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ORIGINAL ARTICLE

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Long-term outcome of patients with Marfan syndrome with previous aortic surgery but native aortic roots

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Key question

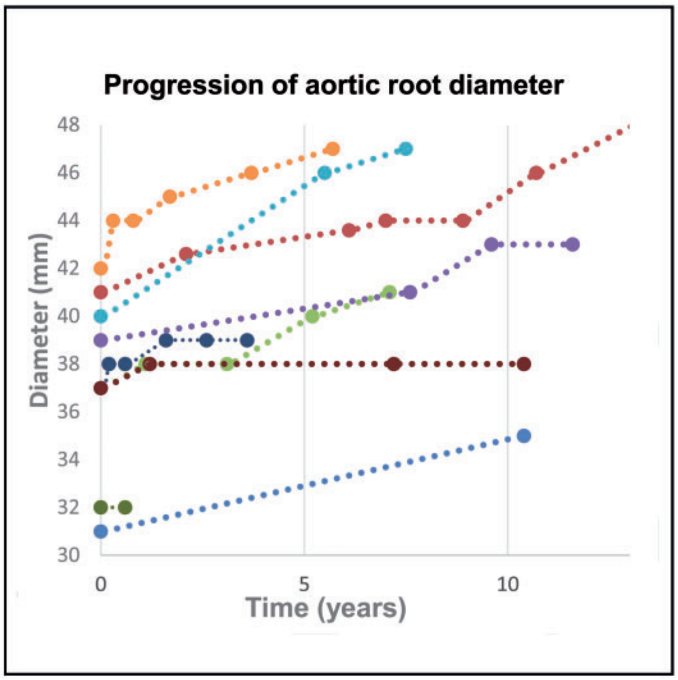
Do all patients with Marfan syndrome need to undergo aortic root replacement over time?

Key finding(s)

10% of patients with previous aortic surgery will be free from aortic root replacement until the sixth decade of life.

Take-home message

Although there is a steady increase in aortic root diameters in patients with Marfan syndrome throughout their lifetime, 10% remain free from root surgery.



Abstract

OBJECTIVES: The goal of this study was to report the long-term outcomes of patients with Marfan syndrome who had aortic surgery on any aortic segment except for the replacement of the aortic root itself.

METHODS: An observational retrospective single-centre study was conducted with 115 Marfan syndrome patients who underwent 189 major aortic interventions from 1995 until 2018. Patients without aortic root replacement were identified and aortic root growth was analysed over time.

RESULTS: Eleven of 115 patients (9.5%) did not have aortic root replacement during a follow-up of 10.5 [standard deviation (SD) 5.7] years and a mean age at last follow-up of 53.9 (SD 13.4) years. Patients without root replacement did not suffer less frequently from any type of acute aortic dissection (type A 27% vs 25%, *P* = 0.999; type B 36% vs 25%, *P* = 0.474). Patients with native aortic roots did not undergo fewer

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aortic interventions than those with aortic root replacement [12/11, mean 1.09 (SD 0.54) operations/patient vs 177/104, mean 1.7 (SD 1.3); P = 0.128]. Progression of the aortic root dimension was 0.5 (SD 0.3) mm/year in the group of patients with native aortic roots.

CONCLUSIONS: Current data suggest that 10% of patients with Marfan syndrome with previous aortic surgery will be free from aortic root replacement until the sixth decade of life.

Keywords: Marfan syndrome • Aortic root • Aortic surgery • Aortic dissection

ABBREVIATIONS

CI	Confidence interval
CT	Computed tomography
MFS	Marfan syndrome
SD	Standard deviation
SE	Standard error

INTRODUCTION

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by mutations in the gene encoding for the extracellular matrix protein fibrillin-1 [1] leading to dysregulation of the transforming growth factor-beta signalling pathway [2]. Aortic root dilatation and subsequent root replacement are thought to be integral parts of the natural history of patients with MFS. Ever since the first aortic root replacement performed by Bentall in 1968 [3] and the valve-sparing aortic root replacement techniques described by David (1992) and Yacoub (1993), an increasing number of reports have focused on the surgical management of aortic root aneurysms in this patient population [4], whereas data concerning MFS patients with native aortic roots remain scarce. The goal of this study was to report the long-term outcomes of patients who underwent aortic surgery on any aortic segment except for replacement of the aortic root itself.

PATIENTS AND METHODS

Data from 115 consecutive MFS patients fulfilling the 2010 revised Ghent criteria who underwent 189 major aortic operations and were followed at this institution since 1995 were analysed retrospectively (Fig. 1). Eighty percent of these patients carried pathogenic mutations. Patients were included if they had undergone at least 1 intervention on any segment of the aorta. Patients were evaluated using electrocardiographically gated computed tomography (CT) angiography. During follow-up, magnetic resonance imaging was performed to reduce the radiation exposure. Using multiplanar reformatting, the maximum aortic root diameter was measured perpendicular to the axis of the left ventricular outflow tract. Patients were analysed with regards to freedom from aortic root interventions during follow-up. Aortic root growth was measured over time. The study was approved by the regional ethics committee (approval no. 2019-01534). Informed consent was waived because of the retrospective nature of the study and because the analysis used anonymous clinical data. All data were gathered in a standardized database using the Research Electronic Data Capture system. An observational design was used that conformed with the Strengthening the Reporting of Observational Studies in Epidemiology statement [5].

Statistical analyses

Values are given in mean/median, standard deviation (SD)/standard error (SE)/range, when appropriate. In addition to descriptive statistics, data underwent a Kaplan–Meier survival analysis, determining aortic root intervention-free survival as well as overall survival. T0 was determined as the time of the first aortic operation. Analysis was performed using Prism version 8.00 for Windows (GraphPad Software, La Jolla, CA, USA). The Fisher's exact test was used to compare categorical variables. Univariable comparison between the 2 groups (native root and root replacement) was done using the log-rank test, whereas the number of aortic interventions in the 2 groups was compared using an unpaired *t*-test. A Fine and Gray competing risk analysis was performed to assess death as a competing factor for the event aortic root surgery. Finally, a linear regression analysis was performed to look for a correlation between initial root dimension and growth rate. Tests were conducted without adjustment or a prespecified plan for multiple testing and were exploratory in nature.

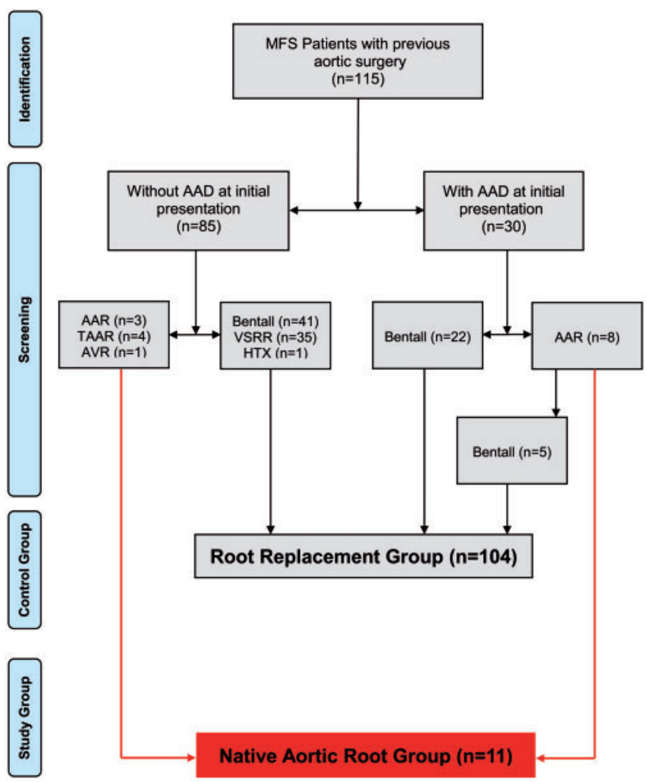

Figure 1: Flow chart showing patient selection. AAD: acute aortic dissection; AAR: ascending aortic replacement; AVR: aortic valve replacement; HTX: heart transplant; MFS: Marfan syndrome; TAAR: thoraco-abdominal repair; VSRR: valve-sparing root replacement.

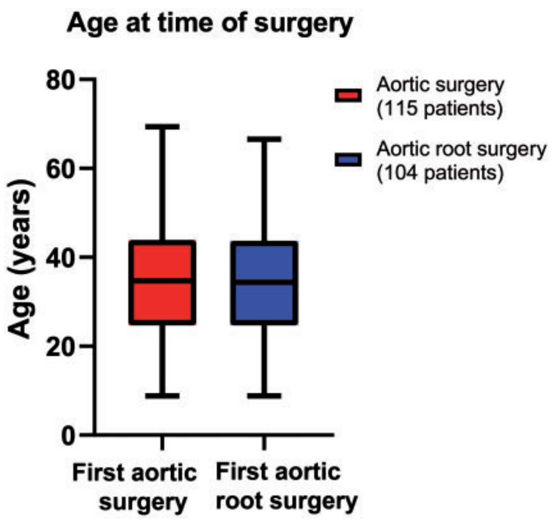

Figure 2: Box-and-whiskers plot showing age at time of first aortic surgery and first aortic root surgery.

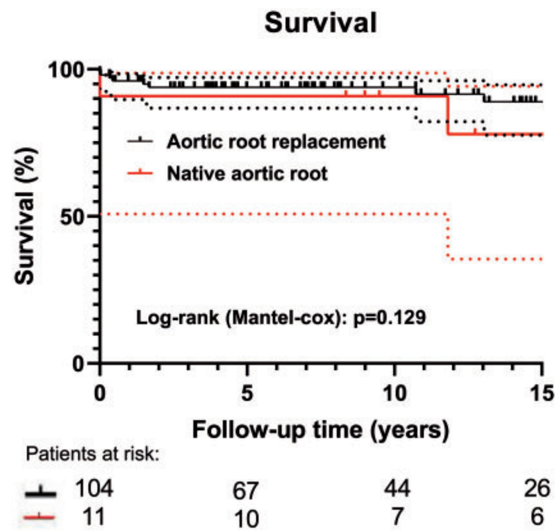

Figure 4: Kaplan–Meier curves with 95% confidence intervals demonstrating overall survival of these 2 groups.

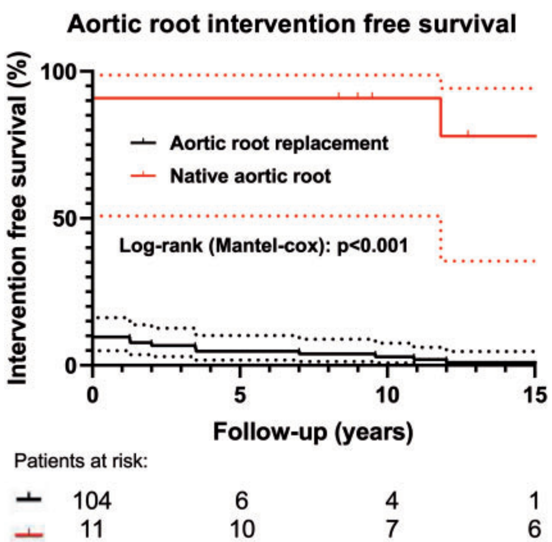

Figure 3: Kaplan–Meier curves with 95% confidence intervals demonstrating the aortic root intervention-free survival of the 2 groups.

RESULTS

A total of 115 patients with MFS were followed for a mean duration of 9.7 (SD 7.6) years. The mean age at the first aortic surgical procedure was 35.2 years (SE 1.2) [95% confidence interval (CI) 33–38] whereas the mean age at the first aortic root procedure was 34.8 years (SE 1.3) (95% CI 32–37) (Fig. 2). Eleven out of 115 (9.5%) patients did not undergo aortic root replacement during the follow-up period of 11.3 (SD 6.0) years, and the mean age at last follow-up was 53.1 (SD 13.1) years in the native aortic root group. Aortic root intervention-free survival of the entire patient population was 13% (SE 3.1), 11% (SE 2.9), 7.7% (SE2.6) and 3.8% (SE 2.3) at 5, 10, 15 and 20 years, respectively (Fig. 3). Death prior to aortic root replacement in the native group was excluded as a competing event through a Fine and Gray analysis, which demonstrated a subhazard ratio of 1.3 and a non-significant χ^2 test result of 0.59.

Aortic root replacement was performed in 104 patients who were followed for 9.7 (SD 7.7) years. There was no significant difference in follow-up duration between the 2 groups ($P = 0.758$). The mean aortic root diameter at the time of surgery was 51 (SD 11) mm. A modified Bentall procedure was performed in 68 (65%) patients, whereas 35 (34%) patients underwent valve-sparing procedures (David, $n = 30$; Yacoub, $n = 5$) [6]. One patient had a heart transplant due to concomitant end-stage heart failure. In the group of patients with aortic root replacement, 17 had thoraco-abdominal aortic repairs whereas 22 arch procedures were performed in 21 patients. Eleven reoperations were required following valve-sparing procedures: 6 aortic valve replacements, 3 redo-root replacements and 1 revision of the proximal anastomosis due to pseudoaneurysm formation.

One patient had a biological aortic valve replaced 3 years after a Yacoub procedure because of progressive aortic valve insufficiency. The same patient had a Bentall procedure 7 years later because of early graft degeneration. Five patients had aortic root replacement as a secondary aortic procedure following ascending aortic replacement for a Stanford type A dissection due to progressive dilatation or aortic valve regurgitation, respectively.

Survival

There were no significant differences (Fig. 4) in survival among patients with native aortic roots compared to those who had root replacements. Survival in the aortic root replacement group at 1, 5, 10 and 15 years was 96% (SE 1.9), 93.8% (SE 2.4), 93.8% (SE 2.4) and 88.9% (SE 4.1), whereas survival in patients with native aortic roots was 90.9% (SE 8.7), 90.9% (SE 8.7), 90.9% (SE 8.7) and 72.7% (SE 17.7). Patients without root replacement did not have significantly fewer types of acute aortic dissections [type A aortic dissection 27% (3/11) vs 25% (27/104), $P = 0.999$; type B aortic dissection 36% (4/11) vs 25% (26/104), $P = 0.474$]. Of note, none of the patients in the native aortic root group who had a type A aortic dissection was known to have an enlarged aortic root or ascending aorta. At the time of the operation, the aortic

Table 1: Overview of the 11 patients with native aortic roots at the end of the follow-up period

Gender	BMI	AD type A	AD type B	Extracardiac manifestations	First intervention	Second intervention	Age at last FU	Root size at baseline (mm)	Root size at last FU (mm)	Radiological FU duration (years)
m	25				TAR		54	31	35	10.4
f	21.4		x	S/p spine surgery	TAAAR	MVR	45	41	48	13.1
m	21.8				AVR		34	37	41	7.1
f	22		x	S/p bilateral amotio retinae	AAA		68	39	43	11.6
f	24.9				AAR, CABG		67	40	46	7.5
m	23.7	x			AAR		44	42	47	5.7
m	22.2		x		AAR, AVR, MVR		51	37	39	3.6
f	17.9			Severe bilateral myopia	AAR, MVR		45	37	39	10.4
m	19.8		x		TAR, DAR	TAAAR	Died at 53	32	32	0.6
m		x			AAR	DAR	Died at 50	-	-	-
f		x			AAR, TAR		Died at 82	-	-	-

Colours correspond to curves in Fig. 5.
AAA: abdominal aortic replacement; AAR: ascending aortic replacement; AD: aortic dissection; AVR: aortic valve replacement; BMI: body mass index; CABG: coronary artery bypass grafting; DAR: descending aortic replacement; FU: follow-up; MVR: mitral valve repair; TAAAR: thoraco-abdominal aortic aneurysm repair; TAR: total arch replacement.

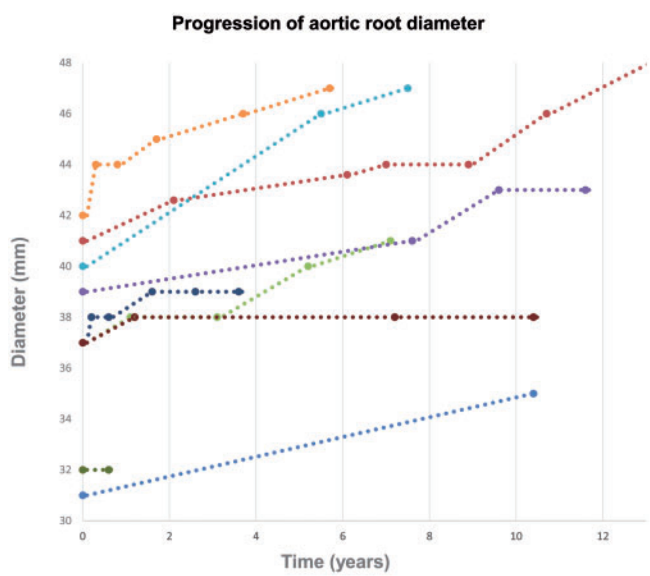

Figure 5: Progression of aortic root diameter (in millimetre) in patients with Marfan syndrome with native aortic roots (9/11 patients) during the follow-up period (in years).

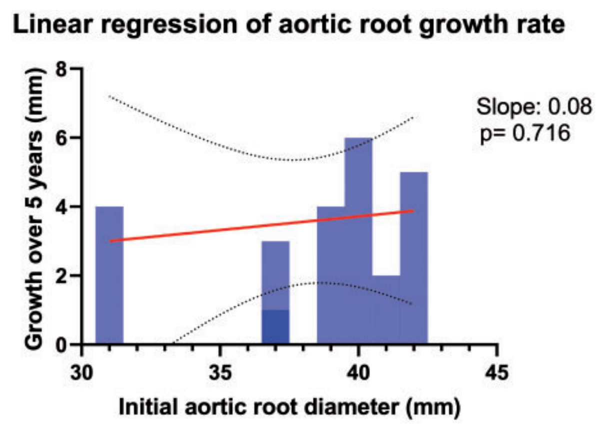

Figure 6: Linear regression of the aortic root growth rate in correlation with the initial root size over 5 years in 7 patients. Note that 2 patients had an initial root size of 37 mm.

root was not severely dilated and the diagnosis of MFS was not yet established.

There was no statistically significant difference between the 2 groups regarding the number of aortic interventions performed. Patients in the native aortic root group underwent 1.09 ± 0.54 aortic procedures (n = 12/11) compared to 1.7 ± 1.3 (n = 177/104) in patients with root replacement (P = 0.128). Replacement of the ascending aorta was the most common aortic intervention and was performed in 54% (6/11) of patients in the native aortic root group. Details regarding procedures in patients with native aortic roots are shown in Table 1.

The diagnosis of MFS was made preoperatively in only 2 patients of the native root group: A 35-year-old woman presented with severe mitral valve regurgitation due to bileaflet prolapse. She exhibited a very mild phenotype including dilatation of the ascending aorta without involvement of the aortic root or aortic valve. It was decided to replace only the ascending aorta at the time of mitral valve repair. The initial aortic root diameter was 37 mm and reached 39 mm after 10 years of follow-up.

A 24-year-old woman with a history of postpartum type B aortic dissection and subsequent need for thoraco-abdominal repair underwent mitral valve repair due to symptomatic severe mitral valve regurgitation 14 years later. The aortic root diameter at the time of valve repair was 43 mm. At the end of the 27-year follow-up period, the maximum aortic root diameter was 48 mm.

Mortality

There were 3 deaths during the follow-up period in the native root patient group: (i) a 50-year-old man died during emergency surgery for a descending aortic rupture 4 days after ascending aortic and partial arch replacement due to type A dissection; (ii) an 81-year-old woman had an aortic arch rupture 11 years after aortic valve and ascending aortic replacement following subacute type A aortic dissection. The patient refused surgical treatment and died 4 days later. (iii) A 53-year-old patient developed multi-organ failure after redo thoraco-abdominal repair 16 years after distal arch and descending aortic repair.

Aortic root growth

Imaging of the aortic root was available for all patients. For 1 patient, the preoperative CT scans were not available for review. Echocardiography showed a non-dilated aortic root. Reassessment using CT scanning at the 10-year follow-up examination demonstrated a maximal aortic root diameter of 36 mm. Results are shown in Fig. 5. The mean aortic root growth rate in MFS patients with a history of aortic surgery but with native aortic roots was 0.5 ± 0.3 mm/year. The specific values of the individual patients show homogeneous growth over time. Using linear regression analysis (Fig. 6) in 7/11 patients who had imaging follow-up for at least 5 years, we could show that there was no significant correlation ($P = 0.716$) between the initial root dimension and the rate of dilatation. However, there was a trend towards a slight acceleration (slope of 0.08) that could only be confirmed in a larger patient cohort.

DISCUSSION

Acute aortic dissection due to an aortic root aneurysm is the leading cause of death in patients with MFS. Although this situation is unfortunately still true for patients who are unaware of their disease, acute type A dissection is rare in MFS patients who are closely followed in a specialized centre. In a large series of 732 patients published by the Paris group, the event rate was 0.17% per year. Surgery was recommended at an aortic diameter of 50 mm [7]. Most larger MFS series focus on the various aspects of the aortic root aneurysm and the technical aspects of aortic root surgery. In a recent series of 165 patients with MFS operated on at Johns Hopkins Hospital, Baltimore, MD, USA, patients were only included in the study if they had undergone aortic root replacement at this institution and independently of any aortic interventions that occurred before this event [6]. Aortic root aneurysm is one of the determining phenotypic features of MFS, and it is therefore often assumed that all MFS patients will undergo aortic root surgery at some point. Nevertheless, while caring for patients with MFS over a long period of time, we have seen that not all patients have to undergo aortic root surgery or even have a severely dilated aortic root despite a clear diagnosis of MFS [8]. Because all patients in the study had aortic surgical procedures, patients with a familial form of ectopia lentis syndrome without cardiovascular involvement are excluded by default. In a recently published report by the Yale group, the average mean annual growth rate in 78 patients with MFS was 2.6 ± 0.5 mm/year, with a wide range of 1.3–3.5 mm. The authors demonstrated that large aneurysms grow faster, an effect also seen in patients who do not have MFS [9]. The average aortic root growth seen in our study is in line with the results of a large observational study from the Netherlands with 221 Marfan patients. In this study, average aortic root growth rate was 0.42 mm/year in men and 0.38 mm/year in women. The Dutch group also improved their linear model by distinguishing fast- (1.5 mm/year in men and 1.8 mm/year in women) and slow-growing (0.36 mm/year in men and 0.27 mm/year in women) aortic roots. However, the patients in the Dutch registry were in general much younger than those in our study, with a median age of 25 years in men and 27 years in women [10]. The average age at the time of root replacement in one of the largest MFS experiences published to date by the Hopkins group was 35 years and therefore in line with our current results [11]. Given the preceding data, the number of patients who had aortic root surgery in a group of MFS patients is directly dependent on the age of the patients included. To avoid this bias, we only included patients who already had interventions on any aortic segment. Only by doing this did it become possible to compare those patients with and without aortic root replacement.

Our current report highlights several interesting points: About 10% of MFS patients will be free from aortic root replacement up to the sixth decade of life. These patients do not seem to have a high risk for acute aortic root dissection when they are seen regularly within a dedicated follow-up programme. The aortic root seems to grow linearly over time; we have seen no case of rapid expansion. In our view, these findings are important for decision-making in patients with suspected MFS but with a small aortic root who are undergoing aortic surgery as well as patients with unrepaired aortic roots in whom the ascending aorta was already replaced.

There was no difference regarding the number of magnetic resonance imaging/CT controls between the 2 groups. Most patients with unrepaired roots suffered from acute aortic dissection and needed close follow-up for this condition. The most important finding regarding these patients is the importance of making sure that they are never lost to follow-up. Even in patients with a stable aortic situation we recommend follow-up at least every third year. We have all seen patients who were lost to follow-up and then presented with a difficult-to-treat complication years after aortic surgery.

Indeed, we sometimes have difficulties deciding whether to replace the root in adolescent patients with MFS presenting with a severe myocardial infarction but an aortic root diameter of only 30 or 35 mm. Obviously, there is no clear answer to this problem. The current data indicate that the aortic root is continuously growing throughout the entire lifetime of these patients, regardless of whether the patient has already undergone surgery, and that aortic events are rare. Therefore, the indication for concomitant aortic root replacement is a function of age at a given aortic root diameter. It is a continuum: The larger the root and the younger the patient, the higher the risk that the patient will come back for a surgical procedure. We certainly try to perform a genetic analysis before the operation in elective cases to have a better understanding of how the aorta will develop over time. But, of course, the majority of adult patients with MFS do have aortic root aneurysms that clearly have to be addressed.

Furthermore, there are patients presenting electively with isolated ascending aneurysms. Although we all have the classical pear-shaped root in mind when thinking about MFS patients, the presentation can vary widely. Nowadays, the majority of the young patients with aneurysms undergo genetic testing and the detection rate of FBN1 mutations is much higher than it was 20 years ago.

We have learned that an acute event in patients with unrepaired aortic roots in whom the ascending aorta was already replaced seems unlikely as long as the aortic root is small. None of the 3 deaths in the native aortic root group was caused by dissection or rupture of the aortic root. Furthermore, there was no difference in the overall survival between the groups. Therefore, prophylactic replacement in diameters below the accepted thresholds for surgery does not seem to be necessary, even in patients with MFS. Current guidelines recommend elective aortic root replacement in MFS patients without risk factors at 50 mm. Reasons to intervene earlier are family history of dissection, diameter increase of 3 mm/year or severe aortic regurgitation. In female patients with MFS wishing to conceive, the threshold varies between 40 and 45 mm, depending on the guidelines. The recommended threshold in a redo situation is 55 mm, although these are not specific guidelines for MFS patients [12, 13]. With growing experience and prolonged life expectancy of MFS patients even after surgery for type A dissection, we now increasingly deal with patients with complex aortic disease from the aortic root to the aortic bifurcation. Every intervention performed has therefore to be seen within the larger context of the unrepaired aortic segments. This study therefore provides a small but important piece of information for clinicians taking care of patients with MFS. Current research [14] and findings in the field of genetics might contribute in the future to identifying more phenotype-determining modifier combinations. However, in the described population, genetic differences, if they existed, did not contribute to a difference in phenotype as shown by the non-significant differences in the numbers of procedures and the incidence of aortic dissection.

Limitations

This study has all the limitations that are inherent in a retrospective study. We analysed a highly selected patient subpopulation. The study as such is certainly underpowered to detect differences in survival but, because we were able to report a complete follow-up with a mean follow-up time of more than a decade, there is certainly some merit in this analysis, despite its exploratory nature. Furthermore, 2 different imaging modalities (MRI and CT scan) were used, which may have contributed to differences in assessing aortic root size.

CONCLUSIONS

Current data suggest that 10% of patients with MFS will be free from aortic root replacement to the sixth decade of life despite having undergone previous aortic surgery. Nevertheless, there is a slow but steady increase in aortic root dimension in all patients over the entire follow-up time. In the present population, patients with native aortic roots do not have a less severe vascular phenotype as measured by the number of aortic interventions performed. Patients with MFS remain at risk for aortic root events throughout their lifetime and preemptive surgery according to current guidelines is strongly recommended.

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Conflict of interest: none declared.

Author contributions

Selim Mosbahi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing—Original draft; Writing—review & editing. **Murat Yildiz:** Formal analysis; Investigation; Validation; Visualization. **Paul-Philipp Heinisch:** Formal analysis; Resources; Validation; Visualization; Writing—review & editing. **Bettina Langhammer:** Resources; Supervision; Validation; Visualization. **Silvan Jungi:** Investigation; Supervision; Validation; Visualization. **Thierry P. Carrel:** Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Florian S. Schoenhoff:** Conceptualization; Formal analysis; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

Reviewer information

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