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## CLINICAL RESEARCH

# Surgical management of patients with Marfan syndrome: Evolution throughout the years

Évolution des indications de la chirurgie chez les patients présentant un syndrome de Marfan

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*Abbreviations:* MFS, Marfan syndrome; TGF- $\beta$ , transforming growth factor-beta.

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**MOTS CLÉS**

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Dilatation aortique ;  
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Chirurgie aortique ;  
Chirurgie valvulaire  
mitrale

**Summary**

*Aim.* — To evaluate the evolution of surgical management in a large population of patients with Marfan syndrome.

*Methods.* — This is a retrospective study of patients fulfilling the Ghent criteria for Marfan syndrome, who visited the Centre de référence national pour le syndrome de Marfan et apparentés and underwent a surgical event before or during follow-up in the centre.

*Results.* — One thousand and ninety-seven patients with Marfan syndrome, according to international criteria, came to the clinic between 1996 and 2010. Aortic surgery was performed in 249 patients (22.7%; 20 children and 229 adults), including the Bentall procedure in 140 patients (56%) and valve-sparing surgery in 88 patients (35%); a supracoronary graft was performed in 19 patients (7.6%), usually for aortic dissection. During the past 20 years, the predominant reason for aortic surgery has switched from aortic dissection to aortic dilatation, while age at surgery has tended to increase (from  $32.4 \pm 11.9$  years to  $35.2 \pm 12.4$  years;  $P=0.075$ ). Mitral valve surgery was performed in 61 patients (5.6%; six children and 55 adults), including 37 valvuloplasties (60.6%) and 18 mitral valve replacements (29.5%). No significant difference was observed when comparing mitral valve surgery before and after 2000.

*Conclusion.* — Surgery performed in patients with Marfan syndrome has switched from emergency surgery for aortic dissection to elective surgery for aortic dilatation; this is associated with surgery performed at an older age despite the indication for surgery having decreased from 60 mm to 50 mm. No significant evolution was observed for mitral valve surgery.

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**Résumé**

*But.* — Apprécier l'évolution de la prise en charge chirurgicale des patients présentant un syndrome de Marfan.

*Méthodes.* — Étude rétrospective portant sur les patients qui ont été vu au Centre national de référence pour le syndrome de Marfan et apparentés, remplissant les critères de Ghent et ayant subi une intervention chirurgicale avant ou pendant leur suivi dans le centre.

*Résultats.* — Mille quatre-vingt dix-sept patients présentant un syndrome de Marfan selon les critères internationaux ont été vus entre 1996 et 2010. La chirurgie aortique a été pratiquée chez 249 (22,7% ; 20 enfants et 229 adultes), soit une intervention de Bentall ( $n=140$ , 56%), soit une intervention préservant la valve aortique ( $n=88$ , 35%). Chez les 19 derniers patients (7,6%), un tube sus-coronaire a été mis en place, en règle pour dissection aortique. Au cours des 20 dernières années, l'indication principale de la chirurgie a changé de dissection aortique à dilatation aortique, ce alors que l'âge de la chirurgie avait tendance à augmenter ( $32,4 \pm 11,9$  ans vs  $35,2 \pm 12,4$  ans, avant et après 2000 ;  $p=0,075$ ). La chirurgie valvulaire mitrale a été pratiquée chez 61 patients (5,6% ; six enfants et 55 adultes), à type de plastie chez 37 (60,6%) et de remplacement valvulaire chez 18 (29,5%). Les chiffres restent similaires avant et après l'année 2000.

*Conclusion.* — La chirurgie réalisée chez les patients présentant un syndrome de Marfan et autrefois principalement une chirurgie d'urgence pour dissection est maintenant surtout une chirurgie programmée pour dilatation aortique. Cela alors que les patients sont opérés plus tard alors que le seuil chirurgical a baissé de 60 à 50 mm. Les indications et le type de chirurgie mitrale n'ont pas évolué.

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**Background**

Marfan syndrome (MFS) is a connective tissue disorder with dominant autosomal inheritance and a prevalence of around 1/5000, mostly related to mutations in the gene coding for fibrillin 1 [1]. The cardinal features of 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]. Much progress has been made in the understanding of this disease, with the recognition of the role of fibrillin 1 [1], the

description of new pathologies related to mutations in transforming growth factor-beta (TGF- $\beta$ ) receptors [4–6], the implication of the TGF- $\beta$  pathway in aneurismal aortic diseases, etc. [7]. Advances have also been made in the global care of MFS patients, with the installation of "Centres de référence" and "Centres de compétence", through the "Plan maladies rares". In parallel, the life expectancy of MFS patients has improved by 30 years over the past 30 years [8], probably as a result of better recognition of the disease, diffusion of medical therapy (including beta-blockers) and monitoring of the aortic root diameter, allowing for

preventive aortic root replacement [9,10]. However, the modification of patient care during this period is not documented other than by surgical series, i.e. reflecting the evolution of care in specific high-volume centres. Besides, because the populations studied were usually not completely characterized according to international criteria, the series mostly comprise aortic aneurysm patients rather than MFS patients.

Here we take advantage of a large MFS population followed in a multidisciplinary medical clinic caring for MFS patients throughout the territory according to modern standards, to study the evolution of surgical care over the years.

## Methods

### Population

All patients who came to the Centre de référence pour le syndrome de Marfan et apparentés between 1996 and 2010 were considered for this retrospective study, which was performed using the patient files. Diagnosis of MFS was based upon the Ghent criteria, which were evaluated systematically in all patients, except for mutation screening and dural ectasia detection, which were performed only when considered necessary for diagnosis or optimal patient or family care. To be included in this study, patients had to have a confirmed diagnosis of MFS and to have undergone a surgical event (either aortic or mitral). This is therefore a series of consecutive patients seen in our outpatient clinic who had been operated on because of MFS.

Surgery could have been performed either before the patients came to the Centre de référence or during follow-up, in different places, although usually in France.

### Surgery

#### Aortic surgery

Only surgery of the ascending aorta was considered in this study. Aortic surgery was divided into supracoronary grafting versus replacement of the sinuses of Valsalva. Within surgery including replacement of the sinuses of Valsalva, valve-sparing surgery was distinguished from the Bentall procedure using either a bioprosthesis or a mechanical aortic valve. The reason for surgery was also evaluated (aortic dissection or aortic dilatation). Because aortic valve regurgitation is secondary to aortic dilatation in this population and requires surgery for an aortic diameter above our surgical threshold (50mm), aortic surgery was considered to be performed for aortic dilatation even if in a few patients aortic regurgitation may have been the revealing factor.

#### Mitral valve surgery

Mitral valve replacement was distinguished from mitral valve preservation.

### Data presentation and statistics

Descriptive data are presented as mean value  $\pm$  standard deviation or frequency and percentage, as appropriate. The  $\chi^2$  test was used to compare percentages and the Wilcoxon rank-sum test was used to compare age at surgery before and after 2000.

## Results

A total of 4218 patients were screened for MFS in our clinic between 1996 to 2010; 57% lived in Paris or a close suburb, while the remainder came from all over the French territory. Of these, 1097 fulfilled the Ghent criteria for MFS (540 men and 557 women); 356 were first seen as children (i.e. aged < 18 years) and 741 were first seen as adults; the mean age at last consultation was  $32.2 \pm 16.7$  years.

Surgery of the ascending aorta was performed in 249 patients, i.e. 22.7% of the whole population, comprising 20 children (5.6% of the children) and 229 adults (30.9% of the adult population). Aortic surgery included aortic valve replacement in 140 patients and aortic valve sparing in 88 patients (two unknown). In the remaining 19 patients (7.6%), a supracoronary graft was performed, i.e. in 92.4% of the patients, the sinuses of Valsalva were replaced. The reason for surgery was aortic dilatation in 67% of patients and aortic dissection in the remaining 33%. A supracoronary graft was performed mainly when aortic dissection was the reason for surgery (14/19 patients).

Surgery of the mitral valve was performed in 61 patients (5.6%), comprising six children (1.7% of the children; five valvuloplasties and one mitral valve replacement) and 55 adults (4.8% of the adults; 37 valvuloplasties and 18 mitral valve replacements).

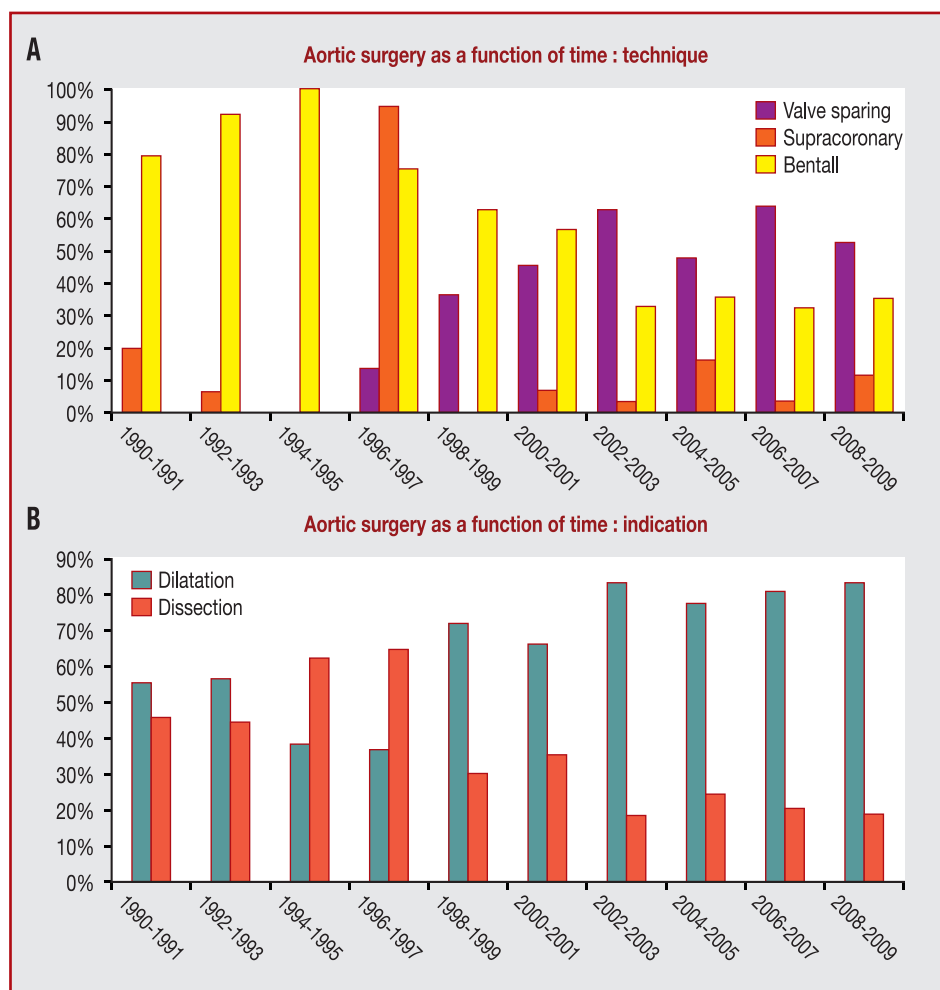
During the past 20 years, important changes in surgical practice have occurred (Fig. 1): The main reason for aortic surgery has changed from aortic dissection to aortic dilatation (which represented 54% of aortic valve surgery before 2000 vs 77% after 2000;  $P < 0.0001$ ). The type of aortic surgery has switched from aortic valve replacement to aortic valve-sparing surgery (18% before 2000 vs 59% after 2000;  $P < 0.0001$ ). However, these changes were not due to earlier aortic surgery as the patients who had operations on the ascending aorta before 2000 tended to be slightly younger than patients operated on during or after 2000 ( $32.4 \pm 11.9$  years vs  $35.2 \pm 12.4$  years;  $P = 0.076$ ; Fig. 2).

When comparing the 146 patients who were operated on before their first visit to our centre with the 103 patients operated on after their first visit to our centre, many variables differed: age at first visit to our centre was older ( $38.0 \pm 11.7$  years vs  $31.3 \pm 12.3$  years;  $P < 0.01$ ), reason for surgery was more frequently aortic dissection (43.0% vs 8.8%;  $P < 0.01$ ) and aortic valve replacement was more frequent (80.8% vs 35.7%;  $P < 0.001$ ), whereas surgery was performed at a similar age ( $33.4 \pm 11.8$  years vs  $34.9 \pm 12.8$  years;  $P = 0.33$ ).

The percentage of mitral valve surgery in which valvuloplasty was performed remained roughly stable over the years (65% of mitral valve surgery before 2000 vs 73% after 2000;  $P = 0.46$ ; Fig. 3). The age at which surgery was performed was also similar before and after 2000 ( $29.5 \pm 11.5$  years vs  $30.4 \pm 15.5$  years;  $P =$  not significant; Fig. 2).

## Discussion

Patients with MFS have benefited from many improvements in both diagnosis and care. Diagnosis has improved due to increased awareness of the disease in the medical population and better organization of medical care for patients

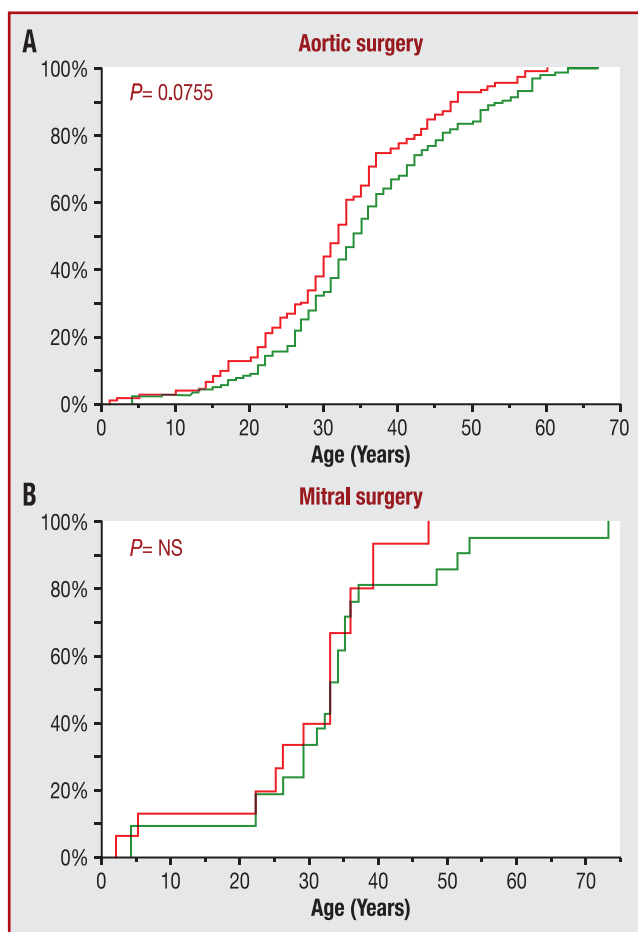


**Figure 1.** Evolution of aortic surgery as a function of time. A. Evolution of surgical techniques: percentage of the population operated on with different surgical techniques according to year. Valve-sparing aortic surgery has become the preferred technique and the Bentall procedure is becoming less frequent; supracoronary grafting remains marginal. B. Evolution of reasons for surgery: percentage of the population operated on for aortic dissection or dilatation according to year. The reason for aortic surgery switched from aortic dissection to aortic dilatation.

with rare diseases, along with voluntary political action in some countries such as France. This has led to an increased rate of familial screening, secondary to an increased understanding of the genetic nature of the disease by the medical community, as well as increased availability of genetic testing, which is used more and more [11]. Echocardiography is now readily available and aortic root follow-up is standardized [12], with clear recommendations being issued [9,13]. Medical care has been standardized, with an indication for beta-blockade in all patients with MFS, or calcium antagonists [14] when beta-blockers are not tolerated. New therapies such as losartan are being tested in randomized trials [15–18]. Aortic root surgery has transformed the prognosis of patients with MFS: before the Bentall procedure was described in 1968 [19] survival was limited by aortic complications [3]. Since the description of the initial technique, numerous improvements have been proposed and more recently, aortic valve-sparing surgery techniques have been described [20–23]. Both medical and surgical improvements have led to an increase in survival expectancy of at least 30 years over the past 30 years [8].

From the surgical viewpoint, reports have been issued by surgical reference centres, indicating the change in their practice from the classical Bentall procedure to valve-sparing surgery: in a study at Johns Hopkins University that included 372 patients, 61% had a valve-sparing procedure in the past 8 years, whereas 85% received a Bentall graft during the first 24 years of the study [24], with excellent results. Other surgical centres have reported results after the Bentall procedure or valve-sparing operations, usually in populations including patients with and without MFS. Recent reports indicate that valve-sparing surgery is a valuable alternative to the Bentall procedure [25].

Our cohort is made up of patients who came at least once to the “Centre national de référence”, as labelled by the French Ministry of Health. Patients came by themselves or were referred to our centre from all over France (57% came from Paris or a close suburb, while the remainder were from other parts of France). Included in this population were patients who were operated on in our centre, as well as patients who had undergone surgery on in other centres, either because they had been operated on before coming to



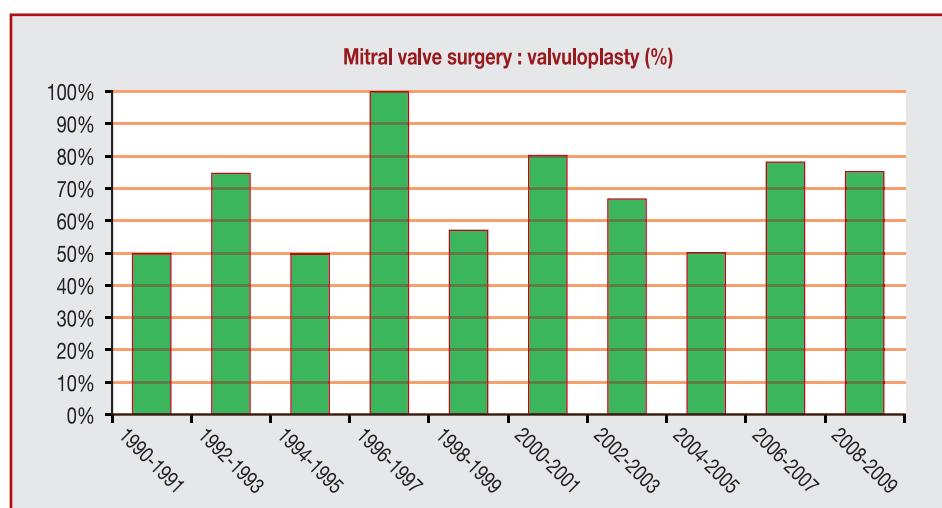
**Figure 2.** Age at which (A) aortic surgery or (B) mitral surgery was performed before and after the year 2000. In red, patients operated on before 2000; in blue, patients operated on after 2000. NS: not significant.

our centre or because of their choice. The cohort therefore provides information on the standard care of the patients and care provided recently by the more up-to-date centres. Three main observations can be made.

There has been a modification of the surgical technique, with a switch from the classical Bentall procedure to valve-sparing operations, while supracoronary grafting remains marginal. Supracoronary grafting is still used in the context of aortic dissection by numerous surgeons.

There has been a modification in the indication for surgery, with a switch from aortic dissection to aortic dilatation as the main reason for performing surgery. This is particularly rewarding for cardiologists because it indicates that diagnosis is now made before an acute (often dramatic) aortic event reveals the disease in a patient. One might think that this would be associated with surgery performed at an earlier age, but mean age at surgery tended to increase when operations performed after 2000 were compared with those performed before 2000. This is particularly impressive as, during the same period, the aortic diameter threshold for prophylactic aortic surgery progressively decreased from 60 mm to 50 mm [13,24–28] and was even lower in some recommendations [29], but not all [30], including a recent recommendation from the ESC [13]. A consensus seems to have been obtained that 50 mm is a reasonable threshold for proposing surgery in a standard patient with MFS [31]. This observation may result from different factors, the most optimistic being that medical therapy (i.e. beta-blockade and information about sports), which is now more widely used because of better recognition of the disease, is effectively delaying the need for aortic surgery in these patients. But it is also possible that other factors are involved, such as increased awareness of the disease in the medical community, better organization of care with the Plan maladies rares and better availability of information for patients, with active associations enabling diagnosis in those with less severe involvement (e.g. through effective familial screening), resulting in a reduced or delayed need for surgery.

There have been no significant modifications in the rate and mode of mitral valve surgery. This would suggest that



**Figure 3.** Evolution of mitral surgery as a function of time: percentage of the population operated on with valvuloplasty or mitral valve replacement according to year. No clear trend is apparent.



no major improvement in mitral valve surgery has been made during this period. We have to recognize first that the numbers are much lower, as only a small percentage of the population will undergo mitral valve surgery whereas almost 25% of our population have already undergone aortic surgery despite their young age (32.7 years). Furthermore, mitral valvuloplasty was described by Carpentier well before the new valve-sparing surgery for the aortic root, and mitral regurgitation is associated with symptoms that allow recognition of mitral regurgitation whereas aortic dilatation remains asymptomatic until aortic dissection occurs, as aortic regurgitation is rarely symptomatic in this population (because of moderate severity).

## Limitations

This study included patients who came to the Centre de référence pour le syndrome de Marfan et apparentés and therefore did not include all patients with MFS in the French territory. It is true that recognizing all patients with MFS remains a challenge, as indicated by the fact that the prevalence proposed for the disease has not been established after systematic screening of an unselected population, because its polymorphic nature renders systematic screening cumbersome and practically impossible on a large scale. Therefore, bias is possible in the selection of the population included in this study and the evolution of the surgery reported here could also reflect evolution in the referral bias. This appears to be unlikely, because also included were patients who came only once and patients who were operated on earlier or in other places, and because the Plan maladies rares has allowed clear recognition of the Centres de références throughout the territory.

## Conclusions

Our data illustrate that up-to-date care, including familial screening, yearly echocardiographic follow-up, systematic beta-blockade and scheduled surgery when the aortic diameter reaches 50 mm, has resulted in a change from emergency to elective surgery in patients with MFS. It is probable that other improvements are going to appear: on the medical side, there is great hope for losartan [32]; and on the surgical side, some new techniques have been proposed and are in the evaluation phase [33].

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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