European Journal of Cardio-Thoracic Surgery 48 (2015) 931–936
doi:10.1093/ejcts/ezu553 Advance Access publication 9 February 2015

ORIGINAL ARTICLE

Cite this article as: Schoenhoff FS, Langhammer B, Wustmann K, Reineke D, Kadner A, Carrel T. Decision-making in aortic root surgery in Marfan syndrome: bleeding, thromboembolism and risk of reintervention after valve-sparing or mechanical aortic root replacement. Eur J Cardiothorac Surg 2015;48:931–6.

Decision-making in aortic root surgery in Marfan syndrome: bleeding, thromboembolism and risk of reintervention after valve-sparing or mechanical aortic root replacement†

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Received 26 September 2014; received in revised form 2 December 2014; accepted 10 December 2014

Abstract

OBJECTIVES: Valve-sparing root replacement (VSRR) is thought to reduce the rate of thromboembolic and bleeding events compared with aortic root replacement using a mechanical aortic root replacement (MRR) with a composite graft by avoiding oral anticoagulation. But as VSRR carries a certain risk for subsequent reinterventions, decision-making in the individual patient can be challenging.

METHODS: Of 100 Marfan syndrome (MFS) patients who underwent 169 aortic surgeries and were followed at our institution since 1995, 59 consecutive patients without a history of dissection or prior aortic surgery underwent elective VSRR or MRR and were retrospectively analysed.

RESULTS: VSRR was performed in 29 (David $n = 24$, Yacoub $n = 5$) and MRR in 30 patients. The mean age was 33 ± 15 years. The mean follow-up after VSRR was 6.5 ± 4 years (180 patient-years) compared with 8.8 ± 9 years (274 patient-years) after MRR. Reoperation rates after root remodelling (Yacoub) were significantly higher than after the reimplantation (David) procedure (60 vs 4.2%, $P = 0.01$). The need for reinterventions after the reimplantation procedure (0.8% per patient-year) was not significantly higher than after MRR ($P = 0.44$) but follow-up after VSRR was significantly shorter ($P = 0.03$). There was neither significant morbidity nor mortality associated with root reoperations. There were no neurological events after VSRR compared with four stroke/intracranial bleeding events in the MRR group (log-rank, $P = 0.11$), translating into an event rate of 1.46% per patient-year following MRR.

CONCLUSION: The calculated annual failure rate after VSRR using the reimplantation technique was lower than the annual risk for thromboembolic or bleeding events. Since the perioperative risk of reinterventions following VSRR is low, patients might benefit from VSRR even if redo surgery may become necessary during follow-up.

Keywords: Aortic surgery • Marfan syndrome • Valve-sparing surgery • Aortic root surgery • Connective tissue disease

INTRODUCTION

Aneurysm of the aortic root is the hallmark feature of Marfan syndrome (MFS), an autosomal dominant connective tissue disorder imposed by mutations in the gene encoding for the extracellular matrix protein fibrillin-1 [1, 2]. Although patients with MFS exhibit skeletal, ocular and cardiovascular manifestation, aortic aneurysm determines mortality in this patient population [3]. In 1968, Hugh Bentall introduced a technique to replace the aortic root using a mechanical prosthesis sewn into a Dacron graft. Low morbidity and mortality rates in MFS patients undergoing elective root surgery using a modified Bentall procedure have fostered the concept of prophylactic aortic root surgery to prevent acute aortic dissection and its sequelae [4]. When valve-sparing root surgery (VSRR) was introduced into clinical practice, it was an intriguing concept for the young Marfan patient population requiring elective surgery.

But it was soon realized that MFS patients present with an inherent weakness of the aortic valve cusps itself that is usually not seen in other patient populations presenting with aortic root aneurysm. Patients frequently present with fenestrations, small tears at the commissures and elongated free margins. Although one can argue that this is just the result of stress due to the dilated aortic

† Presented at the 28th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Milan, Italy, 11–15 October 2014.
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root and enlargement of the annulus which will cease after the root has been reconstructed, the issue of longevity of VSRR in MFS persists. This is an important issue in adult patients where a sufficiently large prosthesis can be easily implanted and is expected to last a lifetime. Therefore, we and others, while embracing VSRR in other patient populations, have been a bit more cautious in performing this procedure in patients with MFS.

Owing to the almost normal life expectancy of MFS patients in the current era, the risk for thromboembolic and bleeding events due to life-long oral anticoagulation following mechanical aortic root replacement (MRR) is becoming more and more of an issue and VSRR seems an attractive option to reduce these risks. But as VSRR carries a certain risk for subsequent reinterventions, decision-making in the individual patient can be challenging.

AIM

Aim of this study was to investigate the risk of bleeding, thromboembolism and reintervention after VSRR or MRR in MFS patients.

PATIENTS AND METHODS

Data from 100 MFS consecutive patients (mean age at initial surgery 35.6 ± 14 years, range 9–69 years, 59% male patients) fulfilling Ghent criteria who underwent 169 major aortic operations and were followed at this institution since 1995 was retrospectively analysed. Patients who underwent genetic testing and were FBN1 negative retrospectively underwent TGFBR1 and R1 testing and those who tested positive were excluded.

For the current study, 59 patients without a history of dissection or prior aortic surgery who underwent elective VSRR or MRR could be identified.

Patients are followed up in our MFS clinics 3, 6 and 12 months after surgery and then, depending on the findings, at least once per year. Patients were evaluated using echocardiography and ECG-gated, CT angiography to plan surgery, as a follow-up in patients with dissections and in patients undergoing surgery on an emergency basis. In benign cases or after uneventful elective surgery, MR imaging was performed to reduce cumulative radiation exposure.

Furthermore, a phone interview was conducted according to a standardized questionnaire that was sent to the patients in advance. Individual informed consent was obtained and patients were asked if we were allowed to contact their primary care provider regarding recent developments, changes in medication or CT scans that have been performed outside our institution. Hereby, a 97% completeness of follow-up was achieved. This study was approved by the institutional review board and individual informed consent from the patient or, in case of minors, the parent or the legal guardian was obtained.

Statistical analysis

Values are given in mean ± SD, when appropriate. In addition to descriptive statistics, data underwent a Kaplan–Meier survival analysis, with either aortic reintervention, cerebrovascular event or death as an event, followed by a log-rank test to compare the event risk for patients with aortic root replacement by either MRR or VSRR. Analysis was performed with Stata version 12 software (StataCorp, College Station, TX, USA).

Indication for surgery

As previously prescribed, since 1995 we have gradually lowered our threshold to recommend elective aortic root surgery from initially 50–55 mm until the early 2000s, to 50 mm and now to 45–50 mm in patients suitable for VSRR or progressive dilatation of more than 5 mm per year [5]. If the aorta at the level of the inominate artery was 35 mm or larger, repair was extended into the arch by performing a hemi-arch or total arch replacement [6]. If aortic regurgitation was present and the aortic root size was less than 45 mm, indication for surgery depended on the extent of regurgitation and hence left ventricular dimensions. Prophylactic root replacement was suggested in women wishing to conceive if the aortic root size exceeded 40 mm [7].

Techniques for aortic root replacement

Aortic root replacement in the MRR group was performed as a modified Bentall procedure with reimplantation of coronary buttons using a commercially available mechanical composite graft. In the majority of patients, an SJM mechanical valve (St Jude, St Paul, MN, USA) in a Gelweave Valsalva vascular prosthesis (Vascutek, Renfrewshire, UK) was used.

Valve-sparing root replacement (VSRR) was performed in suitable candidates using the Yacoub remodelling technique in the early experience followed by exclusive use of the David reimplantation technique since the late 1990s. We have essentially been using the David I procedure consistently over the years with exception of the introduction of the Valsalva graft in the early 2000s. Reasons not to perform VSRR in patients with MFS were severely enlarged annuli (>30 mm), bicuspid or pseudo-bicuspid valves and multiple or large fenestrations of the leaflets or partial detachment of the commissures.

Postoperative anticoagulation

After uneventful MRR, patients were started on phenprocoumon on the 1st postoperative day while a prophylactic dose of unfractionated heparin (10 000 IU/d) was maintained until target INR was reached. If patients were not within target range on the 5th postoperative day, heparin was given in a therapeutic dose. Patients after VSRR were started on low-dose acetylsalicylic acid on the 1st postoperative day. Recently, low-dose acetylsalicylic acid for 3 months was added to the regimen in patients with MRR.

RESULTS

Primary aortic root interventions

In 59 patients without a history of dissection or prior aortic surgery who underwent elective root replacement, VSRR was performed in 29 and MRR in 30 patients. In VSSR, the remodelling technique was used in 5 patients and the reimplantation technique in 24. In VSRR, no cusp repairs were performed. Concomitant mitral valve repair was performed in 2 patients. The mean age in the MRR

group was 36 ± 12 years compared with 27 ± 12 years ($P = 0.004$) in the VSRR group. The mean aortic root size was 48 ± 5.4 mm (40–65 mm) in the VSRR group compared with 54 ± 12 mm (37–90 mm) in the MRR group ($P = 0.014$).

Aortic valve regurgitation (none/mild/moderate/severe) was present in 45/41/14/0% of patients in the VSRR and in 27/27/40/6% of the MRR group ($P = 0.02$).

Reinterventions on the aortic root

The mean follow-up after VSRR was 6.5 ± 4 years (180 patient-years) compared with 8.8 ± 9 years (274 patient-years) after MRR. Aortic root reoperation rates after the remodelling (Yacoub) procedure were significantly higher than after the reimplantation (David) procedure [3/5 (60%) vs 1/24 (4.2%), $P < 0.0001$]. Freedom from reintervention on the aortic root in VSRR using the remodelling technique at 5, 10 and 15 years was 40% compared with 94% at 5 years when using the reimplantation approach (Fig. 1).

The mean time to reoperation was 1.6 years in the reimplantation compared with 3.8 years in the remodelling group. All reinterventions were performed due to progressive aortic valve insufficiency. MRR was performed in 3 patients. In 1 young patient, first aortic valve replacement was performed, followed by MRR 7 years later. There were no reinterventions on the aortic root in patients after MRR. No patient presented with endocarditis or valve thrombosis throughout follow-up.

The need for reintervention after the reimplantation procedure (0.8% per patient-year) was not significantly higher than after MRR ($P = 0.44$) but follow-up after VSRR was significantly shorter ($P = 0.03$). There was neither significant morbidity nor mortality associated with root reoperations.

Non-root reinterventions

The only non-root reoperation in the VSRR group was mitral valve replacement in 1 patient, whereas in the MRR group there was 1 mitral valve replacement, 1 total arch replacement and 1 infrarenal aortic aneurysm repair. In the VSRR group 2/29 suffered from type B dissection but none required thoraco-abdominal surgery, whereas in the MRR group 8/30 experienced type B dissection ($P = 0.04$) and 5 required thoraco-abdominal aortic replacement.

Bleeding and thromboembolism

There were no neurological nor other bleeding or thromboembolic events after VSRR compared with four stroke/intracranial bleeding events in the MRR group (log-rank, $P = 0.11$), translating into an event rate of 1.46% per patient-year following MRR. The rate of freedom from cerebrovascular events in the MRR group at 5, 10 and 15 years was 92%, 92 and 83% compared with 100% in the VSRR group, respectively (Fig. 2). The following cerebrovascular events were observed: (a) stroke with hemiparesis 12 years after elective MRR and 8 years after diagnosis of type B dissection. The patient subsequently recovered except for a residual hypoaesthesia of the leg and underwent thoraco-abdominal surgery for progressive dilatation 2 years after the stroke; (b) chronic subdural haematoma with acute bleeding 1 year after MRR. The patient developed acute type B dissection 9 years later and subsequently underwent thoraco-abdominal surgery for progressive dilatation; (c) stroke with hemiparesis and aphasia after arch replacement, which was performed 16 years after MRR and (d) massive intracerebral bleeding 5 days after acute type B dissection and 5 months after uneventful MRR.

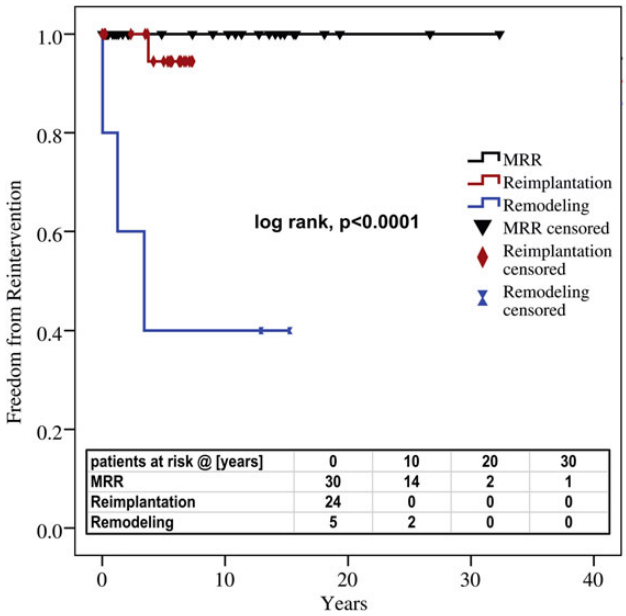

Figure 1: The Kaplan–Meier curve depicting significant differences in freedom from reintervention on the aortic root in patients undergoing VSRR using the remodelling technique compared with the reimplantation technique and MRR. VSRR: valve-sparing root replacement; MRR: mechanical aortic root replacement.

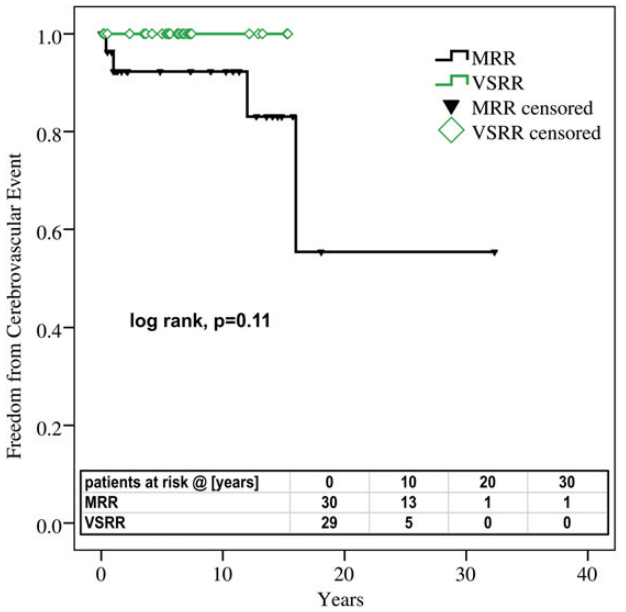

Figure 2: The Kaplan–Meier curve depicting freedom from cerebrovascular events in patients who underwent either VSRR or MRR. VSRR: valve-sparing root replacement; MRR: mechanical aortic root replacement.

There was 1 patient with pulmonary embolism 1 year after MRR. The patient developed acute type B dissection 6 years later and subsequently underwent thoraco-abdominal surgery for progressive dilatation.

Re-exploration due to bleeding was necessary in 1 patient in each group. Following MRR, 2 patients developed pericardial

effusion. One patient in the VSRR group developed a retrosternal haematoma and underwent CT-guided drainage. There was no patient with non-cerebral major haemorrhage or gastrointestinal bleeding. There was only 1 patient with a minor bleeding event several days after tooth extraction.

In the VSSR group, 5 (17%) of the patients were discharged with coumadin due to postoperative atrial fibrillation (recurrent or longer than 48 h). None of these patients experienced a thromboembolic or bleeding event while being on coumadin.

Mortality

There were no significant differences in survival between patients who underwent MRR or VSRR (log rank, $P = 0.41$). Overall 30-day, 6-month, 1-year and late mortality rates were 1.7, 3.4, 3.4 and 8.5%, respectively (Fig. 3). Operative mortality in patients requiring aortic root reintervention after failed VSRR was zero.

There were four deaths in the MRR group compared with one death in the remodelling and none in the reimplantation group. Causes of death were (a) massive intracerebral bleeding 5 days after acute type B dissection and 5 months after uneventful MRR, (b) malignant arrhythmia during the postoperative course in a young man with a severe form of MFS and concomitant dilative cardiomyopathy who underwent aortic root replacement, concomitant mitral valve replacement and tricuspid valve repair, (c) multiorgan failure after non-cardiac surgery 21 years after MRR and 32 years after mitral valve replacement, (d) aortic rupture after type B dissection 2 years after uneventful MRR and (e) congestive heart failure complicated by sepsis 13 years after VSRR.

DISCUSSION

Elective root replacement using a tube graft with a mechanical valve is a safe operation and has contributed to the increased survival of MFS patients over the past decades [4, 8, 9]. Perioperative

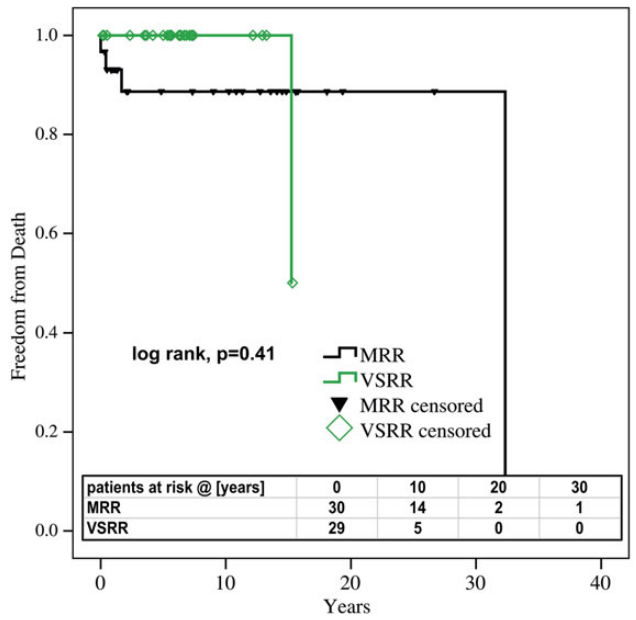

Figure 3: The Kaplan–Meier curve showing no significant differences regarding survival in patients who underwent either elective MRR or VSRR. VSRR: valve-sparing root replacement; MRR: mechanical aortic root replacement.

complications are rare and operative mortality has become an exceptional event. Furthermore, it is a very durable solution; in our cohort, there was no reoperation on the aortic root. Prosthetic valve endocarditis is often mentioned but, in our series, there was no case of endocarditis within the past 20 years.

Several studies with larger patient populations report a low incidence of thromboembolic complications during follow-up. Radu *et al.* report on 100 patients after MRR with a mean age of 65 years and an event rate of 3.6 per 100 patient-years [10]. In a large cohort of patients with 242 mechanical and 64 biological root replacement from the Yale group, freedom from bleeding, stroke and distal embolism was 91% at 10 years [11]. Although these patients were generally older and had more comorbidities than most MFS patients, in a study by Karck *et al.* comparing 74 MRR and 45 VSRR in MFS patients, 24% of survivors in the MRR group experienced bleeding or thromboembolic events during follow-up [12].

In the largest series of MFS patients to date, Cameron *et al.* report that among 372 patients, thromboembolism was the most common late complication after aortic root replacement but only occurred in patients with MRR. The actuarial rate of freedom from thromboembolism was 96.3, 93.3, 91.0 and 89.8% at 5, 10, 15 and 20 years, respectively [8].

Although most studies suffer from uneven follow-up, VSRR has already demonstrated superiority in terms of thromboembolic events and bleeding. The Hopkins group compared outcomes in 140 MFS patients undergoing either MRR ($n = 56$) or VSRR ($n = 84$). Thromboembolic events were significantly more frequent in the MRR group (9 vs 1%, $P = 0.03$) but the rate of dissection, which certainly influences the thromboembolic rate, was much higher in the MRR group (16 vs 1%, $P = 0.001$) [9]. Nevertheless, other groups report similarly positive results [13, 14].

Unfortunately, most thromboembolic events are associated with neurological impairment which significantly reduces the quality of life and puts the patients' ability to lead an autonomous life at risk. Furthermore, perioperative stroke is, besides congestive heart and multiorgan failure, also a major determinant in morbidity and mortality in redo aortic surgery. Therefore, in our opinion, the thromboembolic event rate after MRR has to be compared with the rate of reintervention after VSRR and the risk associated with the reintervention itself to allow a balanced decision. To achieve comparable results, we excluded patients with prior aortic interventions or patients who initially presented with acute dissection since these factors are known to increase the thromboembolic event rate.

The reintervention rate after VSRR may certainly be influenced by the aggressiveness with which this approach is pursued by each centre. In our practice, VSRR was adopted very early for children but we remained hesitant in the adult population due to the inherent weakness of the aortic cusp tissue in MFS. Furthermore, many MFS patients presented at a time when the annulus was already significantly enlarged, the cusp stretched and a durable repair seemed unlikely. In our series, patients with VSRR had significantly smaller root diameters and less aortic regurgitation compared with those who underwent MRR. The fact that there is considerable overlap indicates the importance of other parameters. Although some surgeons expressed their views that MFS itself is not a risk factor of VSRR failure anymore [13], a large international registry from the Aortic Valve Operative Outcomes in Marfan Patients Study Group found that the outcome of VSRR in MFS is mostly likely different from that in non-MFS patients [15]. After including 316 MFS patients from experienced centres, 7% of

VSRR patients had developed grade 2 AR after the first year, which is a worse outcome compared with non-MFS patient populations.

Although, over the past decade, VSRR has certainly become the method of choice in young MFS patients in our centre, we still do not take the possibility of failure lightly and maintain a rather conservative approach. Despite the increasing awareness for connective tissue disease, many patients are only diagnosed at a point when the aortic root size already far exceeds the recommended threshold for intervention, thereby limiting the possibility of sparing the valve.

In the current analysis, the annual failure rate of VSRR is actually lower than the risk for a thromboembolic event or stroke. Obviously, this analysis is severely limited by the low occurrence rate of both events, but is similar to results from a large meta-analysis that analysed 11 observational studies reporting valve-related morbidity and mortality after MRR or VSRR in patients with MFS and a study size of $n>30$ to reflect the centre's experience [16]. In this analysis, including 1385 MFS patients, the thromboembolic event rate was 0.7% per year after MRR compared with 0.3% per year after VSRR. Reintervention rates were significantly higher in the VSRR group compared with the MRR group (0.3/year vs 1.3%/year). But when looking only at the subgroup of patients who underwent VSRR using the reimplantation technique, the annual failure rate equals the thromboembolic event rate of 0.7% per year after MRR. Outcomes after VSRR depend on patient characteristics, surgical skill and aggressiveness with which the approach is pursued. Therefore, to be able to make an informed decision, the surgeon and the patient have to consider the expected failure rate after VSRR and compare it with the rate of thromboembolic events after MRR, which may also vary according to patients' characteristics in each centre.

CONCLUSION

In the current study, the calculated annual failure rate after VSRR using the reimplantation technique was lower than the annual risk for thromboembolic or bleeding events. As the perioperative risk of reinterventions following VSRR is low, the patient might benefit from VSRR even if redo surgery may become necessary during follow-up.

ACKNOWLEDGEMENTS

We thank Brigitta Gahl, University Hospital Berne, for statistical assistance.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

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Dr D. Cameron *(Baltimore, MA, USA):* Dr Schoenhoff, thank you very much for this beautiful presentation which sheds more light on the debate between Bentall and valve-sparing procedures for Marfan aortic root aneurysms.

The study shows that both of these surgical approaches have very low operative risk and that survival out to ten years is virtually identical. You've also shown, as others have, that the remodelling operation is not a good operation for Marfan syndrome because it does not stabilize the annulus and predisposes to late aortic regurgitation.

You've also shown that the Achilles heel of the Bentall is the continuing but low risk of thromboembolic complications, and the Achilles heel of the valve-sparing is the risk for reoperation for aortic regurgitation. But, importantly, you've quantified those risks which are actually very low, about 1% per year, slightly higher for the risk of thromboembolism in Bentall, slightly less for the risk with valve-sparing. But they're both low at the end of ten years, patients essentially have a low risk of either complication and so are being asked to 'pick their poison', whether they would rather have a reoperation or a stroke. Most would rather have a reoperation.

There are some limits of the study. Of course, your follow-up is less than ten years, so it's not really a long-term follow-up. And most of your Bentalls were in the early part of the series, so there is historical bias.

We at Johns Hopkins have done a similar analysis of our experience and have found nearly identical results, which I find very encouraging. I want to point out some remarkable aspects of the clinical care that you provided. You had no episodes of prosthetic valve endocarditis in the Bentalls over the last 20 years. That shows again that the standard has been set very high by the Bentall procedure. You have also had no operative mortality in any patients, even the root

reoperations. You have set the bar very high for root surgery in Marfan syndrome.

I have three questions. The most provocative finding of this study was a significantly higher risk of distal aortic dissection in the mechanical valve Bentall patients compared to valve-sparing, which suggests that the mechanical valve may impart more stress on the descending aorta. Could you to comment on that?

I also want to ask you to comment on why you think your risk of prosthetic endocarditis is so low. It may speak to the close follow-up you provide your patients.

Finally, who does not get a valve-sparing at your centre now? Are issues like ventricular function and concurrent mitral disease figured in? How do you decide for whom the valve-sparing is not really the right operation?

Dr Schoenhoff: Indeed, there is a higher risk for type B dissection in patients after mechanical root replacement. At the 2013 meeting of the American Heart Association, we presented data that tried to answer the question of whether a patient with a proximal repair has a higher risk for subsequent type B dissection, which was not the case. But at that time, we didn't differentiate between valve-sparing and mechanical root replacement.

When we reanalyzed the data for this manuscript, we became aware that there is a significant difference. I think the easy answer would be to say that MFS patients undergoing an elective Bentall procedure have a more severe phenotype, and this is why they're more likely to suffer from type B dissection. But I'm not sure if that is actually the case. Maybe after all, as you suggested, it's the fact that we implant a mechanical valve which has a different flow pattern, which results in more shear stress for the downstream aorta. But I will certainly look into that in the near future.

And regarding the thromboembolic event rate?

Dr Cameron: Yes. The thromboembolic rate was actually a little higher than in other series. But your prosthetic valve endocarditis rate was much less. Could you comment on that?

Dr Schoenhoff: Regarding the thromboembolic event rate, I think that due to the small numbers, one event more or less changes percentages quite substantially. If you look at other series, such as the Hannover series with 75 mechanical root replacements and 45 valve-sparing, among the survivors, 24% of patients had some form of thromboembolic events. And in your own series of 140 Marfan patients, you had an overall thromboembolic event rate of 9%. In the largest study to date, a meta-analysis published in Heart 2011 with 1400 patients, the event rate was roughly 1% per year, so I think we are not that far apart.

Regarding endocarditis, I have no idea why that is the case. I also noticed that in your series, you have several patients that came in with a thrombosed valve. This is also something we haven't seen. I think maybe we care for a slightly different patient population in Switzerland. It's a small country. Most patients have their primary care provider whom they regularly see and check their anticoagulation. If there is anything that is slightly abnormal, they are referred to their cardiologist or we see them in our outpatient clinic. So there might be a little bit closer follow-up. Other than that, I have no idea why that is because of the endocarditis.

And regarding your last question?

Dr Cameron: Who doesn't get a valve-sparing?

Dr Schoenhoff: I think that Dr Carrel, that our department still has a fairly conservative approach towards valve-sparing in the Marfan patients. I think this is justified.

As you can see, just recently, the Aortic Valve Operative Outcomes in Marfan Patients study was published, and it showed that 7% of patients had grade II aortic regurgitation after one year. These were all expert centres, and I think this is much more than you would expect in a non-Marfan population. So I think it's justified to be a little bit more restrictive.

I think that we would not necessarily be inclined to perform a valve-sparing in a patient who already has a very severely enlarged annulus or in a patient who has large, thin, stretched cusps with multiple fenestrations and/or partial detachment of the commissures. Moreover, I think we would be careful in a patient with a very asymmetrical sinus.

With regard to bicuspid valves, if it's a very symmetrical valve, we might try, but if it's asymmetric and has some calcification, I think we would rather go for the Bentall procedure.

Dr T. Sioris *(Tampere, Finland):* Did some of them receive cusp reinforcement or cusp plication, free-edge reinforcement with Gore-Tex or suture or cusp plication?

Dr Schoenhoff: So whenever the need arises to perform extensive cusp repair or to correct for any major asymmetries, I think we would choose rather to do a Bentall procedure. And in this series, as far as I know, there was no reinforcement of the free margin in any patient.