Management of Aortic Disease in Marfan Syndrome

A Decision Analysis

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Background: Marfan syndrome is a relatively common heritable disorder of connective tissue that affects numerous organ systems, but the most severe complication is aortic aneurysm and dissection. A variety of medical and surgical approaches are available for managing the cardiovascular complications. Our objective was to compare elective composite graft surgery, elective valve-sparing surgery, and medical management for patients with both Marfan syndrome and thoracic aortic disease on the basis of life expectancy with differing diameters of the aortic root and rate of increase in the aortic root size.

Methods: A Markov decision analysis model was constructed to compare the 2 surgical options with watchful waiting with medical therapy.

Results: For our base-case analysis of a 20-year-old patient with Marfan syndrome and thoracic aortic aneurysm, the aortic valve-sparing option was preferred. It extended life expectancy to 73.8 years compared with the medical treatment option (71.4 years) and with the composite graft surgery (72.7 years). Our results show that there is a better outcome for a patient with an aortic root diameter between 3.0 and 3.5 cm with early prophylactic surgery than with deferred or emergency surgery. Medical treatment was preferred when the aortic root diameter was smaller than 3.0 cm.

Conclusions: Although long-term follow-up data are not yet available, it appears that advances in the technique of valve-sparing surgery have made it the preferred option to composite graft, primarily to avoid the complications of anticoagulation. Our study indicates that patients who have an aortic root diameter of larger than 3.0 cm should be considered for prophylactic aortic surgery.

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MARFAN SYNDROME (MFS), first described by the French pediatrician Antoine Marfan in 1896,[1] is an autosomal dominant inherited disorder of connective tissue associated with mutations in the fibrillin-1 gene.[2,3] Multiple tissues and organs, including the heart and aortic root,[4] are affected in MFS. Prognosis is mainly determined by progressive aortic root dilatation, potentially leading to aortic dissection and rupture.[5] In the 1970s, most patients with MFS died prematurely of aortic rupture or aortic regurgitation, often by the third decade of life.[5] Over the past few decades, however, developments in medical[6] and surgical management[7] of aortic disease in MFS, as well as better recognition of the syndrome, have resulted in markedly improved life expectancy up to approximately 70 years.[8,9]

More than 30 years ago, Halpern and colleagues[10] suggested a potential benefit of β-adrenergic blockade in protecting the aortic root in MFS. One prospective, randomized trial of propranolol[11] and several retrospective studies of other β-blockers and calcium channel antagonists[12,13] have supported this notion. Specifically, long-term oral treatment with β-adrenergic blockade both reduces the rate of aortic root dilatation and delays or prevents the development of aortic regurgitation and dissection.

Surgical treatment of the dilated or dissected aortic root in MFS has evolved over the past 30 years as well. The first important advance was the composite graft, consisting of a prosthetic valve fixed in a vascular conduit to which the coronary arteries were anastomosed. This technique, first devised by Bentall and De,[7] was so effective in reducing surgical mortality that some centers began prophylactic repair to prevent aortic dissection.[14] The continued excellent results in many reports worldwide have led to a progressive lowering of the aortic root diameter at which prophylactic repair is recom-

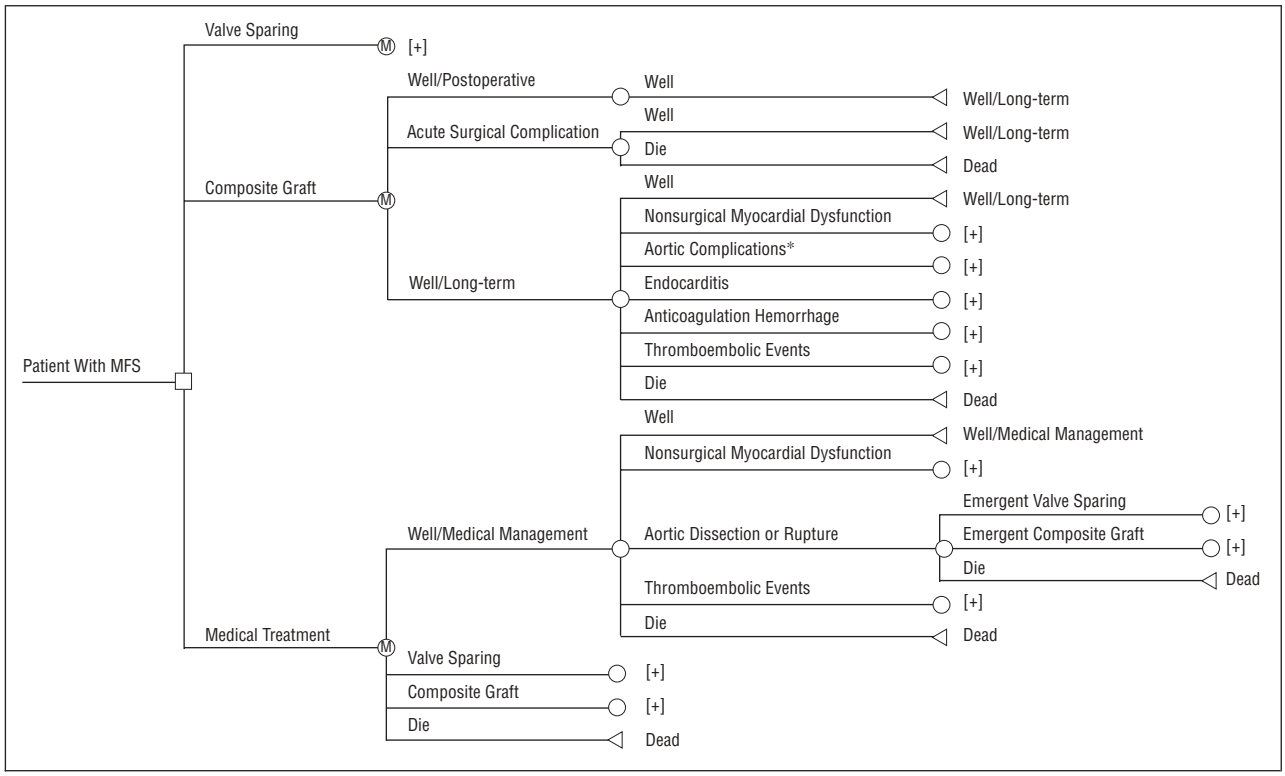

Figure 1. Simplified Markov decision analysis model. A square represents a decision node, and circles represent chance nodes. Circles with "M" inside represent Markov nodes, and triangles represent terminal nodes. The plus sign in brackets represents that continuation of tree branches is not shown. For illustrative purposes, only the subtrees for the composite graft and medical treatment option are shown. Patients could either die from or be treated successfully for medical events after the "well/long-term" state. If treated successfully, they would return to the well/long-term state. The asterisk indicates to include aortic aneurysm, dissection, rupture, or moderate to severe aortic valve insufficiency. MFS indicates Marfan syndrome.

mended.[8] The major complications directly related to composite graft repair are the morbidity associated with the lifelong need for oral anticoagulation and the small but real risk of endocarditis. Aortic homografts, composed of cryopreserved human cadaveric tissue, have been 1 alternative for very young patients or others who are at high risk of complications from anticoagulation.[8] However, homograft valves calcify and stiffen over time and rarely last more than a decade without needing to be replaced. Various techniques to preserve the native aortic valve while replacing the dilated sinuses of Valsalva and proximal ascending aorta have been introduced.[14,15] The obvious advantages of so-called valve-sparing procedures are avoidance of anticoagulation and a very low risk of thromboembolism and endocarditis. However, early approaches to valve-sparing ("remodeling" techniques) carried a substantial risk of early dilatation of retained sinus tissue and the appearance of aortic regurgitation.[16] Continued surgical evolution to the "reimplantation" techniques currently being used have seemingly improved short-term outcomes.[17] No randomized trials among any of these various surgical approaches and no direct comparisons of medical vs surgical therapy have been conducted. Furthermore, no formal clinical trials are likely to be performed.

In an attempt to investigate the outcomes, measured as life expectancy, of these various approaches to treating patients with MFS, we conducted a Markov decision analysis. The results provide support, in addition to personal and anecdotal experience, for the optimal management of individual patients.

METHODS

THE MODEL AND ASSUMPTIONS

We developed a Markov decision analysis model that compared 3 management strategies: (1) elective composite graft surgery, (2) elective valve-sparing surgery, and (3) medical treatment. The model was constructed using DATA Professional (Tree Age Software Inc, Williamstown, Mass). A hypothetical cohort of 20-year-old people with MFS was followed over their lifetimes. The life expectancy of patients was modeled by iterating the decision whether to operate on a yearly base. In the first year, patients were assigned to 1 of 3 strategies. With each 1-year cycle, patients moved to a different state or back to the same state depending on the probabilities of clinical events. Patients who were assigned to either the composite grafting or valve-sparing options underwent an elective operation. If patients in the valve-sparing group developed postoperative aortic complications that could not be controlled medically, they underwent another operation with a composite graft. Patients who started out in the medical management group were treated medically, and if they developed aortic dissection or rupture, they later received an emergent operation. In this situation, we assumed that 80% of patients had composite graft surgery and 20% of them received valve-sparing surgery. Patients in each group could die of either MFS-related causes, such as aortic complications, postoperative complications, myocardial dysfunction, endocarditis, thromboembolic events, anticoagulant hemorrhage, or non-MFS problems typical of the population at large. Our primary outcome measure was life expectancy in years. Only events associated with a risk of mortality affected the final outcomes. Morbidity or quality of life was not modeled.

Figure 1 illustrates a simplified and truncated version of the Markov decision analysis model that we constructed for the study. **Table 1** summarizes the key variables, the base-case estimates, and the range of values used in the sensitivity analysis of the model.[8,17-32]

DATA SOURCES

Most model parameters were determined from the published literature, except for 1 variable that was estimated by expert opinion as described in the following section. For key variables, the MEDLINE databases from 1966 to 2004 were searched by using the terms *Marfan syndrome, aortic root, dissection, composite graft,* and *valve-sparing surgery*. More than 100 articles were reviewed for data that could be used to generate estimates of 76 parameters (Table 1). This analysis incorporated recent data on valve-sparing surgery that has markedly improved the results and decreased the reoperation rate for long-term aortic complications.[16,17,23]

ANNUAL RISK OF AORTIC DISSECTION OR RUPTURE WITHOUT PROPHYLACTIC AORTIC SURGERY

Because no literature was available for this variable, we constructed a questionnaire to poll recognized experts in the field to estimate the annual risk of aortic dissection in a 20-year-old patient with MFS under various clinical scenarios. The questionnaire included 3 domains: the aortic root diameter varying from 3, 4, 5, 6, to 7 cm; the increase in aortic size from 0, 2, to 5 mm in the preceding year; and the presence or absence of family history of aortic dissection or rupture. Experts were asked to give their presumptive probabilities of aortic dissection in each combination of 3 domains. Using the responses from 5 recognized experts in MFS, we calculated average risk of aortic dissection in the given various patient scenarios (**Table 2**). An alternative source for these data would be meta-analysis if published estimates were available.

SENSITIVITY ANALYSIS

In general, the results obtained from a decision analysis depend on the accuracy of the data used to estimate the probabilities and outcomes. Even with data from very large population-based studies, it is rarely the case that estimates are known with complete certainty. To validate the decision analysis model, we performed sensitivity analysis, which examines the results when key variables are assigned values at the extremes of their possible ranges. We completed 1-way sensitivity analysis on all model variables over the full range of estimates as determined from the literature and expert opinion. Two-way sensitivity analyses were conducted using variables that were determined to be critical in 1-way sensitivity analyses.

Table 1. Base-Case Estimates and Ranges Used for Analysis*

Variable	Probability Base Case (Range), %/y	Reference
Annual risk of aortic dissection in Marfan patients		Expert opinion†
Without family history of aortic dissection	2.6 (0.1-50.0)	
With family history of aortic dissection	3.7 (0.1-50.0)	
Mortality of nonelective procedures		
Valve-sparing operation for aortic dissection	13.3 (5.6-18.2)	18, 19
Composite graft operation for aortic dissection	11.0 (5.6-18.0)	8, 18
Mortality of elective procedures		
Valve-sparing operation	0.1 (0-1.0)	8, 19-22
Composite graft operation	1.5 (0.7-3.3)	8, 18
Incidence of late aortic complications†		
After valve-sparing operation	5.8 (0-15.0)	8, 19, 23, 24
After composite graft operation	2.2 (1.3-4.0)	25
Reoperation for aortic complications		
After valve-sparing operation	3.2 (0-6.2)	17, 19, 23, 26
After composite graft operation	1.4 (0.5-3.0)	8, 27
Mortality of reoperation		
After valve-sparing operation	0.8 (0.8-10.0)	19, 26
After composite graft operation	4.5 (3.5-6.0)	24
Incidence of endocarditis		
After valve-sparing operation	0.2 (0-0.8)	24, 26
After composite graft operation	0.6 (0.5-1.5)	8, 17
In the composite group		
Incidence of anticoagulation hemorrhage‡	1.7 (0.2-3.0)	8, 24, 28-31
Mortality of anticoagulation hemorrhage	2.9 (0.03-3.0)	18, 30, 32
Incidence of thromboembolic complications		
After valve-sparing operation	0.03 (0-0.4)	8, 17
After composite graft operation	0.7 (0.5-2.0)	8, 17

*Only 18 of 76 key variables are listed.
†See "Methods" section for description.
‡Incidence of anticoagulation-related hemorrhage does not increase until the age of 75 years.[28,29]

RESULTS

BASE-CASE ANALYSIS

Using our model, we estimated life expectancy for 20-year-old people with MFS, varying the size of the aortic root and the rate of aortic dilation. In our base-case analysis, a patient with or without family history of aortic dissection or rupture was assumed to have an aortic root diameter of 5 cm and an increase in aortic root diameter of 2 mm in the preceding year. Our results show that the valve-sparing option extended life expectancy to 73.8 years compared with composite graft surgery (72.7 years) and the medical treatment option (71.4 years). If a patient has a family history of aortic dissection or rupture, the life expectancy in the medical treatment group would be shorter (70.6 years).

As the diameter of the aortic root increased from 3 to 7 cm, the life expectancy of patients with MFS decreased as shown in **Figure 2**. In our model, the aortic root size did not affect the outcome of 2 surgical options. The

Table 2. The Survey Results*

Aortic Root Diameter, cm	Probability of Aortic Dissection According to the Increase in Diameter in the Preceding Year, %					
	Without Family History of Aortic Dissection			With Family History of Aortic Dissection		
	0 mm	2 mm	5 mm	0 mm	2 mm	5 mm
3	0.3 (0.1-1.0)	0.3 (0.1-1.0)	0.5 (0.1-2.0)	0.7 (0.1-2.0)	0.7 (0.1-2.0)	1.1 (0.1-4.0)
4	0.7 (0.1-1.0)	1.0 (0.1-2.0)	1.5 (0.7-2.0)	1.2 (0.1-2.0)	1.5 (0.1-3.0)	2.1 (1.0-4.0)
5	2.0 (1.0-5.0)	2.6† (2.0-5.0)	4.9 (3.0-7.5)	3.1 (2.0-5.0)	3.7† (3.0-5.0)	7.3 (5.0-10.0)
6	9.2 (4.0-25.0)	10.6 (5.0-25.0)	15.6 (7.0-35.0)	11.8 (5.0-30.0)	13.4 (7.0-30.0)	18.2 (10.0-40.0)
7	20.2 (8.0-35.0)	21.8 (10.0-35.0)	28.8 (12.0-50.0)	24.9 (10.0-40.0)	26.2 (12.0-40.0)	33.6 (15.0-50.0)

*Numbers in parentheses are the range of the expert opinion.
†Used for the base-case analyses.

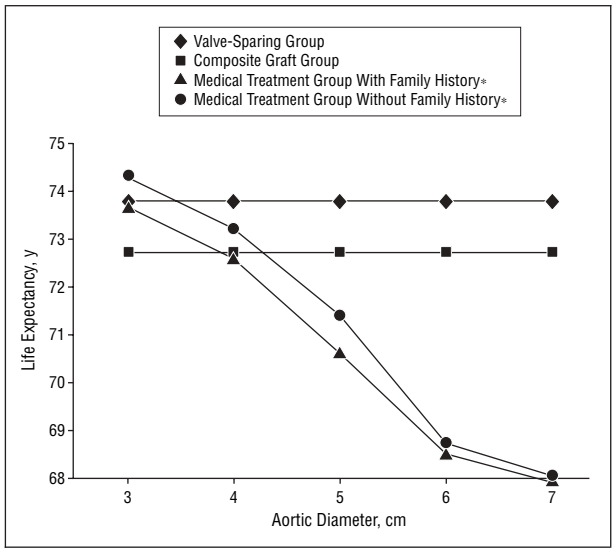

Figure 2. Changes in life expectancy in relation to the size of the aortic root (rate of aortic dilatation: 2 mm/y). The asterisk indicates with/without family history of aortic dissection or rupture.

medical treatment option was preferred for a patient with less than 3.5 cm of aortic root diameter in the absence of family history of aortic dissection and for a patient with smaller than 3.0 cm of aortic root diameter in the presence of family history of aortic dissection.

REASSESSMENT OF LIFE EXPECTANCY

We modeled a 20-year-old patient reevaluated after 5 and 10 years in terms of life expectancy. Because we assumed the aorta dilated at a linear rate of 2 mm per year, the patient who initially had an aortic root diameter of 3 cm attained 4 cm of aortic root diameter by the age of 25 years. Thus, the estimated life expectancy for a 25-year-old patient was 74.0 years with medical treatment if the patient did not have family history of aortic dissection or rupture. If a patient had a family history of aortic dissection or rupture, the life expectancy with the medical management decreased to 73.5 years. If the patient received elective surgery at the age of 25 years, the life expectancy would be 73.5 years after the composite graft surgery and 74.5 years after the valve-sparing surgery (**Table 3**). These results suggest that we can postpone prophylactic surgery in the patient with an initial aortic root diameter of 3 cm until the age of 25 years if family history of aortic dissection is not present. Extending the analysis to when the patient became 30 years old, the life expectancy would decline in the medically treated group to 73.3 years without family history of aortic dissection or rupture and 72.6 years with family history of aortic dissection or rupture. By contrast, the life expectancy was 74.2 years in the composite graft group and 75.1 years in the valve-sparing group. Results using 4- or 5-cm aortic root diameter at initial presentation and calculating life expectancy every 5 years were similar. The slight decline in life expectancy of a 25-year-old compared with a 20-year-old reflects modest nonlinearity of rupture estimates in these 2 age groups. Furthermore, age of presentation did not affect the management decision for elective surgery within the range that we investigated.

SENSITIVITY ANALYSES

In 1-way sensitivity analysis of the parameters given in Table 1, we found that our results were sensitive to 2 important variables. The medical treatment strategy was the best option for a 20-year-old patient with MFS and aortic disease until their risk of aortic dissection or rupture reached 0.7% per year. **Figure 3**A illustrates the result of sensitivity analysis on the probability of aortic dissection or rupture in the medical treatment group. One-way sensitivity analysis on the probability of late aortic complication after valve-sparing operation (Figure 3B) showed that the valve-sparing option would be preferred unless the incidence of late aortic complications, such as aortic dissection, rupture, dilatation, or insufficiency after initial valve-sparing surgery, exceeds the threshold of 12% per year. Two-way sensitivity analysis did not reveal any significant interaction between the variables.

LIFE EXPECTANCY IN THE MEDICAL TREATMENT GROUP

The risk of aortic dissection is believed to be predominantly influenced by 3 factors: aortic root diameter, rate of aortic root enlargement, and family history of aortic dissection or rupture. **Figure 4** illustrates the overall

Table 3. Life Expectancy by Aortic Root Diameter and Treatment*

	Life Expectancy, y					
	Without Family History of Aortic Dissection or Rupture			With Family History of Aortic Dissection or Rupture		
Strategy	Age, 20 y	Age, 25 y	Age, 30 y	Age, 20 y	Age, 25 y	Age, 30 y
Medical treatment						
3 cm†	74.3	74.0	73.3	73.7	73.5	72.6
4 cm†	73.2	72.4	71.0	72.6	71.7	70.7
5 cm†	71.4‡	69.9	70.3	70.6‡	69.7	70.2
Composite graft	72.7‡	73.5	74.2	72.7‡	73.5	74.2
Valve sparing	73.8‡	74.5	75.1	73.8‡	74.5	75.1

*The rate of increase in aortic diameter is 2 mm per year. The presence of family history of aortic dissection or rupture does not change life expectancy in either the composite graft or valve-sparing group.
†Initial aortic root diameter.
‡Base-case analysis results.

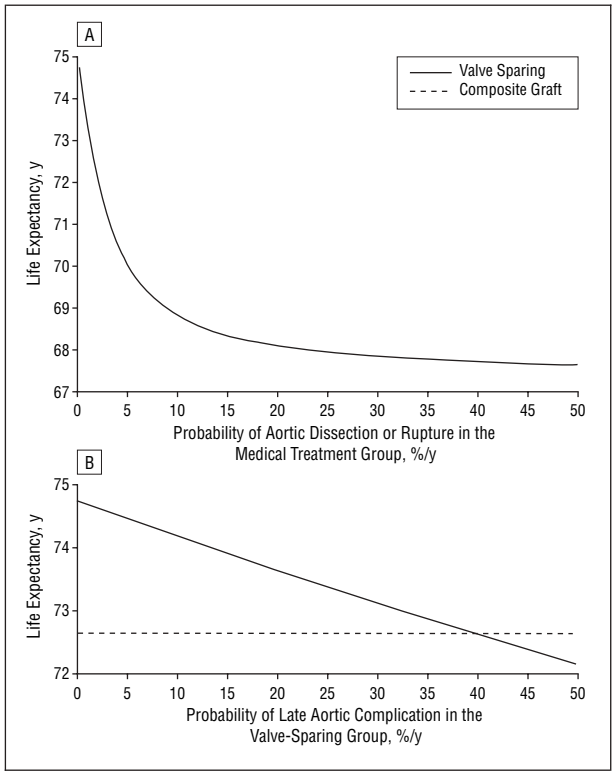

Figure 3. A, The effect of the risk of aortic dissection or rupture on life expectancy of the medical treatment group; B, the effect of the incidence of late aortic complication after valve-sparing surgery on life expectancy.

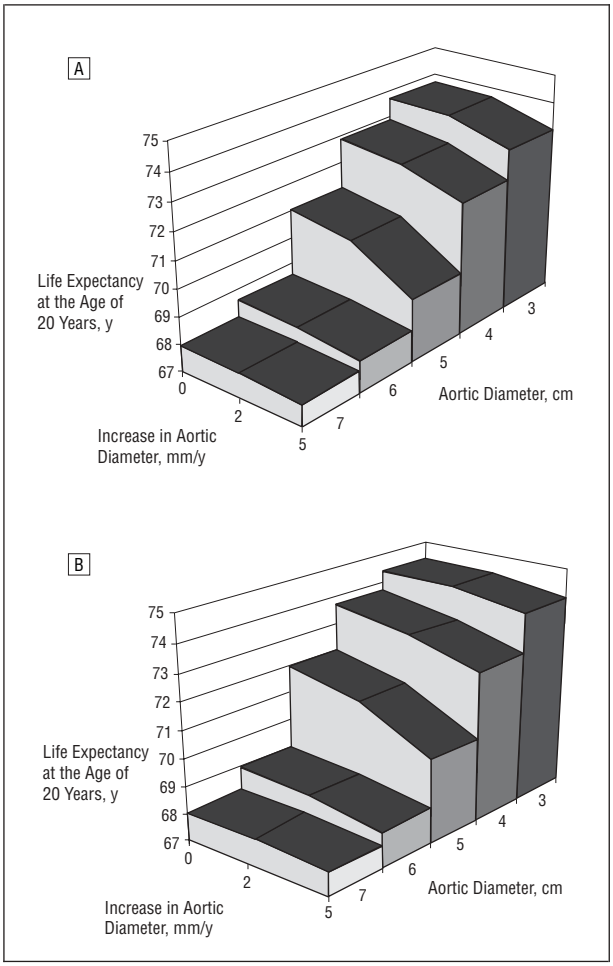

Figure 4. The effect of changing an aortic root diameter and a rate of aortic root enlargement on life expectancy. A, With family history of aortic dissection or rupture; B, without family history of aortic dissection or rupture.

combined impact of these factors on life expectancy of a patient with MFS in the medical treatment group.

As expected, patients with a smaller aortic root diameter, less increase in aortic root size during the preceding year, and no family history of aortic dissection had greater life expectancy. In the absence of a family history of aortic dissection or rupture, a patient who had an aortic root diameter of 3 cm and no change in aortic size in the preceding year had a life expectancy of 74.4 years with medical therapy.

Aortic root diameter had the greatest impact on life expectancy in any given clinical condition. The presence of family history of aortic dissection or rupture decreased life expectancy more in a patient with a small size of the aorta (0.7 years with an aortic root diameter of 3 cm vs 0.14 years with an aortic root diameter of 7 cm). The change in the aortic root diameter from 0 to 5 mm in the previous year caused the biggest drop in the patient group with an aortic root diameter of 5 cm and no

family history of aortic dissection or rupture (1.9 years) and had very little effect in patients with an aortic root diameter larger than 5 cm.

COMMENT

The purpose of our decision analysis was to determine the optimal management of aortic disease in MFS and to decide when to pursue prophylactic aortic surgery. Our analyses show that elective surgery increased life expectancy of patients without family history of aortic dissection or rupture more than watchful waiting with medical management when the aortic diameter was between 3.0 and 3.5 cm. For patients with a family history of aortic dissection or rupture, elective surgery can be a better option even with a smaller aortic root diameter (Figure 2). Because surgical risk and lifestyle issues are different for each patient, these conclusions should be viewed as general guidelines and not specific recommendations.

Compared with the current criterion for prophylactic aortic root replacement, which is an aortic root diameter of 5.0 to 5.5 cm,[6] our results show that elective repair should be considered even earlier. In addition to the aortic root diameter, the rate of aortic dilatation and family history of aortic dissection or rupture are the most important factors in determining the life expectancy of patients with MFS.

Older results that used higher estimates of aortic complications after valve-sparing surgery tended to favor the composite graft option. New data, however, suggest that valve-sparing surgery done with the current aortic valve reimplantation technique has a significantly lower rate of aortic complications. Our study showed that valve-sparing is preferred to composite graft when the aortic complication rate after valve-sparing surgery is 12% or less.

There are several limitations in this study that could bias the results. First, no randomized trial comparing the outcome of these 2 surgical procedures among centers and surgeons has been conducted. Also, because the valve-sparing operation is a newer procedure than composite grafts, the sample sizes and the length of follow-up in the studies that we analyzed were relatively small. To minimize the possible influence of preexisting bias in the literature that we used, we performed 1-way sensitivity analyses for all the parameters in our decision analysis tree with a broad range of variables.

Second, in our model, we assumed a constant rate of aortic dilatation and a fixed reassessment interval of 5 years. We also assumed a linear relationship between aortic diameter and risk of dissection and rupture. Because of these assumptions, our model may differ from actual clinical practice. However, without these assumptions the model would be too complex for analyses and interpretation. We also assumed a fixed mortality and morbidity rate for each surgical procedure when in fact the rates of these complications could differ with increasing aortic diameter and increasing patient age at operation. Quality of life was not considered in our model, but it might favor the valve-sparing option over the composite graft because it avoids lifelong anticoagulation.

Third, for our analysis, we needed a probability of aortic dissection at a given set of clinical parameters. It is known that the risk of aortic dissection is dependent on the aortic root diameter, the rate of aortic root enlargement, and the presence of family history of aortic dissection or rupture.[6,9,21] However, the exact impact of these factors on the risk of aortic dissection is not presently established in the literature. To obtain more precise estimates of this important variable, we surveyed experts in the field. The estimates from the experts were more variable at larger aortic root diameters, indicating that current knowledge surrounding this issue remains unclear. Because the sensitivity analyses revealed that the probability of aortic dissection was the most important factor in determining life expectancy, further clinical research on this parameter and other key variables should be done to better inform clinical decision making.

CONCLUSIONS

Our results suggest that valve-sparing surgery is a better choice than composite graft surgery for aortic disease in patients with MFS largely as a result of significant improvement in operative mortality and the rate of long-term aortic complications after valve-sparing surgery. Life expectancy in MFS may be improved by considering earlier prophylactic aortic surgery than what is currently prescribed.

This study highlights the need for further research in this area. Future research should be directed toward finding the direct impact of aortic root enlargement on the risk of aortic dissection, the average rate of aortic root dilatation, the number of patients with MFS who died before they have emergency surgery, and the cause of death in detail after any kind of prophylactic aortic operation. Our study also suggests that an aggressive program to prevent aortic complications by serial echocardiogram and early prophylactic surgery may improve life expectancy for patients with aortic disease secondary to MFS.

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