Late complications and distal growth rates of Marfan aortas after proximal aortic repair†

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Abstract

OBJECTIVES: Conflicting results have been reported on late aortic growth and complication rates of the descending thoracic aorta in patients with Marfan syndrome (MFS) after proximal aortic surgery.

METHODS: Of 198 Marfan patients followed up regularly, 121 (43% David-I, 7% David-II, 11% supracoronary replacement, 52% mechanical conduit, 8% arch replacement) were analysed after proximal aortic surgery retrospectively. 97% had MFS1, 3% MFS2 (Loeys-Dietz-Syndrome); 56% were male and the mean age was 35 ± 13 years. 65% were initially operated on for root/ascending aortic aneurysms and 35% for aortic dissections. Using automated computed tomography angiography and magnetic resonance angiography cross-sectional analyses, the mean diameters of the distal arch, mid-descending and distal supradiaphragmatic descending thoracic aorta were measured at early and late follow-up (mean 6.3 years for aneurysms and 4.7 years for dissections). The mean duration of clinical follow-up was 7.6 years and the cumulative clinical follow-up comprised 894 patient-years.

RESULTS: At 20 years, overall freedom from distal aortic complications and/or reintervention was 76% (51–86%) for aneurysms and 52% (28–71%) for dissections (P = 0.03). In non-dissected aortas, distal aortic growth was significant, but minimal: arches grew from 25.2 ± 0.6 to 26.3 ± 0.8 mm (P = 0.01), mid-descending aortas from 22.2 ± 0.5 to 24.9 ± 1.2 mm (P = 0.05) and distal descending aortas from 22.1 ± 0.7 to 24.2 ± 1.4 mm (P = 0.02, 0.58 mm/year ± 0.5 mm). Dissected distal aortas increased by a mean of 0.3 ± 0.5 mm/year. Dissection (P < 0.001), urgent procedure (P = 0.02) and hypertension (0.052) were associated with larger distal aortic diameters at late follow-up and more significant aortic growth over time.

CONCLUSIONS: Late distal complication rates are low for patients initially presenting with aneurysms. The risk of late distal reoperation is dictated by the initial pathology and by the presence of an initial dissection and not by faster distal aortic growth. Strategies to completely restore a non-dissected anatomy might improve late surgical outcome in Marfan’s syndrome.

Keywords: Marfan syndrome • Aortic aneurysm • Aortic dissection • Aortic root surgery • Prosthetic aortic replacement • Thoracic aortic stent-grafting

INTRODUCTION

The Marfan syndrome (MFS) is a heritable autosomal dominant connective tissue disease with variable penetrance and is diagnosed on the basis of the revised 2010 Ghent criteria [1]. Although it is linked to a variety of clinical presentations and complications, including mitral valve leaflet prolapse or peripheral arterial aneurysms, thoracic aortic disease is most feared because of its morbidity and mortality. Of major concern are aneurysms of the thoracic and the thoraco-abdominal aorta, in particular of the aortic root and the ascending aorta [2] and the high incidence of Stanford Type A and Type B aortic dissections.

Aortic dissections and thoracic aortic aneurysm rupture have been limiting life expectancy in MFS patients to a median of ~30 years in the past [3]. However, improvements in perfusion strategy, organ protection during thoracic aortic surgery and surgical techniques including composite valved grafts and valvesparing aortic root replacement allow for prophylactic aortic root surgery as the first-line treatment for MFS patients with aortic root or ascending aortic aneurysms [3–5].

In contrast to the well-characterized short- and long-term outcome of aortic root and ascending aortic surgery in MFS patients, the fate of the aorta distal to left subclavian artery in MFS patients after surgery of the aortic valve and of the proximal aorta is not well characterized. Conflicting results have been reported on distal aortic growth, early and late distal aortic complications as well as reintervention rates [6–9].
The aim of this study was to investigate distal aortic growth rates and clinical outcome by means of a retrospective single-centre study (University Heart Center Freiburg in Freiburg and Bad Krozingen) on a cohort of 121 patients with confirmed MFS, who had all undergone proximal aortic surgery.

MATERIALS AND METHODS

Patients and procedures

This retrospective investigation was approved by the institutional review board. As of May 2012, 198 patients with confirmed MFS were followed up at the Heart Center Freiburg University’s Marfan Clinic. Patients from both clinics in Freiburg and Bad Krozingen (Heart Center Freiburg University) were included. Of these, 121 have a surgical history of proximal thoracic aortic surgery for aortic aneurysms or Stanford Type A dissections, constituting the final study population. Surgery was performed between July 1981 and May 2012. Late distal aortic procedures were performed between January 1996 and June 2012. In all the patients, MFS was confirmed according to the revised Ghent criteria from 2010 [1]. Testing included clinical evaluation and, if necessary, genetic testing.

Primary surgical procedures

Proximal aortic procedures included composite valved graft (Conduit, Bentall), David I and David II (Yacoub, Remodelling) procedures, supracoronary ascending aortic replacement as well as full arch and hemiarch replacements (Table 1). David I (Fig. 1) and David II procedures were performed as described elsewhere [4]. A minority of patients underwent modifications of these techniques (Table 1), as follows: modification of the classic David I reimplantation procedure using one single small tube graft includes isolated David-type reimplantation of a single sinus and supracoronary ascending aortic replacement above the other two sinuses. Modification of the David II (Remodelling) procedure was a ‘Uni-Yacoub’ replacing only one single sinus of Valsalva, mostly in the setting of an acute dissection. Composite valved graft procedures, supracoronary ascending aortic replacement and arch procedures were performed according to the standard protocol. Selective cerebral perfusion during deep hypothermic circulatory arrest was routinely established via a cardiopulmonary bypass graft on the innominate or right subclavian artery.

Secondary procedures and definitions

The ‘distal’ aorta is herein defined as the aorta distal to the left subclavian artery, including the distal aortic arch and the descending thoracic aorta. Late distal procedures included conventional open prosthetic replacement of the thoracic descending aorta and thoracic endovascular aortic repair (TEVAR). The indication for distal procedures was based on recent guidelines and the clinical situation of the patient. In most cases, a diameter of >5.5 cm was the indication for a distal aortic intervention.

Follow-up

At our institution, patients with confirmed diagnosis of MFS are routinely followed up at a dedicated out-patient clinic on an annual basis or earlier if indicated. Prospective acquisition of follow-up information constituted the basis for the study presented herein, while only selected patients were contacted via phone.

CT-angiographic surveillance and morphometric analysis of the distal thoracic aorta

According to our institutional policy, patients with known MFS are followed up by transthoracic echocardiography and cross-sectional imaging, including magnetic resonance imaging (MRI) and computed tomography (CT), on an annual basis. Institutional data bases were searched for available imaging data. Data sets were assessed by a radiologist with 4 years of experience in reading CT and MR angiographies, blinded to patient-identifying information. For analysis of aortic growth, thin-sliced data sets (slice thickness of ≤1 mm) were included into the analysis. Distal aortic diameters were assessed at three standardized anatomic locations distal to the left subclavian artery, at the level of the thoracic descending aorta (slice thickness of ≤1 mm) were included into the analysis. Distal aortic diameters were assessed at three standardized anatomic locations distal to the left subclavian artery, at the level of the

Table 1: Baseline patient characteristics at the time of initial surgery (n = 121)

<table>
<thead>
<tr>
<th>Basic clinical characteristics</th>
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<tbody>
<tr>
<td>Age, mean ± SD (range)</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
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<tr>
<td>Height, mean ± SD</td>
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<tr>
<td>Weight, mean ± SD</td>
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<tr>
<td>BMI (kg/m²), mean ± SD</td>
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<tr>
<td>BSA*(m²), mean ± SD</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Diabetes mellitus, n</td>
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<tr>
<td>LVEF (%), mean ± SD</td>
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<tr>
<td>Urgent procedure*, n (%)</td>
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<tr>
<td>NYHA &gt;II, n (%)</td>
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<tr>
<td>MFS 1, n (%)</td>
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<tr>
<td>MFS 2 (LDS), n (%)</td>
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<tr>
<td>Bicuspid aortic valve, n (%)</td>
</tr>
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</table>

Primary aortic pathology

- Aortic root aneurysm, n (%) | 52 (43)
- Ascending aortic aneurysm, n (%) | 15 (12)
- Root and tubular ascending aortic aneurysm, n (%) | 11 (9)
- Isolated sinus of Valsalva aneurysm, n (%) | 4 (3)
- Acute Type A dissection, n (%) | 31 (26)
- Subacute Type A dissection, n (%) | 5 (4)
- Chronic Type A dissection, n (%) | 3 (2)

Aortic valve function at initial procedure

- Clinically significant aortic stenosis, n (%) | 1 (1)
- Aortic regurgitation ≥II (moderate), n (%) | 55 (45)

Type of initial surgery

- Isolated aortic valve replacement, n (%) | 4 (3)
- Composite valved graft, n (%) | 52 (43)
- David I, n (%) | 43 (35)
- David II, n (%) | 7 (6)
- Supracoronary ascending aortic replacement, n (%) | 11 (9)
- Hemiarch or full arch replacement, n (%) | 10 (8)

Primary aortic pathology, aortic valve function at the time of the initial procedure and type of initial aortic surgery.

*BSA according to Dubois and Dubois.

Urgency at initial operation.

SD: standard deviation; BMI: body mass index; BSA: body surface area; LDS: Loeys-Dietz syndrome; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; MFS: Marfan syndrome.
mid-descending thoracic aorta and at the supradiaphragmatic level of the descending thoracic aorta (Fig. 1). For measurements CT data sets were transferred to a dedicated postprocessing workstation (Aquarius iNtuition, TeraRecon, San Mateo, CA, USA) and analyses by multiplanar reformations oriented perpendicular to the aortic axis. Mean diameters were obtained as area-derived diameters by means of planimetry (Fig. 1).

High quality, thin-slice and gated CTA imaging was available in 90 (74%) of the included patients. Mean distal aortic growth was analysed using imaging data of 60 patients (50%) who had high-quality scans available perioperatively as well as at late follow-up (33 male, mean age 35 ± 12 years).

End points

The following end points were investigated: death, infectious complications (composite end point including proven aortic valve endocarditis or sepsis), central nervous thrombo-embolic complications (composite end point including transient ischaemic attacks, ischaemic stroke and intracranial haemorrhage), distal aortic dissection and reoperation. Cross-sectional imaging end point was distal aortic growth (mean diameters at three different aortic levels).

Statistical analysis

Continuous variables are reported as means ± 1 standard deviation (SD). Categorical variables are reported as frequencies and their percentages. Paired and unpaired Student’s t-tests and one-way analysis of variance (ANOVA) were used to test for differences in continuous variables, as appropriate. Actuarial survival, freedom from clinical adverse events and distal reinterventions were analysed using Kaplan–Meier analysis and logrank calculations. The Cox-stratified and proportional hazard models were used for assessment of clinical variables impacting on reoperation. Risk factors for large distal aortic diameters at late follow-up as well as for distal aortic growth over time were tested using t-tests and ANOVA. Statistical analyses were performed using SigmaStat (Systat, San Jose, CA, USA).

RESULTS

Patient demographics and baseline characteristics for all the included 121 patients are listed in Table 1. The clinical follow-up was 97% complete, with 4 patients who were lost to follow-up. The mean follow-up was 7.6 years (range 0.05–28 years). The cumulative clinical follow-up comprised 894 patient-years.

Survival and morbidity

Overall survival was 96% (95% CI 88–98%) at 5 years, 84% (71–90%) at 10 years and 80% (71–88%) at 15 years. At 20 years, overall survival was 70% (60–83%) with 13 patients remaining at risk. Patients after elective surgery for aneurysm seemed to have better late survival, but this was not statistically significant (Fig. 2). Kaplan–Meier curves depicting survival and freedom from other adverse events are illustrated in Fig. 3. Freedom from
Central nervous deficits was 90% (80–94%) at 10 years and 73% (50–87%) at 20 years, as illustrated in Fig. 3. Freedom from infectious complications was 85% (74–92%) at 10 and 80% (63–89%) at 20 years with 11 patients remaining at risk (Fig. 3).

Adverse aortic events and reoperations—predictors of distal reoperation

Primary distal aortic procedures stratified for the different primary aortic pathologies and for the initial ascending aortic and/or aortic root procedures are illustrated in Fig. 4. Patients presenting with acute, subacute or chronic Type A dissections had significantly higher distal reoperation rates compared with patients who underwent initial surgery for an aneurysm (P = 0.03, Fig. 2). The presence of initial dissection was significantly associated with distal reoperation. In addition, mean distal aortic diameters at the late follow-up and increase of mean diameters over time were found to be associated with higher distal reoperation rates (see Table 2). A total of 19 distal aortic procedures were performed at a mean of 9.7 ± 7 years after initial surgery (0.06–23.5 years). Two TEVARs and three open surgical procedures were performed in patients after aneurysm repair at 10 ± 0.9 years and at 4.8 ± 3.5 years, respectively. In patients who underwent initial surgery for Type A dissection, 4 TEVAR and 10 open surgical aortic repairs were performed at 7.5 ± 11 and at 12.2 ± 6 years, respectively. The indications for late reoperations

Figure 2: Top: comparative survival of patients presenting with aneurysms and dissections at the time of initial surgery. Bottom: Kaplan–Meier curves showing comparative freedom from distal aortic procedures (including the distal aortic arch, mid and distal descending thoracic aorta) for patients initially presenting with proximal aortic aneurysms and dissections.

Figure 3: Kaplan–Meier survival curves (n = 121 Marfan patients). Top: endpoint was central nervous deficits (CND), including transient ischaemic attacks, strokes and intracranial haemorrhage. Bottom: endpoint was infectious complications, including infectious endocarditis and sepsis.
were chronic dissecting aneurysm in 9, thoraco-abdominal aortic aneurysm (TAAA) in six and acute Type B dissection in 4 patients. Late TEVARs were performed for Type B dissection in 4 patients (two acute, two chronic), for one dissecting infrarenal abdominal aortic aneurysm and for one TAAA.

Distal aortic size and predictors of distal aortic growth

Patients initially operated on for aneurysms had a mean distal aortic growth of 0.58 mm/year ± 0.5 mm. After initial aortic repair
for Stanford Type A dissections, the mean progression of aortic size was 0.3 mm/year ± 0.5 mm. This accounts for all the patients who had peri- and postoperative high-quality CT Scans available, which were suitable for our radiological assessment (50%, \(n = 36\) aneurysms, \(n = 20\) dissections). The overall mean values of distal aortic diameters at the three different anatomic levels stratified for dissection vs aneurysm are shown in Fig. 5. For both pathologies, distal aortic growth was significant, but not profound (Fig. 5). Different percentiles of mean diameters are shown in Fig. 6 for the different pathologies. The highest variability of mean aortic diameters at late follow-up was found at the distal descending thoracic aortic level for both aneurysms and dissections. The only covariates associated with a larger mean distal aortic diameter at late follow-up were dissection at initial operation \((P < 0.001)\) and urgent initial procedure \((P = 0.02)\), while chronic arterial hypertension was not significantly associated \((P = 0.05)\). See Table 2 for all the tested covariates. We did not identify any risk factors associated with a larger mean increase of distal aortic diameters (Table 2).

**DISCUSSION**

*Clinical results after proximal aortic surgery in patients with Marfan syndrome*

In 2009, Cameron et al. reported on their 30-year experience in aortic root surgery for MFS, with 372 MFS patients operated between 1976 and 2006. As the most common reasons of late death \((n = 74, 19.9\%),\) actuarial survival at 20 years was 75.6%, the group identified late dissection or rupture of the residual

<p>| Table 2: Tested covariates for distal aortic reoperation and distal aortic growth |
|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Covariate</th>
<th>(P)-value</th>
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<tbody>
<tr>
<td>Tested covariates (Cox proportional hazards model) for distal aortic reoperation</td>
<td></td>
</tr>
<tr>
<td>Dissection</td>
<td>0.029</td>
</tr>
<tr>
<td>Large mean distal aortic diameter</td>
<td>0.003</td>
</tr>
<tr>
<td>Distal aortic growth (difference of mean distal aortic diameter)</td>
<td>0.034</td>
</tr>
<tr>
<td>Urgent procedure</td>
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<tr>
<td>NYHA</td>
<td>0.999</td>
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<tr>
<td>LVEF</td>
<td>0.487</td>
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<td>Hypertension</td>
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<td>BSA</td>
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<tr>
<td>BMI</td>
<td>0.244</td>
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<tr>
<td>Aortic crossclamp time</td>
<td>0.226</td>
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<tr>
<td>Aortic arch replacement</td>
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<tr>
<td>CPB time</td>
<td>0.563</td>
</tr>
<tr>
<td>ACE–I</td>
<td>0.463</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.145</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tested covariates (ANOVA) for distal aortic growth</th>
<th>(P)-value (^a)</th>
<th>(P)-value (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissection</td>
<td>0.686 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Urgent procedure</td>
<td>0.909 0.024</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.464 0.052</td>
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<tr>
<td>ACE–I</td>
<td>0.689 0.762</td>
<td></td>
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<tr>
<td>Beta-blocker</td>
<td>0.789 0.417</td>
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<tr>
<td>Sartan</td>
<td>0.627 0.266</td>
<td></td>
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<tr>
<td>Root replacement</td>
<td>0.230 0.685</td>
<td></td>
</tr>
<tr>
<td>Arch replacement</td>
<td>0.314 0.109</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Mean difference between preoperative and late CTA evaluation. \(^b\)Mean distal aortic diameter at late follow-up.

NYHA: New York Heart Association class; LVEF: left ventricular ejection fraction; BSA: body surface area; BMI: body mass index; CPB: cardiopulmonary bypass.

*Figure 5: Mean aortic diameters stratified for initial aortic pathology and aortic segment. Aneurysms include isolated sinus of Valsalva, root, ascending tubular and combined aortic root and tubular aortic aneurysms. Dissections include acute, subacute and chronic Type A dissections. The asterisks indicate statistical significance.*

*Figure 6: Median (black line in box), 10th (lower end of bar), 25th (lower end of box), 75th (upper end of box) and 90th (upper end of bar) percentiles of mean aortic diameters stratified for aneurysms (upper image) and dissections (lower image). The asterisks indicate single outliers. Arch: distal arch; mid: mid-descending thoracic aorta; Distal: distal descending thoracic aorta; Pre: preoperative.*
aorta or iliac arteries, as well as arrhythmias [3]. Late survival in our series was comparable with these results. Actuarial freedom from reoperation on the residual aorta was 82.2 and 72.1% at 15 and 20 years, respectively [3]. This equals our results for patients initially treated for aneurysmal disease, while freedom from reoperation was much lower (52% at 20 years) for patients after dissection in our cohort.

Predictors of distal aortic growth and reoperation after proximal surgery in patients with Marfan syndrome

In 2008, Girdauskas et al. from Leipzig reported on fifteen MFS patients who underwent distal reinterventions late after aortic root surgery (between 2 months and 10 years postoperatively) [10]. All underwent secondary open surgery on the descending aorta, 80% for dissecting distal aneurysm after initial surgery for Type A dissection, similar to other reports [6]. The authors identified initial Type A dissection as the only independent risk factor for distal re-intervention. Another study supporting the body of evidence that Type A dissection has a strong impact on mid-term and late distal aortic complications and late reoperation rates is a report from Zierer et al. [11]. The group reported on 201 patients who underwent repair for acute Type A dissection, of whom 10 had the MFS [11]. Aortic growth was present in 49% of patients with a mean yearly growth rate of 5.3 ± 4.5 mm. The group concluded that aortic enlargement can occur as late as more than a decade after the initial procedure. These growth rates are profoundly different to our results, supposedly because we included all patients (also the ones without any growth) into our average calculations which were the basis for our statistical analyses.

Although several clinical studies have been performed in order to characterize predictors of distal aortic complications in MFS [3, 6, 10], reports on actual aortic growth for different pathologies in MFS are sparse. The rationale of our study was to retrospectively analyse the clinical results of a large MFS cohort with the clinical follow-up out to 20 years on the one hand, and to provide exact measurements of early and late distal aortic size (multiangulated area-derived mean diameters) on the other hand. This study was pivoting at the interdependence between aortic complication rates, initial pathology and actual aortic diameter. Distal reoperation was significantly linked to the presence of an initial dissection, in concordance with other reports [3, 6, 10, 12]. The mean distal aortic size at the time of late follow-up and the mean change of diameters over time were found to be linked to reoperation, too. However, diameters were at the same time significantly larger in patients with dissections. Aortic diameters started out larger in patients with dissections, but the growth over time was not profoundly different from that in patients with aneurysms. Moreover, the growth rates of dissected aortas were found to be significant but not very profound. For those reasons, we conclude that the presence of an aortic dissection is the one main important risk factor for distal reoperation, and not primarily distal aortic growth. This conclusion implies that distal dissection should be treated early and with the goal of a complete as possible restoration of a non-dissected distal aortic anatomy in Marfan patients. An aggressive, early surgical treatment of the dissected aortic arch and descending aorta might improve late outcome of these patients, if these procedures can be carried out with acceptable perioperative outcome at the respective institution.

The Baltimore group found that the most profound effect on late reoperation rates was generated by the presence of dissection at the time of the initial procedure as well [3]. Survival was compromised by about a third at 20 years when dissection was present, underlining the importance of a proactive surgical approach to prevent dissection. At 20 years, patients who had a dissection at the first operation had freedom from reoperation of 40% at 20 years vs 77% in others. The presence of a dissection nearly doubled the risk that a patient needed another operation at 20 years [3].

Several other risk factors for distal aortic growth and reintervention in MFS have been reported. Among them are large proximal size at the time of surgery, large distal ascending aortic size at the time of surgery, as well as distal aortic distensibility [13, 14]. Some authors have hypothesized that a rigid proximal tube graft may lead to higher distal mechanical stress, which puts the distal aorta at risk especially in MFS patients [3]. In addition, previous proximal surgery [15, 16], hypertension and aortic valve regurgitation have been described as risk factors for distal aneurysm formation. In our cohort, hypertension was associated with larger distal size, too, although probably because of its close pathophysiological interrelletion with aortic dissection. We did not consider aortic valve functional haemodynamics as a covariate for our Cox model because of the diversity of aortic valve and aortic root treatments. In addition, the presence of a patent false lumen has been reported to be a risk factor for distal aortic growth [11]. We did not assess structural risk factors like partial or full thrombosis of the false lumen, although these factors might play an important role. These important factors will be analysed in future studies and are currently incorporated in our local MFS database.

The Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Registry (GenTAC) is a National Institutes of Health-funded multicentre database and biorepository that enrols patients with genetically triggered thoracic aortic aneurysms [7]. Among other prognostic factors in MFS reported by the GenTAC group were beta-blocker therapy, hypertension at follow-up and initial aortic size. Beta-blocker therapy in our analysis was not found to be linked to adverse clinical outcome or aortic growth. However, only a minority of patients lacked antihypertensive long-term therapy in our cohort.

It remains unclear whether there is a true difference between the natural history of the distal Marfan’s aorta and the outcome of the distal aorta after proximal surgery. The question whether proximal aortic surgery can effectively decrease the risk of distal aortic growth and late distal aortic complications still needs to be answered [16]. In addition, it is unclear what role timing of the proximal repair and size criteria in surgical decision-making play in preventing distal aortic complications in these patients [17].

Sporadic dissection of a normal caliper aorta vs complicated aneurysm—same hereditary basis but different entities

Patients undergoing elective surgical repair of an aortic root aneurysm that has been followed up for months or years might constitute a profoundly different patient substrate compared with Type A dissection patients undergoing emergency repair. These groups should probably not be compared even if rigorous
matching for clinical and morphological (for example aortic size) criteria has been carried out. At least, sporadic dissection in MFS without primary aneurysm should probably be analysed completely separately from MFS aneurysms and dissected aneurysms. Reported differences in distal reintervention rates [10] probably reflect the multifaceted differences between those two different entities, although they share the same hereditary basis.

Are stent-grafts an appropriate therapy in patients with Marfan syndrome?

The adequacy of endovascular stent-graft repair in patients with intrinsic hereditary connective tissue disorders is currently debated [18, 19]. In the presented cohort, 6 patients were treated with TEVAR as a second-step procedure, which is about a third of distal reinterventions. At the time of the analyses, conclusive statements on the outcome after TEVAR were not possible. We performed TEVAR for both acute and chronic Type B dissections or TAAA only if these patients were poor open surgical candidates for anatomical or other patient-related reasons. However, TEVAR may not be considered standard of care in Marfan patients, especially in cases of chronic or asymptomatic aortic disease. Tissue quality of the aortic media involving loss, rarefaction and qualitative changes of elastic lamellae and other fibres in the extracellular matrix might put these patients at an increased risk of mid-term and late aortic complications, but this still needs to be clarified [20]. If there is a vital indication in an unstable patient, for example in an acute complicated Type B dissection, TEVAR is a reasonable alternative treatment. Placement of thoracic stent-grafts in patients with chronic dissections or asymptomatic aneurysms might be hazardous and its rationale is still debated; for example, Nordon et al. [21] reported on chronic dissections in MFS patients treated with TEVAR. The group from Rostock reported on 5 patients with MFS who were treated with distal aortic stengrafts for subacute or chronic Type B dissection after initial composite valved graft (n = 4) and Yacoub remodelling (n = 1) [18]. The incidence of complications in the complete cohort was not reported [18] and with only 2 patients remaining at risk after 5 years in this report, the true outcome needs to be determined in more studies comprising larger numbers of patients.

Potential role of medical therapy

Finally, the potential of evolving medical prophylactic therapy using beta-blockers, AT I-receptor-antagonists and ACI-inhibitors needs to be mentioned [22]. Clinical and experimental results suggest a promising future for these therapies [23]. Results from studies in different mouse models and clinical results indicate that AT II blockade [24] and AT I antagonism [25] are possibly effective pro-active measures to avoid aortic growth and complications in MFS patients. As mentioned earlier, in our cohort, the majority of patients were on antihypertensive therapy involving a beta-blocker in almost all the cases, and ACE-I in a majority, rendering inclusion into the statistical modelling futile.

Study limitations

We herein report on a single-centre experience. Prospective acquisition of follow-up data was performed in the dedicated Marfan Clinic of the Heart Center Freiburg University (Freiburg and Bad Krozingen). Consequently, only partial telephone follow-up was necessary and performed in selected patients, while most of the follow-up information was readily available. Although the clinical follow-up was close to complete (98%) only about half of the patients had high-quality CT scans available peri- as well as late postoperatively. While overall 75% had high-quality scans available, only those 50 patients could be included into comparative analyses of aortic diameters. However, basic patient characteristics did not differ profoundly between this sub-cohort and the rest of the patients. Owing to selection of the three standardized levels of aortic segments for area-derived mean diameter measurements, small localized aneurysms could have been missed.

CONCLUSIONS

Irrespective of the underlying initial aortic pathology, growth of the distal thoracic aorta after proximal repair in Marfan patients is significant, but not profound. Late distal complication rates are low for patients initially presenting with aneurysms. The risk of late distal reoperation is dictated by the presence and nature of an initial dissection and not primarily by faster distal aortic growth.

Conflicts of interest: none declared.

REFERENCES

APPENDIX. CONFERENCE DISCUSSION

Dr F. Schoenhoff (Berne, Switzerland): In our own experience, as well as in other large series of Marfan patients, the main reason for repeated reinterventions after elective proximal repair is the occurrence of a type B dissection during follow-up, which is often characterized by rapid aortic dilation within the first year after the event. So I was wondering if you could comment on the number of patients in your series who suffered from type B dissection after elective root surgery, and whether you observed an accelerated growth rate which may have contributed to the fact that, in your series, patients undergoing elective surgery had a higher growth rate than those with acute dissection, which is kind of counter-intuitive.

And second, as you had already mentioned, stent-grafting in patients with Marfan syndrome is somewhat controversial. And since you had a substantial number of stent-grafting (one-third of your reoperations have been stent-grafts), I was wondering if you could provide us with any CT data regarding the growth of the stented aortic segments during the course of your follow-up.

Dr Kari: Thank you. That is a very good question. We had two patients with Marfan syndrome who had 100 reoperations, and we came to the same kind of conclusion as yours. Dissection is definitely (we all know that now), a very important risk factor for Marfan patients to be reoperated on. In our experience, Marfan patients had a four-fold risk of being reoperated on distally than the non-Marfan dissected patients, and a six-fold higher risk than Marfan patients operated on electively.

My question is, would you suggest, as we did (but without any real statistical basis), that in Marfan patients with acute dissection, the aortic replacement should be extended to the total arch in order to reduce the risk of late distal operations?

Dr Kari: That is an implicit conclusion from the data that we have. If your rate of patients who re-enter as early as possible a non-dissected anatomy, of course, after you take the patient to the OR and fix the type A dissection, then you might even think about stent-grafts for the aortic arch, uncovered stent-grafts, that completely restore a dissected anatomy at an early time point.

Dr Bachet: And you wouldn’t hesitate to use stent-grafts in Marfan patients, even dissected? Isn’t this a little dangerous or, let’s say, off-label use?

Dr Kari: It is off-label, at least we don’t have any mid-term or long-term results and that will be interesting to see. It’s difficult to really obtain valid conclusions on that because randomized trials are difficult to perform and it’s going to take many years to acquire a body of evidence on these Marfan patients, because not many stent-grafts are put in Marfan patients. I think it will be several more years until we can say what the actual role of stent-grafting in Marfan patients should be, or is.

Dr Bachet: But why not using the classical elephant trunk? Because we saw yesterday that the results are not so bad, they are even quite good.

Dr Kari: That probably depends on the centre and on the surgical skills that are present in the respective surgical centres.

Dr C. Etz (Leipzig, Germany): Just for clarification, you are suggesting that Marfan tissue that has suffered a dissection, once you deploy the stent-graft, is going to be more stable than Marfan tissue that was not dissected previously?

Dr Kari: Not exactly. What I’m saying is that if, after you fix the type A dissection, you create an anatomic situation without any residual dissection, so you place the stent-graft (and we have two or three cases in Freiburg where we saw that with covered stent-grafts), you can achieve really good results at an early time point, then this patient might have a much lower risk for re-intervention or reoperation at a later point in time.

Dr Etz: But it is still a Marfan patient. So if you have the scar tissue, you think the Marfan is more stable and that’s the conclusion of it.

One last question that’s more technical. We just analysed our data from Leipzig (excluding Marfan patients) with regard to the cannulation site in type A aortic dissection. And the interesting result that we found was that if you perfuse in an antegrade fashion, as opposed to a retrograde fashion, from the femorals, that the group that was initially perfused antegradely had a better long-term outcome and a lower incidence of reoperations. Our conclusion was that probably there are re-entry tears and that distal perfusion may introduce a secondary injury to the descending aorta. What is your perfusion concept, is it different in Marfan’s as opposed to other patients?

Dr Kari: No, it’s not different.

Dr Etz: It’s the same?

Dr Kari: It’s the same.

Dr Etz: And routinely, are you using retrograde perfusion at all?

Dr Kari: We have very low rates of distal perfusion.

Dr T. Schachner (Innsbruck, Austria): Did you analyse your group of patients with regard to different Marfan phenotypes and their growth rates of the aorta?

Dr Kari: That is a very good question. We had two patients with Loeys-Dietz syndrome. And it’s correct that the new criteria say that Loey-Dietz syndrome needs to be sorted out before you can actually say that someone has Marfan. Those two patients are in the cohort, but those are the only two patients who have a non-classical Marfan.

Dr E. Weigang (Mainz, Germany): I’m not sure if we can leave your conclusion and your statement like this. We have recently published our recommendations in the EACTS/ESC position paper. Our interdisciplinary group’s clear statement is ‘Don’t use any stent-grafts in Marfan patients.’ The only exception is as a bailout procedure or if you have a complication after open replacement, and both ends of your stent-graft are in the vascular graft. When you review all the literature, you will see that stent-grafts in the distal end in the valve result in complications during follow-up. This makes me wonder how you reached your conclusions; we will see what you report after the next follow-up with these patients. That will be interesting.

Dr Kari: I guess that depends on the risks and hazards associated with open, conventional aortic arch replacement and the respective centres.