Early and Long-Term Results of a Valve-Sparing Operation for Marfan Syndrome

Emma J. Birks, BSc, MRCP; Carole Webb; Anne Child, MD; Rosemary Radley-Smith, FRCP; Magdi H. Yacoub, PhD, FRS

Background—We have previously described the experience, rationale, and development of a valve preserving technique, but its role in patients with Marfan syndrome has not previously been defined. Here, we attempt to determine the early and long-term results, timing, and determinants of outcome of this operation in patients with Marfan syndrome.

Methods and Results—Since 1979, 82 patients (73.2% of all patients with Marfan syndrome undergoing resection of aneurysm of the ascending aorta) were operated on using this technique. Ages ranged from 2 to 69 years (mean, 33.9 years). In all, there were 4 early deaths (4.9%), 2 with acute dissection and 2 with chronic aneurysm operated on as emergencies. There were no early deaths in 67 patients operated on electively. Actuarial survival for patients operated for chronic aneurysm was 94.2%, 94.2%, and 94.2% at 1, 5, and 10 years, respectively; that for acute dissection was 72.7%, 63.6%, and 63.6%; and that for chronic dissection was 100%, 85.7%, and 75.0%. The probability of needing reoperation was 5.7%, 17.3%, and 17.3% at 1, 5, and 10 years. There were no instances of infective endocarditis or thromboembolic complications except in 2 patients operated on early in the series who had cusp extension. At the end of the follow-up, trivial or no aortic regurgitation was demonstrated in 33.3%, mild in 45.6%, moderate in 21.1%, and severe in 0.

Conclusions—Valve-sparing operations are feasible in most patients with Marfan syndrome; they are applicable to patients with both dissection and chronic aneurysm. The early and long-term results are encouraging. Results are better in the absence of dissection, and prophylactic operation is warranted in some cases.

(Circulation. 1999;100[suppl II]:II-29–II-35.)

Key Words: aneurysm ■ valves ■ aorta

Marfan syndrome is an autosomal dominant heritable disorder of connective tissue that results in skeletal, ocular, and cardiovascular manifestations. The diagnosis, which has been the subject of several publications,1-5 is made by clinical and genetic criteria. The prognosis in Marfan syndrome is determined mainly by pathological changes in the aortic root and ascending aorta, which frequently involve the aortic valve. Changes in the aortic valve mechanism are due largely to secondary aortic wall disease. To date, there is no agreement on the type and timing of surgical treatment of aortic valve and root disease in Marfan syndrome. Most patients undergo composite replacement of the aortic root and valve with a Bentall procedure.6-14 However, all available valve substitutes carry a significant incidence of valve-related complications such as hemorrhage, thromboembolism, infection, and compromised hemodynamics. These complications could be particularly relevant in patients with Marfan syndrome because of the young age, possible existence of left ventricular disease, diffuse arterial pathology, tendency to arterial dissection or leakage, and occasional need for orthopedic operations. In 1979, we developed a valve-conserving operation for patients with aneurysm or dissection of the aortic root that preserves the dynamic structure and function of the aortic valve mechanism.15 This operation and that described by David and Feindel16 are being applied with increasing frequency to patients with different types of aortic root pathology. Application of the valve-sparing operation to patients with Marfan syndrome has not been adequately studied. The purpose of this article is to analyze and study the feasibility and the early and long-term results of applying our type of valve-sparing operation to patients with Marfan syndrome.

Methods

Patients
One hundred twelve patients with Marfan syndrome and aneurysm of the ascending aorta were operated on by 1 surgeon between September 1979 and November 1998. Eighty-two (73.2%) underwent the valve-conserving operation. Marfan syndrome was diagnosed according to the revised criteria of De Paepe and colleagues.2 There was involvement of the ocular system in 32 patients (39.0%), the skeletal system in 63 (76.8%), and the presence of a positive family history in 35 (42.7%). Patients were 2 to 69 years of age (mean, 33.9±1.7 years); 17 patients were <18 years of age. There

From the National Heart and Lung Institute at Imperial College of Science, Technology and Medicine, Middlesex, UK.

Correspondence to Magdi Yacoub, FRS, Professor of Cardiothoracic Surgery, National Heart and Lung Institute, Heart Science Centre, Royal Brompton and Harefield Hospital, Harefield, Middlesex, UB9 6JH, UK.

© 1999 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
were 50 men and 32 women. All patients were considered for a valve-sparing operation regardless of the size of the aneurysm or annulus. Patients with severe secondary retraction or calcification of the aortic valve cusps were considered unsuitable for repair. In an additional 6 patients, repair was attempted, but the valve was replaced at the same operation. Residual regurgitation was judged to be due to severe secondary changes in the cusp in 5 of these patients (despite initial assessment) and the use of a large Dacron tube (30 mm) for a relatively small root in 1.

The mode of presentation was chronic aneurysm of the ascending aorta or root in 54 patients (65.8%), chronic dissection in 17 (20.7%), and acute dissection in 11 (13.4%). The operation was performed as an emergency in a total of 15 patients (18.3%). Thirty-seven patients were asymptomatic but were judged to have a poor prognosis because of the rate of enlargement or size of the aortic root, a strong family history of rupture at a young age, or coexisting pregnancy. NYHA status was class I in 37 patients (45.5%), class II in 8 (9.8%), class III in 30 (36.6%), and class IV in 7 (8.5%). The preoperative degree of aortic regurgitation was evaluated by a set of clinical and echocardiographic criteria and judged to be none or trivial in 13 patients (15.9%), mild in 18 (22%), moderate in 42 (51.2%), and severe in 9 (11%). Mean preoperative aortic root size was 5.7 ± 0.3 cm. Forty-seven patients were on β-blockers either preoperatively or immediately postoperatively. Fifteen patients (18.3%) had a previous history of hypertension. Cardiothoracic ratio on the preoperative chest x-ray was <0.55 in 49 and >0.55 in 23. One patient was 17 weeks' pregnant at the time of operation.

A preoperative echocardiogram was performed in all patients and coronary angiography was performed in those over the age of 40. Three patients (3.7%) had associated CABG surgery, and 6 (7.3%) had associated mitral valve repair. Mean cardiopulmonary bypass time was 116.1 ± 3 minutes; mean cross-clamp time was 85.7 ± 2 minutes.

Patients were followed up regularly at our hospital. A clinical examination, ECG, chest radiograph, and 2D echocardiogram were performed. For patients living overseas, up-to-date information was obtained from the referring physician. No patients were lost to follow-up.

Surgical Technique
The technique used in this series has been previously described in detail. It consists of excision of all the diseased aortic wall of the ascending aorta and all 3 sinuses to a level 1 mm above the crown-shaped aortic “annulus.” A Dacron tube with 3 tongue-shaped processes is then used to resuspend the aortic valve and reconstitute the sinuses (Figure 1).

Statistical Analysis
The Kaplan-Meier product limit was used to estimate long-term survival. The influence of different potential risk factors on survival was evaluated by use of univariate analysis with the log-rank test and Cox proportional-hazards model and multivariate analysis with the Cox proportional-hazards model. The effect of preoperative aortic root size and early postoperative aortic regurgitation on the incidence of reoperation was evaluated by use of the nonparametric Mann-Whitney test. A value of P ≤ 0.05 was used to indicate significance.

Results

Mortality
The 30-day (early) mortality for the whole group was 4.9%. Of the 4 early deaths, 2 were patients with acute dissection; 1 died of subarachnoid hemorrhage and 1 of redissection. Two were patients with chronic aneurysm, both operated on as an emergency because of severe heart failure and low cardiac output syndrome; both died of low cardiac output. There were no early deaths in 67 patients operated on electively. Early mortality rates for patients operated on for acute dissection, chronic aneurysm, and chronic dissection during the whole period were 18.2%, 3.7%, and 0%, respectively.

During a follow-up period varying from 30 to 6983 days (mean, 1998 days; median, 1105 days), there were 8 late deaths. Overall actuarial survival rates were 92.3%, 87.3%, and 84.3% at 1, 5, and 10 years (Figure 2). There were 4 late deaths in the chronic dissection group, with actuarial survival rates of 100%, 83.7%, and 75.0% (Figure 3), and only 1 late death in the chronic aneurysm group, with actuarial survival rates of 94.2%, 94.2%, and 94.2%. There were 3 late deaths in the acute dissection group, with actuarial survival rates of 72.7%, 63.6%, and 63.6%. The causes of these late deaths are
shown in Table 1. Survival in the 37 asymptomatic patients was excellent as shown in Figure 4. Survival rates in 47 patients on β-blockers either preoperatively or immediately postoperatively were 97.9%, 95.4%, and 95.4%, which were superior to those not on β-blockers (84.9%, 77.0%, and 71.1%; Figure 5). Furthermore, duration of treatment with β-blockers seemed to be important, and only treatment of patients for >6 months seemed to affect survival (although this did not quite reach statistical significance). Univariate analysis of patient- or operation-related possible predictors of late death after operation (Table 2) identified NYHA functional class IV, emergency surgery, absence of β-blockers, and presence of symptoms as poor predictors of survival. Multivariate analysis confirmed these risk factors and found age to be another poor predictor of survival.

Postoperative Aortic Valve Function
The presence and degree of aortic regurgitation in the survivors were assessed by echocardiographic criteria. At the end of a follow-up period ranging from 30 to 6983 days (mean, 1998 days; median, 1105 days), it was judged to be absent or trivial in 32.8%, mild in 44.8%, moderate in 22.4%, and severe in 0. Aortic valve function tended to be stable, with progression occurring more often in patients who had
mild or moderate residual regurgitation immediately after operation (Table 3). Mean postoperative aortic root size was 2.8±0.3 cm at last follow-up. The first patient with a large aneurysm of the ascending aorta operated on in 1979 has normal aortic function (as assessed clinically and by echocardiography) 19 years after the operation and has recently retired from her job as a physician. Furthermore, after a major car accident 2 years after operation, she underwent aortic angiography, which showed “normal” aortic root, coronary ostia, and valve function.

Reoperation
During a follow-up period from 30 to 6983 days (mean, 1998 days), 11 patients underwent reoperation on the aortic valve mainly for residual or recurrent regurgitation. Four patients had valve replacement with a St Jude’s valve, 3 with a Starr Edwards valve, and 4 with a homograft. The cumulative probability of undergoing reoperation was 5.7%, 17.3%, and 17.3% at 1, 5, and 10 years. Freedom from reoperation is shown in Figure 6. One patient died 52 days after reoperation with a Starr Edwards valve of left ventricular failure. Preoperative aortic root diameter was not a risk factor for incidence of reoperation.

阀-related Complications
Routine anticoagulation was not used in this series; no thromboembolic complications or endocarditis was encountered, except in 2 patients operated on early in the series who had additional cusp extension with calf pericardium. One developed endocarditis 5 years after surgery and was successfully treated by valve replacement; the other developed 1 episode of thromboembolism (left ventricular thrombus 6 years after surgery).

Bicuspid Aortic Valves
Of the 82 patients, 4 (mean age, 35 years) had bicuspid valves, which in the absence of cusp retraction were not considered a contraindication for repair. Of these, 1 presented as an emergency with severe heart failure and low cardiac output syndrome and died on the first postoperative day of low cardiac output. The other 3 are alive and well with no or minimal aortic regurgitation at latest follow-up (mean, 2673 days).

Mitral Valve Involvement
In all, 10 patients underwent mitral valve repair: 2 (2.4%) before, 6 (7.3%) at the same time as, and 2 (2.4%) after the valve-conserving operation.
Other Arterial Pathology

Four patients (4.9%) previously had repair of a descending aortic aneurysm. Six patients (7.3%) subsequently had a descending aortic aneurysm repair, 2 of whom died after the repair. Three patients had fatal uncorrected descending aortic dissections after the valve-conserving operations at 46, 890, and 5046 days after surgery that caused their deaths.

Symptomatic Status

An improvement in symptomatic status observed early, as assessed by NYHA class, was maintained in most patients, with 89.9% of those at latest follow-up being in class I, 7.2% in class II, 2.9% in class III, and 0 in class IV.

Table 2. Possible Predictors of Survival Investigated by Univariate Analysis

<table>
<thead>
<tr>
<th>Possible Predictors of Survival</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>0.96</td>
<td>0.93–1.00</td>
<td>0.07</td>
</tr>
<tr>
<td>Family history</td>
<td>0.37</td>
<td>0.1–1.35</td>
<td>0.13</td>
</tr>
<tr>
<td>Skeletal manifestations</td>
<td>2.79</td>
<td>0.36–21.7</td>
<td>0.33</td>
</tr>
<tr>
<td>NYHA class</td>
<td>8.79</td>
<td>2.54–30.4</td>
<td>0.0006</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Severity of aortic regurgitation</td>
<td>0.53</td>
<td>0.17–1.67</td>
<td>0.28</td>
</tr>
<tr>
<td>greater than moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency operation</td>
<td>7.08</td>
<td>2.24–22.4</td>
<td>0.0009</td>
</tr>
<tr>
<td>Use of β-blockers</td>
<td>0.23</td>
<td>0.06–0.89</td>
<td>0.0330</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>1.09</td>
<td>0.97–1.23</td>
<td>0.015</td>
</tr>
<tr>
<td>Preoperative aortic root size</td>
<td>1.00</td>
<td>0.95–1.05</td>
<td>0.15</td>
</tr>
<tr>
<td>Associated procedures</td>
<td>1.44</td>
<td>0.31–6.67</td>
<td>0.63</td>
</tr>
<tr>
<td>Cross-clamp time</td>
<td>1.00</td>
<td>0.97–1.04</td>
<td>0.89</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Significant by multivariate analysis: relative risk=0.94, 95% CI=0.90–0.98, P=0.007.

Cardiothoracic Ratio

Postoperatively, diminution in heart size as indicated by a reduction in the cardiothoracic ratio observed early tended to be maintained, except in the patients who developed aortic regurgitation.

Echocardiogram Measurements

Analysis of serial echocardiograms showed a postoperative reduction in left ventricular end-systolic dimensions (a mean preoperative value, 41.5 mm; at 6 months, 36.8 mm; at 5 years, 35.8 mm, which was maintained) and end-diastolic dimensions (mean preoperative value, 60.2 mm; at 6 months, 53.2 mm; at 5 years, 53.6 mm, which was maintained). An improvement in fractional shortening was also observed (preoperative mean value, 30.7%; at 6 months, 31.5%; at 5 years, 33.3%, which was maintained).

Discussion

This study documents the feasibility, pattern of survival, aortic valve function, and recurrence of arterial pathology in patients with Marfan syndrome over a period of ≥19 years. We have shown that valve-conserving operations are feasible in ≥70% of patients with Marfan syndrome undergoing aortic root operations. Although the microfibrillar abnormality caused by mutations of the fibrillin gene affects many...
structures in the body, including the valve cusps, the main problem results from progressive dilatation dissection or rupture of the aortic wall, and aortic regurgitation results from dilatation of the aortic sinuses and sinotubular junction. The valve cusps are usually functionally normal, with sufficient cusp tissue for the enlarged aortic orifice, particularly during the early phases of the disease, but undergo secondary changes in patients with long-standing aortic regurgitation who develop retraction of the cusp, rendering repair difficult or impossible. Earlier operation could therefore increase the application of this operation to virtually all patients with Marfan syndrome.

Repair durability has been good in patients with Marfan syndrome, particularly in the absence of secondary changes and in those with effective repair immediately after operation. Earlier operation could enhance durability because the operation could alter mechanical loading, which might influence connective tissue degradation by metalloproteinases. Preservation of the valve has many advantages, including maintenance of the extremely sophisticated, dynamic structure of the aortic outflow, which could influence left ventricular function, coronary flow, and cardiac output and possibly result in better survival and quality of life. Because patients with Marfan syndrome are usually younger and potentially have compromised left ventricles, the low incidence of valve-related complications and lack of need for anticoagulation have particularly important implications for the quality of life in these patients. In addition, they may require orthopedic or further arterial interventions that could be rendered hazardous by the anticoagulation necessitated by use of a prosthetic valve.

Early mortality was 4.9% for the whole group, and there were no early deaths in 67 patients operated on electively. Overall survival rates were 92.3%, 87.3%, and 84.3% at 1, 5, and 10 years, respectively, but survival was dependent on the original type of disease, with actuarial survival rates of 94.2%, 94.2%, and 94.2% in patients undergoing resection of chronic aneurysm. Patients with acute dissection had actuarial survival rates of 72.8%, 63.6%, and 63.6%, and those with chronic dissection had rates of 100%, 83.7%, and 75.0%. These figures compare favorably with those reported for composite replacement of the aortic root with prosthetic valves, although in the absence of a control group in our study, any meaningful comparison with patients having composite valve replacement or the David operation is difficult.

Results were better in the absence of dissection; survival in those with chronic aneurysm was superior to survival in those with acute dissection. Those with chronic dissection initially had an excellent survival, but with time, survival began to parallel that of acute dissection, suggesting that the presence of an intimal tear affects outcome.

Survival in the asymptomatic group was excellent, suggesting that early operation in high-risk patients (such as a rapid rate of enlargement or size of the aortic root, a strong family history of rupture at a young age, or coexisting pregnancy) is warranted. In this series, successful “prophylactic” resection of a large aneurysm of the root was performed in a patient 17 weeks’ pregnant. Maintenance of normothermia, high perfusion pressure, and continuous monitoring of fetal heart rate resulted in maintenance of pregnancy, which resulted in the delivery of a normal baby. In our series, treatment with \( \beta \)-blockers either preoperatively or immediately postoperatively was associated with improved survival. The survival rates for those on \( \beta \)-blockers were 97.9%, 95.4%, and 95.4% at 1, 5, and 10 years compared with 84.9%, 77.0%, and 71.1% for those not on \( \beta \)-blockers. These results support previous evidence that treatment with \( \beta \)-blockers has a protective effect.

Our analysis identified several risk factors for poor survival that could help to improve patient selection and timing of the operation. Our study showed age, NYHA
functional class IV, emergency surgery, absence of β-blockers, and presence of symptoms as poor predictors of survival. The pattern of early and late survival after repair can be expected to improve further because of increased experience, the use of preoperative β-blockers, and earlier operations, as suggested by these predictors of survival. Improved survival in the asymptomatic group (Figure 4) suggests that prophylactic operation is warranted in some cases. The number of late deaths in this series caused by dissection of the descending thoracic aorta indicates that a follow-up of these patients, which includes imaging of the entire aorta, is mandatory.

In conclusion, we have demonstrated that valve-conserving operations are feasible in most patients with Marfan syndrome and can be used in patients with both acute and chronic dissection and aneurysm. The early and long-term results are encouraging, and results are better in the absence of dissection, which suggests that prophylactic operation is warranted in high-risk patients.

Acknowledgments
We would like to thank John Smith of Tissue Typing and Derek Robinson of the Department of Statistics at the University of Sussex for performing the statistical analysis. We would like to thank Jacqui Scott for her invaluable help. We would like to thank the British Heart Foundation for their support; M. Yacoub is a British Heart Foundation Professor of cardiothoracic surgery, and Dr Birks is an investigator for the statistical analysis. We would like to thank Jacqui Robinson of the Department of Statistics at the University of Sussex for performing the statistical analysis. We would like to thank John Smith of Tissue Typing and Derek Robinson of the Department of Statistics at the University of Sussex for performing the statistical analysis. We would like to thank Jacqui Scott for her invaluable help. We would like to thank the British Heart Foundation for their support; M. Yacoub is a British Heart Foundation Professor of cardiothoracic surgery, and Dr Birks is a research fellow in cardiology supported by the British Heart Foundation.

References
Early and Long-Term Results of a Valve-Sparing Operation for Marfan Syndrome
Emma J. Birks, Carole Webb, Anne Child, Rosemary Radley-Smith and Magdi H. Yacoub

_Circulation_. 1999;100:II-29-II-35
doi: 10.1161/01.CIR.100.suppl_2.II-29
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/100/suppl_2/II-29

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/