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VALVULAR HEART DISEASE (TL KIEFER, SECTION EDITOR)

Valvular Disease in Marfan Syndrome: Surgical Considerations and Management

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Abstract

Purpose of Review Detail the current strategies for the management of valve dysfunction in Marfan syndrome (MFS), understand the limitations of surgical interventions, and delineate the likely direction of future innovations.

Recent Findings Significant advances in both medical and surgical management of MFS have been made over the last 50 years. This has resulted in improved overall outcomes. As MFS patients age, new clinical challenges that were once rare have emerged and can require complex care strategies. Medical management has seen advances and focuses on anti-impulse and molecular-based pharmacotherapy, along with close monitoring with serial imaging to minimize acute aortic dissection risk by selecting appropriate timing of prophylactic surgical intervention with increasing aortic dimensions. Ongoing trials are evaluating other potential drug therapies with the ultimate goal of targeted treatment.

Summary Over the last 50 years, significant advances have been made in the understanding and management of MFS. A move to prophylactic surgery for aortopathy and valve disease has progressed from a valve replacement to a valve-sparing strategy in many cases. However, the durability of these repairs is variable and the possibility of reintervention looms.

Keywords Marfan syndrome · Valvular disease · Surgical management · Connective tissue disorder

Introduction

Marfan syndrome (MFS) is an autosomal dominant, multi-system connective tissue disorder associated with a fibrillin-1 (FBN1) gene mutation [1]. The syndrome has wide ranging effects on multiple systems and a variable expressivity. The incidence of MFS is 2–3 per 10,000 individuals [2]. In approximately 27% of cases, the mutation is de novo with the affected individual having no family history of the disease, and the diagnosis is made clinically with the use of the Ghent criteria [1]. The Ghent nosology evaluates the skeletal, cardiovascular, ocular, pulmonary, skin manifestations along with family history, as well as the results of genetic testing, and uses a scoring system to establish the diagnosis. Some findings develop with age, which makes the nosology less useful in young patients. The typical Marfan patient is young, tall, and thin framed with long limbs, arachnodactyly, possible pectus deformities, and scoliosis [1]. The patient may also have a family history of connective tissue disorder, sudden death, aortic aneurysms, or dissections. The cardinal cardiovascular findings of MFS are a dilated aortic root with resultant aortic valve regurgitation, and mitral valve prolapse with or without regurgitation. The cardiovascular findings are responsible for the major morbidity and mortality in this patient population [3].

Major advances in the management of Marfan syndrome have been made over the last 40 years. Before the introduction of composite aortic valve and root replacement by Bentall and DeBono in 1968, the average life span of a MFS patient was approximately 40 years [4]. A move toward valve-sparing surgical techniques, first described by Yacoub in 1993 and David and Feindel in 1992, was also a critical milestone for this frequently young patient population in whom a mechanical surgical valve was generally preferred given durability concerns with bioprosthetic valves [5, 6]. Valve-sparing techniques, particularly in the aortic position, have been found to

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be a safe and effective strategy that avoids the thromboembolic and hemorrhagic complications associated with mechanical valves [7]. The focus of this review is the current management and surgical strategies for valvular disease in the MFS patient.

Marfan Syndrome Medical Management

The fibrillin-1 (FBN-1) gene was discovered to be the cause of Marfan syndrome in 1991 by Dr. Dietz et al. at Johns Hopkins University [8]. Fibrillin is found in many types of tissues including the heart valves, myocardium, and blood vessels. It is the main structural component of microfibrils, which comprise the supporting scaffold for the deposition of elastin. Abnormalities in the FBN-1 gene cause weakness in tissues that lead to abnormalities seen in MFS patients. The most common abnormalities in the cardiovascular system are aortic root dilation leading to eventual aortic valve regurgitation and mitral valve prolapse with or without regurgitation [2]. The main goal of medical management for MFS is to delay the progression of aortic dilation with anti-impulse and directed molecular therapy, and in doing so, limit the risk of aortic dissection and delay the development of aortic regurgitation.

Early diagnosis is key in the management of MFS. The diagnosis may be suspected in children, but the MFS phenotype is progressive and patients need to be followed closely for a definitive diagnosis to be made. Until prophylactic surgery is recommended, medical management including serial imaging, exercise restriction, and pharmacotherapy with beta-blockers and angiotensin receptor blockers (ARB) are employed. The ACCF/AHA guidelines for the management of aortic dilation in MFS suggest an echocardiogram at the time of diagnosis of MFS and 6 months later to demonstrate stability of the aortic dilation. Subsequently, annual imaging should be performed if stability has been shown. More frequent imaging is needed if the maximal aortic diameter is 4.5 cm or greater, or if there is significant growth from baseline. Computed tomography (CT) is the imaging modality of choice given widespread availability and speed, followed by magnetic resonance imaging (MR) and echocardiographic examination. Measurements are acquired perpendicular to the axis of flow and using the external diameter with CT and MR [9].

After a randomized controlled trial in 1994 comparing propranolol to no therapy in patients with MFS revealed a slower rate of aortic root dilation and a reduction in aortic complications, beta-blockade became the foundation of modern medical management [10]. While beta-blockade has become a mainstay of medical treatment in MFS, two large meta-analyses came to opposing conclusions about the effectiveness of the treatment. Gersony et al. found no evidence of clinical benefit of beta-blockade therapy, while Gao et al. found beta-blockers did slow the rate of aortic dilation in MFS [11, 12]. The rationale behind beta-blocker treatment is reasonable; however, there is room for further investigation into what has become a treatment cornerstone.

More recently, losartan, an ARB, has gained popularity in the treatment of MFS. FBN-1 has been shown to be a regulator of the cytokine transforming growth factor β (TGF-β) [13]. TGF-β signaling is upregulated in mice models of MFS, and histologic examination of the aortic tissue in these mice reveals fragmentation of the media and disarray of the elastic fibers [14]. Grossly, these MFS mice have progressive and marked aortic dilation. Losartan has been shown to attenuate the TGF-β signaling pathway. When MFS mice were treated with losartan, there was a significant decrease in the growth rate of the aortic root similar to wild-type mice. Additionally, the treated mice had less disruption of their aortic wall architecture when compared to MFS mice treated with placebo [14]. However, a randomized controlled trial comparing losartan to atenolol in children and young adults with MFS and dilated aortic roots found no difference in the rate of aortic root dilation over a 3-year period. There was also no difference in the rate of aortic root surgery, aortic dissection, or death [15]. This study lacked a control group, but one could conclude that either pharmacologic choice is a reasonable option. In contrast, Groenink et al. showed a reduction in preoperative rates of aortic root dilation in patients treated with losartan compared to a control group [16]. More studies are needed to assess the optimal pharmacologic strategy.

Marfan Syndrome, the Aortic Root, and the Aortic Valve

The vast majority of Marfan patients have some element of aortic root ectasia, and approximately 60–80% will have documented aortic root dilation [2] (Table 1). Both the ACCF/AHA and the European Society of Cardiology recommend prophylactic root surgery at a diameter of 5.0 cm unless there is a personal or family history of dissection, in which case surgery should be performed at 4.5 cm or above [9, 17]. Pregnancy in MFS is associated with an increased risk of dissection secondary to hemodynamic and hormonally induced changes on the elastic fibers of the aortic wall. Women with MFS contemplating pregnancy are considered at increased risk for dissection when the aorta is greater than 4.0 cm and are strongly encouraged to undergo prophylactic repair prior to pregnancy if the aorta is $\geq$ 4.0 cm [17].

Since the introduction of prophylactic surgery for aortic root replacement, the survival of patients with MFS has increased dramatically [18]. The original method for composite aortic root and valve replacement, described in 1968 by Bentall and DeBono and later refined by Kouchoukos, entails the replacement of the aortic valve and root with a mechanical valved-conduit and reimplantation of the coronary arteries as

Table 1 Frequency of cardiovascular manifestations in Marfan syndrome patients, with 60–80% found to have aortic root dilatation and up to 68% with mitral valve abnormalities

Lesion/feature	Symptoms	Frequency	Complications	Comments
Aortic root dilatation	None	60–80%	Aortic dissection	Dissection rare in children < 10 years old
				Diagnostic feature in those < 40 years old
Pulmonary artery dilatation	None	76%	Dissection rare	Regurgitation may be intermittent
Mitral regurgitation/prolapse/-annular calcification	Palpitations Chest pain dyspncea	52–68%	Arrythmias Endocarditis Ventricular dysfunction	
Descending aorta dilatation	None		Aortic dissection	Rare in childhood
				May contribute to dissection risk
Endothelial dysfunction/abnormal aorta elasticity	None	80–100%	Increased vascular stiffness	
Tricuspid valve prolapse	None unless severe	4%	May progress requiring repair	Severe disease uncommon except in infantile type
Left ventricular dysfunction	Dyspnea	36% in infantile type Up to 100%	Diastolic. May be progressive to systolic dysfunction	May occur despite normal valves
	Reduced exercise tolerance	Severity varies		
Arrhythmias	Palpitations Collapse	Up to 20–30%	May cause sudden death	Associated with ventricular dilatation
Coronary artery aneurysm	Chest pain			
	Myocardial infarction	< 1%	Only described in adults	More common than in normal population
Atrial septal defect	None	4%	May need surgical repair	

(From: Stuart AG, Williams A. Arch Dis Child. 2007; 92 (4):351–6. https://doi.org/10.1136/adc.2006.097469, with permission from BMJ Publishing Group Ltd.) [2]

orthotopic buttons [19, 20]. This has been shown to be a safe and durable repair and has been considered the gold standard surgical treatment for root aneurysm for decades [21]. Gott et al. carefully examined what was essentially the worldwide experience for aortic root replacement in MFS from 1968 to 1996 at 10 aortic centers in North America and Europe and found an exceptionally low 30-day mortality rate of 3% [22]. Of the 675 patients included in the study, the vast majority of them, 604 patients, underwent a composite-graft replacement. The trade-off for a durable solution to aortic insufficiency with a mechanical valve was complications with hemorrhage and thromboembolic events associated with the lifelong anti-coagulation requirements. This has been shown to be a risk of 0.7%/year [7].

As noted above, in an effort to preserve the native aortic valve and avoid the aforementioned complications associated with lifelong anti-coagulation, Yacoub and David popularized various valve-sparing root replacement (VSRR) techniques [6, 23]. These techniques have been modified over the course of the last 20 years, but the principle remains the same: excise the dilated root tissue, preserve the native valve leaflets, and re-implant the coronary artery buttons. Two main methods predominate at aortic centers around the world, root remodeling (Yacoub procedure) and root reimplantation (David procedure). Regardless of the method utilized, the quality of the native aortic valve tissue remains a concern in this patient population. Histochemical examination of the aortic valve leaflets of MFS patients reveals the pathognomonic abnormalities of FBN-1 [24]. As such, the long-term durability of valve-sparing repairs is a subject of ongoing investigation. It is important to note that the presence stress fenestrations in these valves may indicate irreparable damage, and replacement may be indicated depending on the severity, although this is a topic of debate [21, 25••]. Several examples of the wide range of aortic valve leaflet morphology in MFS is demonstrated in Fig. 1.

As mentioned, Yacoub originally described the root remodeling procedure, in which the aneurysmal sinuses are removed and a scalloped graft is sewn directly to the remnant sinus tissue and valve commissures [23]. This method preserves the sinus anatomy of the aortic root but does not provide support of the aortic annulus. This may therefore predispose to late annular dilation and potentially aortic valve insufficiency, as was noted by Cameron et al. in a series of aortic root

replacements in the MFS population performed over a 30-year period [21]. To address this issue, some centers reinforce the aortic annulus during the remodeling procedure with an annular wrap or annuloplasty. The available short-term data shows this method can be an effective adjunct to the remodeling approach, but further investigation is ongoing [26]. The David reimplantation technique, however, supports the aortic valve and annulus within a fixed Dacron conduit and prevents late dilation of the aortic annulus, thereby preserving coaptation of the native leaflets [6]. This has been shown to be a safe and durable operation and has become the procedure of choice for valve-sparing root replacement in MFS patients at most aortic centers [21, 25••, 27, 28]. Recent modifications to the procedure involve the use of a Valsalva graft that replicates the aortic sinuses and maintains the native root geometry [29]. Further investigation is needed to understand the effects of this modification, if any, on the durability of the repair.

Bendetto et al. produced an exhaustive meta-analysis examining the surgical management of MFS patients with aortic root disease in 2011 and found an increased risk for reintervention with valve-sparing techniques, while valve replacement techniques were associated with an increased risk for thromboembolic events; there was no difference in the incidence of endocarditis. Additionally, when reimplantation was widely adopted the incidence of reintervention was less evident [7]. More recently, Flynn et al. conducted another meta-analysis comparing valve-sparing and valve replacement surgery in MFS patients undergoing aortic root replacement. The authors found no difference in reintervention rates but did observe a significantly greater incidence of thromboembolic events, late hemorrhagic complications, and endocarditis in patients undergoing valve replacement surgery [30•]. These results may indicate that with increased experience at centers for aortic surgery, the durability of valve-sparing repairs is improving.

One of the limitations of valve-sparing strategies is a lack of reproducibility and standardization in the approach. There exists great variety in valve quality, amount of cusp prolapse, presence of leaflet fenestrations, and overall root geometry amongst the MFS population with aortic root disease (Fig. 1). This translates into enormous operative variability and the need for extensive experience with the procedure to ensure successful and durable results. El-Khoury and his group developed a classification system for the mechanisms of aortic insufficiency (AI), similar to the Carpentier classification of mitral insufficiency, to aid in standardizing approaches to aortic valve repair. They found that cusp restriction (Type III AI) was predictive of repair failure and recurrent insufficiency [31]. They also noted that for patients with types I and II insufficiency (functional annular dilation with cusp prolapse

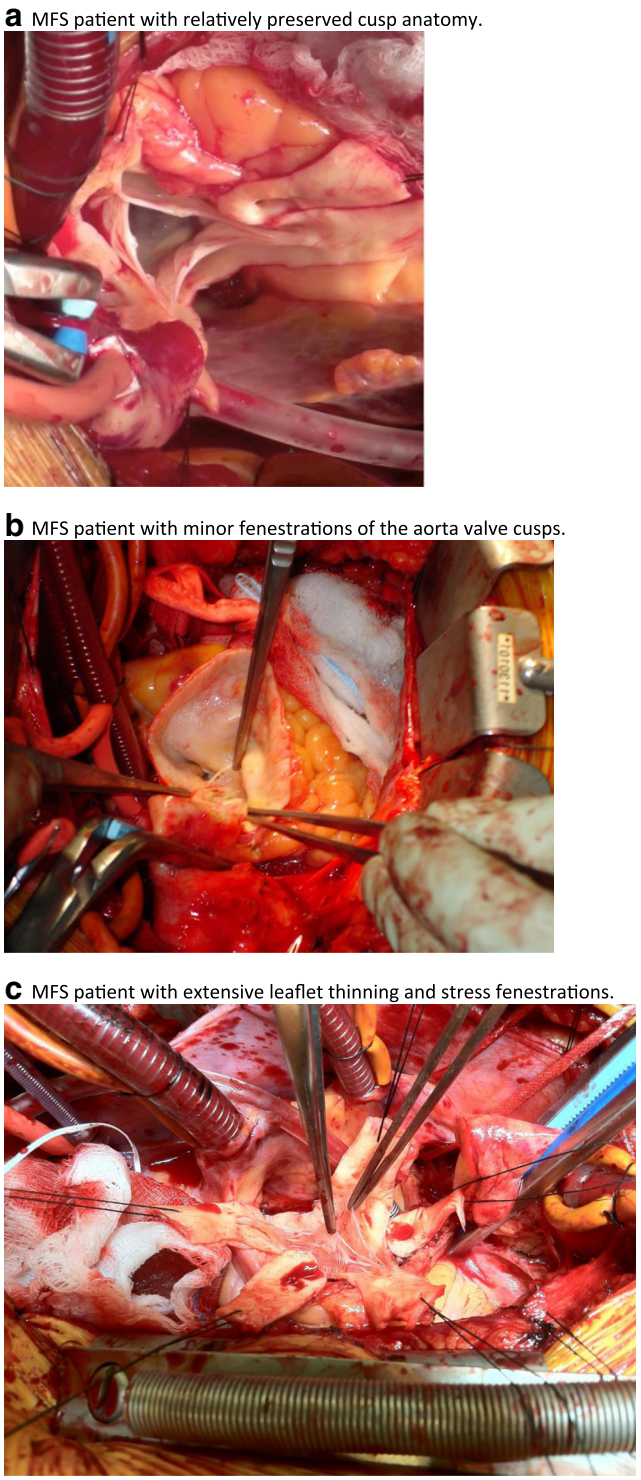

Fig. 1 Aortic valve leaflet morphology demonstrating wide range of tissue quality and cusp abnormalities that play a role in the potential for aortic valve repair and valve-sparing root replacements. **a** MFS patient with relatively preserved cusp anatomy. **b** MFS patient with minor fenestrations of the aorta valve cusps. **c** MFS patient with extensive leaflet thinning and stress fenestrations

or perforation but not restriction), there was 91% freedom from reoperation at 8 years. A detailed summary of the classification is provided as well as the corresponding recommendation for repair approach (Fig. 2).

Newer devices such as the FDA-approved HAART 300 (BioStable, Austin, TX) annuloplasty ring are also intended to help standardize and simplify aortic valve repair. This device is implanted below the native leaflets and restores normal annular geometry as determined by direct intraoperative measurement of cusp free margin lengths. The ring prevents annular dilation, facilitates subsequent correction of cusp prolapse if present, and has been shown to be a safe and effective adjunct in aortic valve repair [32]. As such, the ring allows for a more standardized approach to aortic valve repair. Further, the device allows for use of the simpler remodeling (Yacoub) technique of VSRR in the MFS population, as late annular dilation is prevented by the annuloplasty ring. Finally, there may be the potential for future interventions if a valve repair fails, as the ring may provide a scaffolding for the deployment of a transcatheter valve. This valve-in-ring strategy is still under investigation and more work is needed to confirm the safety and feasibility of this technique.

For MFS patients who have significant intrinsic cusp pathology precluding a valve-sparing strategy, valve replacement surgery remains the gold standard. However, mechanical valve composite grafts carry a lifelong risk of hemorrhage and thromboembolic events [4, 7, 21, 30•, 33]. Puskas et al. conducted a prospective randomized trial to test the safety of a less aggressive anti-coagulation strategy for the On-X aortic valve (CryoLife, Inc., Kennesaw, GA) and found the INR can be safely maintained between 1.5 and 2.0 without an increase in thromboembolism rates when combined with aspirin therapy [34]. Therefore, these findings suggest the potential to attain the durability benefits of a mechanical valve while limiting the anti-coagulation risks with a less aggressive INR goal. As such, it is our preference to use the On-X mechanical valved-conduit for this reason when a Bentall is necessary in the typically young MFS patient.

Marfan Syndrome and Mitral Valve Disease

While aortic root dilation and risk of acute dissection remains the major source of morbidity and mortality in the MFS patient, significant mitral valve disease is also a common finding in this population. In fact, mitral valve prolapse (MVP) and resultant insufficiency is the most common cardiac manifestation in childhood and can present as one of the first indicators of the disease [35]. Overall, the incidence of MVP in Marfan syndrome has been reported to be approximately 80% and is less benign than in the general population, progressing to severe mitral valve regurgitation (MR) or endocarditis more frequently overall [36]. As surgeons strive to spare the aortic valve, the dysfunctional mitral valve poses a significant challenge. Similar concerns regarding the quality of the mitral valve leaflets in MFS persist as they do in aortic valve disease, calling into question the durability of repairs.

Mitral valve prolapse has a prevalence of 2–3% in the general population, and there is a risk of progression to severe regurgitation, endocarditis, and heart failure [37]. Current guidelines for recommending surgery in Marfan patients are the same as in non-Marfan patients; however, MFS patients tend to present earlier in life. Mitral operation is indicated in Marfan patients for chronic severe MR in the symptomatic patient or in the asymptomatic patient if repair has a > 95% probability, if the ejection fraction is < 60% due to mitral

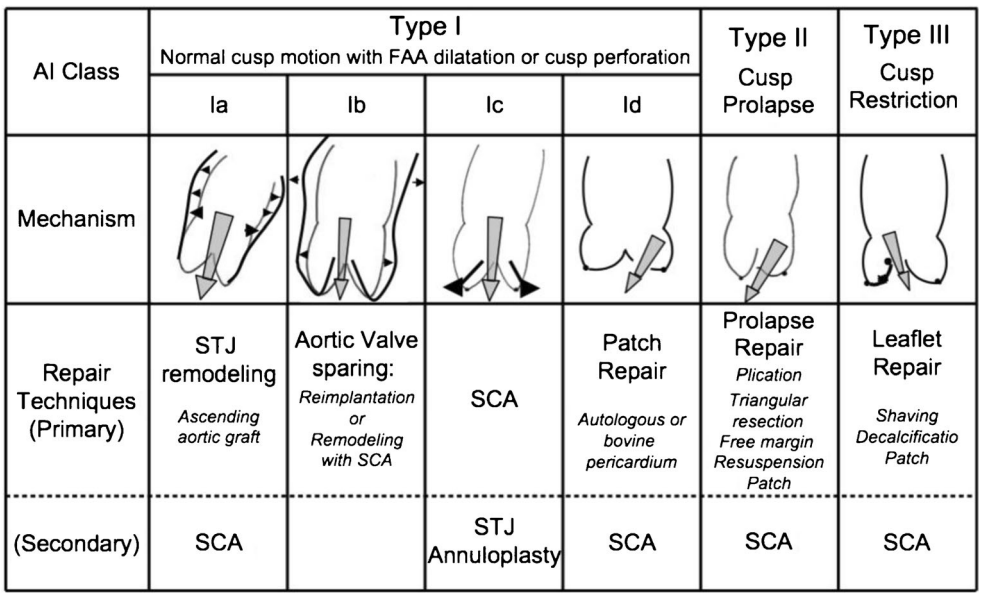

Fig. 2 Repair-oriented functional classification of aortic insufficiency (AI) with description of disease mechanism and repair techniques. *FAA*, functional aortic annulus; *STJ*, sinotubular junction; *SCA*, subcommissural annuloplasty (From: Boodhwani et al. J Thorac Cardiovasc Surg. 2009;137(2):286–94. doi:https://doi.org/10.1016/j.jtcvs.2008.08.054, with permission from Elsevier) [31]

disease, if the left ventricular end-systolic diameter is ≥ 4 cm due to mitral disease, or possibly if atrial fibrillation or pulmonary hypertension are present. Additionally, mitral valve surgery is reasonable in patients with moderate MR when undergoing cardiac surgery for other reasons [38]. Mitral valve repair has been shown to be a durable and superior strategy relative to replacement in most myxomatous disease of the mitral valve [39, 40]. Notably, however, the morphology and natural history of mitral valve disease in the MFS patient differs from that of the myxomatous disease patient. Bhudia et al. examined mitral valve surgery in the MFS patient and found that MFS patients had less posterior leaflet prolapse, more bileaflet prolapse, had overall longer and thinner leaflets, and underwent mitral valve repair less frequently than patients with myxomatous disease (59% vs. 94%) [40].

With current information, the techniques of mitral repair for MFS patients are the same as those for non-MFS patients. Given the higher incidence of bileaflet prolapse and Barlow's disease in MFS patients, Marfan mitral repairs can be as simple as annuloplasty alone, but can also involve work on both leaflets including artificial chords, chordal transfer, leaflet resection, sliding leaflet plasty, Alfieri stitch, and multiple cleft closures. In the general population, bileaflet prolapse is less likely to be repaired than is posterior prolapse, and bileaflet mitral repairs may be less durable than posterior leaflet repairs [41, 42]. Barlow valves in particular are more likely than other forms of prolapse to have significant bileaflet thickening and calcification that can complicate repair and impair durability.

In the aforementioned study by Bhudia et al., mitral valve repair was found to be a safe and durable option for the properly selected MFS patient [40]. Helder et al. found in a retrospective study of 61 consecutive patients with MFS undergoing surgery for mitral regurgitation over 5 decades, that mitral repair was associated with significantly better 10-year survival without increased risk for reoperation when compared to mitral replacement [43]. The advantages of mitral repair over mitral replacement are in principle not different from non-MFS patients.

Given that 80% of MFS patients have some element of MVP, this finding is a critical factor to consider when these patients present for aortic root surgery. Further, it is an issue not well defined in the literature but one becoming more pressing in the era of prophylactic surgery and valve-sparing techniques. Kunkala et al. looked at 166 MFS patients with MVP who underwent aortic root replacement and found that while 69% of the patients had MVP, only 20% of these patients had moderate to severe mitral regurgitation, all of whom underwent concomitant mitral valve surgery without an increase in risk [44]. Of the patients who did not undergo concomitant mitral surgery, subsequent mitral valve intervention was not required within their 2-year follow-up. Cameron et al. studied 372 MFS patients undergoing aortic root replacement and found 49 of them underwent concomitant mitral valve surgery with no operative mortalities [21]. Gillinov and associates looked at 118 patients undergoing concomitant aortic root and mitral valve surgery, 34 of whom had MFS [45•]. The operative mortality was 1.7% with 10- and 15-year survivals of 79% and 71%, respectively, and reoperative rates at 5 and 10 years of 4% and 12%. Their group routinely involved both aortic and mitral valve surgical specialists in each case and felt this strategy contributed to their success, and this has been the approach at our institution as well. In summary, at busy aortic centers with appropriate expertise, combined aortic root and mitral valve surgery for moderate to severe regurgitation appears to be a safe and effective strategy.

Nonetheless, data are limited regarding repair versus replacement of the mitral and aortic valves when BOTH valves are being operated in MFS patients. Several common situations should be considered:

1. In the young MFS patient needing mitral replacement with a mechanical prosthesis, one could argue that a mechanical valved-conduit for the aortic valve has the advantage of a lower risk of reoperation versus aortic valve repair. These patients will require lifelong anticoagulation for the mechanical mitral valve, and therefore, aortic valve repair likely offers little advantage in this scenario. The reciprocal of this scenario is not necessarily true, however, i.e., the patient with an irreparable aortic valve but potentially repairable mitral valve. In this situation, the decision regarding concomitant mitral valve repair versus replacement should be based upon the likelihood of a durable mitral valve repair given the reduced anti-coagulation requirements of a mechanical aortic versus mitral prosthesis.

2. A more difficult situation is those MFS patients needing complex MV repair and with a large aortic root potentially amenable to VSRR. This combined procedure typically will require a longer cardiopulmonary bypass and cross-clamp time, and decision-making should therefore be individualized based on the patient's age, ventricular function, previous cardiac surgery, and other comorbid conditions [45•, 46]. The authors have tended toward double valve replacement in these patients if MV repair would be very complicated with significant risk of late failure.

3. Some MFS patients needing mitral surgery may have an aortic root that is only modestly dilated (< 4.5 cm) without surgical aortic valve disease. If complex mitral repair is planned and felt likely to succeed, then one could consider minimally invasive mitral repair first, followed by a VSRR later when the root enlarges to a diameter meeting surgical criteria. If the mitral valve needs replacement, then one could argue for concomitant mechanical

valved-conduit aortic root replacement if the root is ≥ 4 cm to avoid later reoperation.

4. Finally, in an emergent setting with severe MR (i.e., acute type A dissection in a MFS patient), one could argue for replacement of both the mitral and aortic valves to expedite a complex operation and minimize the potential for high-risk reoperation.

Conclusions

Treatment strategies for the cardiovascular complications of MFS have evolved over the last century, and what was once a predictably fatal condition has seen survival rates that approach those of the general population. While the literature on beta-blockade therapy is somewhat inconsistent, there is a solid rationale behind implementing pharmacotherapy early with serial imaging for detecting progressive aortic dilation and/or valve dysfunction, and thereby allowing early intervention in the elective setting [11, 12]. Further investigation into the ideal medical treatment for MFS is needed, and areas such as ARB therapy have shown promise [15, 16]. The introduction by Bentall and DeBono of the technique for aortic root replacement spurred an effort to prophylactically operate on MFS patients and resulted in excellent outcomes [19]. However, the implications of lifelong anti-coagulation for a mechanical valved-conduit, including bleeding and stroke risks, again motivated surgeons to innovate. As such, valve-sparing techniques have become more of a mainstay in this patient population at referent aortic centers, and outcomes in these high volume centers have been excellent [7, 25••]. Concern remains for the resilience of valve repair, both aortic and mitral, in a population with valves comprised of abnormal tissue but, thus far, have proven to be a safe and durable option that avoids anti-coagulation. However, there is significant variation in both valve and root anatomy, as well as surgeon comfort and experience with valve repair. Newer devices aim to standardize and simplify aortic valve repair and offer the potential scaffolding for future transcatheter reinterventions if late failure of the repair occurs. Finally, thoughtful consideration needs to be given regarding the optimal surgical approach for the MFS patient with combined aortic and mitral valve disease so as to minimize the risks of reoperation as well as lifelong anti-coagulation.

Compliance with Ethical Standards

Conflict of Interest Ryan P. Plichta, Donald D. Glower, and G. Chad Hughes declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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