Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit

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Abstract

Objective: Allograft conduits are used for reconstruction of the right ventricular outflow tract in congenital heart malformations (biventricular repair) and autograft procedures. A retrospective evaluation of allograft reconstruction of the right-ventricular-outflow-tract reconstruction was conducted and a cross-sectional quality of life study was performed. Methods: Between August 1986 and March 2009, 509 allografts (435 pulmonary and 74 aortic) were implanted in 463 pediatric and adult patients (308 right-sided congenital heart malformations and 155 autograft procedures). Perioperative and follow-up data were collected and analyzed. Kaplan–Meier analyses were done for survival, valve-related re-operation, and valve-related events. Cox regression analysis was used for evaluation of potential risk factors. Results: The mean age at allograft implantation was 19 years (1 week–66 years). Mean follow-up was 9 years (2 days–22 years). Forty-eight patients died during follow-up. Patient survival was 93% at 10 years and 88% at 15 years. A total of 63 re-operations were required for allograft dysfunction in 58 patients. Freedom from valve-related re-operation was 89% at 10 years and 81% at 15 years. Freedom from valve-related events was 86% at 10 years and 74% at 15 years. Younger patient age (p = 0.007) and the use of an aortic allograft (p < 0.001) were identified as independent risk factors for allograft re-operation. Patients between 14 and 40 years scored significantly lower on ‘physical functioning’ and ‘general health’ subscales than the general Dutch population, but scored better on the subscales ‘emotional role functioning’ and ‘bodily pain’. Except for the subscale ‘general health’, on which patients within our study population scored lower, patients between 41 and 60 years had comparable average scores as the general Dutch population. The older patient group (61 years or older) had a better average score on the subscale ‘bodily pain’ and similar scores on other subscales with respect to the general Dutch population. Conclusions: Right-ventricular-outflow-tract reconstruction with an allograft conduit can be performed with good patient survival, acceptable long-term allograft durability, and good perceived quality of life.

Keywords: Pulmonary valve; Quality of life; Heart-valve-prosthesis implantation; RVOT reconstruction

1. Introduction

Reconstruction of the right ventricular outflow tract (RVOT) is performed in patients with congenital heart disease when there is no adequate continuity between the right ventricle and the pulmonary circulation. The use of an ‘aortic’ valve allograft for pulmonary valve replacement was introduced in 1966 [1]. But it was not until 1983 that Ross et al. introduced the ‘pulmonary’ valve allograft for pulmonary valve replacement [2]. This has resulted in an ever-increasing application of allografts. Nevertheless, a tendency toward allograft degeneration over the years is still apparent [3]. Degeneration of the pulmonary valve allograft can eventually lead to clinically relevant pulmonary stenosis (PS) and pulmonary regurgitation (PR). PR is usually well tolerated in childhood. However, recent long-term studies have demonstrated that, in adults, PR may lead to progressive right ventricular (RV) dilatation and, with time, to RV dysfunction, exercise intolerance, ventricular tachycardia, and sudden cardiac death [4–6]. Further improvement for this still growing population of patients with congenital heart disease is mandatory to be able to optimize their life expectancy and quality of life (QoL).
Long-term results of RVOT reconstruction with pulmonary allografts have been scarcely reported thus far. Furthermore, no study has reported on QoL in patients after RVOT reconstruction. QoL has emerged as an increasingly important outcome parameter for several reasons: it provides a precise indicator of overall health status of the individual patient, and higher QoL is associated with improved disease-specific prognosis and also with increased survival [7,8].

The aim of the present study was to assess clinical outcome over time in patients, who received an allograft in the RVOT at our institution. In addition, a cross-sectional assessment of QoL in these patients was done.

2. Methods

2.1. Patient population

Between August 1986 and March 2009, 509 allografts (435 pulmonary and 74 aortic) were implanted in 463 pediatric and adult patients (308 right-sided congenital heart malformations and 155 autograft procedures). Our series represents a heterogeneous group in which the common denominator was the need for a right-sided allograft conduit. Patients were classified according to their primary diagnosis (Table 1). A first allograft was implanted in 463 patients, a second in 41, a third in four, and a fourth in one.

2.2. Operative techniques

Timing of surgery was determined in a regular heart team meeting between the (congenital) cardiologists and cardiac surgeons during which all cases were discussed. The decision as to whether to operate or not was based on contemporary clinical practice. The surgical procedures were performed using standard cardiopulmonary bypass with moderate hypothermia, myocardial protection with crystalloid cardioplegia (St. Thomas Hospital solution), and, in most cases, topical cooling. If associated intracardiac procedures were not required, the reconstruction was done without cross-clamping of the aorta. Using the interposition technique, the allograft was sewn between the right ventricle and pulmonary artery in most cases (n = 502). In seven patients, the allograft was implanted between the right-sided left ventricle and the pulmonary artery. Distal and proximal anastomoses were made with a running polypropylene suture. Twenty-one patients needed a distal extension to ensure proper connection. For this purpose, an allograft patch (n = 12), an autologous pericardial patch (n = 3), or a prosthetic patch (n = 6) was used. A proximal extension of the allograft was necessary in 112 patients. In these cases, an allograft patch (n = 47), the anterior-mitral-valve leaflet of the aortic allograft (n = 26), a pericardial patch (n = 27), or a prosthetic patch (n = 12) was used. In all cases, attempts were made to implant the allograft away from the sternum to prevent compression or distortion.

2.3. Allograft properties

The Rotterdam Heart Valve Bank provided most of the allografts (n = 410), which were allocated by Bio Implant Services, Leiden, the Netherlands. Preparation and storage methods have been described earlier [9]. The National Heart Hospital, London, England, provided 19 fresh and four cryopreserved allograft conduits. The remaining allografts were shipped from the Hospital Clinic I, Barcelona, Spain (n = 47); the Karolinska Homograft Bank, Stockholm, Sweden (n = 6); the Deutsches Herzzentrum, Berlin, Germany (n = 26); and Herzzentrum Nord Rhein Westphalen, Bad Oeynhausen, Germany (n = 1). The patient’s body surface area was used as a guideline to determine the allograft diameter. No attempt was made to achieve ABO blood type or human leukocyte antigen (HLA) type matching.

2.4. Data collection

All patients, who receive an allograft for RVOT reconstruction at Erasmus MC, are systematically registered in a dedicated relational database (Microsoft Access 2007). After implantation of the allograft, patients were seen at regular intervals by their cardiologists, with the exception of 12

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD or total no.</th>
<th>Range or percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>19 ± 15</td>
<td>1 week–66 years</td>
</tr>
<tr>
<td>Age &lt; 1 year</td>
<td>60</td>
<td>12%</td>
</tr>
<tr>
<td>Age 1–18 years</td>
<td>208</td>
<td>41%</td>
</tr>
<tr>
<td>Age &gt; 18 years</td>
<td>241</td>
<td>47%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>301</td>
<td>59%</td>
</tr>
<tr>
<td>Female</td>
<td>208</td>
<td>41%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>46 ± 27</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.41 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve pathology</td>
<td>170</td>
<td>33.4%</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>152</td>
<td>29.9%</td>
</tr>
<tr>
<td>PA or PS, VSD</td>
<td>63</td>
<td>12.4%</td>
</tr>
<tr>
<td>Discordant ventriculoarterial connection with PA or PS</td>
<td>51</td>
<td>10.0%</td>
</tr>
<tr>
<td>Common arterial trunk</td>
<td>44</td>
<td>8.6%</td>
</tr>
<tr>
<td>PA or PS with intact septum</td>
<td>26</td>
<td>5.1%</td>
</tr>
<tr>
<td>Aortic atresia with biventricular heart</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Total</td>
<td>509</td>
<td>100%</td>
</tr>
</tbody>
</table>

PA: pulmonary atresia; PS: pulmonary stenosis; and VSD: ventricle septum defect.
patients who migrated to other countries or were living abroad. In September 2009, vital status of all patients was acquired from municipal civil registries with a response rate of 97%.

All follow-up data of patients with congenital heart malformations (biventricular repair) were collected retrospectively from hospital records. The autograft patients are part of a prospective cohort study. In addition, questionnaires with information about occurrence of any cardiovascular event since last known follow-up were sent to all living patients in October 2009. These questionnaires were completed and returned by 94% of the patients. Patients who did not complete and return the questionnaires (6%), were censored at the most recent known follow-up. The day of implantation was considered the starting point of patient survival. Endpoints in patient survival were death or last follow-up date. Patients lost to follow-up were censored at last date of follow-up. The starting point of allograft survival was the day of implantation; the endpoint was the occurrence of events during follow-up or last follow-up date. The cause of death was registered and reported according to the guidelines for reporting mortality and morbidity after cardiac valve interventions [10]. This study was approved by the institutional review board of Erasmus University Medical Center (MEC-2008-371) and all patients provided informed consent.

2.5. QoL assessment

QoL was measured with the Short Form 36-Item Health Survey (SF-36) [11]. The SF-36 is the most widely used and evaluated health outcomes measure and has extensive evidence for its validity and reliability in multiple populations. The SF-36 assesses eight health-status domains (i.e., physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this total by the range of scores and then transforming the raw scores to a scale from 0 to 100 [11]. A higher score on the SF-36 subdomains represents a better functioning; a high score on the bodily pain scale indicates the absence of pain. The scale has good reliability, with Cronbach α ranging from 0.65 to 0.96 for all subscales [12].

In August 2009, all surviving patients who were 14 years or older (n = 236) received the SF-36 (Dutch version) questionnaire by mail and were asked to return the completed questionnaire. Patients living abroad or of whom up-to-date contact specifications were not available were excluded. A total of 198 (84%) patients completed the SF-36 questionnaire. The results of perceived QoL in the patients after RVOT reconstruction were compared to Dutch population norms [13]. To be able to compare the QOL assessed in patients after RVOT reconstruction with the QOL of the general Dutch population, we subdivided the study group into different age categories (14–40 years, 41–60 years and 61–70 years).

2.6. Statistical analyses

Patient data were entered into a computerized relational database (Microsoft Access 2000). Statistical software Statistical Package for Social Sciences (SPSS) for Windows version 10 (SPSS Inc, Chicago, IL, USA) was used for data analysis. Actuarial survival was determined using the Kaplan–Meier method [14]. For all tests, a p-value of less than 0.05 was considered significant.

The log-rank test was used for univariate assessment of the effect of potential risk factors on patient survival, freedom from valve-related re-operation, and freedom from valve-related events. To investigate independent risk factors for mortality and morbidity caused by allograft failure, the Cox proportional hazard model was used. Risk factors were selected with a backward stepwise method (required significance of p > 0.10 for elimination from the model and p < 0.05 for retention in the model). With regard to implantation position, all autograft procedures were labeled as anatomic, and any other allograft implantation for reconstruction of the RVOT was labeled as extra-anatomic.

Young age at time of implantation (Fig. 1(a)), small allograft diameter (Fig. 1(b)), extra-anatomic position of the allograft, young donor age (Fig. 1(c)), and an aortic allograft were considered to be potential risk factors for allograft dysfunction [3,15–17].

The results of the SF-36 questionnaire were compared with the population norms by the Wilcoxon rank-sum test with Bonferroni correction. This latter correction indicates that the allowable significance level for each SF-36 subscale was p < 0.00625 (0.05/8 subscales).

3. Results

3.1. Patient and donor characteristics

The baseline characteristics of the study population are shown in Table 1. The donor group consisted of 280 male and 214 female donors with a mean age of 37 ± 18 years (median, 42; range, 0–65 years). The characteristics of 15 donors could not be traced. Mean allograft diameter was 22 ± 4 mm (median, 23; range, 10–31 mm). Of the 509 allografts, 493 were cryopreserved, and 16 were fresh. Nineteen (3.7%) allografts were reduced in size by bicuspidalization before they were used for RVOT reconstruction; their size was included as two-thirds of the original size.

3.2. Follow-up

The mean follow-up time was 9 ± 6 years (median, 9; range, 0–22 years). Total number of patient-years was 4680.

3.3. Mortality

Fifteen patients (3%) died within 30 days of operation. The causes of early death were heart failure (n = 5), bleeding (n = 4), hypoxic encephalopathy (n = 1), respiratory insufficiency (n = 1), pulmonary thrombo-embolism (n = 1), multi-organ failure (n = 1), severe congenital bronchomalacia (n = 1), and arrhythmia (n = 1). All deaths were nonvalve related. None of these allografts showed signs of degeneration at pathologic examination. Univariable logistic regression analysis revealed that the need of preoperative ventilation support (hazard ratio (HR) 6.08; 95% confidence
interval (CI) 1.23—29.95; \( p = 0.027 \), the need of preoperative inotropic drug support (HR 8.38; 95% CI 2.12—33.03; \( p = 0.002 \)), and undergoing urgent or semi-urgent operation (HR 6.56; 95% CI 2.19—19.66; \( p = 0.001 \)) are independent risk factors of early mortality. In a multivariable logistic regression analysis, only undergoing urgent or semi-urgent operation (HR 6.56; 95% CI 2.19—19.66; \( p = 0.001 \)) could be identified as an independent risk factor of early mortality.

Thirty-three patients died later than 30 days after implantation. Six of these deaths were valve related. In one patient, calcification of the allograft valve conduit caused stenosis resulting in acute right-heart failure 1.2 years after the operation. Endocarditis destroyed the allograft in two other patients after 51 days and 7.4 years, respectively, resulting in right-ventricular failure. One patient died due to severe pulmonary valve insufficiency and arrhythmia 3 months after the operation. One patient died due to severe pulmonary valve insufficiency resulting in heart failure 2 years after the operation. One patient died from sudden, unexplained, unexpected death without further clinical data or autopsy 5.5 years after the operation.

The causes of non-valve-related late death were heart failure (\( n = 12 \)), respiratory insufficiency (\( n = 2 \)), sepsis (\( n = 2 \)), myocardial infarction (\( n = 1 \)), arrhythmia (\( n = 1 \)), pulmonary hypertension (\( n = 1 \)), pancreatitis and heart failure (\( n = 1 \)), and hypoxic encephalopathy (\( n = 1 \)), while the cause was unknown in six patients. Patient survival was 97% (95% CI 95—98%) at 1 year, 93% (95% CI 90—95%) at 10 years, and 88% (95% CI 83—92%) at 15 years (Fig. 2).

Univariable Cox regression analysis revealed that undergoing urgent or semi-urgent operation was the only risk factor for late death (HR 3.94; 95% CI 1.83—8.48; \( p < 0.001 \)).

### 3.4. Morbidity

During follow-up, 99 valve-related events were reported. Sixty-three allograft replacements were required for allograft dysfunction in 58 patients (mean age 18.8 ± 11.2 years). Among the patients who needed an allograft replacement, allograft dysfunction was related to structural valve failure in 56 re-operations, nonstructural failure in three re-operations, and allograft endocarditis in four patients. In the group of patients with structural valve failure, 42 valves were replaced due to stenosis, eight valves due to regurgitation and six valves because of both stenosis and regurgitation.

In the group of patients with nonstructural valve failure, the extension of the conduit caused stenosis near the proximal anastomosis of the allograft in one patient, one patient suffered from supravalvular stenosis near the distal anastomosis, and, in one allograft, a false aneurysm in one sinus was responsible for the regurgitation. Freedom from
valve-related re-operation was 89% (95% CI 86—92%) at 10 years and 81% (95% CI 76—86%) at 15 years (Fig. 3).

Three patients underwent a re-operation for allograft failure but without replacement of the allograft. In two of these patients, the extension material causing allograft stenosis was removed, and, in one patient, a pulmonary allograft patch was used for enlargement of the RVOT. Endocarditis was diagnosed in eight patients. Thirteen patients underwent a percutaneous pulmonary valve replacement. Balloon dilatation of the pulmonary allograft was needed in nine patients, and, in three patients, the diagnosis of cerebrovascular accident was made. Freedom from any valve-related event or re-operation was 86% (95% CI 82—89%) at 10 years and 74% (95% CI 68—78%) at 15 years (Fig. 4).

3.5. Risk factors

Univariate analysis identified younger patient age (HR 1.06; 95% CI 1.04—1.09; p < 0.001), extra-anatomic position of the allograft (HR 2.67; 95% CI 1.42—5.02; p = 0.002), the use of aortic allograft (HR 6.40; 95% CI 3.89—10.53; p < 0.001), younger donor age (HR 1.05; 95% CI 1.03—1.06; p < 0.001), and smaller allograft diameter (HR 1.21; 95% CI 1.14—1.27; p < 0.001) as potential risk factors for valve-related re-operation.

Donor age and allograft diameter were not included in a multivariable analysis, as they were significantly correlated with patient age at the time of operation (p < 0.01).

After multivariable analysis, younger patient age (HR 1.04; 95% CI 1.01—1.06; p-value: 0.007) and the use of aortic allograft (HR 4.17; 95% CI 2.39—7.27; p < 0.001) were identified as independent risk factors for allograft re-operation.

3.6. Quality of Life

After Bonferroni correction for multiple tests, young adult patients (age category 14—40 years), who underwent an RVOT reconstruction, scored significantly lower on 'physical functioning' and 'general health' scales. However, compared with the general Dutch population, this patient group scored better on 'emotional role functioning' and 'bodily pain' scales. No major differences could be found between the perceived QoL in this patient group and the QoL of the general Dutch population for the other measured SF-36 scales (Fig. 5(a)).

In adult patients (age category 41—60 years), no substantial differences could be found for most of the scales between the perceived QoL of our study population and the general Dutch population, except for the 'general health' scale on which the study population scored a lower average (Fig. 5(b)).

Compared with the general Dutch population, patients older than 61 years of age scored significantly better on the 'bodily pain' scale. No major differences could be found in this group for other scales between the study population and the general Dutch population (Fig. 5(c)).

4. Discussion

The present study evaluated the long-term clinical outcome of RVOT reconstruction with an allograft conduit. Our results show that this procedure can be performed with excellent results in terms of patient survival and acceptable long-term allograft durability. The results of our experience with RVOT reconstruction have been reported earlier by our institution [18]. The additional value of the present study is reporting the long-term clinical outcome of RVOT reconstruction in a larger group of patients with a follow-up time up to 22 years. Furthermore, the health-related QoL in patients after RVOT reconstruction has been assessed in the present study.

4.1. Survival

In the present study, patient survival was 93% (95% CI 90—95%) at 10 years and 88% (95% CI 83—92%) at 15 years. These survival rates seem to be slightly better than those reported in the previous studies [16,18—21]. Tweedell et al. reported a survival rate of 88% at 10 years in 205 patients receiving a cryopreserved homograft valve [19]. Bando et al. observed a survival rate of 86% in patients receiving a pulmonary allograft and a survival rate of 80% in patients receiving an
aortic allograft after a follow-up period of 5 years [16]. Hawkins et al. reported a survival rate, which was 81% at 33 months of follow-up [20]. Brown et al. reported recently a survival rate of 80% at 15 years in a non-Ross patient population receiving an allograft conduit [21]. Furthermore, the survival rates in the present study have improved compared with the survival rates reported previously by our own institution [18,22]. Possible explanations for this improvement could be the increasing experience of RVOT reconstruction and the improved overall management of this patient population.

4.2. Re-operation

Compared with previous reports on this patient population, we observed good long-term results in terms of freedom from valve-related re-operations. In the present study, freedom from valve-related re-operation was 89% (95% CI 86–92%) at 10 years and 81% (95% CI 76–86%) at 15 years. Even when taking into account any valve-related event that occurred in our study population, the results were still good. Freedom from valve-related events was 86% (95% CI 82–89%) at 10 years and 74% (95% CI 68–78%) at 15 years. The observed results in our study are more encouraging than those reported by other investigators. In a recent publication, Brown et al. reported a freedom from allograft failure of 60% at 5 years and 43% at 15 years [21]. Niwaya et al. reported a freedom from allograft failure of 82% at 8 years [17]. Stark et al. described 58% and 31% freedom from conduit replacement at 10 and 15 years, respectively [23]. Their relatively young patient population, a large amount of aortic allografts used in the latter series, and use of non-cryopreserved allografts in the early implantation period may perhaps explain these findings.

In an earlier report from our own institution, the freedom from re-operation was 90% at 5 years and 86% at 8 years [18], which was lower than in the present study. A possible explanation for this improvement could be the increasing experience of RVOT reconstruction with an allograft conduit at our institution. Furthermore, we have observed a change in the population of patients receiving an allograft. The number of patients undergoing an autograft procedure or receiving an allograft after a primary tetralogy of Fallot correction has increased.

4.3. Risk factors for accelerated allograft failure

In the Cox regression multivariate analysis, younger patient age and the use of aortic allograft were identified as independent risk factors for accelerated allograft failure. The use of aortic allograft is indeed a well-known independent risk factor in the literature for accelerated graft failure [15,16,18,19]. It has been postulated that a lower content of elastic tissue and a lower amount of total calcium in the wall of the pulmonary allograft in comparison to the aortic allograft can be responsible for this difference [24].

Younger patient age was another independent risk factor for accelerated graft failure in the present study. A plausible explanation for this observation is the fact that the heart will outgrow the allograft after a few years, resulting in the need for re-operation. To prevent this, some authors advise using...
an allograft with a relatively large diameter [25]. However, implanting too large an allograft entails a risk for compression or kinking of the allograft.

Allografts implanted in an extra-anatomic position could only be identified as a potential risk factor in the univariate analysis and not in the multivariate analysis. This is in contrast to an earlier report from our institution [18], and to what other investigators have reported in the past [3,17].

4.4. Quality of life

With the development of advanced surgical techniques and patient survival, QoL is of increasing interest in health care, especially in patients undergoing major surgical operations. The present study shows that the perceived QoL in young adult patients after RVOT reconstruction is impaired on subscale 'physical functioning'. This implies that patients experience more often limitations in lifting, climbing, bending, kneeling, walking, or running than the general Dutch population. Furthermore, this patient group has an impaired score on the 'general health' subscale, indicating that they evaluate their overall health to be lower than in the general population. However, these patients scored better on the 'emotional role functioning' subscale: this indicates that the personal feelings of job performance, or work, or other activities are perceived to be better than in the general population. Furthermore, the intensity and duration of bodily pain and limitations in activities due to pain ('bodily pain subscale') were perceived to be lower. The latter was also the case in patients 61 years and older. The explanation of a better score on the 'bodily pain' subscale could be the fact that a proportion of our patients had experienced limitations in their daily activity before the operation. Symptom relief and the return to the previous lifestyle can probably increase the perception of own health status.

It was interesting to see that, with increasing age, the perceived QoL was more in accordance with the QoL of the general Dutch population. This can be caused by the fact that healthy elderly individuals tend to unconsciously compare their current physical and psychologic performances with those during their younger years.

5. Conclusion

RVOT reconstruction with an allograft conduit can be performed with good patient survival, acceptable allograft durability, and good perceived QoL. Progressive allograft dysfunction with increasing patient follow-up can be expected. Continued long-term surveillance is, therefore, necessary and careful monitoring of patients with pulmonary allografts is warranted.

Acknowledgment

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References

Appendix A. Conference discussion

Dr G. Ziemer (Tuebingen, Germany): The Rotterdam group is known to be one of the most experienced in Europe in dealing with homografts and autografts, as far as the young cardiac patient group is concerned. And so this is a timely effort to present your almost 20-year experience and 463 patients receiving 509 homografts.

I may still be allowed to call these valves and tubes ‘homografts’ because these are transplants in the homologous species, namely, within the same species. I may sound old-fashioned, but anyways.

I will not repeat all the results or discuss how or when the proximal or distal homograft actually requires any elongation and whether this may be better or worse.

I have, however, two principal statements I would like you to comment on or to answer if you feel it is a question.

The first is: If there is anything to be labeled as an anatomical position for the homograft valve substitute in the right ventricular outflow tract, it should not be restricted just to the autograft procedure because I feel for the classical tetralogy patient, the homograft really gets into a physiologic position or anatomic position also.

And if now your extra-anatomic positions comprise only those pathologies like truncus or pulmonary atresia where we really have an extra-anatomic placement of the valve, I just may speculate, if you then compare your extra-anatomic and your anatomic group again, you may see the same differences you have seen in some of your previous publications.

My second statement is, when you looked at your risk factors in the univariate fashion amongst others, you identified younger patient age as well as smaller homograft diameter as such factors. Well, for me both describe the same problem of size, so there is no real difference.

But my question now is: do you have an idea from your data which amount of oversizing, especially for the young and small children, will not be detrimental in the short term by kinking or whatever, but still will provide benefit in the long term and have a longer time of freedom from re-operation?

Dr Mokhles: With respect to your first comment, it would indeed be interesting to investigate this issue with special attention to patients with tetralogy of Fallot. Although it should be noted that in our center, Ross patients received the pulmonary allograft during the first operation, while patients with tetralogy of Fallot received the allografts during the second operation.

Dr Ziemer: Yes. Well, I still would consider this the anatomic position.

Dr Mokhles: Exactly. It would be interesting to examine that, but we have not looked at that yet.

With respect to your second comment, we have indeed included several characteristics in the univariate model to investigate their association with the observed outcome. However, we have tested the correlation between all those variables before using them in the multivariate analyses. In case of significant correlation, the clinically important variable was chosen to be included in the multivariate model.

Furthermore, we have not yet investigated which degree oversizing potentially contributed to a better outcome in our patient population. It is indeed suggested that a relatively large allograft may have a better outcome. However, it should also be taken into account that a relatively large allograft may eventually also result in kinking or compression. But it would be interesting to investigate whether oversizing decreases the rate of re-operations in the long term.