Factors influencing the survival of cryopreserved homografts. 
The second homograft performs as well as the first

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Abstract

Objective: To determine the life span of cryopreserved homografts implanted in the right ventricular outflow tract and the factors influencing it.

Methods: From 1989 through 2003, we reconstructed the pulmonary valve with 301 homografts in 272 patients (median age 13 years; range 4 days–69 years). Indications were tetralogy of Fallot (136), truncus arteriosus (23), Rastelli repair (11), double outlet ventricle (13), endocarditis (5), and the Ross operation (84). Median follow-up was 5.7 years (range 0–14). We analyzed possible predictors of graft replacement by simple and multiple Cox regression.

Results: Actuarial survival was 96\% at 1, 95\% at 5, and 94\% at 10 years follow-up. Three homografts were explanted because of endocarditis (excluded from the analysis). Freedom from explantation was 99.6\% at 1, 94.5\% at 5, and 81.8\% at 10 years. Variables, significantly related to explantation in the univariate analysis, were younger age, small graft size, implantation in a non-anatomical position, the aortic donor homograft, a shorter aortic cross-clamp time and the implantation of a second homograft. In the multiple model, non-anatomical position ($P<0.001$), smaller graft size ($P<0.0001$) or younger age (on square root scale, $P<0.0001$) and clamp time ($P=0.01$) remain as independent risk factors. Immunological variables, like blood group incompatibility, implantation of a second homograft and short warm ischemic time were not significant.

Conclusions: The life span of a cryopreserved homograft is determined by graft size (correlates with age) and the non-anatomical position (correlates with indication). In a specific patient, the second homograft performs as well as the first.

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Keywords: Congenital heart surgery; Biological heart valve; Allograft

1. Introduction

The reconstruction of the right ventricular outflow tract is an essential part of the treatment in congenital heart disease. Cryopreserved homografts became the conduit of choice for this procedure. Homografts, which have an excellent hemodynamic profile, are superior in suturing and tailoring and require no anti-coagulation. Several series reported superb event-free survival rates [1–3]. The homograft longevity depends strongly on the age of the patients. Several authors allude to an immunological role in the biodegeneration of homografts [4–6]. The therapeutic implications of a possible immunological effect on homograft failure are important, as several children need reoperations. We retrospectively analyzed the long-term outcome of homografts in the right ventricular outflow tract to identify the predictors of homograft failure and to identify the possible contribution of an immunological mechanism.

2. Methods

2.1. Patients

From 1989 through 2003, we reconstructed the right ventricular outflow tract with 301 homografts in 272 patients. Ages varied between 4 days and 69 years (median 13 years). Indications were tetralogy of Fallot (136), truncus arteriosus (23), Rastelli repair (11), double outlet ventricle (13), endocarditis (5), and the Ross operation (84).
2.2. Homografts

The implanted homografts were sterile, cryopreserved aortic and pulmonary valve conduits processed by the European Homograft Bank (EHB, Brussels, Belgium). Donor age varied between 0.008 and 64 years (mean 33.41, SD 16 years). The grafts are derived from three types of donors: recipients of cardiac transplantation, multiorgan-donors with non-transplantable hearts and non-beating heart cadavers with a warm ischemia time less than 6 h. They are dissected and decontaminated in a low-grade antibiotic solution containing cefoxitin 240 μg/ml, lincomycin 120 μg/ml, polymyxin B 100 μg/ml, and vancomycin 50 μg/ml. They are immersed in a 10% dimethylsulfoxide solution and left for 30 min in wet ice to allow penetration of dimethylsulfoxide in the tissue. Cooling rate is 1 °C/min down to −40 °C, and 5 °C/min down to −100 °C and is electronically monitored. Then the tissue is transferred into a liquid phase of nitrogen at a temperature below −150 °C and stored for a maximum of 3 years. The median warm ischemic time was 6 h (range 1–24 h); the cold storage time was 54 days (range 11–1109 days).

The grafts were transported in a cooler of liquid nitrogen to the operating theatre and thawed in a water bath before use. We did not attempt to match ABO blood group or gender. Implantation of a pulmonary graft was preferred, but was not always possible because of limited homograft availability. Forty-five of the 301 homografts were aortic grafts (15%).

2.3. Surgical technique

The appropriate homograft size was determined by preoperative echocardiographic measurement of the pulmonary artery diameter. The anatomically largest fitting graft size was used. Homografts sizes ranged between 7 and 29 mm (mean 21.2, SD 4.17 mm). This results in an exponential increase of valve size as related to age with implantation of ‘adult’ sizes from the age of 8 years (Fig. 1).

All implantation procedures were done using support with cardiopulmonary bypass under moderate hypothermia or normothermia. Antegrade crystalloid cardioplegia was used to arrest the heart. All distal and proximal anastomoses were performed with running polypropylene sutures. The homografts were not extended and kept as short as possible. In small children with limited length of pulmonary artery, the homografts were cut with flaps and the distal anastomosis was performed with extensions in the left and right pulmonary artery to avoid restrictions. The proximal anastomosis was positioned at the level of the crista supraventricularis in the case of ventriculo-arterial concordance (anatomic position) and to the anterior free wall of the right ventricle in the case of non-concordance (non-anatomic position). The anastomosis to the right ventricle was enlarged with a right ventricular outflow hood of xenopericardium.

2.4. Follow-up

Patients did not receive aspirin, or any other anti-agregant or anti-coagulant medication. All patients were followed by our referring pediatric (<16 years) or congenital (>16 years) cardiologists. Patients were seen routinely 6 weeks after surgery and then every 6 months. In case of pathologic findings (like an increased gradient, or the onset of pulmonary regurgitation), the patients were asked to return earlier. An instantaneous peak gradient >50 mmHg was considered as a severe stenosis. A pulmonary valve regurgitation grade 3 (on a scale of 4) or more was considered significant. Grading of the pulmonary valve insufficiency was based on the following echo findings: a regurgitation jet restricted to the right ventricular outflow tract (grade 1), a jet reaching into the ventricular body (grade 2), backflow starting from the level of the pulmonary artery bifurcation (grade 3) and backflow starting from the peripheral pulmonary artery branches (grade 4). Follow-up (median 5.7 years; range 0-14) was 97% complete.

According to Emunds, reoperation for increasing pressure gradient due to calcification was considered as structural valve degeneration [10]. The decision to replace the valve for structural valve degeneration depended on the homograft function as well as on the patients’ clinical condition, the reduction in exercise tolerance, right ventricular dimensions, the presence of tricuspid insufficiency and the presence of arrhythmias.

2.5. Analysis of data

The occurrence of homograft replacement is presented with Kaplan-Meier survival curves. Homografts explanted for endocarditis were censored. Cox regressions have been used to verify the relation between different covariates and homograft replacement [7]. The reported P-values are obtained with likelihood-ratio tests. The covariates were grouped into three groups: (1) properties of the homograft (size, aortic or pulmonary graft), (2) immunological variables (second homograft in a patient, blood group incompatibility, time before cryopreservation), and (3) patient-related variables (age, square root of age, gender, aortic cross-clamp time, diagnosis, anatomic position). Then, models were fitted to investigate the effect of the covariates on the replacement time of the homograft separately within each of these three groups. Subsequently, the overall model was created using all available covariates in the following steps: firstly, in the multivariate model
without interaction terms, likelihood-ratio tests were used to eliminate non-significant covariates. Secondly, interactions between covariates significant in the first step were added to the model and again eliminated using the likelihood-ratio tests.

Finally, since some patients underwent two operations, it is not correct to assume that all observations are independent (as the basic Cox model assumes). A gamma-frailty Cox model [8] was fitted to account for possible dependencies between observations on one patient. With this model, the hazard rate of the failure of all homografts on a particular patient is given as the product of a patient-specific quantity Z and a basic hazard rate \( \lambda(t) \):

\[
\text{patient-specific hazard rate } = Z \lambda(t).
\]

The basic hazard rate \( \lambda(t) \) further depends on covariates as in the basic Cox model. In the case that the estimated variance of the Z coefficients does not differ significantly from zero (evaluated by the likelihood-ratio test), dependencies resulting from repeated observations on one patient may be ignored and the basic Cox model may be used [8].

All analyses have been performed with the statistical package R 1.9.1 [9].

3. Results

3.1. Patient outcome

The in-hospital mortality rate for all patients who underwent RVOT reconstruction with a homograft was 2.6% (8/301). Actuarial survival was 96 $\pm$ 1.2% at 1, 95 $\pm$ 1.4% at 5, and 94 $\pm$ 1.5% at 10 years follow-up. Late mortality was related to heart failure (n=6) with or without pulmonary hypertension and one case of sudden death (ventricular tachycardia). Three homografts were explanted and replaced because of endocarditis (excluded from the analysis).

3.2. Homograft survival

An increasing calcification of the wall of the homograft, resulting in increasing peak systolic gradients, was the common expression of degeneration of the grafts. Actuarial freedom from significant stenosis was 99 $\pm$ 0.4% at 1, 94.9 $\pm$ 1.4% at 5, 83.4 $\pm$ 3.3% at 10 and 58.6 $\pm$ 7.9% at 12 years follow-up. Significant pulmonary regurgitation was rare and always secondary to more distal stenosis. Actuarial freedom of regurgitation was 92.6 $\pm$ 2.2% at 10 years.

All patients with significant stenosis underwent catheterization to validate the diagnosis and to dilate or stent the area of maximal stenosis.

The decision to replace the valve for structural degeneration depended on the homograft function as well as on the patients’ clinical condition, the reduction in exercise tolerance, right ventricular dimensions, the presence of tricuspid insufficiency and the presence of arrhythmias. The mean gradient over the homografts before replacement was 59 $\pm$ 10 mmHg. Actuarial freedom from explantation for degeneration was 99.6 $\pm$ 0.4% at 1, 94.5 $\pm$ 1.7% at 5, and 81.8 $\pm$ 4.1% at 10 years (Fig. 2).

3.3. Factors influencing homograft survival

The univariate importance of the possible predictors of replacement of the homograft for degeneration was evaluated in separate Cox’s relative risk models. A smaller graft size, an aortic donor graft, a second homograft implantation, younger recipient age, younger donor age, a shorter cross-clamp time, a non-anatomic position, truncus arteriosus and non-Ross procedures were significantly related to homograft replacement in these univariate analyses (Table 1).

The Cox’s models using only covariates from each specific group (homograft features, immunological variables, patient-specific variables) yielded the following results. From predictors giving specific homografts features (size, aortic or pulmonary graft), only ‘size’ suffices to explain the time to homograft replacement. Similarly, from a set of immunological variables (second homograft, blood group incompatibility, ischemic times), only second homograft suffices. Finally, in describing homograft replacement with only patient characteristics, an additive model with square root of age + position + aortic clamp time optimizes the prediction which is not improved by any interaction term.

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft size (bigger vs. smaller by 1 mm)</td>
<td>0.77 (0.71, 0.83)</td>
</tr>
<tr>
<td>Pulmonary vs. aortic donor graft</td>
<td>0.26 (0.13, 0.50)</td>
</tr>
<tr>
<td>Cold ischemia (longer vs. shorter by 1 day)</td>
<td>1.00 (1.00, 1.00)</td>
</tr>
<tr>
<td>Warm ischemia (longer vs. shorter by 1 h)</td>
<td>1.02 (0.95, 1.11)</td>
</tr>
<tr>
<td>Second vs. first homograft</td>
<td>3.15 (1.20, 8.31)</td>
</tr>
<tr>
<td>Compatible vs. non-compatible BG</td>
<td>1.30 (0.66, 2.67)</td>
</tr>
<tr>
<td>Older vs. younger age (by 1 year)</td>
<td>0.84 (0.79, 0.91)</td>
</tr>
<tr>
<td>Gender (female vs. male)</td>
<td>0.89 (0.45, 1.77)</td>
</tr>
<tr>
<td>Clamp time (longer by 10 min vs. shorter)</td>
<td>0.90 (0.81, 1.00)</td>
</tr>
<tr>
<td>Non-anatomic vs. anatomic position</td>
<td>8.88 (4.34, 18.15)</td>
</tr>
<tr>
<td>Truncus vs. non-truncus</td>
<td>10.95 (5.36, 21.55)</td>
</tr>
<tr>
<td>Ross vs. Non-Ross</td>
<td>0.00 (0.00, 0.00)</td>
</tr>
<tr>
<td>Older vs. younger donor age (by 1 year)</td>
<td>0.94 (0.92, 0.97)</td>
</tr>
</tbody>
</table>

In a multiple regression, only age or size, non-anatomic position and clamp time remain significant.
The overall prediction of the time to the replacement of the homograft is optimally carried out by the model with three variables without use of interaction terms: ‘square root of age’, ‘position’ and ‘aortic clamp time’ (Table 2). Further, the correlation between ‘square root of age’ and ‘graft size’ allows the use of the same prediction model with the use of ‘graft size’ instead of ‘square root of age’ (Table 3). The variable ‘position’ expresses the anatomic or non-anatomic position of the graft. This variable depends strongly on the underlying diagnosis. Truncus arteriosus, repairs of double outlet right ventricles and Rastelli operations are typical cases, where the graft is placed in a non-anatomical position. Similarly, the longer aortic cross-clamp time is a reflection of diagnosis. Ross procedures, resulting in the longest cross-clamp time, had a very low incidence of homograft replacement.

A Kaplan–Meier homograft survival curve for the different age groups illustrates the importance of age (Fig. 3). Homograft longevity is excellent for the oldest group (>16 years) of patients with a freedom of replacement of 99.0 ± 1.0% at 10 years.

The variance of the frailty coefficients did not appear to be significantly different from zero ($P=1.00$ for the model of Table 2 and $P=0.17$ for the model of Table 3). Also, the estimates of the regression parameters only negligibly differed from those given in Tables 2 and 3. These findings imply that basic Cox models without the use of the frailty component can be used.

### 3.4. Gamma-frailty Cox models

The models of Tables 2 and 3 were checked for the effect of ignored dependencies arising from the fact that some patients contributed by two homografts replacement to the dataset using the gamma-frailty Cox models. In both models,

<table>
<thead>
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<th>Regression parameter ± SE</th>
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</thead>
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<tr>
<td>Square root of age (higher vs. lower)</td>
<td>$-0.782 ± 0.171$</td>
</tr>
<tr>
<td>Non-anatomic vs. anatomic position</td>
<td>$1.252 ± 0.404$</td>
</tr>
<tr>
<td>Clamp time (longer by 10 min vs. shorter)</td>
<td>$-0.222 ± 0.086$</td>
</tr>
</tbody>
</table>

Optimal model for prediction ‘square root of age’ + ‘position’ + ‘clamp time’. The variable ‘position’ expresses the anatomic or non-anatomic position of the graft. This variable depends strongly on the underlying diagnosis. Truncus arteriosus, repairs of double outlet right ventricles and Rastelli operations are typical cases, where the graft is placed in a non-anatomical position. Similarly, the longer aortic cross-clamp time is a reflection of diagnosis. Ross procedures, resulting in the longest cross-clamp time, had a very low incidence of homograft replacement.

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### 4. Discussion

In homograft explant studies, early loss of cellular elements and tissue architecture has been observed [11–14]. Koolbergen et al. indicated that cryopreserved homografts lose their cellular components within their first year after implantation [11]. They showed no IgG or C3 depositions in the explanted grafts. Valve tissue cellularity consisted mainly of ingrown host cells 1 year after the implantation. It is therefore logical to assume that the superior clinical performance of cryopreserved homografts is mainly a result of the preservation of the collagenous skeleton and components of the extracellular matrix.

**Table 2**

Multivariate Cox regression 1

<table>
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</tbody>
</table>

Alternative optimal model for prediction ‘square root of age’ + ‘position’ + ‘clamp time’.

**Table 3**

Multivariate Cox regression 2

<table>
<thead>
<tr>
<th>Regression parameter ± SE</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft size (bigger vs. smaller by 1 mm)</td>
<td>$-0.212 ± 0.045$</td>
</tr>
<tr>
<td>Non-anatomic vs. anatomic position</td>
<td>$1.346 ± 0.410$</td>
</tr>
<tr>
<td>Clamp time (longer by 10 min vs. shorter)</td>
<td>$-0.181 ± 0.075$</td>
</tr>
</tbody>
</table>

Alternative optimal model for prediction ‘graft size’ + ‘position’ + ‘clamp time’.

Fig. 3. A Kaplan-Meier homograft survival curve for the different age groups illustrates the importance of age. Homograft longevity is excellent for the oldest group (>16 years) of patients with a freedom of replacement of 99.0 ± 1.0% at 10 years.

Fig. 4. A Kaplan-Meier homograft survival curve for the first (full line) and the second (dotted line) homograft in the subgroup of patients ($n=29$) who received two homografts. The second homograft performs as well (or better) than the first. Clearly, patients are older when they receive the second graft.
Pathologic evidence of an immune reaction is lacking. Clinical studies failed to identify a relation between ABO mismatching and homograft failure [1].

However, Dignan and colleagues showed in a series of 162 patients that the immune response influences the life span of the aortic valve homograft [5]. They indicated in a multivariable analysis that age, time between homograft procurement and cryopreservation and HLA-DR mismatching are significantly related to homograft failure. Similarly, in a series of 96 homografts implanted in the RVOT, Baskett et al. identified an aortic homograft and a short preservation time as significantly related to reoperation and young age. ABO mismatch and diagnosis were associated with echocardiographic valve failure [4]. The possible underlying mechanism is a T-cell response initiated by non-self HLA-DR on endothelial and dendritic cells [6]. This mechanism could explain some of these observations. A shorter time between homograft procurement and cryopreservation results in more viable cells and hence, a worse homograft outcome. Aortic donor grafts contain more dendritic cells than pulmonary homografts and are therefore more linked to graft failure if placed in the RVOT. Younger age is associated with more active immune system. Based on the fact that homografts are quickly decellularized, we have to assume that this immune response happens immediately after the implantation and that this reaction determines the late outcome (8-10 years later). Some studies described indeed an early substantial donor-specific allogeneic response in recipients of aortic homografts [15].

Still, it is remarkable that in all series, the impact of this immunological reaction on homograft function and longevity remains small, if at all detectable. This is in contrast to well-known risk factors such as graft size and diagnosis. In addition, similar studies showed no significant effect of HLA matching on homograft longevity [16,17]. The trauma of surgery and blood transfusion can be disturbing agents to detect the graft-related immune responses. The most important observations concern series with exclusively aortic allografts [5,15]. Younger patients might have a more active immune system; they are as well at a higher risk to outgrow their grafts. Our results indicate an overwhelming effect of graft size (and consequently age) and diagnosis. Both factors and their derivatives determine the outcome by themselves. The effects of other factors (aortic donor graft, second homograft) are completely suppressed. Clearly, the patients undergoing a redo operation to get their second homograft were already at a higher risk in terms of diagnosis. The univariate observation that the second homograft degenerates quickly is no argument for an immunological mechanism. In the multiple analysis, the effect of a second homograft disappeared. ABO mismatching and short ischemic time were (even in a univariate analysis) completely irrelevant. So, it seems from our results, as well as from other series, that the clinical relevance of this immunological reaction is limited [1,16,17].

We were unable to determine anti-HLA antibodies or HLA mismatch in this retrospective analysis and cannot exclude its possible role in the degeneration process. Considering the limited availability of homografts, HLA matching of donor and recipient is extremely difficult. HLA antigens are polymorphic, with 16 discrete antigens in the important HLA-DR group.

Several groups propose the use of xenografts or alternative methods to restore the continuity between the right ventricle and the pulmonary artery [18-23]. The clinical results of homografts in the RVOT remain extremely good. The 10-year freedom from graft replacement for patients older than 16 years was 99% in our series. At this moment, we have no xenografts or alternative techniques to compete with these observations. Xenografts have the advantage of availability, and alternative techniques can be considerably beneficial in cost. In terms of clinical results, the homograft remains the gold standard. Based on our findings, we see no reason to avoid a second homograft in a redo operation.

References

Appendix A. Conference discussion

Dr G. Stellin (Padova, Italy): It was not clear from your presentation whether all your homografts have been implanted in the pulmonary position. Was it so?

Dr Meyns: Yes.

Dr Stellin: Second question: it’s not clear whether they were all pulmonary homografts or you have used some aortic homografts in the pulmonary position. Could you please clarify this issue?

Dr Meyns: I mentioned that 15% were donor aortic grafts.

Dr Stellin: Okay. I probably missed that. I’m sorry.

Dr Meyns: But they were all implanted in the pulmonary position, right ventricular outflow tract.

Dr W. Mrowzynski (Poznan, Poland): Don’t you think that ABO group compatibility is rather coarse variable to assess a correlation between immunological and clinical outcomes?

And the second question is, what was the number of explanted homografts? Because I didn’t see it.

Dr Meyns: Well, yes, I really think that an ABO incompatibility is a very crude way of looking at an immunological reaction. And as I showed, it did not turn out to be significant. I think if there is an immunological reaction, we’re going to have to look at the HLA reactions. I agree completely.

Secondly, concerning the percentage that had to be explanted, there was a 10-year freedom of 81%. So 19% at 10 years has to be explanted.

Dr D. Ross (Edmonton, Alberta, Canada): I don’t disagree with much of your talk except the HLA-DR portion. We published last year in the JTCVS our series of homografts, and we found that matching at least one of the DR sites was protective against failure; not a huge effect, but about 25%. And in a very small center with very small numbers, we started matching. We could match probably a quarter to half of our patients at least one DR site.

The point is you can’t change the effective age. You have to operate when you do. You can’t change the diagnosis. But this is something you can change. And the side effect of it is you’ll avoid sensitizing those children, which may be a bigger problem down the road if they do come for a transplant or something. Otherwise, I agree very much with your talk.

Dr Meyns: I know of your work and that’s why I admitted that we did not look, and we could not look, retrospectively at the HLA antibodies. And I think, indeed, what we have noticed here, that on a clinical level age and indications have an overwhelming effect. But if we try to fine-tune the therapy, like you did in your group, the only thing we can do, I think, is to look at the HLA reactant.

The main message I want to bring here, that I don’t really see a need to go to alternative methods like xenografts, or alternative operations, as is often advocated. I think that you have to protect the superior results of the homografts.

Dr M. Helvind (Copenhagen, Denmark): I have two questions for you. The first concerns the indication for changing the homograft. You state various indications. The major one, or the most important one, being stenosis. But your mean gradient was below 60 mmHg. I wonder if you could be precise about when you choose to change the homograft.

The other one concerns the balloon dilatation of the stenotic homograft. In my experience, it’s very difficult to do a successful balloon dilatation in a calcified homograft. Do you have another experience in that regard?

Dr Meyns: Yes, the indication to replace a graft, I agree, it’s always a subjective one and it’s a clinical decision. So the gradients are, of course, the reason why everybody is alerted. And as I said during the talk, the things that we take into account is the exercise tolerance of the patient at that moment, right ventricular dimension, and if there is sign of tricuspid insufficiency, meaning that if there is a gradient, but all the other three factors are fine, we just wait and see. And assuming, of course, that the dimensions of the right ventricle increase, we decide to go on with homograft replacement. But I agree, this is a clinical decision taking into account these different items.

Concerning the ineffectiveness of balloon dilatation, I agree completely with your statement. It seems to bring very little time gain.

Dr B. Williams (Toronto, Ontario, Canada): Could you clarify for me your data about use of a second homograft. I think this is a very important issue for all of us. It is unclear whether one failed homograft should preclude success with a second one.

The data that you showed has an odds ratio for failure of the second homograft that was quite substantially increased. And yet your multivariable analysis failed to confirm that. And yet, by definition, patients having a re-operation must be older and they almost unquestionably have a larger size homograft. So I don’t understand why a second homograft was not a risk factor for early failure in your multivariable analysis.

Dr Meyns: Yes, this is indeed a key point, because this is what we are specifically aiming at: Should we use a second homograft when the first one failed? And as age is so important and these redo operations are older, why does it not come out in the multivariate analysis?

Well, it seems to be in the other factor, which seems to be determined, it’s the diagnosis. These are the patients with the truncus arteriosus and the Rastelli repairs. And by their diagnosis and the non-anatomic position of the homograft, they take the risk of the failure. And so if you consider diagnosis and age, the second operation completely disappears as being a risk factor.

Dr A. Mesklishvilli (Berlin, Germany): Do you think that is possible instead of replace the homograft with another homograft, just to place a transannular patch in these children with mostly hypertrophic right ventricle to avoid, especially in small ones, to avoid repeat operation before older age?

Dr Meyns: You mean not to put the homograft in the first place and then try to gain time in the beginning?

Dr Mesklishvilli: Yes.

Dr Meyns: Yes, I can agree with that strategy, yes.

Dr G. Ziemer (Tuebingen, Germany): I just may end with a minor technical question. You said you do it all in cross-clamping and cardioplegic arrest. But why do you do this in redoes where you have no ventricular septal defect? You could do it on a beating heart.

Dr Meyns: I agree completely. This is an analysis we did in the year 2003. And also, I said that we do it under moderate hypothermia. It can as well be done under normothermia and with ventricular fibrillation.

Dr Ziemer: It may be especially good for bad right ventricles.

Dr Meyns: Right, or a beating heart.