Dissection in Marfan syndrome: the importance of the descending aorta

Lea Mimoun1, Delphine Detaint1, Dalil Hamroun2, Florence Arnoult1,3, Gabriel Delorme1, Mathieu Gautier1, Olivier Milleron1,4, Catherine Meuleman1,5, François Raoux1,6, Catherine Boileau1,7,8, Alec Vahanian1,9, and Guillaume Jondeau1,6,9*

1Service de Cardiologie, Centre de référence pour les syndromes de Marfan et apparentés, Hôpital Bichat, AP-HP, 46 rue Henri Huchard, 75018 Paris, France; 2INSERM U827, Univ Montpellier 1, France; 3Explorations fonctionnelles, Hôpital Bichat, AP-HP, 75018 Paris, France; 4Service de Cardiologie, CHU Le Raincy-Montfermeil, 10 rue du Général Leclerc, 93370 Montfermeil, France; 5Service de Cardiologie, Hôpital St Antoine, AP-HP, 75012 Paris, France; 6Hôpital Marie Lannelongue, 133 Avenue de la Résistance, 92350 Le Plessis Robinson, France; 7INSERM U698, Hôpital Bichat, 75018 Paris, France; 8Hôpital Ambroise Paré, Laboratoire Central de Biochimie d’Hormonologie et de Génétique moléculaire, AP-HP, 92100 Boulogne, France; and 9Université Paris 7, Paris, France

Received 19 June 2010; revised 6 September 2010; accepted 13 October 2010; online publish-ahead-of-print 8 December 2010

Aims
To better characterize patients with Marfan syndrome who have survived an acute aortic dissection and to estimate the risks of events in the descending aorta. Up until now, this portion of the aorta has not been well studied but is gaining importance due to improved patient survival.

Methods and results
We report a retrospective cohort of 100 Marfan patients who survived an aortic dissection. Dissection occurred in either the ascending aorta (AscAo) (n = 37), the descending aorta (DescAo) (n = 20), or both (Asc + DescAo, n = 43). During a mean follow-up of 9.8 ± 6.0 years (complete for 88% of the patients), 17 patients died and 52 had a clinical event (new aortic dissection, surgery, ischaemia, haemorrhage), 60% of which involved the descending aorta. Event-free survival was similar whatever the location of the aortic dissection. However, a better event-free survival was observed when no dissected portion of the aorta remained after surgery, which was the case in 62% (23/37) of the AscAo patients (30% incurred an event vs. 86%; P = 0.008 by log-rank test).

Interestingly, the diameter of the ascending aorta was below the surgical threshold in 60% of the patients who incurred a dissection of the descending aorta, and within the normal range in 25%.

Conclusion
The descending aorta may dissect whatever the diameter of the ascending aorta. The descending aorta is the location of most late clinical events after any dissection of the aorta. The rate of clinical events is much lower when all the dissected aorta has been removed in patients with AscAo dissection.

Keywords
Marfan syndrome • Aortic dissection • Descending aorta

Introduction
Marfan syndrome (MFS) is a connective tissue disorder with autosomal dominant inheritance and a prevalence of around 1/5000, mostly related to mutations in the gene coding for fibrillin 1 (FBN1).1 Fibrillin 1 is a ubiquitous protein and FBN1 mutations induce modifications in many organs. The cardinal features of the MFS involve the ocular, cardiovascular, and skeletal systems,2 but aortic enlargement and dissection, mostly of the ascending aorta, was the primary cause of early death before 1970.3 However, the life expectancy of MFS patients has improved by 30 years over the last 30 years4,5 as the result of medical therapy and monitoring of the aortic root diameter allowing for preventive aortic root replacement.6 Therefore, complications other than those occurring in the ascending aorta are becoming more important in patients with the MFS.

It is well recognized that both the ascending and descending aorta are abnormal in the MFS: fibrillin 1 is present in the entire aortic wall—both ascending and descending—and the aorta has been repeatedly shown to possess abnormal elastic properties at the abdominal level.7–9 Dilatation or dissection of the descending aorta is regarded as the most serious complication of the disease.10 However, the diagnosis of descending aortic dissection and its management have not been clearly defined.11 A recent study conducted by our group has highlighted the fact that the descending aorta is the most frequent location of late events in patients with Marfan syndrome.12

We report a retrospective cohort of 100 Marfan patients who survived an aortic dissection. Dissection occurred in either the ascending aorta (AscAo) (n = 37), the descending aorta (DescAo) (n = 20), or both (Asc + DescAo, n = 43). During a mean follow-up of 9.8 ± 6.0 years (complete for 88% of the patients), 17 patients died and 52 had a clinical event (new aortic dissection, surgery, ischaemia, haemorrhage), 60% of which involved the descending aorta. Event-free survival was similar whatever the location of the aortic dissection. However, a better event-free survival was observed when no dissected portion of the aorta remained after surgery, which was the case in 62% (23/37) of the AscAo patients (30% incurred an event vs. 86%; P = 0.008 by log-rank test).

Interestingly, the diameter of the ascending aorta was below the surgical threshold in 60% of the patients who incurred a dissection of the descending aorta, and within the normal range in 25%.

Conclusion
The descending aorta may dissect whatever the diameter of the ascending aorta. The descending aorta is the location of most late clinical events after any dissection of the aorta. The rate of clinical events is much lower when all the dissected aorta has been removed in patients with AscAo dissection.

Keywords
Marfan syndrome • Aortic dissection • Descending aorta

* Corresponding author. Tel: +33 1 40 25 68 11, Fax: +33 1 40 25 67 32, Email: guillaume.jondeau@bch.aphp.fr
Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oup.com.
Methods

Population

All patients who came to our outpatient clinic between 1996 and 2008 were considered for this retrospective study performed using the patient files. Diagnosis of the MFS was based on Ghent criteria, which were evaluated in all the patients, although mutation screening and dural ectasia were performed only when felt necessary. Evaluation of diagnostic accuracy according to the revised Ghent nosology (retrospective evaluation) was also performed. Inclusion criteria of our study were age >18 years, confirmed diagnosis of the MFS, and presentation and survival of an aortic dissection. This is, therefore, a series of consecutive patients seen in our outpatient clinic, who had both aortic dissection and the MFS.

According to the extent of the first aortic dissection they presented with, patients were classified as one of three groups: ascending aorta alone (AscAo), entire aorta (Asc + DescAo), or descending aorta alone (DescAo). The limit between ascending and descending aorta was defined by the left subclavian artery. The AscAo group was subdivided according to the completeness or incompleteness of the dissected aorta removal. In the other groups (Asc + DescAo and DescAo), no patients had complete removal of the dissected aorta due to the medical management of the dissected descending aorta.

Collection of data

Clinical and demographic data were collected at three points: at the time of (i) the first aortic dissection, (ii) the first visit to our centre after the first aortic dissection (echocardiographic data obtained at this time were used for all the patients), and (iii) the end of the follow-up which was set at 1 September 2009 (either the last visit to our clinic or a phone call to the patient or family member when necessary). Current standard follow-up proposed for the patients following dissection of the descending aorta includes complete imaging of the aorta (i.e. both thoracic and abdominal) after 3 months, 6 months, and yearly thereafter. This can be done using a CT scanner (ECG-gated MSCT, with contrast injection) or a 3D MR angiography with injection of gadolinium chelate.

After aortic dissection, when the diagnosis of the MFS was recognized, the medical treatment included (i) beta-blocker therapy, which is systematically given in our outpatient clinic to all Marfan patients (with or without aortic dissection), (ii) ACE-I when tolerated, and additionally (iii) diuretics or other antihypertensive agents when necessary so that systolic blood pressure remains <120 mmHg. This is systematically verified by ambulatory measures of blood pressure. This protocol is in keeping with the recent recommendations (AHA). Echocardiography

All patients underwent protocolized comprehensive echocardiographic examination. Two-dimensional parasternal long-axis views at the end-diastole were used to measure aortic diameters according to the method of Roman et al. at four levels: aortic annulus, sinuses of Valsalva, supra aortic ridge, and proximal ascending aorta 1–2 cm above the aortic ridge. Z-scores were calculated using Roman monograms.

Echocardiographic data obtained during the first visit after the occurrence of the aortic dissection were used.

Data presentation and statistics

Descriptive data are presented as median value (25–75th) or percentages as appropriate. Aortic diameters are expressed in absolute values in millimetres and as Z-score (number of standard deviation above the mean) according to Roman et al. Comparisons between groups used either the non-parametric test (Kruskall–Wallis) or χ² as appropriate. Regarding the follow-up analysis, we analysed a combined endpoint of mortality or cardiac events (aortic surgery, symptomatic extension of the dissection, ischaemic or haemorrhagic event, aortic valve replacement, aortic rupture or pre-rupture). Survival curves were constructed using Kaplan–Meier analysis and comparison between groups used the log-rank test. P-values <0.05 were considered significant. The statistical software used is Jump 7.0.1.

Results

Population

One hundred adult Marfan patients underwent an aortic dissection and survived the event. They represent 12.8% (100/791) of the Marfan population seen in our clinic over the 1996–2008 period. In half of the patients [51 (51%)], the MFS was already diagnosed at the time of the dissection.

Aortic dissection was localized to the AscAo in 37 patients, Asc + DescAo in 43, and DescAo in 20 patients. All these patients fulfilled the criteria according to the revised Ghent nosology (see Supplementary material online, Table S1). Genetic screening was performed in 71 patients, allowing recognition of an FBN1 mutation in 57 (80%), a TGFBR2 mutation in 6 (8%), and a TGFBR1 mutation in 1 (1.4%). No difference in age of occurrence of aortic dissection [39 (30–44) vs. 37 (32–45) vs. 32], sex (51 vs. 57% vs. 1/1 female), or evolution (data not shown) could be found according to the gene affected (FBN1 vs. TGFBR2 vs. TGFBR1). Table 1 shows the clinical characteristics of the patients according to the location of the dissection. Patients who presented a DescAo dissection were significantly older than other patients. Aortic root replacement for aortic dilatation preceded the first aortic dissection in two patients with AscAo, one patient with Asc + DescAo, and seven patients with DescAo dissections (Figure 1).

Echocardiographic data at first visit after the dissection

Diameter of the aortic root

All patients in the AscAo and Asc + DescAo groups had aortic root replacement prior to the first examination; therefore, aortic root diameters were not available at the time of aortic dissection (Table 1, Figure 2).
Concerning the DescAo group (n = 20), seven patients had undergone previous elective aortic root replacement prior to dissection of the descending aorta and one patient had a second dissection on the ascending aorta requiring emergency aortic root replacement before his visit to our centre. Hence, the native aortic diameter at the level of Valsalva was only available for the 12 remaining patients. It was 36.5 (35.0–42.5) mm, i.e. 2.2 (1.7–2.8) SD above the mean according to Roman. This diameter was measured for aortic root dilatation was managed medically.

**Additional procedures included coronary-aortic bypass grafting in four patients.**

**Asc + DescAo group: patients with a dissection of the entire aorta (n = 43)**

Surgery was performed in 42 patients, including 29 Bentall associated with aortic arch replacement in 2 patients; 9 supra coronary grafts associated with aortic arch replacement in 1 patient; 3 valve-sparing procedures associated with aortic arch replacement in 1 patient, and replacement of both the aortic arch and the descending thoracic aorta in 1 patient (Figure 1).

One patient who had a prior elective aortic root surgery performed for aortic root dilatation was managed medically.

Additional procedures included coronary-aortic bypass graft in two patients, mitral valve replacement in one patient, and a mitral valve repair in one patient.

In this group, no patients had complete removal of the dissected aorta.

**DescAo group: patients with a dissection limited to the descending aorta (n = 20)**

Initial management was medical in all patients (Figure 1). However, a replacement of the descending aorta was required in three

---

**Table 1** Population and aortic diameters

<table>
<thead>
<tr>
<th></th>
<th>AscAo (n = 37)</th>
<th>Asc + DescAo (n = 43)</th>
<th>DescAo (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics at the time of the dissection, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20 (54)</td>
<td>21 (49)</td>
<td>12 (60)</td>
<td>0.700</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32 (29–37)</td>
<td>36 (32–45)</td>
<td>40 (36–51)</td>
<td>0.0005</td>
</tr>
<tr>
<td>MFS previously diagnosed</td>
<td>19 (51)</td>
<td>18 (42)</td>
<td>14 (70)</td>
<td>0.109</td>
</tr>
<tr>
<td>Mutations: FBN1/TGFBR2/TGFBR1</td>
<td>17 (46)/2 (5)/1 (3)</td>
<td>28 (65)/3 (7)/0</td>
<td>12 (60)/1 (5)/0</td>
<td>0.687</td>
</tr>
<tr>
<td>Previous elective aortic root surgery</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>7 (35)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Peripartum (% of female)</td>
<td>7 (35)</td>
<td>3 (14)</td>
<td>3 (25)</td>
<td>0.257</td>
</tr>
</tbody>
</table>

| **Clinical characteristics at the time of the first visit to our clinic after dissection** |                 |                       |                 |         |
| Height (cm)          | 181 (172–189)  | 178 (174–188)         | 178 (172–184)   | 0.620   |
| BSA (m²)             | 1.9 (1.7–2.1)  | 1.9 (1.8–2.1)         | 1.9 (1.7–2.1)   | 0.709   |
| Systolic blood pressure (mmHg) | 130 (120–145) | 140 (130–150)         | 140 (112–150)   | 0.084   |
| Heart rate (/min)    | 62 (57–74)     | 66 (60–76)            | 65 (55–72)      | 0.682   |
| Smoking status: former/current | 4 (11)/3 (8) | 9 (22)/ 3 (7)         | 3 (18)/1 (6)   | 0.870   |

| **Aortic diameters at the time of the first visit to our clinic after dissection (mm)** |               |                       |                 |         |
| Delay with the dissection (years) | 2.5 (0.7–9.0) | 1.1 (0.6–7.0)         | 2.9 (0.9–5.4)   | 0.361   |
| Diameters of Valsalva sinus | —             | —                     | 36 (35–42)      |         |
| Diameters of the aortic arch | 26 (24–29)    | 27 (26–31)            | 25 (21–28)      | 0.182   |
| Diameters of the thoracic descending aorta | 22 (20–24)   | 34 (29–40)            | 29 (23–41)      | <0.01   |
| Diameters of the abdominal aorta | 21 (17–27)   | 28 (24–33)            | 30 (22–39)      | 0.019   |

---

**Concerning the DescAo group (n = 20), seven patients had undergone previous elective aortic root replacement prior to dissection of the descending aorta and one patient had a second dissection on the ascending aorta requiring emergency aortic root replacement before his visit to our centre. Hence, the native aortic diameter at the level of Valsalva was only available for the 12 remaining patients. It was 36.5 (35.0–42.5) mm, i.e. 2.2 (1.7–2.8) SD above the mean according to Roman. This diameter was measured for aortic root dilatation was managed medically.**

Additional procedures included coronary-aortic bypass grafting in four patients.

**Asc + DescAo group: patients with a dissection of the entire aorta (n = 43)**

Surgery was performed in 42 patients, including 29 Bentall associated with aortic arch replacement in 2 patients; 9 supra coronary grafts associated with aortic arch replacement in 1 patient; 3 valve-sparing procedures associated with aortic arch replacement in 1 patient, and replacement of both the aortic arch and the descending thoracic aorta in 1 patient (Figure 1).

One patient who had a prior elective aortic root surgery performed for aortic root dilatation was managed medically.

Additional procedures included coronary-aortic bypass graft in two patients, mitral valve replacement in one patient, and a mitral valve repair in one patient.

In this group, no patients had complete removal of the dissected aorta.

**DescAo group: patients with a dissection limited to the descending aorta (n = 20)**

Initial management was medical in all patients (Figure 1). However, a replacement of the descending aorta was required in three
patients because of rapid dilatation of the dissected descending aorta, and a fenestration was performed in one patient because of renal ischaemia.

In this group, no patients had complete removal of the dissected aorta.

Long-term follow-up of MFS patients who survived an aortic dissection (>30 days)

Just over half of the patients, 52 (52%), incurred a clinical event during the follow-up of 9.8 ± 6.0 years. Follow-up was complete in 88% of the patients (death or last visit to our centre after 1 September 2009 or phone call otherwise). Seventeen patients died and 78 events occurred in these 52 patients. Event-free survival was better after complete removal of dissected aorta (Figure 3; \( P = 0.008 \)). Most of the events (60%, 47/78) affected the descending aorta (either symptomatic extension of the dissection to the descending aorta or surgery required by dilatation of the descending aorta) (Figure 1):

- In the AscAo group, 23 patients had complete removal of all dissected aorta. One of these patients died. Nine events occurred in seven of these patients (30%) and six of these
events (67% of events) affected the descending aorta. Fourteen patients from this group had incomplete removal of the dissected aorta, and five of these patients died. Twenty-one events occurred in 12 of these patients (86%) and 12 of the 21 events (57%) affected the descending aorta.

* All patients in the other groups had incomplete removal of the dissected aorta. Among the 43 patients of the Asc + DescAo group, 8 patients died, and 20 (47%) patients incurred 31 events, 17 of which (55%) affected the descending aorta. Among the 20 patients of the DescAo group, 3 patients died, 13 patients (65%) incurred 17 events, and 12 of these (70%) affected the descending aorta.

**Discussion**

Surgical and medical management of the MFS have improved over the last 30 years, allowing patients to survive an acute ascending aortic dissection. The increase in life expectancy has resulted in the emergence of descending aorta complications. We report here the largest series of MFS patients having survived an acute aortic dissection, and our main observations are as follows:

* The descending aorta is affected in two out of three patients during aortic dissection, and is the site of most complications which occur during follow-up.
* Aortic dissection limited to the descending aorta can occur in patients without dilatation of the ascending aorta.
* In the AscAo group, when all the dissected aorta had not been removed, event-free survival was significantly worse.

**Descending aorta dissection**

Dissection of the descending aorta was associated with dissection of ascending aorta in 43% and was isolated in 20% of cases. Similar rates of initial aortic dissection of the descending aorta were reported by others, 18% of the patients registered in the Euro Heart Survey, and 16% of the patients reported by Finkbohner et al.

Although the ascending aorta is the first affected, it is well established that the entire aorta is abnormal in patients with the MFS. This has been suggested by histological studies showing that elastin fibres and microfibrils are important structural components, even if they are found in diminishing quantities from the proximal to the distal aorta. The elastic properties of the abdominal aorta have repeatedly been shown to be abnormal. Because of the benefit of prophylactic aortic root replacement and improved survival of patients, it may be expected that events occurring in the descending aorta will become an increasing problem in this population, and the ability to predict their occurrence in order to prevent them may be of increasing importance.

**Predictors of dissection of the descending aorta**

However, data concerning the prediction of events in the distal aorta are very scarce. The diameter of the aortic root is a key parameter to predict further adverse events. This is true not only for the ascending aorta, but also for the descending aorta: previous indication for aortic root replacement is associated with increased risk of event on the descending aorta, even in the absence of any previous dissection.
Intuitively, the converse is expected (i.e. the absence of risk of dissection of the descending aorta if the aortic root is not dilated). We clearly show that this is not true: >50% of the dissections limited to the descending aorta occurred in patients with aortic root diameter <50 mm. Furthermore, in 25% of cases, the aortic root diameters were within normal limits after adjustments for age, height, and weight according to Roman. The clinical consequence is that prevention of aortic dissection with beta-blockade, today the only established therapy for this purpose, should be proposed to all patients even without dilatation of the ascending aorta.

Besides aortic root diameter, predictors for events occurring in the descending aorta in MFS patients free from aortic dissection include diameter of the distal aorta, aortic compliance, previous aortic root replacement, hypertension, and aortic regurgitation. Previous elective aortic surgery is associated with a larger distal aortic diameter even after adjustment for sex and age, and an increased diameter of the distal aorta is associated with a higher risk of aortic events. This also emphasizes the importance of medical protection of the entire aorta, after prophylactic aortic root surgery. The native aorta remains at risk.

**Descending aorta: localization of complications**

Surviving an aortic dissection clearly places the patient in a high-risk group: 52% of our patients presented an event during a 9.8 ± 6.0 year follow-up period. This rate was 25% during a 5.4 year follow-up period for the 26 patients reported in the Euro Heart Survey.

Furthermore, after an aortic dissection, the descending aorta becomes the main region at risk: it was the site of more than half of the events that we observed, whereas most of the events in non-dissected patients occurred in the ascending aorta. Actually, surgery for dissected aneurysm on the descending aorta or aortic arch if dissected is the most frequent complication observed.

Song et al. indicate that the most powerful independent predictor of late aneurismal change in MFS patients with aortic dissection is the initial diameter of the false lumen at the upper thoracic aortic level. In our population, complete resection of all dissected aortic segments was associated with a better event-free survival (Figure 3). Kazui et al. have shown that an aggressive surgical approach for aortic dissection, including aortic arch replacement, reduced the necessity for late reoperation. In the series of MFS patients reported by Tagusari et al. in the subgroup of patients with a dissection, intact aortic arch was a strong predictor of event-free survival, and replacement of the dissected aortic arch was associated with a reduced number of late reoperations. Several small studies share this observation, suggesting that a complete aortic arch repair should be considered and in particular that aortic arch replacement should be performed when the aortic arch is dissected.

**Implications**

Although the descending aorta appears to have become an important target for management in patients with the MFS, the recommendations proposed are poor, mainly due to the absence of data. Accounting for the difficulties of surgery on the descending aorta, it is clearly impossible to propose this type of preventative surgery without having identified clear prognostic markers. The aortic diameter of a descending aorta remains the best indicator, and current practice is to recommend surgery above 6–6.5 cm or an expansion rate ≥1 cm/year or occurrence of symptoms. Stenting is discouraged in the MFS. Blood pressure should be kept low (systolic blood pressure <120 mmHg) to delay dilatation and the need for risky surgery, and strict control should be evidenced using ambulatory measurements.

The goal, however, should be to prevent dissection of the descending aorta. The first means of ensuring this is to operate on patients with aortic root dilatation before dissection of the ascending aorta occurs, as dissection of the descending aorta is an extension of a dissection of the ascending aorta in more than half of patients. The second is to propose preventative medical management in patients with the MFS whatever the diameter of the ascending aorta (sport limitation and beta-blocker therapy).

**Limitations**

The retrospective nature of our study is a limitation, although a prospective study would hopefully be of limited power due to low event rates with improved patient care. Only patients who survived the first dissection were considered, so we cannot report on operative risk and early deaths. Lastly, owing to the low prevalence of the pathology, aortic dissection occurred from 1987 to 2007, a long period during which surgical techniques, imaging, and medical treatment have improved, so that, hopefully, the ominous prognosis that we report is a pessimistic view of the actual evolution of patients. It remains, however, important and valuable to describe the natural history of the disease.

**Conclusion**

The importance of the descending aorta is under-recognized in the MFS population, and may increase over the years owing to the progress made in the care of the proximal aorta. Twenty per cent of the dissections occurring in our population were limited to the descending aorta. Importantly, this can occur in patients with a non-dilated aortic root or in patients after aortic root replacement, indicating that every patient is at risk and should benefit from medical care including beta-blocker therapy.

After an aortic dissection of the ascending aorta, complete removal of the dissected aorta is associated with a better long-term prognosis. The descending aorta is the place where the majority of the events occurred after a first dissection and should be regularly imaged to evaluate early or late dilatation.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Funding**

This study was supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique).

**Conflict of interest:** none declared.
References


