Mitral Valve Disease in Patients with Marfan Syndrome Undergoing Aortic Root Replacement

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Background—Cardiac manifestations of Marfan syndrome include aortic root dilation and mitral valve prolapse (MVP). Only scant data exist describing MVP in patients with Marfan syndrome undergoing aortic root replacement.

Methods and Results—We retrospectively analyzed data from 166 MFS patients with MVP who were enrolled in a prospective multicenter registry of patients who underwent aortic root aneurysm repair. Of these 166 patients, 9% had mitral regurgitation (MR) grade >2, and 10% had MR grade 2. The severity of MVP and MR was evaluated by echocardiography preoperatively and ≤3 years postoperatively. Forty-one patients (25%) underwent composite graft aortic valve replacement, and 125 patients (75%) underwent aortic valve–sparing procedures; both groups had similar prevalences of MR grade >2 (P=0.7). Thirty-three patients (20%) underwent concomitant mitral valve (MV) intervention (repair, n=29; replacement, n=4), including all 15 patients with MR grade >2. Only 1 patient required MV reintervention during follow-up (mean clinical follow-up, 31±10 months). Echocardiography performed 21±13 months postoperatively revealed MR >2 in only 3 patients (2%). One early death and 2 late deaths occurred.

Conclusions—Although the majority of patients with Marfan syndrome who undergo elective aortic root replacement have MVP, only 20% have concomitant MV procedures. These concomitant procedures do not seem to increase operative risk. In patients with MR grade ≤2 who do not undergo a concomitant MV procedure, the short-term incidence of progressive MR is low; however, more follow-up is needed to determine whether patients with MVP and MR grade ≤2 would benefit from prophylactic MV intervention. (Circulation. 2013;128[suppl 1]:S243-S247.)

Key Words: Marfan syndrome • mitral valve • thoracic aorta

Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue, with an estimated prevalence of ≈1:5000. Since 2010, the diagnosis of MFS has been based on the revised Ghent nosology. Primary cardiac manifestations of MFS include aortic root dilation and mitral valve prolapse (MVP). In adults with MFS, elective replacement of the aortic root is performed if its diameter is ≥50 mm; in patients with an aortic diameter <50 mm, repair is considered if it grows >5 mm per year, if there is significant aortic regurgitation, or if there is a family history of aortic dissection. Great improvements have been made in aortic root replacement because this procedure was initially described >4 decades ago, and the use of valve-sparing root replacement is becoming more common in patients with MFS.

Mitral valve prolapse is the second most common cardiac manifestation of MFS; ≤91% of patients with MFS have MVP. Although MVP may be asymptomatic for a long time, it can present as acute, severe mitral regurgitation (MR) secondary to chordae tendineae rupture. Mitral valve prolapse in patients with MFS who present for repair of an aortic root aneurysm is rarely discussed in the literature. Addressing mitral valve (MV) disease in patients with MFS who are undergoing aortic root replacement is important because of the anatomic relationship between the 2 valves and the potential challenge associated with operating on the MV after aortic root replacement. When patients without connective tissue disorders have MR at the time of aortic root replacement, MV intervention is performed if the severity of the MR is at least moderate. Similarly, MFS patients with MVP may benefit from MV restoration during aortic root surgery. However, clinicians have little data to help guide their decisions regarding the management of MV disease in patients with MFS undergoing an operation to repair ascending aortic dilation and aortic valve dysfunction.

The objective of the current study was to describe the prevalence, severity, and treatment of MV manifestations, as well as postoperative outcomes in MFS patients with MVP who undergo aortic root replacement surgery.

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Methods

Study Design
The current investigation focused on MV disease in patients with MFS. To compare the progression of MR after either aortic valve-replacing (AVR) or aortic valve-sparing (AVS) aortic root replacement, we retrospectively analyzed preoperative echocardiographic data, surgical outcomes, and follow-up echocardiographic and clinical data from a multicenter prospective study.

Study Cohort
The Institutional Review Board of the Mayo Clinic, Rochester, MN, approved our retrospective study and waived the consent requirement. We analyzed data collected from the prospective, multicenter Aortic Valve Operative Outcomes in Marfan Patients (AVOOMP) study.8 Human research review boards approved the AVOOMP study protocol at each of the 19 participating study sites (13 United States and 6 international; Table 1). All enrolled patients provided written informed consent. Three hundred sixteen patients were enrolled in the AVOOMP study between March 2005 and November 2010. The primary indication for surgery was aortic root aneurysm with or without aortic valve regurgitation. Of the 316 enrolled patients, 239 had preoperative echocardiograms available for review. Five patients were excluded from our analysis because of prior MV intervention. Among the remaining 234 patients, preoperative transthoracic echocardiography detected MVP in 166 patients (69%; 93 men; mean age at surgery, 32±13 years). These 166 patients constituted our study cohort.

Aortic root operations were categorized as AVS or AVR according to the final procedure performed, not the intended procedure. Two AVS operations (David IV and remodeling procedures) were converted intraoperatively to AVR; the patients were categorized as having undergone AVR.

Review of Echocardiographic Data
Echocardiography was used to detect MVP and MR and to grade the severity of MR preoperatively and during postoperative follow-up at 6 months, 1 year, 2 years, and 3 years. The severity of MR was graded as none, trivial (0), mild (1), moderate (2), moderate to severe (3), or severe (4).9 All echocardiographic images included in the AVOOMP study were reviewed by one of the authors (H.C.). The diagnosis of MVP was based on 2 echocardiographic criteria: leaflet thickness >0.5 mm and leaflet motion ≥2 mm above the plane of the mitral annulus in the long-axis views.

Statistical Analysis
Descriptive statistics for categorical variables are reported as frequency and percentage, whereas continuous variables are reported as mean±SD or median (range) as appropriate. The Fisher exact test was used to compare MR grades between the AVS and AVR patients. The McNemar test was used to evaluate the agreement between preoperative and follow-up MR grades. Patients were counted as having MR ≥2 if they had this grade at any follow-up visit between 6 months and 3 years. The Kaplan–Meier method was used to estimate freedom from MR >2 at 1, 2, and 3 years. The Wilcoxon rank-sum test was used to compare cardiopulmonary bypass times of patients with and without concomitant procedures. Two-tailed P values were calculated, and P<0.05 were considered statistically significant. Because only a few patients underwent reoperation or had MR during follow-up, no statistical modeling was performed to predict which patients would most benefit from concomitant MV surgery.

Results

Patient Characteristics
Of the 166 patients with MFS who had detectable MVP and underwent aortic root replacement surgery, 15 (9%) had a preoperative MR grade ≥2, 16 (10%) had an MR grade of 2, and 135 (81%) had an MR grade ≤1. The aortic root replacement procedure was AVS in 125 (75%) of the 166 patients and AVR in the other 41 patients (25%). The AVS and AVR surgery groups had similar proportions of patients with a preoperative MR grade ≥2 (P=0.7). Four different types of AVS surgery were performed: 85 patients (51%) underwent a David V procedure, 35 patients (21%) underwent a David I, 4 patients (3%) underwent a David IV, and 1 patient (<1%) underwent a Florida Sleeve.10,11

Of the 166 patients with MFS who had detectable MVP, 33 (20%) underwent concomitant MV intervention during aortic root replacement surgery: 29 had MV repair, and 4 had MV replacement (Table 2). Preoperatively, 15 of these patients (45%) had an MR grade ≥2, 11 (33%) had an MR grade of 2, and 7 (21%) had an MR grade of 1. All patients with an MR grade ≥2 underwent an MV procedure.

The preoperative echocardiograms of all 33 patients who underwent MV repair or replacement were re-evaluated. Thirty-one of the 33 patients had thickened valve leaflets. In addition, 31 patients had bileaflet prolapse; the other 2 patients had predominantly posterior leaflet prolapse. Twenty-seven of the 33 patients had a dilated mitral valve annulus.

The operative reports of these 33 patients were reviewed to determine why patients with MR grade ≤2 underwent MV repair. Of the 7 patients who had initially been diagnosed with grade 1 MR, 3 had more severe MR that was revealed by intraoperative transesophageal echocardiography (TEE), 2 had extremely elongated chordae, 1 patient had ruptured chordae, and 1 patient had a dilated annulus, prompting the surgeon to proceed with MV repair. Among the 11 patients with preoperative grade 2 MR, 4 had more severe valve leakage on intraoperative TEE, 2 had a markedly dilated annulus, 1

Table 1. Distribution of 166 Patients With Mitral Valve Prolapse by Enrolling Site

<table>
<thead>
<tr>
<th>Enrolling Site</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Stanford University</td>
<td>34 (20.5)</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>32 (19.3)</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>20 (12.0)</td>
</tr>
<tr>
<td>New York Presbyterian Cornell</td>
<td>16 (9.6)</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>15 (9.0)</td>
</tr>
<tr>
<td>Baylor College of Medicine</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>University of Leipzig</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>Medical University of Luebeck</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>Institute of Cardiology and Cardiovascular Surgery</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Northwestern University</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Missouri Baptist Medical Center</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Hannover Medical School</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>University of Ottawa</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Loyola University</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Washington University</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Central Maine Heart and Vascular Institute</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Leiden University</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Montefiore Medical Center</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>University of Pittsburgh</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>
had extremely elongated chordae, 1 had a flail chord, 1 had an especially redundant posterior leaflet (especially at P2), 1 had markedly thin scallops, and 1 had sclerosed valve leaflets along with a dilated annulus. Cardiopulmonary bypass times were longer in patients who underwent a concomitant MV operation (249±98 minutes) than in patients who did not (191±78 minutes; P<0.001). Thirteen patients with aortic dissections, 4 acute and 9 chronic, were included in the study cohort (8 Stanford type A and 5 Stanford type B). Only 1 of these patients (who had chronic dissection) had concomitant MV surgery.

During the follow-up period (mean, 31±10 months), only 1 patient required MV reintervention. That patient, a 14-year-old girl, underwent urgent MV replacement 16 days after MV repair surgery (reconstruction with annuloplasty and leaflet resection) because the valve had an MR grade of 4 after the initial operation. The patient had an intraoperative conversion from a valve-sparing David IV procedure to an AVR because of an intraoperative postprocedure aortic regurgitation grade of 3.

Postoperative Follow-Up
Follow-up data collected after the index hospitalization were available for 162 of the 166 patients who underwent aortic root replacement surgery. One 4-year-old patient died of bleeding on the first postoperative day, a 40-year-old patient died of multiorgan failure at 10 months, and a 15-year-old patient died of unknown causes at 17 months; all 3 deaths occurred in patients who underwent MV repair during aortic root replacement surgery. These patients’ cardiopulmonary bypass times were 135, 202, and 211 minutes, respectively, compared with an average time of 203±86 minutes for the rest of the group. Echocardiography performed 21±13 months postoperatively revealed an MR grade ≥2 in only 3 of the 158 patients tested. Two of these patients had preoperative MR grades ≥2 and had undergone operations that included concomitant MV repair; the other patient had a preoperative MR grade of 1 and did not undergo concomitant MV repair. All 3 patients who had a postoperative MR grade >2 had undergone AVS, and none had undergone AVR surgery (P=0.7). Three-year follow-up data were available for 37% of patients. Kaplan–Meier estimates for freedom from MR >2 were calculated, and 99.4%, 98.8%, and 98.2% of patients were alive and had an MR grade ≤2 at 1, 2, and 3 years, respectively.

We also analyzed MR grade in the 133 patients who did not undergo concomitant intervention; follow-up images were available for 130 of these patients. The mean duration of echocardiographic follow-up was 25±14 months. One hundred twenty-three (92%) of these patients had a preoperative MR grade <2. Only 10 (7%) had an MR grade ≥2 at follow-up. The proportion of patients with an MR grade ≥2 did not change significantly between the preoperative time point and follow-up (P=0.1).

Discussion
The reported prevalence of MVP in patients with MFS ranges from 28% to 91% and is thought to be related to a dilated left ventricle and myxomatous degeneration of the valvular tissues secondary to underlying extracellular matrix derangements.12,13 In patients with MFS, MVP reportedly becomes more prevalent with increasing age.14 The echocardiographic criteria for the diagnosis of MVP are single or bileaflet prolapse ≥2 mm beyond the long-axis annular plane and leaflet thickening.13

The biological mechanism for MVP in patients with MFS seems to be related, in part, to a genetically induced reduction in the extracellular matrix binding of latent transforming growth factor-β (TGFβ), which leads to a localized increase in TGFβ activity, resulting in elongation and excessive thickening of the MV leaflets.15 The leaflets’ response to repeated mechanical stress may result in the formation of myxomatous valves, even in patients with MFS. Mitral valve prolapse can lead to serious complications, including MV leakage with secondary left atrial and left ventricular enlargement, atrial fibrillation, heart failure, and stroke.16 Rupture of MV chordae leading to acute MR has also been described and may precipitate the acute onset of heart failure or the need for urgent or emergent MV surgery.17–19

In our study, 166 (69%) of the 239 patients with MFS who underwent elective aortic root repair and had echocardiograms to review were found to have MVP, but only 15 (9%) of these patients had an MR severity grade >2. This pattern seems to be similar to the reported frequency of MVP in patients without connective tissue disorders.15 Although patients with MVP more frequently have MR than those without MVP, the MR is usually trivial or mild.16

To determine whether an MR grade ≥2 is an adequate threshold for recommending MV intervention concomitant with AVR or AVS aortic root replacement, we examined data from those patients who did not undergo concomitant MV intervention. None of these patients required subsequent MV surgery during our follow-up period. Also, only 7% of patients had a more severe MR grade during postoperative follow-up than they had preoperatively. Of the 33 patients who underwent concomitant MV surgery, only 1 required a subsequent MV procedure, which was performed early in the postoperative period because of a failed MV repair.

In MVP patients without connective tissue disorders, risk factors associated with cardiovascular mortality include moderate-to-severe MR and an ejection fraction <50%.

Table 2. Concomitant Mitral Valve Procedures

<table>
<thead>
<tr>
<th>Mitral Valve Procedure</th>
<th>AVS Root Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AVS</td>
</tr>
<tr>
<td>Annuloplasty</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Annuloplasty with leaflet resection</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Reconstruction without annuloplasty*</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Reconstruction with annuloplasty*</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Reconstruction with annuloplasty and leaflet resection*</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Replacement</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>22 (100%)</td>
</tr>
</tbody>
</table>

Values are expressed as number (percentage). AVR indicates aortic valve replacing; and AVS, aortic valve sparing.

*Reconstruction describes a variety of mitral valve repair techniques, including triangular and quadrangular resection, Alfieri suture repair, and sliding advancement plasty of the posterior leaflet.
Secondary risk factors for cardiovascular events in the same population are a left atrial dimension ≥40 mm, flail MV leaflets, atrial fibrillation, and age ≥50 years. Although there are no data regarding the risk factors for cardiovascular events in patients with MFS, some of the aforementioned risk factors are probably important in these patients as well. Our patients had few cardiovascular events during the relatively short follow-up period; thus, we were not able to determine the risk factors associated with such events. However, we did observe that all 3 deaths after aortic repair occurred in patients who underwent MV procedures.

The question of whether MVP should be addressed by MV repair rather than replacement is an important one. For patients with MVP who do not have MFS, the risk of requiring MV reoperation after MV repair versus MV replacement is similar at 5, 10, and 15 years postoperatively. In the current study, the only MV reoperation was probably necessitated by a technical issue, because the patient developed severe MR soon after the operation. We favor MV repair when the patient’s anatomy is suitable, but mechanical MV replacement is a reasonable option for select Marfan patients with significant associated mitral regurgitation who are undergoing mechanical prosthetic AVR, because these patients will require long-term anticoagulation with warfarin. In our study, of the 4 patients who underwent mechanical MV replacement, 3 of them also underwent mechanical AVR.

**Study Limitations**

The retrospective nature of the current study limited the types of analysis we could perform and, therefore, the inferences we could make. For example, this study design prevented us from performing echocardiograms to look for specific dimensions or to obtain the best images for making those measurements. Because the study data were collected at multiple institutions, variability in echocardiographic technique and image quality is a potential concern, but we attempted to offset this variability by having one of our authors perform an additional review of all images. Also, the follow-up period was too short to answer questions regarding MV repair durability. Mitral valve prolapse is associated with only trivial-to-mild MR in most cases. We only had a few patients (n=3) with an MR grade ≥2 and only 1 patient who underwent MV reintervention. This did not allow us to develop any predictive models regarding which patients would most benefit from a concomitant MV operation.

A prospective study focusing specifically on MVP with a larger patient cohort and longer follow-up would better enable us to make recommendations regarding which risk factors should prompt prophylactic concomitant MV intervention in MFS patients with MVP who are undergoing AVR or AVS aortic root replacement surgery. The continuing follow-up planned for the current MFS cohort may provide important information in the future. Currently, such a retrospective study with long-term follow-up is probably our most feasible option for developing more precise recommendations on this topic.

**Conclusions**

In the current study, MVP was present in 69% of patients with MFS who underwent aortic root replacement with either AVR or AVS techniques. Twenty percent of the patients with MVP underwent an MV procedure concomitant with aortic root replacement. Short-term results suggest that combining these procedures in patients with MVP and an MR grade >2 is reasonable. Operative risk was not significantly increased by the addition of MV repair or replacement. Also, in patients who did not undergo concomitant MV procedures, subsequent MV procedures were rare, suggesting that MV operations may not be necessary for patients with lower MR grades. The type of aortic root replacement, be it valve sparing or valve replacing, did not have an appreciable effect on postoperative MV function. Longer follow-up is needed to determine whether prophylactic MV intervention at the time of aortic surgery might be beneficial for patients with MVP and an MR grade ≤2.

**Acknowledgments**

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**Disclosures**

J. Coselli received research support (significant) from Vascutek Ltd, a Terumo Company; Medtronic, Inc.; and WL Gore & Associates; He is a consultant/advisory board (modest) member of Cook Medical, Inc; Vascutek Ltd, a Terumo Company; Edwards Lifesciences; Medtronic, Inc.; and WL Gore & Associates. The other authors report no conflicts.

**References**

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