Comparison of aortic root replacement in patients with Marfan syndrome

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Abstract

Objectives: Although the aortic-valve-sparing (AVS) reimplantation technique according to David has shown favorable durability results in midterm and long-term studies, composite valve grafting (CVG) according to Bentall is still considered the standard procedure. Methods: Retrospectively, we evaluated the results of aortic root replacement of patients with Marfan syndrome (MFS) who underwent surgery between January 1995 and January 2010. MFS was diagnosed using the Ghent criteria. AVS was used in 58 patients and CVG in 30 patients with MFS. AVS was done for aortic-root aneurysm (n = 48) or aortic dissection type A (n = 10). CVG was used for aortic-root aneurysm in 14 patients or aortic dissection type A in 16 patients. The mean follow-up was 3.2 (95% CI: 2.4–4.2) years. Results: In both groups, 30-day mortality was 0%. Three patients (10.0%) in the CVG group required resternotomy for postoperative bleeding versus two patients (3.4%) in the AVS group (p = 0.3). At follow-up, mortality was 10% in the CVG group versus 3.4% in the AVS group (p = 0.3). Re-operation was required in two patients (3.4%) after AVS and in three patients after CVG (10%) (p = 0.3). Three patients (10.0%) who underwent CVG had endocarditis and two patients (6.7%) had a stroke during follow-up, whereas no endocarditis or stroke occurred after AVS. After 14 years, stratified event-free survival was better in the AVS group (event-free survival was 82.3% vs 58.6%, log-rank test p = 0.086), especially after aneurysm (p = 0.057). After 10 years, freedom from aortic regurgitation ≥II in the AVS group was 80% for aneurysm and 50% after dissection (p = 0.524). Conclusion: The reimplantation technique according to David was associated with excellent survival, good valve function and a low rate of re-operation, endocarditis, and stroke. There was a trend to better event-free survival for AVS patients making it the procedure of choice in MFS patients.

Keywords: Marfan syndrome; Aortic root replacement; David; Bentall; Aortic valve sparing; Reimplantation technique

1. Introduction

Marfan syndrome (MFS) is a connective tissue disorder with a prevalence of one in 5000 individuals, which is inherited autosomal dominant with complete penetrance and considerable phenotypic variability with different patterns of organ involvement including the cardiovascular, ocular, skeletal, and pulmonary system, skin, and dura [1]. The high mortality of untreated persons with MFS almost exclusively results from cardiovascular complications such as acute aortic dissection or rupture [2,3]. The average age of death in those dying from MFS in the period of a study of Murdoch et al. was 32 years [3]. With optimized multidisciplinary care and prophylactic aortic root replacement, Marfan patients can achieve a close to normal life expectancy [2].

Prophylactic surgical intervention is the single, definitive measure to prevent dissection or rupture of the aortic root. Compared to high mortality and morbidity after acute aortic events, both early and late survival improve significantly with prophylactic intervention. A study with retrospective review of outcomes from 10 centers has set a composite-graft replacement according to Bentall as the standard aortic root replacement in MFS. The study documented an early mortality of 1.5% and an actuarial survival rate of 84% at 5 years, 75% at 10 years, and 59% at 20 years [4]. Because of the young age at the time of surgery, mechanical aortic valves requiring anticoagulation treatment are often used in MFS patients offering excellent longevity but carrying a risk of hemorrhage, thromboembolism, and endocarditis [4].

The remodeling technique according to Yacoub was introduced in 1979 and the reimplantation-procedure, according to David in 1988 [5,6]. These aortic-valve-sparing (AVS) techniques are an alternative to composite grafting to treat aortic root aneurysm. Because native aortic valve cusps...
are preserved, no anticoagulation is required. So far, the valve-preserving procedures have shown favorable durability in mid-term and long-term studies [7,8]. Reimplantation techniques tend to have better results in MFS than remodeling techniques [8–12]. However, the use of valve-preserving techniques is still being debated in patients with MFS. Fleischer et al. found immunohistochemical abnormalities of fibrillin in aortic valves of Marfan patients and concluded that the widespread use of valve-sparing repairs of aortic root aneurysms in patients with MFS should be carefully re-examined in light of these findings [13]. However, the prospect of avoidance of anticoagulants and a lower risk of thrombembolic complications and endocarditis has convinced many surgeons to favor the reimplantation technique. This study examines the results of the classic reimplantation technique according to David, compared to the standard composite valve grafting (CVG) according to Bentall.

2. Patients and methods

Between January 1995 and January 2010, 88 patients with classical MFS underwent aortic root replacement. MFS was diagnosed using established criteria of the Ghent nosology. As many as 58 patients underwent an aortic valve reimplantation procedure according to David and 30 patients received a composite conduit [6,14]. AVS was done electively for aortic root aneurysm (n = 48) or as an emergency procedure for aortic dissection type A (n = 10). CVG was performed for aortic root aneurysm in 14 patients or for aortic dissection type A in 16 patients (Table 1). Mean follow-up was 3.2 (95% CI: 2.4–4.2) years. Patients were seen in our outpatient clinic every 6 months, including physical examination and transthoracic echocardiography. Endpoints of the studies were death, endocarditis, stroke, and re-operation caused by the reimplanted valve. We evaluated aortic regurgitation (AR) of the reimplanted valve using tranesophageal echocardiography intraoperatively. Transthoracic echocardiography was performed before discharge from hospital and in our outpatient clinic every 6 months [15]. We assessed AR as grade 0 with none, as grade 1 with trivial, as grade 2 with mild, as grade 3 with moderate, and as grade 4 with severe regurgitation. All patients had complete follow-up.

Indications for surgery were an aortic root diameter of 45 mm or more, growth of the aortic root ≥5 mm year−1 or an acute type A aortic dissection. We exclusively used the classical reimplantation technique originally described by David and Feindel (David I) [6]. Valve-sparing reimplantation technique was planned according to the surgeon’s choice. However, the final decision of preserving the aortic valve was made by the surgeon intraoperatively depending on root geometry and aortic cusp condition.

3. Statistical analysis

Data were compared between study groups using Fisher’s exact test or Student’s t-test as appropriate. In the case of asymmetric distribution, values were logarithmized and geometric instead of arithmetic mean values were calculated. Kaplan–Meier analysis and log-rank test were used in a stratified analysis for time-related variables. p Values were reported without correction for multiple testing. Level of significance was set to a two tailed p < 0.05. All statistical analysis was performed using the Statistical Package R version 2.12.1 [7].

4. Results

No patient died within the first 30 days postoperatively. Mean bypass times (p = 0.002) and mean aortic cross-clamp (p < 0.001) times were significantly longer in the AVS group compared to the CVG group. Concomitant procedures are listed in Table 2.

Three patients (10%) underwent re-operations after CVG for prosthetic valve endocarditis. In all of these cases, the aortic root was re-replaced by a biological valve carrying prosthesis. No homografts were used. Two patients (6.7%) had a stroke with hemiplegia of ischemic origin shown by computed tomography (CT) scan. Ultrasound of the carotid arteries showed no signs of stenosis and electrocardiograph (ECG) excluded atrial fibrillation in both patients. Three patients (10%) suffered from valve degeneration and underwent re-operation (Table 3).

Two patients (3.4%) underwent re-operation of the aortic valve after AVS. In both patients, intraoperative waterproof of the reimplanted valve and transesophageal echocardiography showed complete competence of the cusps. Transesophageal echocardiography at discharge showed no signs of AR. The first patient, who initially had AVS for aortic root aneurysm, presented 43 months postoperatively with sudden and severe dyspnea. Transesophageal and transesophageal

Table 1. Preoperative characteristics of Marfan patients undergoing aortic root replacement. AVS = aortic valve sparing; CVG = composite valve grafting.

<table>
<thead>
<tr>
<th></th>
<th>AVS (n = 58)</th>
<th>CVG (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>58</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Mean age (y) (range)</td>
<td>37.7 (18–65)</td>
<td>40.8 (18–71)</td>
<td>0.265</td>
</tr>
<tr>
<td>Males</td>
<td>33 (56.9%)</td>
<td>17 (56.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>48 (82.8%)</td>
<td>14 (46.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type A aortic dissection</td>
<td>10 (17.2%)</td>
<td>16 (53.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Operative data and concomitant procedures in Marfan patients undergoing aortic root replacement. Means (95% confidence intervals) and number of concomitant procedures (percentages) are shown. AVS = aortic valve sparing; CVG = composite valve grafting.

<table>
<thead>
<tr>
<th></th>
<th>AVS (n = 58)</th>
<th>CVG (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracorporeal circulation time (min)</td>
<td>163 (155–171)</td>
<td>139 (122–159)</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>125 (119–132)</td>
<td>91 (79–104)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biological valve</td>
<td>8 (26.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant procedures</td>
<td>18 (31.0%)</td>
<td>8 (26.7%)</td>
<td>0.807</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>2 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>ASD closure</td>
<td>4 (6.9%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tricuspid valve repair</td>
<td>1 (1.7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hemi arch replacement</td>
<td>6 (10.3%)</td>
<td>3 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>Total arch replacement</td>
<td>1 (1.7%)</td>
<td>1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td>1 (1.7%)</td>
<td>2 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve repair</td>
<td>5 (8.6%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>3 (5.1%)</td>
<td>3 (10.0%)</td>
<td>0.406</td>
</tr>
</tbody>
</table>

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Table 3. Early and late results and events after aortic root replacement in Marfan patients. Percentages are given in parentheses. AVS = aortic valve sparing; CVG = composite valve grafting.

<table>
<thead>
<tr>
<th></th>
<th>AVS (n = 58)</th>
<th>CVG (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resternotomy for postoperative bleeding</td>
<td>2 (3.4%)</td>
<td>3 (10.0%)</td>
<td>0.333</td>
</tr>
<tr>
<td>Re-operation of the valve</td>
<td>2 (3.4%)</td>
<td>3 (10.0%)</td>
<td>0.333</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0</td>
<td>3 (10.0%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>2 (6.7%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>1 (1.7%)</td>
<td>3 (10.0%)</td>
<td>0.113</td>
</tr>
<tr>
<td>30-Day-mortality</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death (&gt;30 days)</td>
<td>2 (3.4%)</td>
<td>3 (10.0%)</td>
<td>0.333</td>
</tr>
</tbody>
</table>

Echocardiography displayed severe AR due to a tear affecting the noncoronary cusp. Biological valve replacement was performed within the aortic prosthesis. The second patient had to be re-operated 25 months after AVS due to progressive symptomatic AR caused by prolapse of the left coronary cusp. During re-operation, it was not possible to preserve the native aortic valve again and the valve had to be replaced by a biological valve.

Five patients died during follow-up: three in the CVG group and two in the AVS group. After CVG, one patient died after 6 weeks due to cardiac tamponade of unknown reason. Autopsy showed no bleeding source and international normalized ratio (INR) was within normal range. Two patients died after 13 and 72 months post CVG due to progredient heart failure.

After AVS, one patient died after 10 months of left heart failure. Ejection fraction was already decreased preoperatively. Transthoracic echocardiography showed competence of the reimplanted valve during follow-up. Another patient died due to ventricular arrhythmia 52 months after AVS.

Overall survival estimates after 14 years in those operated for aneurysm was 95.7% in the AVS group and 92.9% in the CVG group (p = 0.398). In those operated for aortic dissection type A, overall survival was 88.9% in the AVS group and 86.5% in the CVG group (p = 0.935). Overall survival was stratified for root aneurysm and dissection type A and did not exhibit differences between AVS and CVG (p = 0.572) (Fig. 1). The event-free survival after aortic root replacement for aneurysm after 14 years was 91.5% in the AVS group versus 77.9% in the CVG group (p = 0.057). After aortic dissection, type A event-free survival was 44.4% in the AVS group and 48.1% in the CVG group (p = 0.427) (Fig. 2). Event-free survival was also stratified for root aneurysm and dissection...
5. Aneurysm durability

were from sparing type I and did not exhibit significant differences between AVS and CVG (p = 0.086).

Doppler echocardiography was performed before discharge and during follow-up examination. All AVS patients were discharged with an AR I or less. 87.9% had an AR < II at last visit (Fig. 3). Kaplan–Meier analysis revealed freedom from AR ≥ II in the AVS group after 10 years of 80% for aneurysm and 50% after dissection (p = 0.524) (Fig. 4).

5. Discussion

Although valve-sparing techniques have shown favorable durability in midterm and long-term studies, its use is still being debated in patients with MFS. We provide a retrospective analysis with a follow-up of up to 15 years in 88 MFS patients with aortic root replacement. The results of this retrospective analysis showed that reimplantation technique was associated with excellent survival and a low rate of reoperations. No patient developed endocarditis or stroke in the follow-up after AVS. There was a trend for less adverse events during follow-up, especially in the subgroup of elective root replacement for aneurysm. The only statistically significant difference in late events was in endocarditis, and not in thrombembolism, death, or re-operation. Despite longer extracorporal-circulation and aortic cross-clamp times, re-erotomy for bleeding was comparable in both groups.

Thus, our data suggest that especially for elective aneurysmal aortic root replacement, the AVS is the technique of choice.

Transcatheter echocardiography revealed good results, even after up to 15 years as expressed by a freedom from AR < II rate of 87.9% (51 patients) at last visit. Of the remaining seven patients, four presented with an AR of II. Of the three patients, who presented with AR III or IV at latest follow-up after AVS, two patients had to be re-operated with AR IV. The one patient with AR III will probably need reoperation in the future. Further long-term follow-up is needed to determine if the AR in the patients with AR II stabilizes on a moderate level or if re-operation is necessary in case of high degree AR. Kaplan–Meier analysis revealed freedom from AR ≥ II in the AVS group after 10 years of 80% for aneurysm and 50% after dissection (p = 0.524).

No in-hospital death was observed in the complete cohort of MFS patients who underwent aortic root replacement. This has been previously described by other groups [8, 16, 17]. The long-term outcome is also comparable. Karck et al. reported in their series of aortic root replacement a 10-year survival of 76% after composite grafting [18], Gott et al. a 15-year survival rate of 76% [4]. Kallenbach et al. stated a 10-year survival rate after aortic valve-sparing reimplantation surgery of 83% [8] and de Oliveira et al. a 10-year survival of 96% in their valve-sparing group and of 87% in their valve-replacing group; the freedom from major AR (>II+ II+) was 75% after 10 years (p = 0.3) [9].

We used the classical reimplantation technique originally described by David and Feindel (David I) exclusively [6]. Susumu et al. demonstrated that the lack of sinuses of Valsalva may lead to increased stress on the aortic cusps during diastole and might predispose to degeneration and late annular dilatation [19–21]. Modifications of the original reimplantation technique aim to imitate the natural sinus of Valsalva [22]. Further follow-up and studies are needed to prove evidence that the creation of neosinuses really improves long-term outcome.

To date, mechanical composite grafting is still the standard for aortic root replacement. During the past few years, biological valve prostheses have become more popular for aortic valve replacement. The fact that there is no need for anticoagulants particularly in woman who want to become pregnant, and the lower incidence of thrombembolic complications, makes the use of biological valve conduits more favorable; but there still remains the risk of degeneration and a potential high-risk re-operation despite good early results even in younger patients. Therefore, valve-sparing operation techniques should be preferred in all patients with aortic root aneurysms, if technically possible, independent of the underlying diagnosis.
There were some limitations in the study. There was a clear trend for better event-free survival after AVS ($p = 0.086$), especially in the subgroup of aneurysm ($p = 0.057$), but our results reached no significance. Although the number of MFS patients operated in our institution is comparably high for a single center, power of this study might be too low to find a significant result.

Majority of AVS procedures were done for aortic aneurysm, whereas composite grafting was performed predominantly in cases with acute aortic dissection. Several reasons might account for these circumstances. Aortic dissection requires emergency intervention. We tend to perform procedures with less extracorporeal circulation-time especially in cases where the aortic arch also requires inspection and replacement. Moreover, stress fenestrations of the aortic cusps or dilated leaflets also occurred with increased aortic root diameters especially in cases with acute aortic dissections; in these cases we prefer to replace the aortic valve. But as our data suggest, results for aortic dissections are comparable for both techniques and therefore justify usage of this procedure. In general, we try to preserve the native aortic valve whenever possible. During the last 2 years, we were able to preserve the aortic valve in all patients who presented with aortic dissection. Our data suggest that especially for the elective aortic root replacement for aneurysm, the AVS is the technique of choice. Long-term durability is excellent after AVS for aortic dissection.

These excellent long-term results after AVS do not support the theory that patients with MFS have a higher risk for postoperative AR due to structural disease of the cusps tissue.

6. Conclusion

The aortic valve reimplantation technique was associated with excellent survival and a low rate of re-operations, endocarditis, and stroke. Despite longer extracorporeal circulation times and cross-clamp times, early results were excellent. Transthoracic echocardiography revealed good results up to 15 years after surgery. There was a trend for better event-free survival as compared to those achieved after conduit replacement. We think that aortic valve reimplantation technique should be favored in patients with MFS whenever technically feasible.

References


Appendix A. Conference discussion

Dr E. Roost (Bern, Switzerland): I have two short questions and one comment.

You had 2 patients with valve degeneration and reoperation after Bentall procedures. When in your follow-up were the valves degenerated? That’s the first question.

Secondly, you have 2 strokes in the Bentall group, and I was wondering whether these patients were on the warfarin or not?

My comment would be that you already mentioned that the two groups aren’t really comparable considering that in the Bentall group almost half of the patients had aortic dissection type A and the other group a little bit less than 20%. So I think these two groups are really different.

And with your statement that event-free survival is better if you compare these two groups, I think that, first of all, your rate of endocarditis is extremely high at 10%, most probably because you have really small groups. But we know from the literature that the cumulative risk or incidence of endocarditis after prosthetic valve implantation is maybe between 2% to 3%, so this 10% is too...
Dr Bernhardt: Concerning your first point, we had 3 degenerated biological valves, occurring between 12 and 14 years of follow-up.

The 2 patients who had a stroke were on warfarin, but they had an ischemic, probably thromboembolic event, so we had no hemorrhagic stroke on CT scan.

Your comment was that both groups were different. As I said, they are significantly different for aneurysm and aortic dissection, that’s right. That’s probably one of the weaknesses in such a retrospective analysis. However, the early mortality was comparable. Maybe we can say we treat two totally different diseases. But the events we had were not related to, let’s say, a remaining dissection in the distal aorta. The deaths and the events were related to the aortic valves. So this is why we can say that the event-free survival is significantly better.

The point is sometimes, as I mentioned in the presentation, it’s a challenge to preserve the aortic valve. When we have cusp enlargement, when we have stress fenestration, sometimes it’s not possible to preserve the native valve. So as long as we can preserve it, I would say from these data, from the retrospective point of view, it’s the technique of choice. As long as we don’t have the long-term data from the prospective study which started 3 years ago in the U.S., with some centers around Europe, we have to rely on all this retrospective data and they are comparable to those published by other groups.

Dr C. Etz (Leipzig, Germany): Quick question regarding the same issue. I find it a very strong statement, when you say that the event-free survival is significantly better with Marfan repair as opposed to the Bentalls.

From studies on young Bentall populations, we know that there is a significant difference in long-term event-free survival between patients who received mechanical as opposed to patients receiving a biological Bentall. I haven’t seen any information on that in the 30 patients you were reporting on. Can you give us a brief idea whether you found differences and how many had mechanical and biological valves?

Dr Bernhardt: Thirty percent had a biological valve. And of them, three had degeneration between 12 and 14 years after replacement.

Dr Etz: And the strokes were in the mechanicals?

Dr Bernhardt: These were mechanicals, that’s right.