Acute Aortic Dissection Determines the Fate of Initially Untreated Aortic Segments in Marfan Syndrome

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Background—The aim of the current study was to investigate incidence and causes of surgical interventions in primarily nontreated aortic segments after previous aortic repair in patients with Marfan syndrome.

Methods and Results—Retrospective analysis of 86 consecutive Marfan syndrome patients fulfilling Ghent criteria that underwent 136 aortic surgeries and were followed at this institution in the past 15 years. Mean follow-up was 8.8±6.8 y. Thirty-day, 6-month, 1-year, and overall mortality was 3.5%, 5.8%, 7.0%, and 12.8%, respectively. Ninety-two percent of patients initially presented with aortic root, ascending aortic or arch lesions, whereas 8% presented with descending aortic or thoraco-abdominal lesions. Primary presentation was acute aortic dissection (AAD) in 36% (77% type A, 23% type B) and aneurysmal disease in 64%. Secondary complete arch replacement had to be performed in only 6% of patients without AAD, but in 36% with AAD (P=0.0005). In patients without AAD, 11% required surgery on primarily nontreated aortic segments (5 of 6 patients experienced type B dissection during follow-up), whereas in patients after AAD, 48% underwent surgery of initially nontreated aortic segments (42% of patients with type A and 86% of those with type B dissection; P=0.0002).

Conclusions—The need for surgery in primarily nontreated aortic segments is precipitated by an initial presentation with AAD. Early elective surgery is associated with low mortality and reintervention rates. Type B dissection in patients with Marfan syndrome is associated with a high need for extensive aortic repair, even if the dissection is being considered uncomplicated by conventional criteria. (Circulation. 2013;127:1569-1575.)

Key Words: aortic dissection, familial connective tissue diseases Marfan syndrome

Marfan syndrome (MFS) is an autosomal dominant disorder affecting ≈1 in 5000 individuals.1 The phenotypic changes of MFS are imposed by mutations in the gene encoding for the extracellular matrix protein fibrillin-1.2 Although patients with MFS exhibit skeletal, ocular, and cardiovascular manifestations, acute aortic dissection attributable to aortic aneurysms still determines morbidity and mortality in this patient population. In a multi-institutional series of 675 patients, 30-day mortality for elective, urgent, or emergency repair was 1.5%, 2.6%, and 11.7% respectively.3

Clinical Perspective on p 1575

Low morbidity and mortality rates in patients undergoing elective root surgery and an increasing awareness for patients with connective tissue disease have continuously lowered the threshold for surgical interventions on the proximal aorta.4 The concept of prophylactic aortic root surgery in preventing acute dissection is well established5 and has contributed to the improved survival of MFS patients over the past decades.6 However, it is not very well understood how this affects the need for further surgical interventions on primarily nontreated aortic segments in the long-term. Several studies suggested a shift of morbidity and mortality toward the distal aorta. Analysis of the Euro Heart Survey database revealed that 31% of interventions in patients with MFS have been performed on the distal aorta,7 and Finkbohner et al6 noted that 18% of primary interventions were attributable to lesions on the distal aorta. It is unclear whether the increased life expectancy in patients with MFS just makes an event on the distal aorta more likely or whether elective root surgery itself might trigger downstream aortic events. In an in vitro model it was suggested that wall tension in the residual aorta increases after prosthetic replacement of the ascending aorta.8

These findings are contrary to our clinical experience in which patients who underwent elective root replacement seemed to have a more favorable long-term outcome compared with patients with a history of acute aortic dissection. The aim of the current study was to determine incidence and substrate for intervention in initially nontreated aortic segments in patients with MFS.
Methods
Data from 86 MFS patients (mean age 35 years, range 8–69 years, 57% male patients) fulfilling Ghent criteria who underwent 136 major aortic operations and were followed at this institution in the past 15 years was retrospectively analyzed. 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 generally evaluated using ECG-gated, CT angiography to plan surgery, as a follow-up in patients with (residual) dissections and in the acute setting. In benign cases or after uneventful elective surgery, MR imaging was performed to reduce cumulative radiation exposure.

Additionally, 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 99% completeness of follow-up was achieved. For analysis, patients were divided in 4 groups (Figure 1): group (1), patients who initially presented without acute aortic dissection; group (2), patients who initially presented with acute aortic dissection; group (3), patients who never experienced acute aortic dissection during follow-up, and group (4), patients who experienced acute aortic dissection initially or at any time during follow-up. This study was approved by the institutional review board and individual informed consent from the patient or, in case of minors, the parent respectively the legal guardian was obtained.

Statistical Analysis
In addition to descriptive statistics, data underwent a Kaplan–Meier survival analysis, with either reoperation or death as an event, followed by a log rank test to compare the event risk for patients with or without history of aortic dissection. Analysis was performed with SPSS version 15.0 software (SPSS, Inc, Chicago, IL).

Indication for Surgery and Surgical Techniques
In patients presenting with aortic root aneurysm, a diameter of 45 to 50 mm or progress of more than 5 mm per year was considered an indication for surgery because 15% of patients with MFS disect at diameters of <50 mm.6–10–12 If aortic regurgitation was present and aortic root size was <45 mm, indication for surgery depended on the extent of regurgitation and hence left ventricular dimensions. In younger women with MFS who want to become pregnant, prophylactic root replacement was considered if aortic root size exceeded 40 mm. Surgical repair of the aortic arch and descending aorta was considered if the diameter exceeded 55 to 60 mm or in case of rapid enlargement (eg, after Stanford type B dissection). There are several procedures available for the treatment of the aortic root in MFS patients; complete root replacement by means of a modified Bentall procedure or a valve sparing root replacement (VSRR) was the treatment of choice13–15 in the current series.

In patients with more advanced stage of disease where dilation of the aorta extended into the aortic arch and descending aorta, arch replacement with or without implantation of an elephant trunk was performed. In patients with acute Stanford type A dissection, the distal anastomosis was performed at least as a hemi-arch replacement using moderate hypothermic circulatory arrest with bilateral antegrade cerebral perfusion.16 If complete arch replacement was necessary, separate reimplantation of the supra-aortic branches using a vascular graft with multiple side-branches was preferred.

Results
Seventy-eight patients (91%) initially presented with aortic root, ascending aortic, or aortic arch lesions, whereas 7 patients (8%) primarily presented with descending aortic or thoraco-abdominal lesions; 1 patient (1%) with aortic root aneurysm and dilative cardiomyopathy underwent heart transplantation as a primary procedure. Cause at initial presentation was acute dissection in 36% and chronic dilative disease in 64%. In the group of patients presenting with acute aortic dissection, 77% of patients presented with Stanford type A dissection and 23% with Stanford type B dissection. In patients with acute Stanford type A dissection, 67% received a composite graft, whereas in 33% of patients only a supra-coronary replacement was performed because the diagnosis of MFS was not established at the time of surgery. In the latter group, 2 of 8 patients needed redo surgery on the aortic root. No VSRR was performed in patients with acute dissection. In patients undergoing elective surgery, 43% of patients received a composite graft, and 50% underwent VSRR. Reasons not to perform VSRR in patients with MFS were bicuspid valve, asymmetrical aortic valve leaflets, and large fenestrations of the leaflets with partial detachment of the commissures.

Re-Intervention on Aortic Root and Aortic Arch
Twenty-one David operations and 5 Yacoub procedures were performed. The rate of reoperation was 1 of 21 patients in the David and 3 of 5 in the Yacoub group, which represents a significantly higher reoperation rate in the remodeling compared with the reinforcement group (P=0.01). All reoperations became necessary because of development of moderate to severe aortic regurgitation. Secondary replacement of the complete aortic arch became necessary in only 6% of patients in group (1) but in 36% of the patients in group (2) (P=0.0005; Figure 2A and 2B).

Distal Aorta
In group (1), 11% of patients underwent surgery in downstream aortic segments, whereas in group (2), 48% patients had to undergo surgery on the distal aorta. Interestingly, 5 of the 6 patients undergoing reinterventions in group (1) experienced type B dissection in the meantime (Figure 3A and 3B). Acute type B dissection occurred in 19% (16/86) of patients. Mean diameter at the time of dissection was 37±8.5 mm (range 19–50 mm). Except for 1 case, the maximum diameter was at the proximal descending aorta. Mean diameter at time of surgery was 64±10.6 mm (range 41–80 mm). This translates into an estimated average growth rate of 16±11.4 mm/6 months after onset of pain. All but 1 patient

Figure 1. Allocation of patients to groups 1 to 4. AAD indicates acute aortic dissection.
One patient developed severe pseudoaortic stenosis with visceral ischemia and underwent surgery shortly after presentation. Mean time between development of type B dissection and surgery was 2±2.7 years, but 67% of patients underwent surgery within the 1st year after the event. Only 1 patient could be identified in whom type B dissection evolved from the distal anastomosis 3 months after elective complete arch replacement.

In the group of patients with a history of dissection, patients experiencing Stanford type B dissection are significantly more likely to undergo surgery on the distal aorta than those with type A dissection (86% versus 42%, P=0.0002).

**Freedom-From-Reoperation and Survival**

Freedom-from-reoperation in group (1) was 86%, 69%, and 27% at 5, 10, and 15 years and 65%, 45%, and 20% at 5, 10, and 15 years, respectively, in group (2) (Figure 4). In group (3), freedom from reoperation was 92%, 86%, and 64% at 5, 10, and 15 years compared with 65%, 42%, and 16% at 5, 10, and 15 years, respectively, in group (4) (Figure 5).

Furthermore, history of dissection at any time during follow-up (group (3)) was not only associated with a higher rate of reoperation but also a predictor of survival in patients with MFS. Survival in group (1) was 93%, 93%, and 93% at 5, 10, and 15 years and 90%, 90%, and 72% at 5, 10, and 15 years, respectively, in group (2) (Figure 6). In group (3), survival was 98%, 98%, and 98% at 5, 10, and 15 years compared with 85%, 85%, and 71% at 5, 10, and 15 years, respectively, in group (4) (Figure 7).

**Other Risk Factors for Re-Intervention**

There were no differences in the incidence of surgical interventions of initially nontreated aortic segments between smokers and nonsmokers (P=0.59). There were no differences in the incidence of surgical interventions of downstream aortic segment between patients who were treated with ACE-inhibitors or angiotensin-receptor blockers and patients without such a treatment (P=0.47). Furthermore, there was no significant influence of β-blockers (BB) or calcium channel blockers (CaB) on either reoperation rate (BB, P=0.26; CaB, P=0.14) or the likelihood of experiencing dissection (BB, P=0.66; CaB, P=0.5).

In patients with high blood pressure (at initial presentation), 12 of 28 patients (43%) needed secondary surgical interventions of the distal aorta, compared with 10 of 58 patients (17%) in those patients without hypertension (P=0.02).
Follow-Up and Complications

Mean follow-up of survivors was 8.8±6.8 years, mean interval between initial and redo-surgery was 5.5±4.6 years. Thirty-day, 6-month, 1-year, and late mortality was 3.5%, 5.8%, 7.0%, and 12.8%, respectively. Intraoperative mortality during the index operation was zero, but 1 patient (1.2%) died during emergency surgery for rupture of the descending aorta 6 days after surgery for type A dissection. The majority of deaths (9 of 11, 82%) occurred in patients with a history of dissection, including 3 patients who experienced type B dissection during follow-up after uneventful elective surgery for aortic root disease. Two patients (18%) without a history of dissection died during follow-up. One was a patient with aortic root aneurysm and severe dilative cardiomyopathy who underwent heart transplantation and died as a result of Non-Hodgkin lymphoma 15 years after the initial surgery. The other patient was 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 and died of a malignant arrhythmia during the postoperative course.

Stroke occurred in 4.2% of patients, all of them in patients with a history of acute aortic dissection. There was no case of paraplegia, but 1 patient with paraparesis. Other complications are shown in Table 1, and causes of death are shown in Table 2.

Discussion

Aortic root disease predisposes MFS patients for the occurrence of life-threatening aortic dissection. Despite the wide availability of screening and prophylactic surgery, 36% of MFS patients operated on in our institution initially presented with acute dissection.

The rate of acute type A dissections in the current series (28%) is comparable with recent studies, where 16% to 28% of the patients present with acute type A dissection. Bentall procedures at initial presentation were performed in 47% of
patients compared with 40% in a similar study. Cameron et al. from Johns Hopkins Hospital recently reported a series of 372 patients over the last 30 years where almost 90% of patients in the last 5 years received VSRR. In our cohort, half of the patients in the nondissection group received a valve-sparing root replacement. Compared with the Hopkins experience, the percentage of patients presenting with acute type A dissection in our institution was much higher; 4.4% versus 28%. In the present series none of the patients with acute dissection underwent a VSRR procedure. We are not opposed to VSRR in patients presenting with Stanford type A dissection, but would only consider performing VSRR in young patients who present with uncomplicated type A dissection without signs of myocardial or visceral ischemia or neurological impairment. Otherwise, a composite graft, which gives predictable long-term results and limits time on cardiopulmonary bypass, is performed.

In 8 patients in our early experience who experienced Stanford type A dissection where the diagnosis of MFS was not established at the time of surgery, there was no significant aortic root dilation and in an emergency situation the procedure was limited to isolated replacement of the ascending aorta. The need for reoperation as a result of aortic regurgitation in our series is significantly higher in the Yacoub than in the David group. As reported by several groups, the rate of annular dilation and valve incompetence is higher with the Yacoub technique than after a David procedure. The remodeling technique represents our early experience with VSRR and was abandoned in favor of the reimplantation technique.

Although endovascular surgery is generally not recommended for MFS patients because of poor tissue quality and ongoing dilation even after technically successful stentgraft implantation, 2 patients with MFS underwent TEVAR to bridge a short aneurysmal segment between 2 polyester grafts.

It is difficult to estimate whether root replacement actually triggers disease progress in downstream aortic segments as has been suggested recently. Re-interventions on the distal aorta after proximal repair resulting from type A dissection are mostly precipitated by residual dissection in the downstream...
aorta. Therefore, no statement regarding the rate of new dissections after successfully repaired type A dissection can be made. There is only 1 patient in the study population with a truly unrelated type B dissection after completely excluded type A dissection. We can only state that in the present series, reoperation on the distal aorta was significantly more frequent in patients with a history of dissection than in patients undergoing elective aortic root surgery.

For MFS patients undergoing elective root repair, type B dissection poses a serious threat throughout follow-up. All except 1 patient in the present study undergoing interventions on the distal aorta after elective proximal aortic repair experienced type B dissection. Only in rare cases there seems to be a direct correlation in terms of a clamp injury or a dissection originating at the distal anastomosis.

Therefore, even if elective root replacement by a prosthesis would constitute a risk factor for downstream aortic dissection (because of the loss of the elastic properties of the root or clamp injuries of the aorta) it is obviously outweighed by the risk of type A dissection if timely proximal repair is not performed.

In a recently published cohort of MFS patients with a history of aortic dissection, Mimoun and colleagues observed a clinical event in 52% of the patients within a follow-up period of 9.8 years. In our present series, reoperations on the distal aorta were significantly more frequent in patients with a history of dissection than in patients undergoing elective aortic root surgery.

In the current study population, 79% of patients underwent genetic testing and 79% of these carried pathogenic mutations. There were no significant differences regarding rate of dissection (32% versus 43%; \(P=0.53\)) or later repair of nontreated aortic segments (26% versus 29%; \(P=1.0\)) between patients with or without pathogenic mutations. Even when looking at these groups of patients separately, the main determinant for later repair of previously nontreated aortic segments was history of acute dissection. In the group of patients with confirmed pathogenic mutations, 76% of patients with a history of dissection underwent later repair of previously nontreated aortic segments, whereas this was the case in 67% of patients without a pathogenic mutation. Of course this observation is biased by the fact that many patients with a clear phenotype, being known for having MFS since childhood, have not been genotyped and mostly undergo elective surgery before acute dissection occurs.

Our 30-day, 6-month, and 1-year (3%, 6%, and 7%, respectively) mortality compares favorably with other published reports, especially considering the higher rate of patients with acute dissection. Our overall mortality is still quite favorable with 13% after a mean follow-up of 8.8±6.8 years. As expected, survival was better in the group without history of dissection, compared with the group with a history of dissection. We think that analyzing late mortality is crucial to optimize treatment of patients with MFS. Although it is not surprising that the majority of deaths are patients with a history of dissection, it seems important to point out that it is not only the direct perioperative mortality that is increased in these patients. Causes of death in patients with a history of dissection included aortic rupture shortly after acute type B dissection, perioperative stroke in type A dissection, intracerebral hemorrhage 4 months after aortic root surgery resulting

<table>
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<tr>
<th>Complications</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Tachyarrhythmia</td>
<td>7 (5.1)</td>
</tr>
<tr>
<td>Hemorrhage needing intervention</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve paralysis</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Phrenic nerve injury</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Postcardiotomy syndrome</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Paraparesis</td>
<td>1 (0.7)</td>
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</tbody>
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<table>
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<tr>
<th>Causes of death</th>
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<tbody>
<tr>
<td>Aortic rupture shortly after acute type B dissection*</td>
</tr>
<tr>
<td>Malignant arrhythmia after mitral valve replacement, aortic root surgery and tricuspid valve repair</td>
</tr>
<tr>
<td>Perioperative stroke in type A dissection*</td>
</tr>
<tr>
<td>Intracerebral hemorrhage 4 mo after aortic root surgery due to type A dissection*</td>
</tr>
<tr>
<td>Stroke during coronary angiography 6 mo after surgery for type A dissection*</td>
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<tr>
<td>Aortic rupture during femoral hernia repair*</td>
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<tr>
<td>Aortic rupture 11 yr after surgery for type A dissection*</td>
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<tr>
<td>Multiorgan failure in Non-Hodgkin lymphoma</td>
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<tr>
<td>Myocardial infarction 3 mo after surgery for type A dissection*</td>
</tr>
<tr>
<td>Rupture of descending aorta 6 days after root surgery for type A dissection*</td>
</tr>
<tr>
<td>Congestive heart failure 5 yr after last surgery*</td>
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</table>

*Asterisk (*) indicates patients with a history of dissection at primary presentation or at any time during follow up. Each cause represents a single patient.
from type A dissection, stroke during coronary angiography 6 months after surgery for type A dissection, aortic rupture during femoral hernia repair, aortic rupture 11 years after surgery for type A dissection, myocardial infarction 3 months after surgery for type A dissection, and rupture of descending aorta 6 days after root surgery for type A dissection.

**Conclusion**

In conclusion, 1/3 of MFS patients still present with acute dissection, despite the increasing awareness of connective tissue disease, improved screening, and the wide availability of elective surgery. Furthermore, our study confirmed that true long-term follow-up is mandatory to avoid adverse aortic events in patients with MFS. The current data suggest that in patients with MFS, the need for surgery on initially nontreated aortic segments is primarily determined by an initial presentation with acute dissection. Furthermore, in patients with MFS, type B dissection constitutes a strong predictor for the need of reintervention in primarily nontreated aortic segments even if the dissection is being considered uncomplicated by conventional criteria.

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**Disclosures**

None.

**References**


**Clinical Perspective**

Aortic root disease predisposes patients with Marfan syndrome (MFS) for life-threatening acute aortic disease. Prophylactic aortic root surgery to prevent acute aortic dissection has contributed to improved survival in MFS patients over the past decades. Despite the wide availability of screening and prophylactic surgery, one-third of MFS patients in our institution initially presented with acute aortic dissection. Almost half of these patients had to undergo reinterventions on the distal aorta compared with only 11% of patients in the group without initial dissection. Interestingly, the majority of patients in the latter group who had to undergo reinterventions experienced type B dissection in the meantime. Patients with Stanford type B dissection are significantly more likely to undergo surgery on the distal aorta than those with type A dissection. In our study, type B dissection occurred in one-fifth of patients at some point during follow-up. In these patients the need for subsequent surgery is driven by rapid enlargement rather than the absolute diameter. Therefore, MFS patients presenting with type B dissection should remain under close surveillance as two-thirds of patients underwent surgery within the first year after the event. In summary, the need for surgery in primarily nontreated aortic segments in MFS is precipitated by an initial presentation with acute aortic dissection. Early elective surgery is associated with low mortality and reintervention rates. Type B dissection in patients with MFS is associated with a high need for extensive aortic repair even if the dissection is being considered uncomplicated by conventional criteria.
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