Type A Aortic Dissection in Marfan Syndrome: Extent of Initial Surgery Determines Long-term Outcome

Running title: Rylski et al.; Aortic Dissection Type A in Marfan’s Syndrome

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Abstract

Background—Data on outcomes after Stanford Type A aortic dissection in Marfan’s Syndrome (MFS) patients are limited. We investigated the primary surgery and long-term results in MFS patients who suffered aortic dissection.

Methods and Results—Among 1324 consecutive patients with aortic dissection Type A, 74 with MFS (58% males, median age 37 (29; 48) years) underwent surgical repair (85% acute dissections; 68% DeBakey I; 55% composite valved graft (CVG), 30% supracoronary ascending replacement, 15% valve sparing aortic root replacement (V-SARR); 12% total arch replacement; in-hospital mortality 3%) at two tertiary centers in the United States and Europe over the last 25 years. Aortic re-intervention with re-sternotomy rate was 24% (18/74) and descending aorta (thoracic+abdominal) intervention – 30% (22/74) at median follow-up of 8.4 (2.2; 12.7) years. Freedom from need for aortic root reoperation in patients who underwent primarily a CVG or V-SARR procedure was 95±3%, 88±5%, 79±5% at 5, 10 and 20 years, and 83±9%, 60±13%, 20±16% in patients who underwent supracoronary ascending replacement. Secondary aortic arch surgery was necessary only in patients with initial hemi-arch replacement.

Conclusions—Emergency surgery for Type A dissection in Marfan patients is associated with low in-hospital mortality. Failure to extend the primary surgery to aortic root and/or arch repair leads to a highly complex clinical course. Aortic root replacement or repair is highly recommended, since supracoronary ascending replacement is associated with a high need (>40%) for root re-intervention.

Key words: Marfan syndrome, acute aortic syndrome
Introduction

Marfan’s syndrome (MFS), an autosomal dominant disorder with variable penetrance based on fibrillin-1 gene mutations (FBN-1), is an important causative factor for acute Stanford Type A aortic dissection in younger patients\(^1,2\). The current American College of Cardiology (ACC) Foundation guidelines recommend prophylactic aortic root surgery in MFS patients when a 4.0 to 5.0 cm ascending aortic or aortic root threshold diameter has been reached as this surgery prevents catastrophic proximal aortic events\(^3\). Due to lack of diagnosis, poor follow-up and the presence of sporadic mutations with variable phenotypic profile, acute aortic dissection is still a frequent and highly lethal initial presentation of aortic pathology in MFS patients. As aortic dissection occurs on average 20 years earlier in MFS patients compared with non-MFS peers\(^1\), ongoing postoperative follow-up and timely, well-planned re-interventions when needed are essential to achieve better life expectancy.

Several groups have described their general aortic surgery experience in MFS patients\(^4,5,6,7\), but to date no large series on Stanford Type A aortic dissection in MFS patients with long-term aortic outcome have been published. Our pooled databases covering 25 years of aortic dissection Type A from two tertiary cardiac centers in the United States and Europe provide a unique opportunity to analyze clinical data on individuals with MFS. In this study we sought to present the outcome of primary surgery in MFS patients who suffered Stanford Type A dissection and to investigate the incidence, causes and results of early and late surgical re-interventions.

Methods

Study population

The institutional review committees at both participating centers approved this study and the
need for informed consent was waived. The Hospital of the University of Pennsylvania in Philadelphia and Heart Center Freiburg University in Freiburg and Bad Krozingen reviewed their aortic dissection databases including patients operated on between 1987 and 2013. The cumulative caseload at both centers was n=1324. Of these, a total of 74 patients (Heart Center Freiburg, 42; University of Pennsylvania, 32; Table 1) with MFS confirmed according to the revised Ghent criteria\textsuperscript{8} underwent surgery for Stanford Type A aortic dissection. Patients were followed-up in the past 25 years at both institutions in MFS clinics in at least 1-year intervals.

**Surgical Techniques**

All patients underwent ascending aortic replacement. In those with established MFS syndrome and in a condition permitting longer cardiopulmonary bypass times (no visceral or cardiac malperfusion, no neurological deficit), valve-sparing root replacement (V-SARR) in the later era was considered whenever the aortic valve was tricuspid, had symmetrical leaflets and there were no large fenestrations of the leaflets. All other patients underwent composite valved graft (CVG) implantation. In patients with unrecognized MFS at the time of surgery, supracoronary ascending replacement with aortic valve resuspension and eventually aortic root reconstruction applying the “neo-media” concept\textsuperscript{9} (in patients operated on in Philadelphia) was performed when the sinus of Valsalva diameter was <$4.5$ cm, there was no dissection entry proximal to the sinotubular junction, and aortic valve was reparable. In all other cases, a V-SARR or CVG procedure was performed. Distal aortic procedures included hemi-arch replacement (open distal anastomosis or aggressive hemi-arch with replacement of the aortic-arch concavity) or, in case of a dissection entry located in the convexity of the aortic arch, total arch replacement was performed using an “island” technique, or separate re-implantation of the supra-aortic branches via a trifurcated vascular graft.
Statistical analysis

Continuous data are presented as median (first quartile; third quartile), categorical variables are given as counts and percentages. Survival and freedom from re-interventions were analyzed using the Kaplan-Meier method. All statistical calculations were performed using SigmaPlot 12 (Systat Software, San Jose, CA).

Results

A total of 74 patients were included. Clinical and operative data are shown in Table 1. At the primary surgery, among patients who received V-SARR operation, 9 underwent aortic valve reimplantation and 2 root remodeling procedures. Among 22 patients who underwent supracoronary ascending replacement, all underwent aortic valve resuspension and 12 received aortic root “neo-media” repair as well. Nine patients (12%) underwent total aortic arch replacement. In-hospital mortality was 3% (2 of 74 patients): one patient died in the operating room of right heart failure and another 6 days after surgery of sepsis and multiorgan failure. Stroke occurred in 4 of 74 patients (5%). One patient suffered paraparesis. In follow-up, 48 aortic re-interventions were performed on 33 of 74 patients (45%). The pattern of replaced aortic segments is shown in Figure 1.

Re-interventions with Secondary Sternotomy

Eighteen patients underwent 23 re-sternotomies for aortic root and/or arch re-interventions. The median interval between the initial operation and the first re-intervention was 8.4 (2.2; 12.7) years. Reoperation rates on the aortic root were associated with the extent of primary aortic surgery. Freedom from need for aortic root reoperation in patients who underwent primarily a CVG or V-SARR procedure was 95±3%, 88±5% and 79±5% at 5, 10 and 20 years, and 83±9%,
60±13% and 20±16% at 5, 10 and 20 years in patients who underwent supracoronary ascending replacement (Figure 2).

In the CVG group, secondary root repair was indicated in 3 patients due to a pseudoaneurysm (1 at the right coronary anastomosis which required second and third re-intervention and 2 patients at the aortic annulus-graft anastomosis), 1 by endocarditis and another one by prosthetic valve thromboembolism. None of V-SARR patients required secondary sternotomy for aortic root re-intervention, however one developed moderate AI 6 years after primary surgery and we decided to replace his valve and took the chance that he had to undergo a second sternotomy for aortic arch aneurysm repair. In the supracoronary replacement group, aortic insufficiency (AI) in 3 and root aneurysm in 3 more patients was the reason for re-intervention. Three more patients with aortic root aneurysm failed to undergo re-intervention: one died of a ruptured abdominal aortic aneurysm, one was a Jehovah’s Witness and declined surgery, another one developed concomitant arch aneurysm and due to severe aortic arch pathology and high operative risk underwent only total arch replacement.

Secondary total aortic arch replacement became necessary in 8 of 74 patients (11%) and together with 5 distal arch re-interventions via lateral thoracotomy, accounted for an 18% overall arch re-intervention rate. No patients required secondary arch surgery after total arch replacement. Freedom from aortic arch reoperation in patients who underwent hemi-arch replacement was 91±4%, 86±5% and 64±10% at 5, 10 and 20 years (Figure 3).

The in-hospital mortality rates were 22% (2 of 9 patients) and 8% (1 of 13) for elective aortic root and arch re-interventions, respectively.

**Interventions on the Descending Aorta**

Twenty-two patients underwent 25 procedures on downstream aortic segments during the
follow-up period. The most common indication was thoracic aortic aneurysm in 17 (including distal arch pseudo- or true aneurysms in 5 patients), followed by abdominal aortic aneurysm in 5, thoracoabdominal aneurysm in 2, and acute aortic dissection Type B in 1 patient. One patient died after emergency thoracic aortic replacement and the second patient died after elective thoracoabdominal repair accounting for 5% (1 of 20 patients) in-hospital mortality in elective cases.

Aortic dissection extension beyond the aortic arch at the time of initial surgery was associated with higher reoperation rates on the descending aorta. Nineteen of 50 (38%) patients with a DeBakey Type I and only 3 of 24 (13%) with a DeBakey Type II dissection required distal reoperation. Freedom from descending aortic reoperation in patients with a DeBakey Type I dissection was 78±7%, 65±8% and 55±9% at 5, 10 and 20 years and in a DeBakey Type II 96±4%, 96±4% and 80±10% at 5, 10 and 20 years (Figure 4), respectively.

Survival
Overall survival was similar in patients who did and did not undergo aortic re-interventions. Survival in patients who required secondary aortic procedure was 87±6%, 73±8% and 62±10% at 5, 10 and 20 years and 88±6%, 72±9% and 63±11% at 5, 10 and 20 years in patients who did not need aortic re-intervention (Figure 5). Survival in patients with a DeBakey Type I dissection was 84±6%, 67±7% and 60±10% at 5, 10 and 20 years and in a DeBakey Type II 100%, 82±9% and 66±12% at 5, 10 and 20 years (Figure 6).

Discussion
Wide availability of screening modalities and the general awareness of connective tissue disease have not yet completely eliminated the risk of aortic dissection, the most catastrophic and often
lethal event in the MFS population. Several major cardiac centers recently reported on their
general experience in aortic surgery on MFS patients. One of their main conclusions was that the
current rate of acute Type A dissection surgery in MFS patients remains very high, ranging
between 16 and 35% of all aortic procedures performed in this cohort\textsuperscript{4, 5, 6, 7}. Herein we report 25
years of international MFS clinical experience in two large cardiac centers with primary surgery
for Stanford Type A dissection and the management of later aortic complications. Our main
observations are:

(i) While surgical treatment for Type A dissection in MFS patients has a very low in-hospital
mortality risk (3%), it is associated with the high risk of later aortic re-interventions (45%).

(ii) Supracoronary ascending replacement at the time of aortic dissection Type A is
associated with high need for root re-intervention when compared with CVG or V-SARR
patients. Leaving the diseased root tissue behind at the time of initial operation leads to the aortic
root’s high complication rates.

(iii) Patients with dissection extending beyond the aortic arch at the initial surgery carry an
increased risk of later re-interventions on the descending thoracic aorta.

Relationship to Previous Studies

Surgical repair of the aorta outcomes have improved dramatically in the past 25 years. In the
most recently published MFS cohorts, Scheonhoff et al\textsuperscript{4} and Cameron et al\textsuperscript{8} reported series of 86
and 372 patients, respectively, with no in-hospital mortality after elective aortic root surgery. Yet
there is very little data on outcome after emergency surgery for Type A dissection in MFS
patients. In the same series from Johns Hopkins Hospital, Cameron et al reported 4.4% (2 of 45
patients) 30-day mortality in MFS patients who underwent urgent or emergent ascending aortic
repair. In a survey of the International Registry of Aortic Dissection, Januzzi et al described 23%
perioperative mortality in a series of 46 patients <40 years of whom 50% had MFS\textsuperscript{10}. In our composite series, in-hospital mortality is relatively low (3%) and compares favorably with the mortality currently reported for the overall aortic dissection population, which ranges between 8 and 20% in high-volume centers\textsuperscript{1,11,12,13}. The low mortality in MFS patients, 85% of whom underwent emergency surgery, may be attributed to the fact that they are on average 20 years younger\textsuperscript{10} than non-Marfan aortic dissection patients, and that they usually do not have the comorbidities typical of older patients.

**Extent of Initial Surgery Determines Need for Aortic Root and Arch Re-interventions**

There is growing consensus that MFS patients operated on Type A dissection should undergo aortic root replacement during the emergency surgery on the proximal aorta\textsuperscript{14,15,16}. However, to date this was a rather intuitive recommendation made according to experiences with non-dissected MFS patients, since the numbers of MFS patients with aortic dissection even at high-volume centers are very low, ranging from 3 to 5% in the entire dissection population\textsuperscript{1,17}. Up to date, no aortic-root preservation outcomes in MFS patients suffering acute dissection have ever been published. In our cohort, 22 patients underwent supracoronary ascending aortic replacement in the emergency setting of acute Type A dissection, as the MFS diagnosis was not known at that time of surgery and their aortic root was non-dilated. Higher need for reoperation on this group’s aortic root (41%) compared to CVG or V-SARR patients (10%), confirms what we and many other groups dealing with MFS patients have intuitively thought, namely that aortic root replacement or repair is highly recommended in MFS patients with a dissected ascending aorta. This statement is additionally supported by the fact, that in-hospital mortality for root replacement or repair at the initial surgery was very low (1.9%). Interestingly, in the root “neo-media” reconstruction group, we noted only one sinus-segment aneurysm requiring re-
intervention. Reinforcing the sinus segment with a Teflon felt placed inside the aortic wall may prevent root dilatation in MFS patients also. However, our patient numbers are insufficient to make a definitive statement.

Several groups reported on outstanding durability of the elective David reimplantation operation in patients with connective tissue disorders. Although both V-SARR techniques (valve reimplantation and root remodeling) are feasible in Type A aortic dissection patients, they are usually done infrequently, as both require long cardiopulmonary bypass times, which can lead to irreversible complications in patients who already present with myocardial or visceral malperfusion, or neurological impairment at the time of admission. Some investigators found that the root remodeling technique is associated with an increased risk of premature failure in MFS patients. In our patients, we performed 11 V-SARR (9 reimplantations and 2 remodelings) procedures, 9 in acute, 1 in subacute and 1 in chronic dissection. We observed no perioperative mortality and only one patient developed moderate AI 6 years after primary surgery; we decided to replace his valve by the chance of second sternotomy for aortic arch aneurysm repair. We believe that V-SARR should be considered in MFS patients with acute Type A dissection, especially those who present with uncomplicated dissection without malperfusion. V-SARR is not only superior to the CVG procedure because it preserves the native valve (avoiding the serious risks of mechanical valves), it also appears to circumvent the risk of later proximal pseudoaneurysm development, a factor we observed in 2 CVG patients and in no patient in the V-SARR group. However, due to small patients’ numbers definitive conclusions on V-SARR versus CVG procedures’ outcomes are not possible.

There is a growing consensus, that replacing the aortic arch during initial surgery for Type A dissection is unnecessary, although it reduces the rate of further arch reoperations.
Our study confirmed this hypothesis. Though aortic arch re-intervention was necessary only in patients with initial hemi-arch replacement, elective arch re-intervention carried an only moderate risk.

**Extension of the Aortic Dissection is Associated With Descending Aortic Re-interventions**

In a recently published cohort of MFS patients undergoing root repair, the Bern group found that the need for distal aortic re-interventions is precipitated by an initial presentation with Stanford Type A dissection\(^1\). Our data suggest more specific conclusions, namely that the need for re-intervention in primarily non-treated aortic segments is determined by the initial extent of Type A aortic dissection, as most re-interventions on the descending aorta were performed on patients with DeBakey Type I dissection. Notably, survival was similar in patients with DeBakey Types I and II, and in patients with and without secondary aortic intervention, suggesting that elective secondary surgery is effective in the treatment of late distal adverse aortic events.

**Limitations**

Patients enrolled to this analysis were operated on within the last 25 years. This might be a limitation of our study, since both surgical and medical therapies made a substantial progress in this time. Although it is the largest series on Stanford Type A aortic dissection in MFS patients, number of events in subgroups of patients by type of surgery was too small to provide adequate power for statistical hypothesis testing.

**Conclusions**

In conclusion, the initial surgical intervention on MFS patients who present with acute Stanford Type A dissection is a low-risk procedure when performed in a cardiac center with extensive aortic surgical experience. Since supracoronary ascending replacement is associated with a high
root re-intervention rate, aortic root replacement or repair during the initial surgery is highly recommended. While the CVG procedure carries risks associated with mechanical valves \textsuperscript{22}, V-SARR, as long as the aortic valve morphology is adequate and the patient’s condition allows longer cardiopulmonary bypass time, appears preferable. Total aortic arch replacement reduces the number of aortic arch re-interventions. However, if secondary aortic arch surgery is performed electively, it carries an acceptable risk. We therefore suggest that an effective strategy to improve long-term outcome in MFS patients with acute Stanford Type A dissection include the David reimplantation procedure whenever it does not raise the overall operative risk, and that arch replacement is not necessary during the initial operation unless there are primary tears in the arch itself.

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Conflict of Interest Disclosures: None.

References:


Table 1. Clinical and operative data

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<tbody>
<tr>
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<td>37 (29; 48)</td>
</tr>
<tr>
<td>Male gender</td>
<td>43 (58)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181 (174; 190)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (69; 84)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (28)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (4)</td>
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<tr>
<td>BAV</td>
<td>3 (4)</td>
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<tr>
<td>Aortic Dissection</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>63 (85)</td>
</tr>
<tr>
<td>Subacute</td>
<td>4 (5)</td>
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<tr>
<td>Chronic</td>
<td>7 (10)</td>
</tr>
<tr>
<td>DeBakey Dissection</td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>50 (68)</td>
</tr>
<tr>
<td>Type II</td>
<td>24 (32)</td>
</tr>
<tr>
<td>Proximal Repair</td>
<td></td>
</tr>
<tr>
<td>CVG</td>
<td>41 (55)</td>
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<tr>
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<tr>
<td>V-SARR</td>
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<td>Distal Repair</td>
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<tr>
<td>Hemi-arch replacement</td>
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<tr>
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<td>13 (24)</td>
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<td>Aortic arch</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Descending thoracic aorta</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>5 (10)</td>
</tr>
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</table>

Categorical variables are given as counts and percentages, continuous as median values (first quartile; third quartile). CVG indicates composite valved graft; V-SARR, valve sparing aortic root replacement; BAV, bicuspid aortic valve. *percentages are given according to all re-interventions

Figure Legends:

Figure 1. Pattern of primarily and secondarily replaced aortic segments in MFS patients who underwent surgery for Stanford Type A aortic dissection. Each vertical column represents one patient. V-SARR indicates valve-sparing aortic root replacement; CVG, composite valved graft.
Figure 2. Freedom from need for aortic root reoperation in patients who underwent initially supracoronary ascending replacement versus those with initial aortic root replacement (CVG) or repair (V-SARR).

Figure 3. Freedom from aortic arch reoperation in patients who underwent primary total aortic arch versus hemi-arch replacement.

Figure 4. Freedom from descending aortic re-intervention by DeBakey type of aortic dissection at the primary surgery.

Figure 5. Survival of patients who underwent aortic re-interventions versus patients without re-interventions. The observation time starts for both groups at the moment of initial surgery.

Figure 6. Survival of patients who underwent surgery for Stanford aortic dissection Type A by DeBakey classification.
### Figure 1

<table>
<thead>
<tr>
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<th>V-SARR</th>
<th>CVG</th>
<th>Supracoronary Replacement</th>
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<tr>
<td>Ascending aorta</td>
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<tr>
<td>Proximal arch</td>
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<td>Distal arch</td>
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<tr>
<td>Descending thoracic aorta</td>
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<tr>
<td>Abdominal aorta</td>
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</tbody>
</table>

- **V-SARR**: Replaced aorta at the primary surgery
- **CVG**: Replaced aorta at the secondary surgery
- **Supracoronary Replacement**: Secondary surgery on already replaced aorta
Figure 2

Survival Analysis

Time (years)

Freedom From Need for Aortic Root Reoperation

Patients at risk:

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>CVG or V-SARR</th>
<th>Supracoronary ascending replacement</th>
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</thead>
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<tr>
<td>0</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
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<td>15</td>
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<td>4</td>
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<tr>
<td>20</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure 3

Survival Analysis

Time (years)

Freedom From Aortic Arch Reoperation

Patients at risk:

Total arch
Hemi-arch

65
42
23
17
10

0
5
10
15
20

0.0
0.2
0.4
0.6
0.8
1.0

Figure 3
Survival Analysis

Time

0 5 10 15 20

Survival

0.0 0.2 0.4 0.6 0.8 1.0

Patients at risk:

DeBakey Type II

DeBakey Type I

Time (years)

0 5 10 15 20

24 19 13 9 6

50 27 15 9 6

Figure 4
Figure 5

Survival analysis graph showing the survival rates over time for patients with and without aortic re-intervention. The graph illustrates the number of patients at risk at each time point:

- No aortic re-intervention:
  - Time (years): 0 to 20
  - Number of patients: 41, 24, 12, 9, 4

- Aortic re-intervention:
  - Time (years): 0 to 20
  - Number of patients: 33, 29, 17, 14, 10
Figure 6
Type A Aortic Dissection in Marfan Syndrome: Extent of Initial Surgery Determines Long-term Outcome


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