Review

Marfan Syndrome: Clinical, Surgical, and Anesthetic Considerations

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Abstract

Marfan syndrome is a multisystem connective tissue disorder, with primary involvement of the cardiovascular, ocular, and skeletal systems. This autosomal heritable disease is mainly attributable to a defect in the *FBN1* gene. Clinical diagnosis of Marfan syndrome has been based on the Ghent criteria since 1996. In 2010, these criteria were updated, and the revised guidelines place more emphasis on aortic root dilation, ectopia lentis, and *FBN1* mutation testing in the diagnostic assessment of Marfan syndrome. Among its many different clinical manifestations, cardiovascular involvement deserves special consideration, owing to its impact on prognosis. Recent molecular, surgical, and clinical research has yielded profound new insights into the pathological mechanisms that ultimately lead to tissue degradation and weakening of the aortic wall, which has led to exciting new treatment strategies. Furthermore, with the increasing life expectancy of patients with Marfan syndrome, there has been a subtle shift in the spectrum of medical problems. Consequently, this article focuses on recent advances to highlight their potential impact on future concepts of patient care from a clinical, surgical, and anesthetic perspective.

Keywords

arterial wall mechanics, cardiac anesthesia, cardiac surgery, heart, mitral valve

Introduction

In 1896, Antoine-Bernard Marfan presented a new hereditary disorder of connective tissue at the annual meeting of the Paris Medical Society.[1] The clinical vignette described a 5-year-old girl with abnormalities in her skeletal system with elongation of the long bones and digits. After this initial description, further aspects were recognized and associated with the initial findings including ectopia lentis and aortic root dilation. This group of clinical characteristics became known as Marfan syndrome (MFS) in 1914, its autosomal dominant inheritance was recognized in 1931, and Bentall and De Bono[2] pioneered the "Bentall" procedure for replacement of the dilated aortic root in 1968.

Marfan syndrome is a connective tissue disease inherited in an autosomal dominant manner and caused mainly by mutations in the *FBN1* gene.[3] This gene encodes fibrillin-1, a glycoprotein that is the main constituent of the microfibrils of the extracellular matrix. Reduced or abnormal fibrillin-1 leads to tissue weakness, increased transforming growth factor β (TGF-β) signaling, loss of cell-matrix interactions, and finally, different phenotypic manifestations of MFS.[4] Its diagnosis can be challenging because many of its features are age dependent, others are frequently seen in the general population, substantial phenotypic variability is commonly observed, and moreover, there is considerable overlap with other connective tissue disorders. Therefore, the diagnosis of patients with MFS should be made according to the newly revised Ghent criteria and requires a comprehensive clinical assessment of multiple organ systems. Genetic testing can be useful in the diagnosis of selected cases.[5]

Epidemiology

The incidence of MFS is hard to define because of the age dependency of many of the features, the common occurrence of some features in the general population (such as scoliosis; lean, tall habitus; mitral valve prolapse; myopia), and shifting

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diagnostic criteria. Nevertheless, it is likely that approximately 1 in every 5000 individuals is affected, although this figure is probably an underestimate.[6] The disease occurs worldwide, with no predilection for either sex or race. It exhibits complete penetrance but variable expression and age dependency. Between one quarter and one third of cases present with no family history of the disease (sporadic cases due to de novo mutations).[7] Because of the high incidence of aortic root aneurysms with an associated risk of life-threatening aortic dissection, the life span is often shortened. Before the successful use of surgical aortic root replacement, death from aortic dissection was far more common than it is today. Medical and surgical advances, improved awareness, and use of presymptomatic monitoring have positively impacted prognosis in patients with MFS. In 1972, the median life expectancy of patients with MFS was reported to be about 45 years.[8] With the introduction of the Bentall procedure, the scenario changed dramatically, and by 1995, the follow-up of 417 patients in a multicenter study revealed that the median survival age had improved to 72 years.[9]

Pathophysiology

Marfan syndrome is an autosomal dominant disorder with high penetrance but variable expressivity. The majority of cases of MFS are caused by a mutation in the *FBN1* gene on chromosome 15 (15q21.1).[10] Fibrillin-1 is a matrix glycoprotein widely distributed in elastic and nonelastic tissues. Fibrillin-1 monomers associate to form complex extracellular macroaggregates, termed microfibrils, which form part of elastic fibers. The microfibrils are believed to confer important biomechanical properties in connecting, anchoring, and maintaining tissues and organs.[11] Interestingly, fibrillin-1 acts as a potent regulator of TGF-β bioavailability, which is a potent stimulator of inflammation, fibrosis, and activation of certain matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9. The relative concentration of active MMPs and tissue inhibitors of MMPs (TIMPs) determines net proteolytic activity. The first degenerative change noted in the aging aorta is cystic medial degeneration, which is an accumulation of mucopolysaccharide cysts within the aortic media that damages the elastin skeleton and leads to loss of vascular smooth muscle cells and that may disrupt the lamellar structure of the media. An imbalance between MMP and TIMP activity leads to proteolysis and aortic wall weakening. Elastin degradation fragments, in addition to inflammatory cytokines, chemokines, and prostaglandin derivates, promote leukocyte recruitment that perpetuates and amplifies the degradation cycle. Together, the inflammatory milieu, elastic fiber fragmentation, medial attenuation, and decreased collagen reduce the structural integrity of the aorta and ultimately result in aneurysmal dilation.[12] Furthermore, reduced or mutated forms of fibrillin-1 have been shown to stimulate the release of sequestered TGF-β and increase its activity.[13] Therefore, the combination of structural microfibril matrix abnormalities, dysregulation of matrix homeostasis mediated by excess TGF-β, and overexpression of MMP-2 and MMP-9 is believed to result in vascular remodeling, characterized by exaggerated elastolysis and abnormal cell-matrix interactions, which in turn are responsible for the phenotypic features of the aorta with MFS[12] (Figure 1).

The role of TGF-β in the pathophysiology of MFS has been further characterized by the therapeutic benefit of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), both known to decrease TGF-β. Early studies in a mouse model of MFS in which the pathological changes in the aortic root closely mimic those seen in humans were used to demonstrate the therapeutic benefit of treatment with TGF-β antagonists in vivo.[14] The development of pathological changes in the aortic wall and the progressive dilation of the aortic root were attenuated or prevented by systemic treatment with a TGF-β–neutralizing antibody or the ARB losartan, which is an antihypertensive medication known to inhibit TGF-β signaling. In comparison, mutant mice treated with the β-blocker propranolol continued to show substantial pathological changes in the aortic wall and had only a moderate reduction in the rate of aortic root dilation. These findings were followed by human studies in which the initiation of ARB therapy resulted in a significant reduction in the rate of change in the aortic root diameter as compared with β-blocker therapy alone.[15]

Cardiovascular Findings

Cardiac disease is a predominant feature of MFS and includes proximal ascending aortic dilation, dilation of the proximal main pulmonary artery, thickening and prolapse of either or both atrioventricular valves, mitral annular calcification, and rarely dilated cardiomyopathy in the absence of severe valvular dysfunction.

Cardiovascular complications are recognized to be the major cause of morbidity and mortality in patients with MFS. Aortic catastrophe, including aortic dissection or rupture (Figure 1), accounts for most of the premature mortality among patients with MFS, a risk that climbs steeply during adolescence and results in death in up to 50% of undiagnosed and untreated patients with MFS by the age of 40 years.

Additional cardiovascular features in MFS include aortic valve regurgitation due to annular enlargement, mitral valve prolapse with or without mitral valve regurgitation, and pulmonary artery dilation in the absence of pulmonary valve stenosis. The prevalence of cardiovascular manifestations in MFS other than aortic dilation is found in about 66% of patients.[16] Compared with patients with myxomatous disease, those with MFS have longer and thinner mitral valve leaflets,

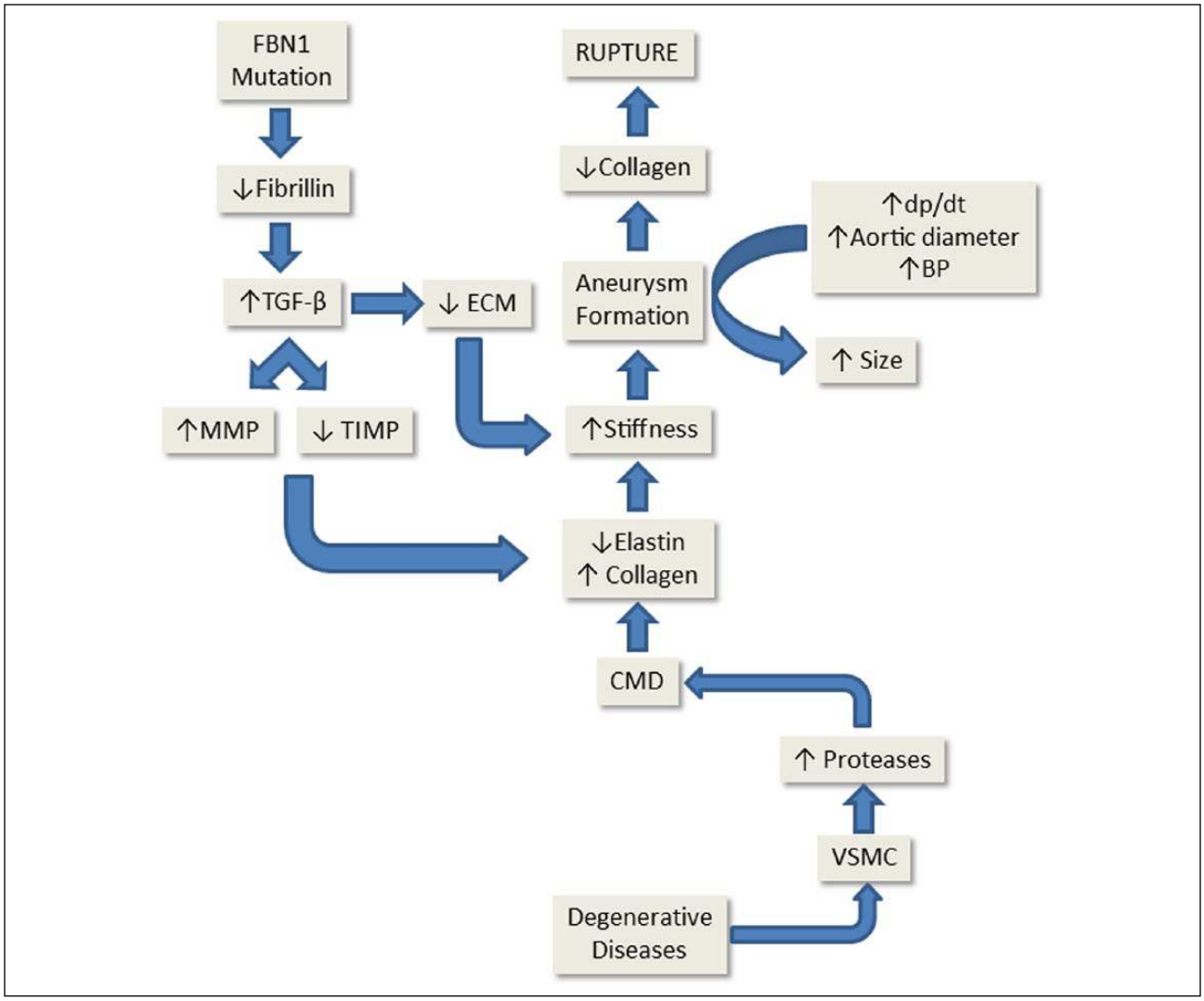

Figure 1. Mechanism of aortic aneurysm formation. Homeostasis of the aortic wall is maintained by several enzymes and growth factors that include TGF-β, matrix metalloproteinases (MMPs), and tissue inhibitors of MMPs (TIMPs).

have less posterior leaflet prolapse, have more anterior or bileaflet prolapse, and present for surgery at a younger age.

In children with early-onset and severe MFS, insufficiency of the mitral valve can lead to congestive heart failure, pulmonary hypertension, and death in infancy; this insufficiency represents the leading cause of morbidity and mortality in young children with the disorder.[7]

Diagnosis

The diagnosis of MFS is challenging and cannot be made by a single molecular test but requires a scoring system that combines various diagnostic items. The 1996 Ghent criteria subdivided diagnostic features into "major criteria," "minor criteria," "organ involvement," and manifestations that only in combination with other manifestations constitute a "major" or "minor" criterion.

Clinical Implications of the Revised Ghent Criteria

The 1996 Ghent criteria were updated in 2010 after data from molecular studies improved our understanding of the pathophysiology of the disease. As a result, several major changes in the diagnostic guidelines were proposed (Table 1)[17]: (1) More weight is given to 2 cardinal features of MFS, namely, aortic root aneurysm/dissection and ectopia lentis. (2) All the other cardiovascular and ocular manifestations of MFS and findings in other organ systems, such as the skeleton, dura, skin, and lungs, contribute to a "systemic score" (Table 1) that guides the diagnosis depending on the presence or absence of aortic disease or ectopia lentis. (3) A more prominent role is assigned to molecular genetic screening for *FBN1* and other relevant genes (eg, TGF-βR1 and TGF-βR2). (4) Some of the less specific

Table 1. Diagnostic Criteria for MFS in Adults According to the 2010 Ghent Classification.

Criteria for Diagnosis of MFS
In the absence of a family history of MFS:
1. Aortic root *Z* score ≥2 AND ectopia lentis
2. Aortic root *Z* score ≥2 AND an *FBN1* mutation
3. Aortic root *Z* score ≥2 AND a systemic score[a] ≥7
4. Ectopia lentis AND an *FBN1* mutation with a known aortic pathological abnormality
In the presence of a family history of MFS (as defined above):
1. Ectopia lentis
2. Systemic score[a] ≥7
3. Aortic root *Z* score ≥2

MFS, Marfan syndrome.
a. Points for systemic score: wrist AND thumb sign = 3 (wrist OR thumb sign = 1); pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1); hindfoot deformity = 2 (plain pes planus = 1); dural ectasia = 2; protrusio acetabuli = 2; reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis = 1; scoliosis or thoracolumbar kyphosis = 1; reduced elbow extension = 1; facial features (3/5) = 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia); skin striae = 1; myopia > 3 diopters = 1; mitral valve prolapse = 1.

manifestations of MFS were either removed or made less influential in the diagnosis (eg, dural ectasia, joint laxity, flat cornea, iris or ciliary muscle hypoplasia, dilation of the pulmonary artery, mitral annulus calcification, recurrent or incisional hernia). (5) The new criteria reinforce the concept that additional diagnostic considerations and testing are required if a patient has sufficient findings to satisfy the criteria for MFS but also shows unexpected findings suggestive of a specific alternative diagnosis (eg, Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome, and the vascular form of Ehlers-Danlos syndrome). (6) The new introduced categories (ectopia lentis; myopia; mitral valve prolapse, borderline and nonprogressive aortic root dilation, skeletal findings, and striae [MASS] syndrome; mitral valve prolapse) cannot be used in patients younger than 20 years, and thus, the term "potential MFS" has been proposed in such patients to take into account that the phenotype may evolve with time.[18]

Imaging the Dilated Aorta

In the past 2 decades, survival has improved for patients with acute aortic syndromes or thoracic aortic aneurysms (TAAs) as a result of technological advances in diagnostic modalities. Current diagnostic techniques for both acute aortic syndromes and TAAs center around the use of computed tomography (CT), transthoracic echocardiography (TTE), and magnetic resonance imaging (MRI).[19] These techniques provide variable information as to the site of origin, extent of dissection, classification of dissection,

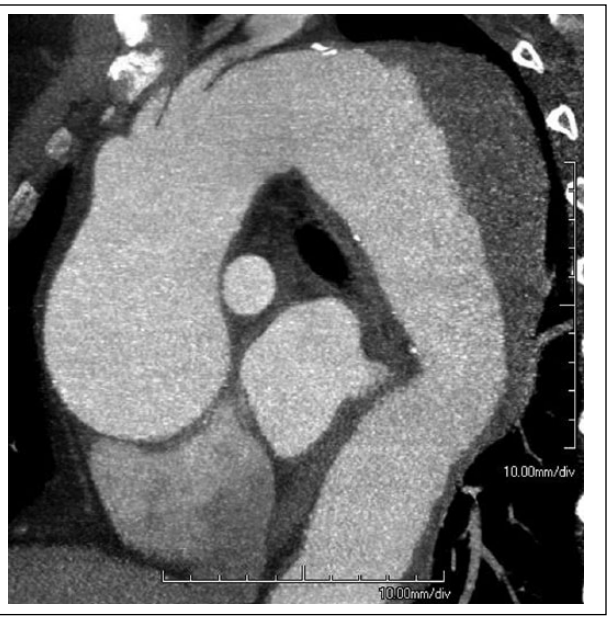

Figure 2. Computed tomography (CT) angiography in Marfan syndrome. Sagittal maximum intensity projection of a CT angiogram performed in a patient with a diffusely aneurysmal thoracic aorta. There are extensive mural thrombi in the descending segment (asterisk).

surrounding areas of hemorrhage if applicable, and other pathological sequelae of the dissection.

The sensitivity of CT scanning approaches enables the detection of both type A and type B TAAs. Spiral CT angiography is currently the most frequently used modality worldwide for diagnosing TAAs: in fact, it is the first diagnostic tool in making the diagnosis in nearly two thirds of patients. Similarly, CT angiography is often used to determine the degree of aneurysmal dilation (Figure 2). However, CT has limitations, as there may be artifacts in the ascending aorta due to cardiac motion as well as streak artifacts that may arise from implanted devices and reduce image quality. In addition, the iodinated contrast load ranges from 80 to 120 mL per study, which can result in contrast-induced nephropathy in select patients. Finally, the use of ionizing radiation, which has dramatically improved over the years, should be taken into account, particularly in younger individuals in whom the accumulated potential cancer risk from repeated imaging is important. Finally, in the setting of type A dissection, CT provides limited evaluation of associated abnormalities in aortic valve function.

Magnetic resonance imaging is an acceptable alternative to CT in stable patients with suspected thoracic aortic disease. Excellent anatomic detail and some information on valvular function are available from MRI. A comprehensive MRI examination of the thoracic aorta may include many components, including black-blood imaging to evaluate

aortic morphology and size and aortic wall contour as well as noncontrast- and contrast-enhanced magnetic resonance angiography using gadolinium-based agents to evaluate the vessel lumen.

Medical Management

β-Blockers

Medical therapy aimed at reducing wall tension through use of β-adrenergic blockade is based on early works demonstrating that the pulsatile nature of the cardiac cycle places significant strain on the aorta, especially within its first 2 cm.[20] The potential benefits of treatment with β-blockers are attributed to a reduction in aortic wall stress caused by their inotropic and negative chronotropic effects and, therefore, a reduction in dP/dt . However, the mechanism through which these drugs exert their protective effects is not well known, and studies on how they influence the elastic properties of the aorta have provided conflicting results.[21] Most studies have provided information that supports a decrement in the aortic dilation rate, but only one study has been able to suggest a mortality benefit.[22] However, the data are scarce, and the findings should be taken with precaution, as the results of a meta-analysis found no benefit in survival using β-blockade.[23]

Current recommendations advise the early use of β-blockers in all patients with MFS, independent of aortic diameter.[21] One of the populations that could potentially benefit the most from treatment with β-blockers is the pediatric population, and the rationale is that treatment with β-blockers may allow surgery to be delayed and, therefore, the eventual implantation of a larger graft, which may in turn avoid the need for reintervention at a later date.[24]

ACE Inhibitors

Recent evidence points toward the potential benefit of ACE inhibitors and selective ARBs as alternatives to standard treatment with β-blockers. The beneficial effects of treatment with ACE inhibitors in MFS are attributed to the control of blood pressure, especially of central pressure, and the reduction of stiffness of the aortic wall.[25] The data stem from an article published in 2005 in which patients with MFS treated with ACE inhibition had a reduced aortic growth rate and a lower event rate compared with those treated with β-adrenergic blocker therapy over a 3-year period. However, it is worth noting that this was nonrandomized, and the doses of drugs were not optimized by any consistent criteria. Nevertheless, blocking the renin-angiotensin system via molecular mechanisms may be beneficial in these patients beyond the control of blood pressure.[15] In the aortic wall, angiotensin II stimulates the proliferation of smooth muscle cells, favors fibrosis, increases the expression of MMP-2 and MMP-9, and reduces apoptosis through binding to the angiotensin type 1 (AT1) receptors. Through binding to angiotensin type 2 receptors, however, angiotensin II exerts an antiproliferative effect.[21] Furthermore, the binding of angiotensin II to AT1 receptors increases the levels of TGF-β and, in turn, the expression of genes regulated by this cytokine. Data from animal models have shown that treatment with AT1 receptor antagonists, such as losartan, reduces TGF-β levels and consequently interferes with some of the processes involved in the pathogenesis of MFS.[14]

Recently, the results of a study set out to assess the tolerability and efficacy of losartan added to β-blockade to prevent progressive aortic root dilation in patients with MFS have been published.[26] In this pediatric population, patients receiving losartan and β-blockade showed aortic root reduction, with the annual dilation rate of the aortic root being significantly lower than that of the β-blockade group. The results of this trial showed that losartan in combination with β-blockade offers more effective protection to slow the progression of aortic root dilation than does β-blockade treatment alone in patients with MFS.

Groenink et al[27] presented the first prospective, multicenter, randomized controlled trial indicating a beneficial effect of losartan in adults with MFS. COMPARE (Cozaar in Marfan Patients Reduces Aortic Enlargement) was designed to test the hypothesis of whether losartan reduces the aortic dilation rate at any of 6 predefined aortic levels in adults with MFS. Additional aims of the study were to examine the effect of losartan on aortic volume and the incidence of aortic dissection, elective aortic surgery, or cardiovascular death. The authors screened 797 patients from 4 Dutch university MFS clinics and used the Dutch national database of adults with congenital heart disease (CONCOR registry) to enroll 233 operated and unoperated patients who were randomized to losartan or no additional treatment. All previously prescribed medication, including β-blockers and calcium channel blockers, was continued after inclusion. Importantly, by design, the trial was open label with blinded assessment of end points. At baseline, patients underwent MRI[19] (or exceptionally, CT) of the entire aorta and again at 3 years of follow-up. Clinical assessment and TTE were performed on an annual basis.

The authors were able to evaluate the rate of aortic root dilation in 145 patients with a native aortic root and show that after 3 years of follow-up, the rate of aortic root dilation was significantly lower in the losartan group compared with that in the control group, with a number needed to treat of 5.3 patients. Regression analysis showed further that change in mean arterial blood pressure or change in systolic blood pressure was not correlated with the rate of aortic root dilation in patients treated with losartan or controls. In patients with prior aortic root replacement, the rate of aortic arch dilation was significantly lower in the losartan group. However, no significant differences in separate clinical end points or the

composite clinical end point could be shown between groups. The results of COMPARE provide additional evidence in favor of the efficacy and safety of losartan in patients with MFS by delaying aortic root dilation of the native aortic root and by decreasing aortic arch dilation in patients with prior aortic root replacement.

Current Recommendations for Medical Management

Given the current knowledge of the pathophysiological mechanisms that lead to aortic enlargement and ultimately to dissection or rupture, it seems likely that future therapy will be directed at the fibrillin-1 gene and/or the TGF-β axis. Current recommendations, however, include β-blocker therapy as the standard of care,[21] and all patients with MFS who can tolerate β-blockade should be treated, regardless of the presence or absence of aortic dilation. Dosage titration is dependent on achieving a resting heart rate of ≤60 bpm if the patient tolerates it. Atenolol administered twice daily is currently the drug of choice in many cases because of its long half-life and it has fewer central nervous system and other side effects due to its relative cardioselectivity.[21] In individuals intolerant to β-blockade, verapamil can be considered a second-line therapy.[28] Given the potential benefit of ARBs in MFS, patients who have need of additional medications to control blood pressure, especially those with chronic dissections, should be treated with losartan in addition to β-blockade.

Surgical Management

The most common cardiovascular surgical features of MFS are mitral valve prolapse and aortic root aneurysm.[24] Mitral valve prolapse is age dependent (more frequent in infants) and more common in women. Although degeneration of the subvalvular apparatus and severe annular dilation present in up to 80% of the patients with MFS, only 25% of these develop mitral valve prolapse and surgical mitral regurgitation.[29] On the other hand, dilation of the aortic root occurs in 50% of adults and, without early recognition and prophylactic surgery, leads to the demise of approximately 50% of these patients by the age of 40 years due to aortic dissection and rupture.[30]

Mitral Valve Prolapse

The surgical approach to mitral valve prolapse in patients with MFS requires particular attention to the location of the cross-clamp.[31] In most cases, there is an alteration of elastin with disrupted, fragmented, and granular fibers from the proximal aorta to the base of the innominate artery. In addition, the possible presence of aortic regurgitation should be taken into consideration when performing cardioplegia to ensure adequate myocardial protection. Intraoperative analysis of the mitral valve will show a mixed pattern of degenerative mitral valve disease with characteristics of patients with fibroelastic deficiency and Barlow disease. The assessment of the subvalvular apparatus reveals the presence of thin, elongated, and sometimes ruptured chordae. The leaflets are thin, without significant myxomatous degeneration and leaflet billowing or thickening, but with excess tissue (diffuse leaflet distention) and severe symmetric annular dilation. These lesions mostly lead to type I or type II leaflet dysfunction. Type I dysfunction implies normal leaflet motion, and the cause of significant mitral regurgitation is isolated severe annular dilation with a central regurgitant jet. Type II dysfunction denotes excess leaflet motion (prolapse) generally secondary to chordal elongation or rupture or myxomatous degeneration of the leaflets (regurgitant jet directed to the opposite site of the prolapsing leaflet).

In patients with type I dysfunction, annular dilation should be corrected with remodeling annuloplasty to restore the native annular size and shape, allowing full leaflet motion. In this regard, placement of the annular sutures mandates complete visualization and identification of the mitral annulus to avoid tearing secondary to the fragility of the tissue. Additionally, special attention should be paid to the posterior leaflet height.[32] Even in the absence of prolapse, leaflet distention (>15 mm) should be corrected to avoid postoperative systolic anterior motion (leaflet displacement or shortening). In patients with type II dysfunction, the presence of tall, distended leaflets and thick prolapsing segments mandates the selection of resection techniques in almost all cases. Although in mild cases, leaflet displacement with chordal techniques (transfer or neochordae) might be sufficient, excessive leaflet distention implies quadrangular resection and annular plication or sliding leaflet plasty. Finally, in patients with coexistent anterior leaflet prolapse, chordal techniques (transfer, transposition, or neochordae) or triangular resection might be performed.[33]

Recent data have demonstrated that it is possible to repair practically all prolapsing valves with a low operative risk (mortality <1%) and the absence of residual mitral regurgitation in high-volume reference centers.[34] In terms of repair durability (assessed by follow-up echocardiography and not by freedom from reoperation), moderate mitral regurgitation due to degenerative disease has been observed to recur at a rate of 1% to 4% per year. Freedom from moderate or greater mitral regurgitation at 5, 10, and 20 years has been shown to be about 95%, 89%, and 69%, respectively.[35]

Aortic Root Dilation

Replacement of the ascending aorta is the only way to prevent fatal complications (aortic dissection and aortic

rupture) in patients with MFS. In general, prophylactic surgery is recommended when the diameter of the ascending aorta at the level of the aortic sinuses reaches 5.0 cm. However, this number might be adjusted due to variation in body surface area among patients. Therefore, patients with an aortic diameter of <2.75 cm/m^2 are considered to be at a low risk of dissection, those with 2.75 to 4.24 cm/m^2 are at moderate risk, and those with >4.25 cm/m^2 are at high risk.[36] In addition, several factors suggest even earlier surgical intervention, including a family history of dissection, increased rate of aortic dilation (>2 mm/y), severe aortic valve regurgitation with left ventricular dilation, and relative feasibility of aortic valve-sparing surgery.[37]

The standard surgical approach for the majority of patients with MFS is the Bentall procedure (Figure 3), which was introduced in 1968 by Bentall and De Bono.[2] The dilated ascending aorta and root are removed and replaced with a Dacron conduit attached to a mechanical aortic valve.[38] Subsequently, both coronary arteries are reimplanted. The results of this procedure have been a benchmark for the many other alternatives that have been used since its inception. In this regard, multicenter studies have documented an early mortality rate of 1.5% and an actuarial survival rate of 84% at 5 years, 75% at 10 years, and 59% at 20 years. In addition, actuarial freedom from thromboembolism and endocarditis at 20 years has been reported to be 93% and 90%, respectively. Our own institutional data have shown survival rates of 87% and 71% at 5 and 10 years, respectively, including patients undergoing reoperative surgery.[39]

Because of the young age at the time of surgery (mean age, 32 years), mechanical aortic valves are selected due to better longevity. Although current mechanical prostheses have superb flow parameters, there is still a need for long-life anticoagulation with its inherent risks. In those patients with medical contraindications that make anticoagulation hazardous, the aortic root and valve can be replaced by conduits with bioprosthesis. However, the durability of these is limited to approximately 10 to 15 years, and reoperation carries an exponential risk with higher operative mortality. This circumstance led to the adoption of techniques[40] to avoid anticoagulation such as valve-sparing techniques, mainly represented by the remodeling or Yacoub technique (Figure 4) and the valve reimplantation or David technique (Figure 5). The first one involves resection and replacement of the sinuses of Valsalva with tailored tongues of the vascular graft and coronary artery reimplantation. The latter involves reimplantation of the native aortic valve into a graft. Furthermore, both of them have surgical advantages and are suitable for different patients. The Yacoub technique is more physiological in that the scalloped graft re-creates the natural sinuses of Valsalva, and the optimal candidate is one with sinus and/or aortic dilation without annular dilation or a major potential for this. On the other hand, the David technique has the theoretical advantage of stabilizing the aortic annulus (which can predispose to postoperative annular dilation and recurrent aortic regurgitation), and therefore, it is indicated in patients with important annular involvement.[41] According to recent reports, 25% of the patients with MFS undergoing valve-sparing procedures have aortic regurgitation at 10 years due to progression of the disease. When compared to the outcomes of Bentall procedures (composite grafting), valve-sparing procedures have lower operative mortality,[42] lower mortality at 5 years (89% vs 96%), and also lower freedom from reoperation at 5 years (92% vs 84%).[43]

Anesthetic Considerations

Preoperative Assessment

The anesthetic approach to patients with MFS undergoing thoracic aneurysm repair depends on the urgency of the procedure. In the symptomatic patient with a leaking or ruptured aneurysm, an emergent indication for surgery will allow for little time to perform more than the basic preoperative assessment, order blood, examine the airway, and discuss the type of surgical procedure to prepare the anesthesia. For an elective operation, however, one must consider careful evaluation of medical history, including a review of all organ systems with close attention to symptomatology inherent to MFS (tall stature, pectus carinatum or excavatum, ectopia lentis, spontaneous pneumothorax, dural ectasia, pathological fracture, scoliosis, protrusio acetabuli, and cardiovascular involvement). At our institution, patients with MFS with cardiovascular involvement are followed in the Aortic Aneurysm Surveillance Program. The progress of the disease is evaluated according to clinical development, and the patient is informed about optimal treatment. If elective surgery is indicated, the patient is scheduled for day admission surgery and before 3 to 7 days is scheduled for re-evaluation in the preanesthetic clinic.[44] All medical information (including details about the location, size, and extent of the aneurysm; functional status of the heart; coronary circulation; presence of an electronic device; central nervous, pulmonary, and renal system evaluation; laboratory and hemostatic competence studies; dental clearance allergies) is collected and electronically sent to all medical personnel involved in the operation. To ensure optimal anesthesia management, close communication between the anesthesia team, surgical team, perfusionist, operating room nurses, and staff in the intensive care unit is necessary. Preoperative antibiotic and antifibrinolytic agents are routinely administered.

Patients with MFS require special considerations regarding the anesthetic technique to avoid extreme hypotension and hypertension, conserve coronary perfusion,

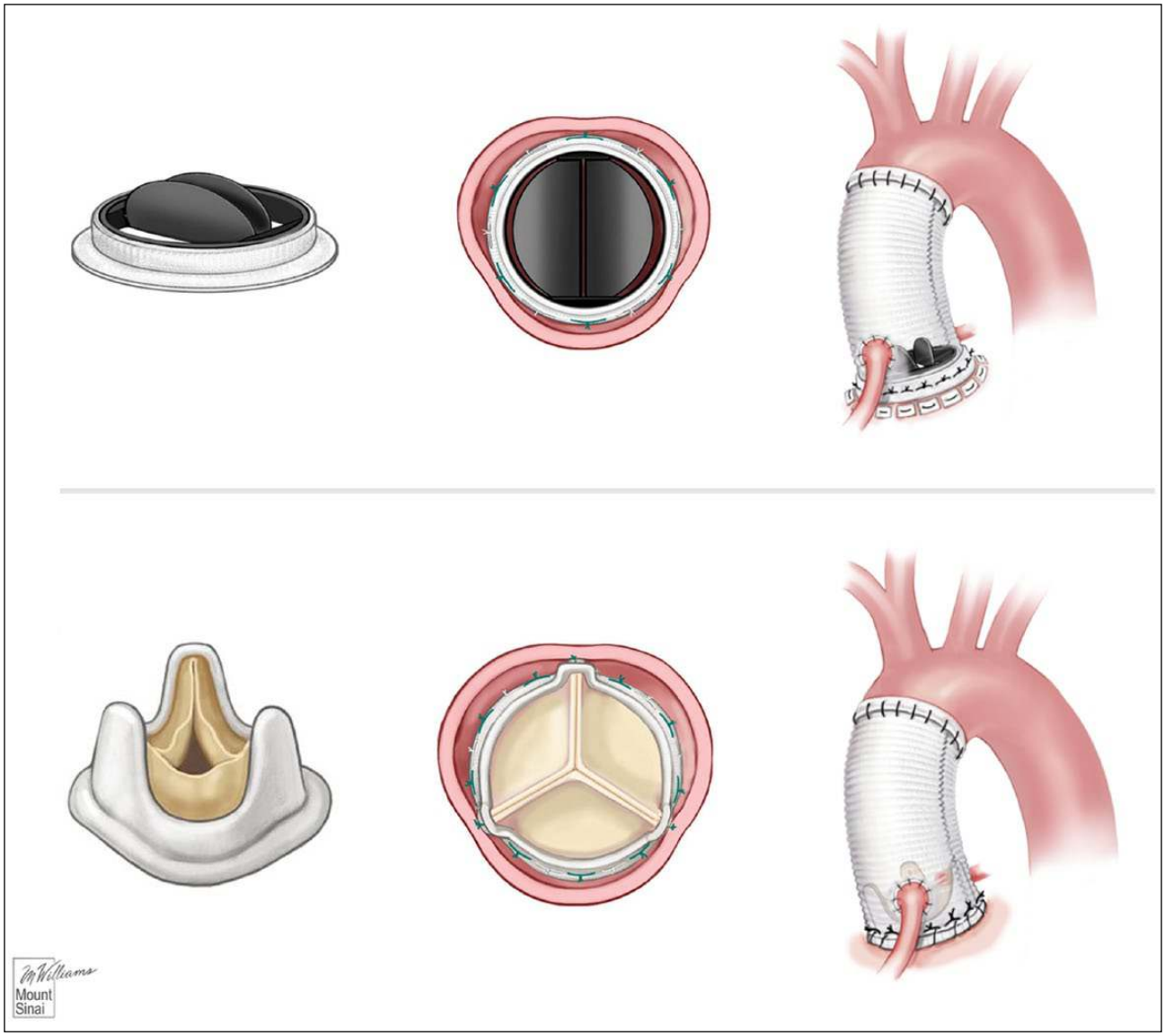

Figure 3. Bentall procedure. The Bentall procedure involves composite graft replacement of the aortic valve, aortic root, and ascending aorta, with reimplantation of the coronary arteries into the graft. This operation is used to treat combined aortic valve and ascending aorta disease, including lesions associated with Marfan syndrome.

and prevent the development of a dissecting aneurysm.[45] Connective tissue of the large arteries is involved in MFS, which lacks elastic fiber integrity. As a consequence, the administration of anesthesia is the only factor that influences the mean arterial pressure. Furthermore, the progressive dilation of the aortic ring may cause dyspnea, angina, and arrhythmia due to aortic regurgitation. Preoperative examination of the airway is critical because the presence of prognathism and a high palate may pose difficulties during tracheal intubation.[46] Finally, complete examination of the joints and evaluation of their laxity are important to avoid dislocations and injuries when positioning the patient on the operating table. This will also be applicable during intubation where excessive traction of the temporomandibular joint should be avoided.[47]

Induction and Monitoring

Standard American Society of Anesthesiologists monitors, consisting of 5-lead electrocardiography and a pulse oximeter, are placed on the patient. The placement of a large-bore intravenous access is imperative, and a rapid infusion system and a cell saver are available in case of aortic ruptures. An invasive pressure monitoring system is connected, and anesthesia is induced with propofol, fentanyl, and midazolam. Before endotracheal intubation, a fiber-optic bronchoscope is

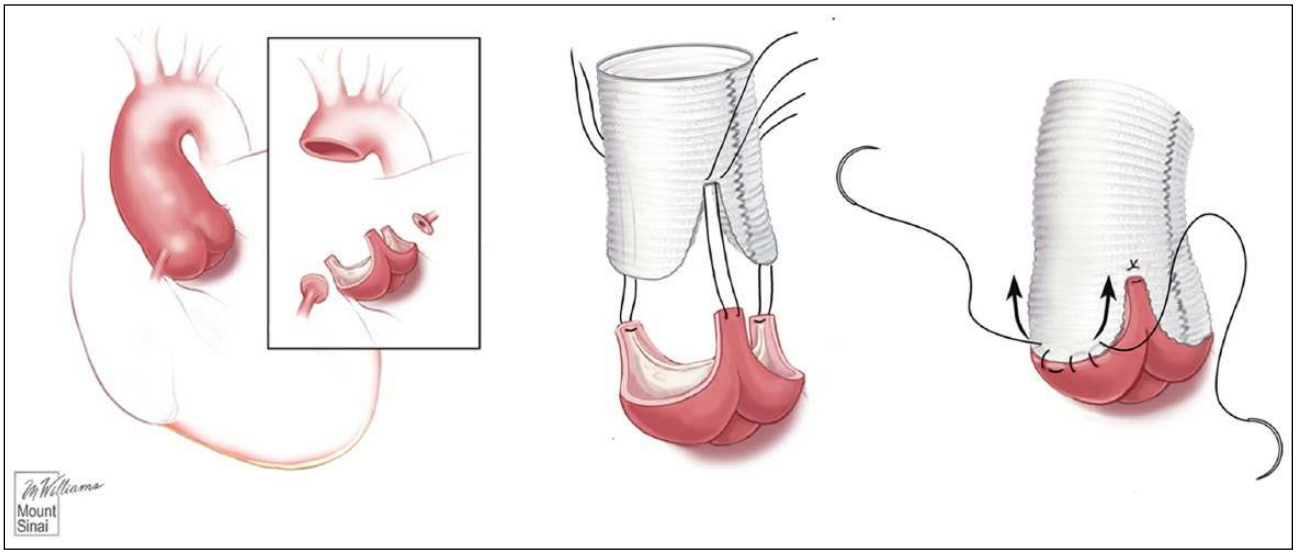

Figure 4. Yacoub technique. The Yacoub remodeling procedure uses a scalloped design to create a new aortic root out of Dacron. This scalloped shape is believed to experience less shear force and, therefore, might be expected to add more longevity and competence to valve-sparing operations.

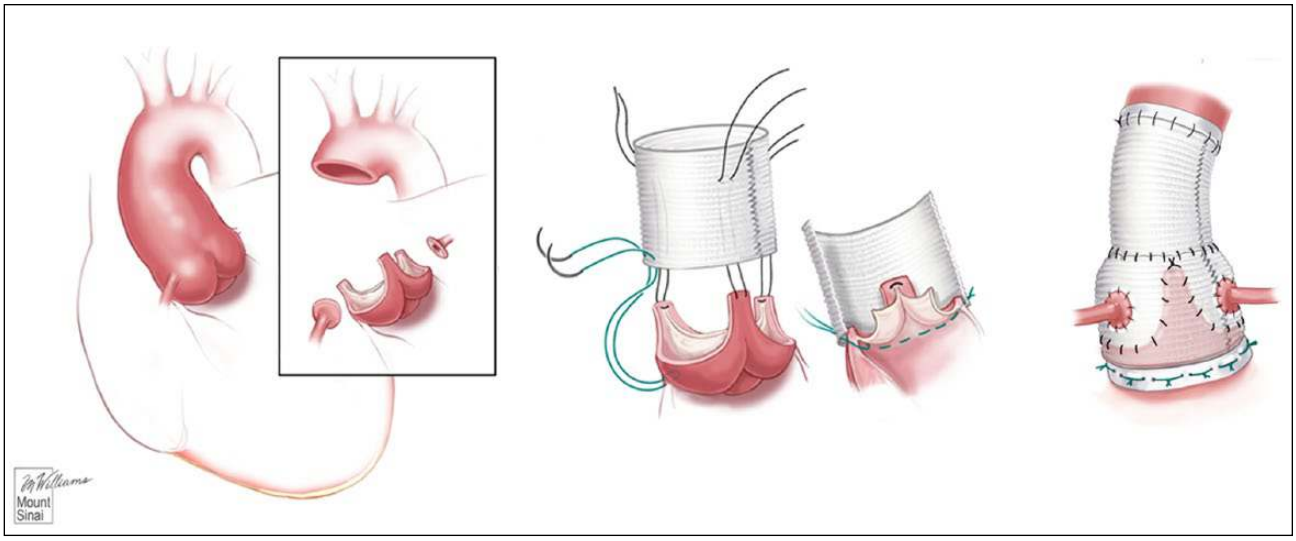

Figure 5. David technique. Also known as the David valve-sparing reimplantation procedure, this technique is used for replacement of the aortic root and ascending aorta only. The aortic valve is not replaced. However, it is reimplanted inside the Dacron tube graft, and both coronary arteries are reattached to the Dacron. In the context of Marfan syndrome, this procedure is suitable for patients if their aortic annulus is not too dilated.

used for inspection of the airway to avoid compression of the aneurysm.[46] Tracheal intubation can be facilitated with the use of succinylcholine or a short-acting nondepolarizing agent. To blunt the hemodynamic response elicited by tracheal intubation, we recommend the generous administration of fentanyl during induction (15-25 μg/kg). The hemodynamic goal is to reduce the stress imposed upon the wall of the aneurysm. This is best achieved by lowering systolic blood pressure as well as inotropy. Volatile agents or neuromuscular blocking agents are generally avoided if somatosensoy evoked potentials or motor evoked potentials monitoring is necessary. In this case, anesthesia will rely on a propofol infusion (50-100 μg/kg/min) to provide anesthetic maintenance.

Once general anesthesia has been induced, the patient is intubated. Correct positioning might be verified with the aid of fiber-optic bronchoscopy. For temperature monitoring, we recommend that 2 different sites be used. A temperature probe is placed into the esophagus for core temperature measurement (this temperature best reflects

the cerebral temperature) as well as a visceral monitoring site (bladder or rectum). For monitoring of central nervous system oxygenation and function cerebral oximetry, monitoring probes are attached to the patient's forehead. Finally, a transesophageal echocardiography probe is placed to obtain important information.

Extracorporeal Circulation Strategies

Hypothermic circulatory arrest (HCA) for repair of the adult aortic arch has become a standard technique in thoracic aortic surgery.[48] Three major neuroprotective techniques in HCA for repair of the adult aortic arch have been championed in the contemporary era: profound hypothermia alone, retrograde cerebral perfusion (RCP), and antegrade cerebral perfusion (ACP). Although profound HCA alone provides excellent neuroprotection in experienced centers, concomitant RCP as part of an integrated protocol for repair of the adult aortic arch has also been shown to provide effective neuroprotection, especially when HCA times are less than 30 to 45 minutes. Furthermore, ACP has also become a mainstream cerebral perfusion adjunct during HCA, especially in the setting of prolonged deep HCA (DHCA) times beyond 30 to 45 minutes. The effectiveness of DHCA depends on the ability of hypothermia to mitigate the metabolic rate, and therefore, achieving adequate cooling becomes crucial for the outcome of the surgery. Taking these considerations into account, we cool the patient until an esophageal temperature of 10°C to 13°C has been reached and the oxygen saturation level in the jugular venous bulb is above 95% (maximal metabolic suppression).[49] Cooling must be a thorough process lasting at least 30 minutes to prevent temperature drifts and ensure adequate hypothermia during reconstruction. Accordingly, the intracranial temperature should be further ensured by circumferentially packing the head with ice. After DHCA, rewarming demands meticulous attention, given that oxygen requirements may outstrip supply. In this setting, systematic gradual rewarming with consistent perfusion temperatures is essential. Finally, to avoid cerebral vasoconstriction after DHCA, stable hemodynamics is required to facilitate optimal oxygen delivery even beyond the immediate postoperative period.[50] Although current series support the safety of a DHCA time of 40 minutes with or without adjuncts, our surgical experience suggests that a duration of DHCA exceeding 30 minutes may result in the occurrence of severe neurological damage.[51]

One more consideration to take into account that is critical in the anesthetic setting of these patients is blood pressure control during aortic cannulation. While some surgeons might feel comfortable cannulating the aorta with a systolic blood pressure of 110 or even 120 mm Hg, it may be prudent to attain systolic blood pressure of 80 to 90 mm Hg for the brief period of aortic cannulation, even if the aorta is of normal dimension.[52]

Special Populations: MFS and Pregnancy

Pregnancy in patients with MFS remains a controversial subject mainly because of the discrepancy in clinical guidelines from different societies. Namely, the 2010 thoracic aortic disease guidelines advocate avoidance of pregnancy if the aortic root diameter exceeds 40 mm and recommend prophylactic aortic root replacement in those who desire pregnancy.[36] The European and Canadian guidelines, however, report an aortic root diameter of 45 mm to be considered safe.[53,54] This discrepancy arises due to the scarcity of data regarding the clinical management of MFS during pregnancy. Recently, however, the results of a study aimed to assess the impact of pregnancy on the rate of aortic growth, and clinical outcomes have been published.[55] The results showed a significantly higher rate of aortic growth documented during pregnancy compared with each woman's prior baseline aortic growth rate. Furthermore, the prevalence of both adverse outcomes and elective aortic surgery during long-term follow-up was higher in those women who experienced a prior pregnancy compared with the matched childless group. Taken together, the available data suggest that women with MFS without previous cardiac complications seem to tolerate pregnancy well, up to an aortic root diameter of 45 mm, with good clinical care before, during, and after pregnancy. Pregnancy, therefore, should be discouraged in women with previous aortic dissection because of the high risk for aortic complications. Moreover, pregnancy causes a slight increase in the aortic root diameter.[56] Finally, women with enlarged aortic root diameters at pregnancy show slightly accelerated aortic root growth with time and therefore should undergo elective aortic root surgery at a younger age.

Conclusions

The last decade has witnessed the discovery of major findings that have provided valuable insight into the understanding of the cellular and molecular mechanisms of MFS. Continued research and combined efforts will lead to further elucidation of the different manifestations of the disease. This cumulative knowledge will undoubtedly translate into individualized and effective pharmacological treatments oriented toward molecular and genetic mechanisms, allowing for tailored medical and surgical approaches to this serious condition.

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