

REPLACEMENT OF THE AORTIC ROOT IN PATIENTS WITH MARFAN'S SYNDROME

VINCENT L. GOTT, M.D., PETER S. GREENE, M.D., DIANE E. ALEJO, B.A., DUKE E. CAMERON, M.D.,
DAVID C. NAFTEL, Ph.D., D. CRAIG MILLER, M.D., A. MARC GILLINOV, M.D., JOHN C. LASCHINGER, M.D.,
AND REED E. PYERITZ, M.D., Ph.D.

ABSTRACT

Background Replacement of the aortic root with a prosthetic graft and valve in patients with Marfan's syndrome may prevent premature death from rupture of an aneurysm or aortic dissection. We reviewed the results of this surgical procedure at 10 experienced surgical centers.

Methods A total of 675 patients with Marfan's syndrome underwent replacement of the aortic root. Survival and morbidity-free survival curves were calculated, and risk factors were determined from a multivariable regression analysis.

Results The 30-day mortality rate was 1.5 percent among the 455 patients who underwent elective repair, 2.6 percent among the 117 patients who underwent urgent repair (within 7 days after a surgical consultation), and 11.7 percent among the 103 patients who underwent emergency repair (within 24 hours after a surgical consultation). Of the 675 patients, 202 (30 percent) had aortic dissection involving the ascending aorta. Forty-six percent of the 158 adult patients with aortic dissection and a documented aortic diameter had an aneurysm with a diameter of 6.5 cm or less. There were 114 late deaths (more than 30 days after surgery); dissection or rupture of the residual aorta (22 patients) and arrhythmia (21 patients) were the principal causes of late death. The risk of death was greatest within the first 60 days after surgery, then rapidly decreased to a constant level by the end of the first year.

Conclusions Elective aortic-root replacement has a low operative mortality. In contrast, emergency repair, usually for acute aortic dissection, is associated with a much higher early mortality. Because nearly half the adult patients with aortic dissection had an aortic-root diameter of 6.5 cm or less at the time of operation, it may be prudent to undertake prophylactic repair of aortic aneurysms in patients with Marfan's syndrome when the diameter of the aorta is well below that size. (N Engl J Med 1999;340:1307-13.)

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IN 1896, A.B. Marfan described a five-year-old girl with long thin legs that he characterized as "spider-like."¹ Over the next 50 years, many other features of Marfan's syndrome were described, including dislocated lenses in 1914, autosomal dominant inheritance in 1931, and aneurysm of the ascending aorta by Taussig and associates in 1943.² In a landmark publication in 1955,³ McKusick provided the comprehensive picture of Marfan's syndrome.

Before the era of open-heart surgery, the majority of patients with Marfan's syndrome died prematurely of rupture of the aorta, often by the third decade of life.⁴ Even after open-heart surgery became established, it was usually reserved for patients with acute aortic dissection or rupture, and results were poor. In 1968, Bental and De Bono described a composite graft-valve procedure in which a prosthetic valve was sewn onto the lower end of a polytetrafluoroethylene (Teflon) tubular graft, which in turn was anastomosed to the aortic annulus; the coronary arteries were then anastomosed to the side of the graft.⁵ This repair completely removes the aortic segment most prone to dissection and rupture.

Nearly 30 years of experience has accumulated since the introduction of this procedure. Therefore, we evaluated the results from several centers with expertise in the performance of aortic surgery for patients with Marfan's syndrome.

METHODS**Patients**

A total of 675 patients with Marfan's syndrome underwent aortic-root replacement at 10 surgical centers (7 in North America and 3 in Europe) between October 1968 and March 1996. To be eligible for entry into the study, patients had to have undergone aortic-root replacement and to have been given a diagnosis of classic Marfan's syndrome; patients with a forme fruste of the syndrome or related connective-tissue disorders were not included. Nine surgical centers submitted information on all patients with Marfan's syndrome who had had aortic-root replacement performed by any surgeon at the centers; one center submitted information only on patients operated on by one surgeon since February 1991, but these patients constituted 95 percent of the patients with Marfan's syndrome who had undergone aortic-root replacement at that institution since 1991.

From the Division of Cardiac Surgery, Johns Hopkins Hospital, Baltimore (V.L.G., P.S.G., D.E.A., D.E.C., A.M.G.); the Department of Surgery, University of Alabama, Birmingham (D.C.N.); the Department of Cardiothoracic Surgery, Stanford University Medical Center, Stanford, Calif. (D.C.M.); the Division of Cardiac Surgery, St. Joseph Hospital, Baltimore (J.C.L.); and the Department of Human Genetics, Allegheny University of the Health Sciences, Pittsburgh (R.E.P.). Address reprint requests to Dr. Gott at the Division of Cardiac Surgery, 618 Blalock Bldg., Johns Hopkins Hospital, Baltimore, MD 21287-4618, or at vgott@csurg.jhmi.jhu.edu.

Other authors were Hans G. Borst, M.D., Division of Cardiothoracic Surgery, Hannover University Hospital, Hannover, Germany; Christian E.A. Cabrol, M.D., Department of Cardiothoracic Surgery, Hôpital La Pitié, Paris; Denton A. Cooley, M.D., Department of Surgery, Texas Heart Institute, Houston; Joseph S. Coselli, M.D., Department of Surgery, Methodist Hospital, Houston; Tirone E. David, M.D., Division of Cardiovascular Surgery, Toronto Hospital, Toronto; Randall B. Griepp, M.D., Department of Cardiothoracic Surgery, Mt. Sinai Hospital, New York; Nicholas T. Kouchoukos, M.D., Division of Cardiothoracic Surgery, Jewish Hospital, St. Louis; and Marko I. Turina, M.D., Department of Cardiovascular Surgery, University Hospital, Zurich, Switzerland.

Follow-up ended on April 1, 1997, and current follow-up data were available for 611 of the 675 patients (91 percent). The mean length of follow-up was 6.7 years (range, 0 to 23). For the 64 patients whose whereabouts were unknown at the end of follow-up, the mean length of follow-up was 4.2 years, and data on these patients were censored at the time of the last follow-up visit. Thirty-two of the patients who could not be located had returned home to another country after surgery.

A total of 604 patients underwent composite-graft replacement according to the method of Bentall and De Bono or a modification of that technique. Twenty-one patients (13 adults and 8 children) underwent placement of a homograft aortic root as the primary procedure, usually to avoid the use of anticoagulation mandated by mechanical prostheses. Fifty patients underwent a valve-sparing procedure; 15 of these patients had aortic dissection (12 acute and 3 chronic) at the time of surgery. Of the 604 patients who underwent a composite-graft procedure, 209 had side-to-side anastomoses of the coronary ostia to the Dacron graft, 149 had direct anastomoses of the coronary artery to the graft, and 34 had a prosthetic interposition graft placed between the coronary ostia and the graft. In the remaining 212 patients, the operative note did not indicate the type of coronary anastomosis used. Further description of these coronary anastomotic techniques may be found in the surgical literature.⁶

Statistical Analysis

Survival and event-free survival curves were calculated according to the Kaplan–Meier method. Risk factors for mortality were determined by a parametric multivariable analysis of the postoperative risk. Clinically important rates are presented, with 95 percent confidence intervals. Computations were made with the use of SAS statistical software that included a program to estimate risks that varied according to time.⁷

RESULTS

Preoperative Characteristics of the Patients

Of the 675 patients with Marfan’s syndrome, 473 (70 percent) were male. The mean age of the patients was 34 years (range, 4 to 73). Two hundred two (30 percent) had a dissection involving the ascending aorta; 99 of the dissections were acute (operation performed within 14 days after the event), whereas 103 were chronic (operation performed more than 14 days after the event). The diameter of the ascending aorta was documented in 524 adult patients; the mean diameter in this group was 6.8 cm (range, 3 to 15). Of these 524 patients, 158 had an aortic dissection with a mean diameter of 7.2 cm. In 73 of these patients with dissection (46 percent), the aortic diameter was 6.5 cm or less. Figure 1 shows the aortic-root diameters in the presence and absence of dissection in the 524 adult patients. Five patients had previously undergone aortic-valve surgery, 33 had previously undergone surgery of the ascending aorta, and 37 had previously undergone both types of surgery.

Operative Results

The 30-day mortality rates are shown in Table 1 according to the urgency of the operation. The 30-day mortality rate among the 455 patients who underwent elective repair was 1.5 percent (7 patients). The rate was 2.6 percent among the 117 patients who un-

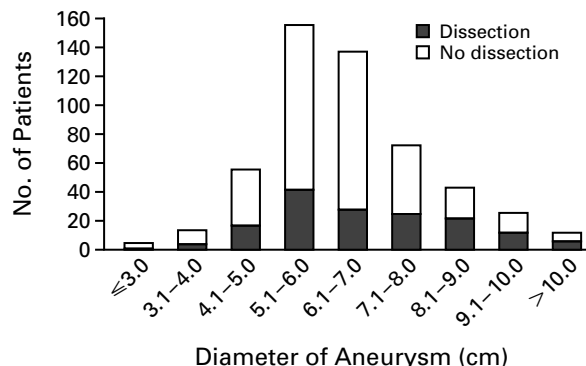


Figure 1. Diameter of the Aneurysm in 524 Adult Patients with Marfan’s Syndrome, According to the Presence of Aortic Dissection.

The diameter of the aneurysm was documented for 524 patients.

TABLE 1. RESULTS OF AORTIC-ROOT REPLACEMENT IN 675 PATIENTS WITH MARFAN’S SYNDROME, ACCORDING TO THE URGENCY OF THE PROCEDURE.

PROCEDURE	NO. OF PATIENTS	30-DAY MORTALITY	
		NO. OF PATIENTS	PERCENT (95% CI)*
Elective repair	455	7	1.5 (0.7–3.3)
Urgent repair (1–7 days after surgical consultation)	117	3	2.6 (0.7–7.9)
Emergency repair (<24 hr after surgical consultation)	103	12	11.7 (6.4–20)
Total	675	22	3.3 (2.1–5.0)

*CI denotes confidence interval.

derwent urgent repair — that is, within seven days after a surgical consultation. The rate was 11.7 percent among the 103 patients who underwent emergency repair — that is, within 24 hours after a surgical consultation.

Eighty-two of the 103 patients who underwent emergency surgery had aortic dissection; 73 of the dissections were acute. The remaining 21 patients underwent emergency surgery because of two or more of the following factors: chest pain, an aneurysm whose diameter exceeded 7.0 cm, or New York Heart Association class III or IV congestive heart failure. The 117 patients who underwent urgent repair had one or more of the following factors: aortic dissection, chest pain, an aneurysm that was larger than 7.0 cm, or New York Heart Association class III or IV congestive heart failure.

Overall, 22 of the 675 patients (3.3 percent) died

within 30 days after surgery. When analyzed according to the type of operation, 30-day mortality among the 604 patients who underwent aortic-root replacement with a composite graft was 3.5 percent (21 patients; 95 percent confidence interval, 2.2 to 5.4 percent). Among the 21 patients who underwent aortic-root replacement with a homograft, the 30-day mortality rate was 4.8 percent (1 patient; 95 percent confidence interval, 0.2 to 26 percent). Among the 50 patients who underwent valve-sparing repair, the 30-day mortality rate was 0 percent.

Twelve of the 22 patients who died within 30 days after surgery had acute or chronic dissection of the ascending aorta. The principal cause of death was low cardiac output postoperatively in seven patients and arrhythmia in six patients. The remaining nine patients died as a result of preoperative aortic rupture (four patients), mediastinitis (one patient), myocardial infarction (one patient), and unknown causes (three patients).

There were 202 patients with ascending aortic dissection at the time of surgery. The 30-day mortality rate was 9.1 percent (95 percent confidence interval, 4.5 to 17 percent) among the 99 patients with acute dissection and 1.9 percent (95 percent confidence interval, 0.3 to 7.5 percent) among the 103 patients with chronic dissection. A total of 185 patients with dissection of the ascending aorta received a composite graft, 15 underwent a valve-sparing procedure, and 2 received a homograft aortic root.

Eighty-one of the patients also underwent a mitral-valve procedure. The overall 30-day mortality rate in

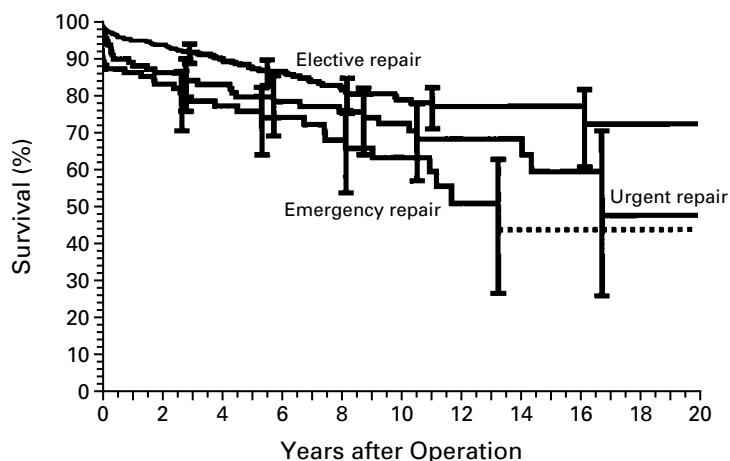
this group was 7.4 percent (95 percent confidence interval, 3.0 to 16 percent). Thirty-five patients underwent concomitant mitral repair with an annuloplasty ring, none of whom died within the first 30 days after surgery. Forty-six patients required concomitant mitral-valve replacement, six of whom died within 30 days postoperatively (13.0 percent; 95 percent confidence interval, 5.4 to 27 percent).

Late Results

A parametric survival analysis showed an initially high risk of death for approximately the first 60 days postoperatively that was followed by a low-risk late phase in which the risk was constant for the duration of the study. The survival rate was 93 percent at 1 year, 91 percent at 2 years, 84 percent at 5 years, 75 percent at 10 years, and 59 percent at 20 years. Figure 2 shows the Kaplan–Meier survival estimates stratified according to the urgency of the procedure.

Dissection or rupture of the residual aorta (or both) and arrhythmia were the leading causes of late death (Table 2). Of the 22 patients who died of dissection or rupture of the residual aorta, 8 (36 percent) had a DeBakey type I dissection (dissection arising in the ascending aorta and extending into the descending aorta) at presentation.

The results of the parametric analysis of the risk of death associated with various factors are shown in Table 3. Previous ascending-aorta surgery (with or without concomitant aortic-valve replacement), urgent repair, and emergency repair were all associated with an increased risk of death within the first 60 days



No. AT RISK										
Elective repair	455	381	294	204	141	97	64	42	17	4
Urgent repair	117	88	74	62	53	41	23	16	8	4
Emergency repair	103	73	57	41	31	21	10	4	3	2

Figure 2. Kaplan–Meier Survival Analysis of 675 Patients with Marfan’s Syndrome, According to the Urgency of the Procedure.

I bars are 95 percent confidence intervals.

TABLE 2. CAUSES OF DEATH MORE THAN 30 DAYS AFTER AORTIC-ROOT REPLACEMENT.

CAUSE OF DEATH	NO. OF PATIENTS
Dissection or rupture of residual aorta	22
Arrhythmia	21
Congestive heart failure	11
Endocarditis	10
Pneumonia	5
Dehiscence of coronary anastomosis	3
Operative encephalopathy	2
Warfarin-induced hemorrhage	2
Miscellaneous*	10
Unknown	28
Total	114

*One patient each died of cancer, the acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, a drug overdose, rejection of transplanted heart, infarct of spinal cord, renal insufficiency, sepsis, trauma, and amyotrophic lateral sclerosis.

after surgery. The presence of New York Heart Association class IV congestive heart failure preoperatively was the only important predictor of the risk of death during the late postoperative phase. The presence of dissection preoperatively was highly correlated with the likelihood of urgent or emergency repair. In the final multivariable equation, age and a history of mitral-valve surgery were not predictive of survival.

Major late complications are presented in Table 4. Thromboembolism was the most common late complication after aortic-root replacement. Of the 27 patients who had thromboembolism, 25 had received a composite graft, 1 had received a homograft aortic root, and 1 had undergone a valve-sparing procedure. One patient had a prosthetic-valve thrombosis

10 years postoperatively but recovered after repeated composite-graft placement. Twelve of the 25 patients with cerebral emboli had a complete recovery. The embolism occurred within 35 days after surgery in 9 of 25 patients and between 3 and 13 years postoperatively in 16 patients. The actuarial likelihood of the absence of thromboembolism among the 593 patients who received a composite graft and who survived the immediate perioperative period was 97 percent at 5 years, 94 percent at 10 years, and 90 percent at 20 years. The linearized rate of thromboembolism among these patients was 0.62 event per 100 patient-years (25 events in 4041 patient-years of follow-up).

Endocarditis developed in 24 patients (Table 4). Fourteen of these patients were treated successfully: seven with antibiotics and four by replacement of the composite graft with a cryopreserved homograft. Three of the four patients whose endocarditis was treated by replacement of the composite graft did not survive. The overall likelihood of the absence of endocarditis was 97 percent at 5 years, 95 percent at 10 years, and 84 percent at 20 years.

Twenty-two of the 653 patients in our study who were discharged from the hospital (3.4 percent) died of late dissection or rupture of the residual aorta. Sixty-three of the 653 patients who were discharged from the hospital (9.6 percent) had late aortic surgery for progressive disease, and 46 were still alive at the time of the last follow-up.

None of the 50 patients who underwent a valve-sparing procedure died in the early postoperative period. The first four valve-sparing operations were performed in Zurich 19 to 29 years ago by Senning and are included in this report. At the time of this writing, one of these patients has moderate aortic insufficiency 20 years after operation, one died of distal aortic rupture 7 years postoperatively, one died of unknown

TABLE 3. MULTIVARIABLE PARAMETRIC HAZARD ANALYSIS OF RISK FACTORS FOR DEATH, ACCORDING TO THE TIME AFTER SURGERY.*

RISK FACTOR FOR DEATH	EARLY PHASE		LATE PHASE	
	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE
Previous ascending-aorta surgery†	5.08 (2.21–11.67)	<0.001		NS
Urgent repair‡	3.33 (1.14–9.79)	0.025		NS
Emergency repair‡	7.40 (2.84–19.30)	<0.001		NS
NYHA class IV preoperatively§		NS	1.78 (1.10–2.88)	0.016

*The early phase is the first 60 days after surgery, and the late phase is the subsequent period (up to 23 years postoperatively). CI denotes confidence interval, NS not significant, and NYHA New York Heart Association.

†This category includes patients who had also undergone aortic-valve replacement and those who had not.

‡The reference category is elective repair.

§The reference category is New York Heart Association class I preoperatively.

TABLE 4. COMPLICATIONS OCCURRING MORE THAN 30 DAYS AFTER AORTIC-ROOT REPLACEMENT.

COMPLICATION AND OUTCOME	NO. OF PATIENTS
Thromboembolism*	27
Complete recovery	13
Mild-to-moderate residual effects	11
Unknown degree of residual effects	3
Endocarditis	24
Successful treatment	14
Antibiotics	7
Homograft aortic-root placement	4
Repeated aortic-valve placement	2
Repeated composite-graft placement	1
Death	10
Treatment with antibiotics	6
Repeated composite-graft placement	3
Homograft aortic-root placement	1
Coronary dehiscence	8
Successful repair	5
Death	3

*Twenty-five patients received a composite graft, 1 received a homograft aortic root, and 1 underwent a valve-sparing operation. One patient had a thrombosed valve, 25 had cerebral emboli, and 1 had a peripheral embolus.

causes 21 years postoperatively, and one was lost to follow-up 12 years after surgery. The remaining 46 patients have been followed for 18 months to 9 years postoperatively. Two of these patients have died (one of amyotrophic lateral sclerosis at 1.8 years and one of pneumonia at 3.7 years). As of this writing, 15 have no aortic insufficiency, 21 have mild-to-moderate postoperative aortic insufficiency, and 1 patient with severe insufficiency required a second operation. The presence or absence of postoperative aortic insufficiency was not recorded in seven patients.

In Senning's early valve-sparing procedures, the left coronary aortic sinus and coronary ostium were left intact. The remainder of the aortic root was replaced with a prosthetic graft, and the right coronary artery was reimplanted into the graft. Sarsam and Yacoub modified this procedure in 1979 by resecting the entire aneurysmal portion of the aortic root and replacing it with a prosthetic graft into which the coronary arteries are implanted.⁸ Two recent variations of the valve-sparing operation have been described by David and Feindel⁹ and David.¹⁰ In the current study, Senning's original valve-sparing procedure was used in 4 patients, the modified procedure of Sarsam and Yacoub⁸ was used in 2 patients, and the modified procedure of David and Feindel⁹ and David¹⁰ was used in 44 patients.

DISCUSSION

The introduction of the composite graft-valve procedure by Bentall and De Bono in 1968 changed the bleak outlook for patients with Marfan's syndrome

and aneurysm of the ascending aorta. Our survey of 10 major surgical centers worldwide indicates that elective repair of such aneurysms in patients with Marfan's syndrome is associated with a low mortality rate (<2.0 percent). On the other hand, the 30-day mortality rate associated with emergency repair was eight times as high.

Kouchoukos and Dougenis have recommended that patients with Marfan's syndrome undergo elective replacement of the ascending aorta when the diameter of the aorta exceeds 5.0 to 5.5 cm.¹¹ Similarly, Coady et al. monitored 230 patients with thoracic aneurysms from 1985 to 1996¹² and found that the odds of rupture or acute dissection are 8.8 times as high among patients with aneurysms of 6.0 to 6.9 cm as among patients with aneurysms of 4.0 to 4.9 cm. They suggest that 5.5 cm is an acceptable diameter for prophylactic resection of ascending aortic aneurysms. Almost half the adult patients with aortic dissection in our study (46 percent) had an aortic diameter of 6.5 cm or less; it is the policy of the centers included in the study to repair these aneurysms prophylactically when the diameter reaches 5.5 to 6.0 cm, regardless of a patient's symptoms.

Often, an adult patient who has an aneurysm with a diameter of 6.0 cm has minimal aortic regurgitation or none at all and is asymptomatic, and aneurysms of this size are frequently not apparent on routine chest films. Unfortunately, every year many patients with Marfan's syndrome and previously unrecognized aneurysms require emergency surgery for acute dissection or sustain fatal rupture before surgery can be performed. Not infrequently such patients had skeletal and ocular changes diagnostic of Marfan's syndrome that were not recognized by the patients' physicians. There is also a widespread misconception that the operative risk is high in patients with Marfan's syndrome, and so patients who have sizable aneurysms are not referred for surgical repair. These circumstances are unfortunate because long-term results after elective repair of the aortic root in patients with Marfan's syndrome are good. The majority resume active lifestyles and have no complications associated with the aortic prosthesis. However, prosthetic endocarditis remains a potentially serious late problem. Since it is commonly associated with the performance of dental work in the absence of prophylactic antibiotics, we recommend that our patients with mechanical prostheses receive parenteral rather than oral prophylactic antibiotics before and after dental procedures. Though composite-graft endocarditis can sometimes be cured with antibiotics, serious infections ordinarily require replacement of the prosthesis with a homograft aortic root. Our results indicate that repeated composite-graft placement is usually an inadequate treatment for endocarditis.

After aortic-root replacement, the residual aorta

must be monitored by serial computed tomography or magnetic resonance imaging. Unfortunately, 22 of our 653 patients who were discharged from the hospital (3.4 percent) died of late dissection or rupture of the residual aorta. In many of these patients, routine serial monitoring of the aorta had not been carried out.

The role of valve-sparing procedures in patients with Marfan's syndrome remains unclear. These procedures, introduced by Senning 29 years ago and popularized by Yacoub and David in recent years, are widely used for other types of patients with ascending aortic aneurysms, but used with caution in patients with Marfan's syndrome. Several surgeons who participated in this study believe that Marfan's syndrome is a contraindication for valve-sparing surgery. There has been concern about the possibility of dilatation of the aortic annulus after the valve-sparing procedure. Recent histologic studies by Fleischer et al. revealed a high degree of structural deterioration of aortic leaflets excised from patients with Marfan's syndrome at the time of aortic-root replacement.¹³ Using an immunofluorescence staining technique, these investigators demonstrated fragmentation and scarcity of fibrillin, a major structural protein in the aortic leaflet, in the excised aortic leaflets. Their findings support a cautious approach to the use of valve-sparing procedures in patients with Marfan's syndrome. The procedure of choice among most surgeons in this study is the composite graft-valve procedure of Bentall and De Bono, but several believe there is a role for valve-sparing procedures among children and young women, the latter because of the risk of anticoagulation during pregnancy. Nevertheless, an unexpected finding in our study was the outstanding long-term results in four patients who had undergone a valve-sparing procedure at the University of Zurich more than 19 years earlier. Also, recently Yacoub et al.¹⁴ described excellent long-term results (September 1979 through April 1997) with the valve-sparing procedure in 68 patients with skeletal manifestations of Marfan's syndrome.

Our survey of surgical repair of the aorta demonstrates that the outlook for patients with Marfan's syndrome has improved dramatically in the past 25 years. Notwithstanding major recent advances in the understanding of the cause of the syndrome,¹⁵ aggressive, preventive medical and surgical management will remain the mainstay of treatment in the near term. Much is still to be learned about the pathogenesis of the condition — for instance, how it is that the mutation of one allele of the fibrillin-1 gene (often so small as to affect only 1 nucleotide out of 10,000 in the coding sequence) in a specific patient adversely affects the extracellular matrix in diverse organs and tissues.^{15,16} Knowledge of the mutation in a patient can allow the identification of relatives at risk for cardiovascular problems before the diagnosis could be established on the basis of clinical criteria.¹⁷

Similarly, molecular testing may identify a relative who does not have the mutation and is therefore at low risk for aortic problems; with this information that person can avoid the expense and inconvenience of repeated evaluation.¹⁸

Recently, it has been shown that targeting the fibrillin-1 gene in the mouse stimulates the vascular phenotype of Marfan's syndrome.¹⁹ One goal of such research is to create a model of the syndrome in a larger animal. The use of somatic gene therapy to correct or ameliorate the fibrillin-1 defect, even in a localized fashion, seems years away, but progress is being made.²⁰ Until more effective methods are developed, patients and their families should understand that cardiovascular complications of Marfan's syndrome can be managed effectively in most cases by moderate restriction of physical activity, β -adrenergic blockade, routine imaging of the aorta, and prophylactic replacement of the aortic root before the diameter exceeds 5.5 to 6.0 cm.^{12,16,21}

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