Aortic regurgitation in Marfan syndrome patients who underwent prophylactic surgery: A single-center experience

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Abstract

Background: Marfan syndrome is an inherited connective tissue disease that causes aortic root dilatation and dissection and requires surgical intervention. Apart from emergent surgery for aortic dissection or aortic aneurysmal rupture, prophylactic surgical intervention can also be administered, depending on the severity of aortic root dilatation. The direct relationship between surgical intervention and aortic regurgitation was seldom mentioned in previous studies.

Methods: A retrospective cohort study was designed to determine the clinical presentations of prophylactic surgery in patients with Marfan syndrome. Between January 2009 and May 2019, 112 patients, adolescents and young adults, treated in the Department of Pediatric Cardiology of Taipei Veterans General Hospital, were enrolled. All patients' sex, body measurements, echocardiography reports, and surgical notes were collected for statistical analysis.

Results: Among the participants, nine patients (8%) underwent the Bentall procedure, and the other 103 did not receive surgical intervention. The operation group had a larger aortic root size (4.89 vs 2.86 cm, $p < 0.001$), more dilated left ventricle (4.81 vs 4.1 cm, $p = 0.002$), and higher prevalence of moderate and severe aortic regurgitation (66% vs 1%, $p < 0.001$) than the nonoperation group.

Conclusion: Among adolescents and young adults with Marfan syndrome, echocardiographic presentation of aortic root dilatation, left ventricular dilatation, and significant aortic regurgitation was significantly associated with prophylactic surgical intervention. According to the study, significant aortic regurgitation should also be considered as an important indication for prophylactic surgery.

Keywords: Aortic regurgitation; Blood vessel prosthesis implantation; Marfan syndrome

1. INTRODUCTION

Marfan syndrome (MFS) is a systemic connective tissue disease inherited in an autosomal dominant fashion. This disease is caused by a mutation in s, a gene that encodes fibrillin-1. FBN1 mutation results in deficits in the extracellular matrix.[1] The weakened connective tissue gradually causes multiorgan symptoms, including musculoskeletal, ocular, and cardiovascular symptoms. Mitral valves prolapse, aortic root dilatation, and aortic dissection are common cardiovascular manifestations of MFS, with the latter two being the leading causes of death in patients.[2]

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Since the Bentall operative procedure was first described by Dr. Bentall and DeBono in 1968,[3] applying this cardiac surgical technique has greatly improved midterm and long-term outcomes of MFS patients with aortic root dilatation or dissection.[3,4] The Bentall procedure, currently considered the standard operation for MFS patients, includes graft replacement of the aortic root and ascending aorta, mechanical valve replacement of the aortic valve, and reimplantation of the coronary arteries to the graft. Following the advancements in surgical techniques, the valve-sparing David procedure, which involves reimplantation of the aortic valve, has gained popularity and is now more widely applied.[5,6]

Although the standard surgical treatment in MFS patients has been standardized, the optimal timing and indications for prophylactic surgery remain uncertain, and these varied across reports. Gillinov et al[7] identified aortic root dilatation and mitral regurgitation (MR) as the two most common surgical indications. The 2010 The American College of Cardiology (ACC)/American Heart Association (AHA)/American Association for Thoracic Surgery (AATS) guidelines recommend elective operation when the internal aortic root diameter exceeds 50 mm, or when there is a rapid growth of the internal aortic root diameter (>5 mm/y), even if it is <50 mm, to avoid acute dissection or rupture.[8] Recent data had suggested early preventive operation

when the aortic root diameter exceeded 45 mm.[9] In addition, surgery has also been indicated in cases with significant aortic regurgitation (AR).[8] While most studies have focused on the aortic root size as an indication for surgery, studies discussing the relationship between AR and surgery are few. The main goal of our research is to determine the relationship between the severity of AR and the incidence of prophylactic surgical intervention.

2. METHODS

A retrospective study was conducted by enrolling patients with MFS treated in the Department of Pediatric Cardiology of Taipei Veterans General Hospital between January 2009 and May 2019. This investigation has been approved by an appropriate institutional review board (IRB), and the IRB approval number was 2021-01-021AC. The inclusion criteria were a diagnosis of MFS according to the original Ghent criteria published in 1996,[10] presence of detailed medical records, and results of a comprehensive transthoracic echocardiography exam. The exclusion criteria were previous aortic surgery, history of aortic dissection, bicuspid aortic valve, congenital or acquired aortic valve dysplasia, and failure to meet the Ghent criteria of diagnosis of MFS. Patients' height and weight were measured, and body surface area was calculated using the Dubois formula. Detailed transthoracic echocardiography data, including aortic root dimensions, left ventricular interdiameter and systolic function, presence of mitral valve prolapses, and severity of mitral and aortic valvular regurgitation, were collected. The aortic root dimensions included the external aortic diameter at the level of the aortic annulus, sinus of Valsalva, sinotubular junction, and ascending aorta on parasternal long-axis view, as shown in the Fig. 1. The maximum aortic root size was defined as the largest dimension among the four levels. Since all patients were adolescents or young adults, their body sizes were similar. Thus the Z-scores of the aortic root were not calculated.

For patients who underwent the Bentall operation, the data, collected during their last outpatient appointment before the operation, were used for analysis. Data for nonoperated patients were collected from their most recent visit.

Mitral valve prolapse diagnosis and grading of MR and AR were based on the 2008 focused update incorporated into the ACC/AHA 2006 guidelines to manage valvular heart disease patients.[11] Based on the color Doppler and angiographic grading, MR is categorized into mild (1+), moderate (2+), and severe (over 3+). Significant AR is defined as regurgitation more severe than grade 2.

2.1. Statistical analyses

The population was divided into two groups, according to the receipt of prophylactic surgical intervention. Statistical analyses were performed using SigmaPlot software, version 12.3 (Taipei Veteran General Hospital), and all tests were considered significant if $p < 0.05$. Continuous variables were displayed as means ± standard deviations, whereas categorical and discrete variables were presented as numbers and proportions.

3. RESULTS

A total of 112 patients with MFS met the inclusion criteria and were enrolled. Among them, nine patients (8.0%) underwent prophylactic Bentall procedure. The remaining 103 did not undergo surgical intervention. The participants were categorized into the operation and nonoperation groups. All detailed results of the statistical analysis are shown in Tables 1 and 2. The demographic characteristics, including the distribution of age, sex, height, weight, and body surface area, were similar between the two groups.

According to the surgical records, the indications for operating were mainly based on the absolute size of the aortic root, instead of the Z-score or rapid progression of aortic root size (>5 mm/y), following the AHA guidelines. All patients in the operation group underwent the classical Bentall procedure, which involved graft replacement of the aortic root and ascending aorta, and mechanical aortic valve replacement. Acute postoperative complications occurred in one case, a 30-year-old woman with acute myocardial infarction due to stenosis over the anastomosis site of the left main coronary artery and aortic graft. The problem resolved a few days after the emergent operation for reanastomosis of the coronary artery and graft. No acute postoperative complications were observed in the other patients ($n = 8$). No midterm complications were noted in any of the nine patients during outpatient follow-up until the present day.

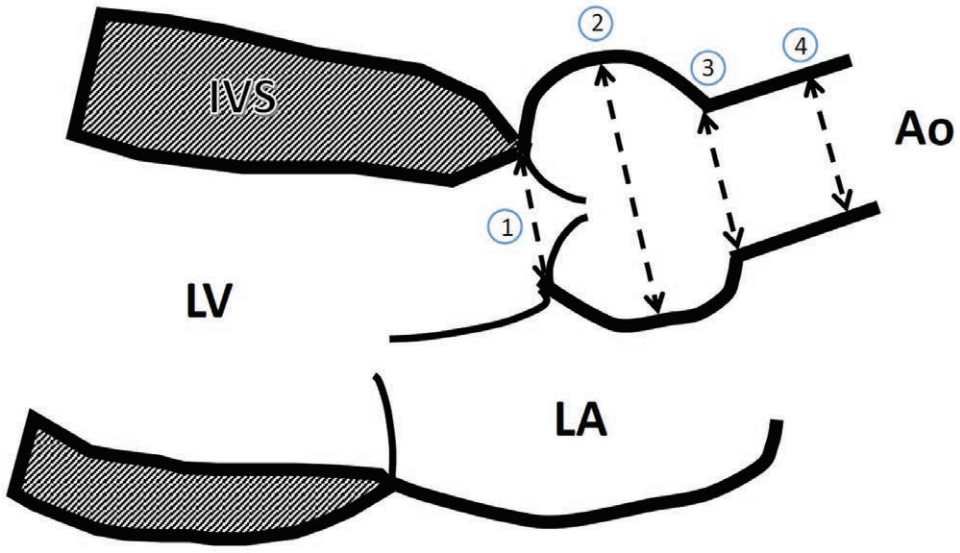

Fig. 1 Standard measuring method of aortic root dimension on parasternal long axis view by transthoracic echocardiography. Ao = aorta; IVS = interventricular septum; LA = left atrium; LV = left ventricle. Number 1 = aortic annulus; Number 2 = Sinus of Valsalva; Number 3 = Sinotubular junction; Number 4 = ascending aorta.

Table 1

Demographic characteristics of the study population

	Operation group (*n* = 9)	Nonoperation group (*n* = 103)	*p*
Age, year-old	30.0 ± 9.9 (15.0-38.0)	18.0 ± 13.0 (17.0-48.0)	0.151
Male/female ratio	1.2	1.1	0.779
Body height, cm	183.0 ± 15.0 (165.0-219.0)	174.0 ± 20.5 (147.0-215.0)	0.098
Body weight, kg	62.0 ± 12.8 (35.0-78.0)	56.0 ± 18.8 (40.0-135.0)	0.231
Body surface area, m^2	1.7 ± 0.2 (1.2-2.0)	1.6 ± 0.3 (1.2-2.8)	0.143

Data are expressed as mean ± standard deviation (minimum-maximum) or numbers.

For the echocardiographic findings, the aortic root sizes were significantly more dilated in the operation group than in the nonoperation group. The aortic roots were measured at the aortic annulus ($p = 0.006$), sinus of Valsalva ($p < 0.001$), or the ascending aorta ($p < 0.001$). The maximum aortic size was also significantly larger in the operation group ($p < 0.001$). Left ventricular assessment showed significantly larger interdiameters in both systolic ($p = 0.008$) and diastolic ($p = 0.002$) phases of the operation group. The left ventricle's systolic function, presented by calculated ejection fraction and fractional shortening, was similar in both groups.

Echocardiographic assessment of the aortic valve showed that all participants had normal tri-leaflet aortic valves, and the operation group had a higher prevalence of significant AR ($p < 0.001$). In contrast, there were no significant differences in terms of the prevalence of mitral valve prolapse and the severity of MR in the two groups.

4. DISCUSSION

In this single-center retrospective study, 112 patients diagnosed with MFS were studied. Increased aortic root size, increased left ventricular interdiameter, and significant AR were associated with prophylactic surgical intervention over a 10-year period.

MFS patients develop AR due to aortic annular dilatation and/or variable degrees of myxomatous aortic valvular degeneration.[12] Physiologically, the progression of AR led to greater regurgitant volume and increased end-diastolic left ventricular pressure. This eventually results in the left ventricle and atrium enlargement. The left ventricular ejection fraction can be maintained initially by a compensatory increase in ventricular contractility, but chronic volume overload leads to myocardial damage that ultimately jeopardizes cardiac output.[13] Considering its direct impact on heart function, AR's severity should be closely monitored, and early surgical intervention to preserve heart function is crucial.[14] In this study, the prevalence of significant AR and left ventricular dilatation was considerably higher in the operation group, demonstrating the effects of AR-related volume overload. These findings suggested that the direct impact of AR on the left ventricle was significant. Moreover, AR was highly prevalent in MFS patients receiving prophylactic surgery. This was seldom mentioned in the reviewed literature. Our findings suggested that in addition to aortic root dilatation, significant AR (grade >2+) should also be considered as an indication for surgical intervention in clinical practice.

Table 2

Echocardiographic characteristics of the study population

	Operation group (*n* = 9)	Nonoperation group (*n* = 103)	*p*
Aortic interdiameter size, cm			
Aortic annulus, cm	2.66 ± 0.95 (1.61-4.71)	1.88 ± 0.38 (1.66-3.13)	0.006*
Sinus of Valsalva, cm	4.40 ± 1.09 (3.31-6.56)	2.85 ± 0.67 (2.72-4.96)	<0.001*
Sinotubular junction, cm	2.65 ± 1.70 (1.80-3.91)	2.07 ± 0.58 (2.08-3.71)	0.053
Ascending aorta, cm	4.30 ± 2.07 (2.56-9.72)	2.65 ± 0.71 (2.05-5.33)	<0.001*
Max aortic size, cm	4.89 ± 1.82 (3.50-9.72)	2.86 ± 0.68 (2.72-5.33)	<0.001*
Max aortic size distribution			
Aortic annulus	0 (0 %)	0 (0 %)	0.682
Sinus of Valsalva	6 (66.7%)	81 (78.7%)	
Sinotubular junction	0 (0 %)	0 (0 %)	
Ascending aorta	3 (33.3%)	22 (21.3%)	
Left ventricular function assessment			
Diastolic inter-diameter, cm	4.81 ± 0.46 (4.25-5.60)	4.10 ± 0.74 (2.98-6.33)	0.002*
Systolic inter-diameter, cm	2.96 ± 0.67 (1.95-4.57)	2.40 ± 0.52 (1.97-4.43)	0.008*
Ejection fraction, %	76.30 ± 12.30 (44.10-90.30)	78.20 ± 7.20 (59.40-90.20)	0.473
Fractional shortening, %	37.00 ± 9.00 (17.60-54.10)	40.00 ± 6.00 (25.90-54.00)	0.242
Valvular function assessment			
AR (< 2+)	3 (33.3%)	102 (99%)	<0.001*
AR (≥ 2+)	6 (66.7%)	1 (1%)	
No MVP	3 (33.3%)	56 (54.4%)	0.388
MVP	6 (66.7%)	47 (45.6%)	
MR			
No	1 (11.1%)	41 (39.8%)	0.155
Mild	7 (77.8%)	58 (56.4%)	
Moderate	1 (11.1%)	2 (1.9%)	
Severe	0 (0%)	2 (1.9%)	

Data are expressed as mean ± standard deviation (minimum-maximum) or number (%).
AR = aortic regurgitation; MR = mitral regurgitation; MVP = mitral valve prolapse.
*Statistically significant.

According to current practice guidelines, the severity of aortic root dilatation is the main indication for surgery.[8] The risk of aortic dissection was positively correlated with the aortic diameter in adults.[15] In this study, aortic root dilatation was assessed by measuring the aortic diameter at different levels of the aorta. The purpose of these meticulous measurements was to determine the most dilated part of the aorta (maximum size of the aortic root) in patients with MFS. Anatomically, the widest part of the natural aortic root is at the level of the sinus of Valsalva. Therefore, this was the most commonly measured site to represent aortic dilatation's severity.[8] According to our data, the maximum size of the dilated aorta was located at the level of the sinus of Valsalva, in accordance with general anatomical findings.[16] However, in about 20% to 30% of MFS patients, the aorta was most dilated at the level of the ascending aorta. This phenomenon was observed in both operation and nonoperation groups. Although the aortic size at the sinus of Valsalva was an appropriate marker of the severity of aortic dilatation, the aortic size at the ascending aorta also reflected the risk of aortic dissection. It may indicate early surgery, even if the sinus of Valsalva is not severely dilated. Therefore, echocardiographic assessment of aortic root dilatation in patients with MFS requires detailed measurements to evaluate the risks and to determine the timing of surgical intervention.

There were no differences in age, height, weight, and body surface area between the two groups. Most participants were in their late adolescence or young adulthood. As a result, age-associated cardiovascular changes were theoretically negligible. The slender physique was attributed to the musculoskeletal manifestations of MFS, known as the Marfanoid habitus. In addition, no patient in the study population was overweight or obese. This reduced confounding factors because obesity was a risk factor of aortic complications in MFS patients.[17]

The cumulative incidence of surgical intervention in our study was 8%, comparable to the prevalence (7.1%, 33/462) reported in France by Hascoet et al.[18] However, in a Spanish study presented by Martín et al,[9] the rate of surgery was nearly doubled (14.1%, 56/397). Upon reviewing the Spanish study, the study group found that the risk of aortic events significantly increased with aortic diameters larger than 45 mm. As a result, they suggested performing elective surgery early, specifically when the aortic root size exceeded 45 mm. This may explain the higher incidence of surgery.[9] This suggestion was reasonable since the elevated risk was documented, and the outcomes of elective aortic root surgery were good in experienced centers.

There are currently two surgical approaches for MFS patients with aortic root dilatation. The classic Bentall operation involves composite valve graft implantation, and the David procedure involves reimplantation of the natural aortic valve. The latter allows freedom from lifelong anticoagulation and risk of thromboembolism, but further reintervention may be necessary due to aortic insufficiency. Previous studies have confirmed the safety and efficacy of valve-sparing operations in selected patients.[3,19–21] A recently published systemic review emphasized the advantages of the valve-sparing procedure in MFS patients. Its long- and short-term results included lower in-hospital, long-term mortality, and lower valve-related reintervention rates.[6] The Bentall procedure is still a routine procedure in most cardiosurgical centers worldwide, including our medical center. All our patients in the operation group underwent the Bentall procedure and exhibited favorable short- and mid-term results during regular clinic visits. An alternative aortic root reconstructive procedure with valve-sparing techniques may be attempted more often in the future, considering its excellent outcomes and promising benefits.

There were some limitations to this study. Due to the retrospective study design, incomplete or missing data were abandoned. As a result, further analyses of other confounding factors were limited. The relatively small sample size and population imbalance between the two groups may have affected the study's statistical power and increased the margin of error. Further research with longer study periods and larger populations is needed to better clarify AR's clinical significance in MFS.

In conclusion, in patients with MFS, aortic root dilatation and further dissection or aneurysmal rupture were common manifestations, and prophylactic surgery was crucial to prevent these complications. The classic Bentall procedure is the current standard technique, and it provided good short-and mid-term outcomes. Echocardiographic presentation of aortic root dilatation, left ventricular dilatation, and significant AR was significantly associated with prophylactic surgical intervention. According to the study, significant aortic regurgitation should also be considered as an important indication for prophylactic surgery.

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