Treatment of Aortic Disease in Patients With Marfan Syndrome
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Marfan syndrome (MFS) is a heritable disorder of the connective tissue with a prevalence of \(~1\) in 3000 to 5000 individuals. The condition is inherited in an autosomal dominant manner with complete penetrance but demonstrates variable expression with significant intra- and interfamilial variation. Approximately 25% of patients do not have a family history and represent sporadic, new mutations for the condition. The cardinal features of MFS involve the cardiovascular, ocular, and skeletal systems. The most life-threatening complication of MFS is thoracic aortic aneurysms leading to aortic dissection, rupture, or both. This article focuses on medical and surgical treatment of aortic disease in patients with MFS and addresses the treatment of aortic disease in children and pregnant women with the condition.

The most common cardiovascular complication in patients with MFS is progressive aortic root enlargement initially occurring at the sinuses of Valsalva. Ascending aortic aneurysm can precipitate acute type A aortic dissection, aortic rupture, aortic regurgitation (AR), or all 3, and these complications were the primary cause of death before the advent of successful preventive therapies. Treatment of the aorta consists of regular imaging to detect and quantify progression of aortic dilation, \(\beta\)-adrenergic receptor antagonist therapy, and prophylactic aortic repair when the dilation reaches a sufficient size to threaten dissection or cause AR. Before the era of open-heart surgery, the majority of patients with MFS died prematurely of rupture of the aorta, with an average life expectancy of 45 years. The success of current medical and surgical treatment of aortic disease in MFS has substantially improved the average life expectancy, extending it up to 70 years.

Cardiovascular manifestations in MFS also include valvular disease involving the mitral valve, aortic valve, or both. Mitral valve prolapse is the most prevalent valvular abnormality, affecting 35% to 100% of patients. Mitral regurgitation is more common in children and women with MFS. It is also important to note that if severe mitral regurgitation prompts surgical repair of the mitral valve, the ascending aorta should be observed carefully postoperatively because hemodynamic stresses on the aorta increase. AR can result from distortion of the aortic valve cusps by the enlarged aortic root and occurs in 15% to 44% of patients.

Other complications of MFS involve the eye, skeletal system, and integument. The lens of the eye is dislocated in \(~50\)% of people with MFS (ectopia lentis) and often is so subtle that it is apparent only with full dilation of the pupil. Myopia is common in MFS, but retinal detachment is a rare complication that may be more common if the lenses are surgically removed. The skeletal features of the disorder include increased height and arm span; anterior chest wall deformities (pectus excavatum or carinatum); long fingers (arachnodactyly) and toes; mild to moderate joint laxity; a narrow, highly arched palate; pes planus; protrusio acetabulum; and vertebral column abnormalities (scoliosis and thoracic lordosis). Dural ectasia (widening of the dural sac, leading to back pain and headache) occurs in \(~60\)% of patients with MFS. Spontaneous pneumothoraces, recurrent hernias, and striae atrophicae also are features of the condition.

MFS results from mutations in the \(FBN1\) gene, which encodes a large glycoprotein of \(~350\) kDa termed...
Fibrillin-1 is a major protein component of extracellular matrix fibrils called microfibrils. Microfibrils are complex structures containing many proteins and are found as isolated aggregates or intimately associated with elastin in elastic fibers. Fibrillin-1 has a complex multidomain structure that includes 47 epidermal growth factor domains, 43 of which have calcium-binding consensus sequences (Figure 1). The protein is encoded by a large gene (>230 kb), which is found on chromosome 15 and consists of 65 exons. A second locus for MFS, termed the MFS2 locus, was mapped to 3p24–25, and mutations in the transforming growth factor-β receptor type II (TGFBR2) recently have been described in patients with MFS, although the significance of the locus for the phenotype has yet to be determined.

More than 100 FBN1 mutations have been described in patients with MFS in the literature, and the UMD-FBN1 mutation database (http://www.umd.be:2030/) contains ~600 FBN1 mutations in individuals with MFS or related conditions (Figure 1). Mutations causing MFS are found in all exons, and other conditions related to MFS can complicate making the correct diagnosis. The syndromes include related conditions that result from FBN1 mutations as detailed previously. In addition, other conditions resulting from mutations in other genes overlap with the MFS phenotype, including familial thoracic aortic aneurysms and dissections, a syndrome in which ascending aortic aneurysms and dissections are inherited in families in an autosomal dominant manner in the absence of the ocular and skeletal features of MFS.

Noninvasive Treatment of Aortic Disease

Monitoring of Aortic Disease in Patients With Marfan Syndrome

The initial evaluation of an individual with MFS should include an echocardiogram to assess the ascending aorta and cardiac valves. Aortic diameter should be measured at the sinuses of Valsalva and related to normal values based on age and body surface area. The severity of the aortic disease is related to the degree of aortic dilation and to the length of the dilated segment, with dilatation limited to the sinuses of Valsalva having a less malignant prognosis than dilation that extends to the aortic arch. An echocardiogram is often recommended 6 months later to determine the rate of enlargement and then annually if stability of aortic size is documented. If the aorta is dilated >4.5 cm, then more frequent imaging should be considered.

Although transthoracic M-mode and 2D echocardiography are the most common techniques used to monitor the size of the aortic root, the precision of the aortic disease in patients with Marfan syndrome. Echocardiography is the most common noninvasive method used to monitor the aortic root and dilated segments. Aortic root disease is defined by aortic root diameter, and the American Heart Association has established guidelines for aortic root size in Marfan syndrome. In addition, other conditions related to the degree of aortic dilation and to the length of the dilated segment, with dilatation limited to the sinuses of Valsalva having a less malignant prognosis than dilation that extends to the aortic arch. An echocardiogram is often recommended 6 months later to determine the rate of enlargement and then annually if stability of aortic size is documented. If the aorta is dilated >4.5 cm, then more frequent imaging should be considered.

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of these measurements are equipment and sonographer dependent because oblique measurements overestimate the true aortic orthogonal diameter (ie, perpendicular to the aortic flow center line in 3D space). Spiral thin-slice CT angiography (CTA) or magnetic resonance angiography (MRA) with 3D reconstructions are precise and should be used if the echocardiogram does not provide adequate aortic images.

The majority of patients with MFS present with enlargement of the ascending aorta or a type A dissection. Rarely, a patient presents with a type B dissection involving the descending thoracic aorta, but no data indicate that enlargement of the descending aorta necessarily precedes dissection. Therefore, serial examination of patients with MFS is focused primarily on assessing the ascending aorta. Routine CTA or MRA imaging of the entire distal aorta is recommended if the descending thoracic aorta is large or has dissected and after repair of the ascending aorta. The poor outcomes of patients with MFS with acute type B dissection, along with lower operative risks, have prompted the recommendation of early surgical repair, even if the dissection is uncomplicated.16

**Treatment With β-Adrenergic–Blocking Agents**

Studies addressing the efficacy of β-blockade in MFS have concluded that such therapy is successful in a subset of individuals.17,18 Overall, medicated patients showed slower aortic root growth (defined as absolute growth rate or growth rate adjusted for age and body size), fewer cardiovascular end points (defined as AR, dissection, or surgery; congestive heart failure; or death), and improved survival rate. Such therapeutic benefit has been observed in all age groups, including young children.18 It is important to note that treated patients continued to have abnormal aortic growth and aortic dissections, and therefore such therapy does not preclude the need for surgical correction. Significant previous aortic root dilatation correlated negatively with therapeutic response.17

In theory, a protective effect of β-blockade could derive from multiple...
mechanisms, including negative chronotropy and decreased rate of volume and pressure change in the ascending aorta resulting from negative inotropy. Imaging and catheterization-based studies have documented each of these potentially beneficial effects in patients with MFS treated with conventional doses of common β-blockers. Most studies have shown relative improvement in ascending aortic stiffness on treatment with β-blockers in a subset of patients with MFS (≥60%) despite the absence of any significant effect on aortic stiffness in controls. Interestingly, selected studies suggested that β-blockade either had no effect or worsened stiffening indexes in ∼35% of individuals with MFS. Increased body weight or an end-diastolic aortic diameter >40 mm was significantly associated with lack of desired response, suggesting that β-blockers must be given at an adequate dose and early in the course of the disease to optimize the potential benefit.

Typical practices call for instituting therapy with β-blockers on attaining diagnostic criteria in someone with a family history of MFS (including aortic involvement) or on recognizing progressive aortic root enlargement (z score >2.0) in a patient with no family history. In older children and adults, the dose is titrated to keep resting heart rate <70 and heart rate after submaximal exercise <100. In the setting of β-blocker intolerance, a trial with a calcium channel blocker is indicated on the basis of a small trial that suggested its efficacy in protecting the aorta in MFS.

Exercise Restriction
Exercise restriction represents a second approach to reduce hemodynamic stress in MFS. Individuals with MFS are encouraged to remain active, with aerobic exercise performed in moderation. Affected individuals should avoid contact sports and competitive sports that routinely require exercise to the point of exhaustion. Most important, they should avoid isometric exercises, including sit-ups, push-ups, and pull-ups, because of the marked elevation in blood pressure that occurs during sustained muscle contraction.

Surgical Treatment of Aortic Disease
Timing of Aortic Surgery
The traditional threshold that prompts the consideration of prophylactic aortic root replacement in patients with MFS has been predicated on aortic size and recommended when the diameter reaches 5.0 cm. The association between increased aneurysm diameter and the risk for dissection or rupture is clearly established, and aneurysm size >6 cm portends a 4-fold increase in the cumulative risk of aortic rupture or dissection in patients with MFS. Factors that will prompt the recommendation for surgery when the aorta is <5.0 cm include rapid growth of the aortic diameter (>1 cm/year), a family history of premature aortic dissection (dissection <5 cm), and the presence of greater-than-mild AR. Some experienced thoracic aortic surgical centers use a ratio of 2x, in which the diameter of the enlarged aortic segment is in the numerator and normal contiguous aorta is in the denominator, to trigger consideration of prophylactic aortic root replacement, but prospective validation of this approach is needed.

Aortic dissection is the leading cause of morbidity and mortality in MFS, and prophylactic surgery is recommended to prevent this complication. Some patients with MFS experience acute dissections when the aortic diameter is <5 cm. These facts highlight the unpredictable nature of aortic dissection in MFS and emphasize the importance of educating patients about the symptoms of an acute dissection.

Composite Valve Graft Repair
Before 1968, the outlook for patients with MFS requiring surgical repair of aneurysms or dissections involving the aortic root was bleak because of the high operative risk, nearly prohibitive bleeding rates, and the frequent occurrence of serious postoperative complications. Bentall and DeBono introduced a method of replacing the aortic valve and ascending aorta simultaneously using a composite valve graft (CVG) and reimplanting the coronary ostia into the graft. Since 1968, the CVG procedure evolved to include full-thickness end-to-side coronary anastomoses as Carrel “buttons” of aorta and a full-thickness end-to-end distal aortic anastomosis, rather than the original “wrap inclusion” or Bentall technique.

The safety, reproducibility, and long-term durability of the CVG procedure have been clearly documented. In 1999, Gott et al reported the outcome of 675 patients with MFS undergoing CVG between 1968 and 1996 at 10 centers with special expertise in thoracic aortic surgery, with the majority of the patients (89%) receiving a CVG. Of the patients, 30% had either an acute or chronic type A aortic dissection. Emergency operations for acute type A dissections were performed on 103 patients (within 24 hours), 117 received an urgent operation (within 1 to 7 days), and 455 were operated on electively. Follow-up averaged 6.7 years and was 91% complete. The 30-day mortality rate was lowest in the elective cohort (1.5%) and highest for emergency operations (11.7%). Previous ascending aortic operation was an independent risk for early death.

Long-term survival was significantly improved when compared with the natural history of aortic disease in these patients (Figure 2). Overall, 93.5% of patients were alive at 5 years, 91% at 10 years, and 59% at 20 years. After 60 days, the hazard of death was low and constant, and the only significant independent risk factor portending a higher probability of late death was congestive heart failure preoperatively (New York Heart Association class IV functional status).

One of the most common causes of late death was dissection or rupture of the residual “downstream” aorta, with only 36% of these late deaths occurring in patients who initially presented...
with an extensive type A dissection. In addition, 10% of the patients subsequently required distal aortic surgery. The need for reoperation on the aortic root was rare. These data highlight the need for frequent serial imaging surveillance of the entire aorta indefinitely in all patients after surgery. Other frequent causes of late death were ventricular arrhythmias, congestive heart failure, prosthetic endocarditis, and other unknown causes.

Among those receiving a CVG and being discharged from the hospital, 90% were free of a thromboembolic (TE) event at 20 years. Most TE complications occurred within the first postoperative month, which emphasizes the importance of assiduous anticoagulation treatment during the early postoperative period. Most surgeons use 81 mg of aspirin daily to supplement warfarin anticoagulation to help reduce the postoperative TE rate. Prosthetic valve endocarditis developed in approximately the same number of patients as in those who had a TE event. Antibiotic prophylaxis surrounding dental procedures is recommended.

In summary, the comprehensive analysis of patients with MFS undergoing CVG clearly demonstrates that elective aortic root replacement is a low-risk and durable procedure when performed in experienced thoracic aortic surgical centers.

Valve-Sparing Aortic Surgical Repair

Because the majority of patients with MFS are relatively young, mechanical valve prostheses in general have been favored, despite the risk of anticoagulation except in special circumstances (eg, reoperation resulting from prosthetic valve endocarditis, children <10 years of age, women wanting to become pregnant). Other surgical procedures have been investigated that preserve the patient’s native aortic valve. Yacoub and subsequently David have pioneered what is generally termed “valve-sparing aortic root replacement.” These 2 surgical approaches are distinct: The Yacoub procedure is referred to as the “remodeling technique,” and the David procedure is the “reimplantation technique.” The remodeling procedure sews the graft to the remaining aortic wall tissue around the commissures after the insertion line of the aortic cusps, thus leaving the annulus mobile (but unsupported) and allowing billowing of the graft, something called “neo-sinuses.” The reimplantation procedure actually fixes the graft to the left ventricular outflow tract at the subannular level and reimplants the valve and the commissures inside the fabric graft, thus fixing the size of the aortic annulus permanently. The newer David-IV and David-V methods create billowing graft neo-sinuses to theoretically minimize diastolic leaflet closing stresses. Both procedures are options for almost all patients with aortic root aneurysms if the aortic valve is structurally normal. If AR is present because of sinotubular junction dilatation or cusp prolapse, then the AR can be corrected by restoring the normal sinotubular junction geometry, shortening the cusp free margin, or both. Structurally abnormal valve cusps are a contraindication for the procedure, and CVG remains the operation of choice for patients who require anticoagulation for other conditions.

Recent outcome reports from both Yacoub’s and David’s institutions indicated that the operative mortality rate for either procedure is low, but the need to return to the operating room for bleeding was 6-fold higher after a Yacoub operation than a David procedure (18% versus 3%). Long-term survival was excellent with either technique, especially for prophylactic aortic repairs. Theoretically, valve-sparing aortic root replacement should be associated with lower morbidity and mortality when compared with CVG because of the complications associated with a mechanical valve. David’s group recently reported lower valve-related morbidity and mortality for as long as 5 to 10 years with a valve-sparing operation as compared with CVG, but further studies are needed to corroborate these findings (Figure 3).

The main issue facing patients and clinicians deciding between CVG versus a valve-sparing technique is the durability of the preserved aortic valve. Data from the Yacoub group indicated that 22% of patients had moderate AR at follow-up (median follow-up of 3 years). The presence of mild AR early after surgery portended a progression to more severe AR over time. The prevalence of late AR was lower in David’s series, but 25% of patients at 10 years had 3+ to 4+ AR. A trend toward less AR favored the David reimplantation technique over the Yacoub technique. Another clinical end point reflecting valve durability is reoperation. In David’s series, it is remarkable

Figure 2. Life expectancy for 675 patients with MFS after surgical replacement of the aortic root. Reproduced with permission from New England Journal of Medicine. Copyright 1999, Massachusetts Medical Society. All rights reserved.
that no valve-sparing patient had yet required reoperation, but only 9 patients remained at risk at 8 years. This result was superior to Yacoub’s experience, in which 17% of patients required reoperation by 10 years (17 patients at risk at 10 years).32

In summary, the valve-sparing aortic root replacement presents patients with MFS with a reasonable alternative to CVG. Survival is excellent with either technique and complications are rare, but the long-term durability of this repair has not been established. Therefore, patients selecting a valve-sparing procedure must accept the risk of possible reoperation in the future.

Surgical Treatment of Distal Aortic Disease After Repair of the Ascending Aorta

After repair of the ascending aorta, studies indicate that the arch and descending aorta are sites for later-onset aneurysms and dissections in patients with MFS, prompting the need for routine imaging of the entire aorta. An MRA or a CTA scan should be done after aortic root repair before discharge and then regularly thereafter. If the distal aorta is stable and no new symptoms are present, then subsequent scanning should be done at least annually and continued despite a lack of appreciable changes. If a previous type A or B aortic dissection occurred, then more aggressive imaging surveillance is essential, and physicians should allow no more than 6 to 12 months between scans because sudden and catastrophic changes can occur unexpectedly even when the aorta is not markedly enlarged. In addition, β-blockers should be continued indefinitely after surgery to reduce the risk for distal aortic problems. Elective surgical replacement of the descending aorta in patients with MFS is safe today, but a risk of paraplegia exists after extensive descending or thoracoabdominal replacement.34 The operative risk is substantially higher when done as an emergency after rupture or dissection. Elective prophylactic graft replacement of the involved aortic segment is recommended if the interval increases in size are sudden (eg, >0.5 to 1.0 cm/year), if symptoms occur, when the aorta reaches 5.5 to 6.0 cm, or when the aortic diameter exceeds twice the diameter of the normal aorta.

Endovascular Stent Grafting of the Aorta

In general, stent grafts should not be used in either the abdominal or the thoracic aorta in patients with MFS or other connective tissue diseases. An exception is previous aortic replacement operations that have been complicated by a late localized false aneurysm. Stent grafting into old synthetic graft “necks” proximally and distally may be a safer alternative than a repeat thoracotomy in selected cases.

Treatment of Aortic Disease in Children and Pregnant Women With Marfan Syndrome

Children

The vast majority of children with MFS (>80%) demonstrate aortic root dilatation, mitral valve prolapse, or both before age 18 years.4,35 In general, the same principles used to treat adults who have MFS are relevant to children, although a small subset of children with an infantile presentation of severe and rapidly progressive MFS do poorly, most often because of severe mitral valve dysfunction. β-Blockers are prescribed either at the time of diagnosis or on documentation of aortic enlargement. A benefit of medical treatment is to delay surgery until the child can accept a graft of sufficient size to accommodate future growth. In children <5 years old, a typical goal is to keep their resting heart rate at <80 and their heart rate after exercise at <110. Monitoring of the dose of β-blockers is necessary during rapid body growth. Although β-blockers are generally well tolerated by infants and children, selected complications (eg, aggravation of asthma or lethargy-induced interference with learning) are increased in this age group. Potential beneficial manipulations can include use of reduced or divided dosing or substitution with a calcium channel blocker. Exercise restrictions do not become meaningful until a child is older but young children can be directed toward sports that focus on skill rather than speed or endurance.

Cardiovascular surgery has been shown to be highly safe and effective in children with MFS.28 In older children, both the composite graft repair and the valve-sparing procedure have shown excellent results for prophylactic replacement of an enlarged aortic root. The desire to avoid chronic anticoagulation in very young children previously mandated the widespread use of aortic homografts. Recently, the valve-sparing procedure has been applied in children as young as 18

Figure 3. Actuarial freedom from valve-related morbidity and mortality (V-R MM) for patients with MFS after aortic root replacement with either a CVG or a valve-sparing procedure. Differences between curves were evaluated with the log-rank statistic. Reproduced with permission from Journal of Thoracic and Cardiovascular Surgery.33 Copyright 2003, Elsevier Inc.
indicate that the risk for dissection is 50% risk of inheriting MFS. Studies distance of the condition (children have a about this risk, along with the inheri-
tation of surgery in adults (~5.0 cm), most surgical centers for MFS do not use absolute aortic size as a criterion for surgery in children. Rapid rate of growth of the ascending aorta (>1 cm/year) is widely used as an indication for surgical intervention in the pediatric population, along with new AR or the need for mitral valve surgery in individuals with substantial aortic enlargement.

Pregnant Women
Women with MFS are at increased risk for dissection during pregnancy and should be counseled before pregnancy about this risk, along with the inheritance of the condition (children have a 50% risk of inheriting MFS). Studies indicate that the risk for dissection is low if the aortic root diameter is <4.0 cm. β-Blockers should be continued during pregnancy, and echocardiograms should be obtained throughout the pregnancy. Cardiovascular complications are more likely if the aorta is >4 cm or if the aortic root diameter increases rapidly in size during pregnancy; this occurs primarily in the third trimester. If possible, surgical repair of an enlarged aortic root should be done prepartum. If there is an enlarged aorta, progressive enlargement of the aorta, or AR, then more aggres-
tive treatment should be pursued, in- cluding close echocardiographic follow-up and consideration of a Caesarean delivery. The decision about the method of delivery depends on indi-
vidual circumstances, but a vaginal delivery can be considered if the patient has no aortic dilation or dissec-
tion. The stress of labor should be reduced by means of epidural anesthesia and efforts should be made to shorten the second stage of labor.

Future Directions in the Treatment of Aortic Disease
Despite a revolution in the understanding of the etiology and pathogenesis of MFS, none of the current treatment modalities derive from this knowledge. Indeed, with the exception of refinement in surgical and imaging tech-
niques, all of the treatment protocols that are in place were conceived and initiated in the 1960s and 1970s. A focus of future therapies will be pre-
venting the pathology in the aortic wall that is characterized by fragmentation and degradation of elastic fibers and loss of smooth muscle cells (SMCs) in the medial layer, or “medial degeneration.” The steps leading from a deficiency of fibrillin-1-containing microfibrils to the observed aortic pathology have begun to be elucidated. Charac-
terization of mice after homozygous Fbn1 gene targeting demonstrates that elastogenesis proceeds despite a severe quantitative and qualitative deficiency of fibrillin-1 microfibrils. Elastic fibers show normal morphology at birth, and fragmentation and loss of elastic fibers is largely a secondary event in these animal models of MFS. This is characterized by a pathogenetic sequence of loss of connecting fila-
ments that normally serve as a struc-
tural interface between elastic lamellae and neighboring SMCs, leading to an altered phenotype of the SMC, which includes altered expression of multiple matrix elements such as increased expression of matrix metalloproteinases MMP2 and MMP9. The net result is the initiation of local elastic fiber de-
struction that correlates temporally and spatially with elastic fiber calcification and infiltration of inflammatory cells into the aortic media. Both increased expression of MMP2 and MMP9 and the presence of inflammatory cells have been demonstrated in the aortic media in aortas of patients with MFS (unpublished data).

Another possible avenue for therapy is based on studies showing that fibrillin-1 and microfibrils regulate the TGF-β family of growth factors (cyto-
kines) that influence many aspects of cellular performance including differenti-
entiation, proliferation, protein pro-
duction, and survival. Data in mice demonstrate that a deficiency of fibril-
lin-1–containing microfibrils results in excessive TGF-β activation and signal-
ing in the developing lung and many other tissues altered in MFS, including the aortic wall. These data develop the paradigm that matrix se-
questration of cytokines is critical to their regulated activation and signal-
ning, and perturbation of this function can contribute to the pathogenesis of diseases such as MFS.

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