increased.

These findings may suggest that the younger patient is at the time of transplantation, the greater is the magnitude of early increase and subsequent decrease in ventricular mass with the remodeling process. Significant decrease in cardiac dimensions, volumes, and mass, during the first year post-transplantation clearly showed that the ventricles remodeled. This remodeling consisted primarily of regression of end-diastolic diameters, end-diastolic dimensions and volumes, and myocardial mass. The trigger that initiates regression is likely to include the load-modulation of ventricular mass [14]. By one year after the transplantation, the LV mass had decreased significantly from the original mass 30 days post-transplantation, suggesting that the heart undergoes more extensive adaptive changes mediated by pressure and volume factors. It is likely that both neurohumoral factors and intrinsic myocyte responses to the altered pressure and volume load contribute to these altered hemodynamic adaptations.

There was no correlation between donor age and the amount of increase in heart dimensions, such that it is highly possible that only neurohumoral variables, myocardial growth factor, gene expression, and adaptation of heart of the recipient circulatory demands dictate the growth and remodeling of the heart. Previous investigators [18] suggested that these changes may be due to exposures to elevated circulating catecholamines after cardiac denervation, chronic volume overload, and graft ischemia.

The determinants of myocardial growth have not been defined. Zak [13] demonstrated that differentiation and growth of the heart are governed by two sets of factors, intrinsic or time-dependent factors, which include myogenesis and cardiac looping, and are very important in the early stages of embryonic cardiac development occurring in the absence of hemodynamic influences. Extrinsic factors are related to the cardiac performance responding to functional demands, such as compensatory hypertrophy that follows an increase in hemodynamic load. As the body weight doubles at 6 months and triples by 1 year of age, the cardiac weight increases similarly [15]. The fetal period of myocardial growth is characterized by mitotic division, and cellular proliferation continues in the early postnatal period with a rapid decline. Further growth is characterized by increase in cell diameters. The signal to cease proliferation is unknown. The potential for proliferation to be ‘restimulated’ remains an intriguing concept supported by the work of Chien [16] in which the activation of cardiac target genes resulted in embryonic gene expression.

Circulating humoral factors, including growth factors, proto-oncogenes, cyclic nucleotides, and steroid hormones have profound effects on cellular growth. Adrenergic input is
another stimulant to myocardial hypertrophy. The absence of re-innervation of the donor heart has been reported [17].

In this study, we have demonstrated that even in the presence of delayed linear growth, normal cardiac chamber growth occurs. Because ventricular systolic and end-diastolic dimensions may be more dependent on volume loading conditions than on increase in cell size, our long-term results are confirmative. The restrictive physiologic function observed at 1 month post-transplantation normalized over a period of 1 year, adapting to the recipient circulation. This suggests that hearts can adapt rapidly to altered pressure and volume loads and show marked remodeling over time to maintain the circulatory burden.

This evidence that the transplanted heart has the ability to adapt to new hemodynamic burdens suggests that, regardless of the donor-to-weight recipient ratio, the donor hearts could rapidly adapt to the new hemodynamic environment and that, after the immediate post-transplant period, the allografts could maintain an appropriate circulation according to the recipient's circulatory demands.

From a clinical standpoint, the results of this study indicate that the use of oversized or undersized donor hearts within a certain range appears to be well tolerated after orthotopic heart transplantation. Our policy in pediatric heart transplantation is that donor can be 4 times larger than the recipient, but should not be much smaller to sustain the immediate post-transplant hemodynamics. Tang et al. [18] reported that use of smaller allografts does not affect recipient's short- and long-term survival, and smaller allografts could therefore be accepted in pediatric heart transplantation. Patel et al. [19] reported that weight ratio did not predict mortality after heart transplantation after controlling for known risk factors, propensity score adjustment, and propensity score matching. Fullerton et al. [20] also reported that large size mismatches appear to be well tolerated in infants and pediatric heart transplantation.

The observed normal cardiac growth in this study supports the interplay between hemodynamic load and circulating factors in determining appropriate cardiac growth in a young, growing population.

These observations do not support the contention that donor-recipient size ratio plays a dominant role in cardiac growth.

In this regard, another interesting and challenging issue may be fostered. In our study, we have proven that cardiac growth of transplanted hearts occurs linearly with somatic growth in general. Does growth occur in those transplanted adult hearts? These are evidently mismatched hearts when implanted to children. Why do they shrink in size within months to 1 year after their implantation? These hearts, which have been denervated and subjected to a barrage of immunosuppressants, have already gone over their potential for cellular hyperplasia. We have chest X-rays of these patients showing the large heart occupying such a small chest cavity (Fig. 3(a)), but after a time period, they have reduced in size, and eventually fit (Fig. 3(b)) according to the BSA of the recipient over time. It is indeed a provocative issue, and we are very much concerned to look for possible explanations as to what cellular mechanisms could be responsible. At this point in time, based on our data at hand and existing albeit scant literature, we can only postulate that there could be some molecular signal pathways or feedback mechanisms, which exist, directing this interesting response. The question of the proportional cardiac shrinkage of an adult heart transplanted in a small chest cavity, eventually enlarging its dimensions over time in relation to bodily growth of its recipient, probably as a result of time-dependent genetic factors including cardiac morphogenesis and myocyte hypertrophy, or because of extrinsic hemodynamic demands result in subsequent cardiac enlargement remains unresolved in this study. We have only the numbers (dimensions and z scores) to prove it, but we would not be able to provide the

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Fig. 3. a. Chest X-ray of a child transplanted with an adult heart. b. Chest X-ray of the same child 30 days after transplantation.
underlying mechanisms. As of now, be as it may, we may only surmise that the shrinkage in transplanted adult hearts within a certain period of time that conforms to the somatic growth of the recipient is a physiological adaptation to pressure and volume demands of the growing body.

5. Study limitations

We did not study the effects of immunosuppression, hemodynamic performances, frequency and severity of acute and chronic rejections, myocardial fibrosis, and myocyte damage in correlation with the changes in cardiac dimensions. While peak systolic wall stress was not considered in the present study, an exploration of changes in peak systolic wall stress post-transplant, which is BSA dependent, would be an important addition to the existing body of information. These issues are the subjects of ongoing researches in our center.

6. Conclusions

The adaptation of the donor heart to the recipient circulation following transplantation is a dynamic process. This study demonstrates that the transplanted heart undergoes normal growth in diastolic dimensions, volumes, and myocardial mass over time appropriate for body growth after cardiac transplantation in infants and children. This myocardial growth occurs despite immunosuppression and denervation. Ventricular remodeling occurs by temporally reversible increase in ventricular diameter, volume, and mass several weeks following transplantation, the extent of which is predicted by physiological requirements of the developing child as demonstrated in the normalization and increase in dimensions and volumes over time.

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References


Appendix A. Conference discussion

Professor C. Schiensak (Freiburg, Germany): The results of this interesting study emphasize ventricular remodeling following pediatric or infant transplantation. Knowledge of the normal increase in LV mass in the first weeks after cardiac transplantation seems very important in the critical evaluation of LV mass change as a criterion for allograft rejection. However, your findings are not new but confirm results of other groups, and I refer to the Loma Linda group who analyzed this phenomenon prospectively in a large patient cohort.

There are three questions. First, how about patients with signs or proof of rejection? Did you exclude them from your analysis?

Second question, for your study you analyzed echo data retrospectively over a time period of more than 20 years. I wonder if follow-up is complete and, if not, you should mention that in your data sheets.

And the third question, the data on ventricular dimensions as shown in your graphics now, which are the core data of your whole analysis, are misleading. Please comment on the meaning of right ventricular end-diastolic dimensions which range from 50 down to zero.

Dr Delmo Walter: Your first question?
Professor Schlensak: The first question concerns signs of rejection. Did you exclude those patients from the retrospective study?

Dr Delmo Walter: We did not exclude; they are in fact included. But we did not study or evaluate the effects of rejection on the cardiac dimensions or on the chamber growth. That’s why I mentioned it in my study limitations, we did not particularly focus on that area.

But all those patients having acute or chronic rejection were included. In fact, in my manuscript I mentioned that we had five patients who had several repeat rejections and had a higher dose of immunosuppressants and steroids and hence they exhibited delayed growth. But when we actually look at the echocardiographic dimensions such as the end-diastolic diameter and ventricular mass, the growth or the change in cardiac dimensions were still appropriate for the body surface area.

The second question?

Professor Schlensak: The second question was whether follow-up is complete. You referred to 30 days, 1 month, 2 to 4 years, and 10 years follow-up in echo data in a retrospective study over 23 years.

Dr Delmo Walter: Yes, the follow-up is complete. We have been doing transplantation for more than 23 years; however, I only included those patients who had follow-up until 10 years. Because some patients, of course, were 17 years old during the time that transplantation was performed, so I included only one year from those patients. These 17 year olds do not grow anymore after that.

And the rest of the patients, of course had complete follow-up. They may not be regular, like annually, but they had echocardiographic studies every now and then. So that’s why I stratified this in follow-ups of 1 year, 2 to 5 years and 6 to 10 years.

And the third question?

Professor Schlensak: The third question was that the end-diastolic dimensions are a little bit misleading. You have a range from 50 down to zero. Please comment on the zero, I don’t understand that.

Dr Delmo Walter: Where is that again?

Professor Schlensak: Right ventricular end-diastolic dimensions. If you look at the left columns, I don’t understand that it goes to zero or below zero, the range of the columns. What is zero dimension in an echo? I’m a surgeon and probably I misunderstood.

Dr Delmo Walter: I am a surgeon too, and I also don’t understand.

J. Pepper (London, UK): Is the graph inaccurate?

Dr Delmo Walter: I am sure it is accurate. This was already given by the statistician and I really never had a thorough look at it. But the range was written 0 to 47 and 0 to 63.

Professor Schlensak: But zero dimension?

Dr Pepper: You can’t have a zero dimension in a structure.

Professor Schlensak: It’s very small.

Dr Pepper: It’s moving into the field of particle physics, I think.

Dr Delmo Walter: I’m sorry, but I will thoroughly look at the numbers again, because I think there was a mistake somewhere in my data input.

Professor Schlensak: You should critically look at those figures again.