Aortic Diseases

Medical Management of Marfan Syndrome

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Marfan syndrome is an autosomal dominant, multisystem disease characterized by long bone overgrowth and other skeletal abnormalities, dislocation of the ocular lens, pneumothorax, decreased skeletal muscle mass, mitral valve prolapse, and dilatation of the aortic root. Antoine Bernard-Jean Marfan first described the syndrome in 1896 in a young patient with peculiarly long and thin digits (subsequently termed *arachnodactyly*), elongated limbs (which he termed *dolichostenomelia*), and congenital contractures of multiple joints. Because of the latter feature, this patient may really have had congenital contractural arachnodactyly, a connective tissue disorder not described until 1968. For the half century subsequent to Marfan's report, features in other systems were described in patients with thin, elongated limbs: mitral valve disease in 1912; dislocation of the ocular lens in 1914; ruptured aortic aneurysm in 1918; aortic root dilatation and dissection in 1943; and autosomal dominant inheritance in 1949. Manifestations occur in many other tissues and organs and are increasingly being recognized as patients survive to older ages.[1]

An accurate incidence has been impossible 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 diagnostic criteria. Several conditions that were once classified as Marfan (eg, homocystinuria, Loeys-Dietz syndrome) are recognized now as clearly distinct. However, Marfan syndrome is clearly one of the more common, potentially lethal Mendelian conditions with an estimated prevalence of 1 case per 3000 to 5000 individuals. This figure does not appear to vary with ethnicity or geography.[2]

Mutations in the gene (*FBN1*) that encodes the extracellular matrix protein, fibrillin-1, cause classic Marfan syndrome.[3] Up to one third of cases have neither parent affected and represent de novo mutations in either the gamete from their mother or father. Heterozygosity for a mutation in *FBN1* can also produce a variety of overlapping phenotypes with Marfan syndrome. No robust genotype-phenotype correlations have emerged, despite >1000 mutations being analyzed.[4] Mutations in the middle region of the gene, exons 24 to 32, tend to predict more severe cardiovascular problems at all ages. Other families or sporadic patients in which some of the features of Marfan syndrome occur, but typically without ectopia lentis, have mutations in 1 of 2 genes (*TGFBR1* and *TGFBR2*) that encode receptors for the cytokine transforming growth factor-β (TGF-β).[5–7]

Diagnosis

The diagnosis of Marfan syndrome continues to evolve. Existing criteria[8,9] are in the process of being revised, based on a workshop held in Brussels, Belgium, in early 2007. Both clinical and molecular genetic criteria have a role in assigning the label of Marfan syndrome with confidence.

Clinical Criteria

In 1998, the Ghent criteria specified characteristics of the phenotype and genotype that can be assessed through history, bedside examination, imaging, and molecular genetic testing.[9] "Major criteria" carried more diagnostic weight and included features not commonly found in the general population (such as ectopia lentis, aortic root aneurysm, and dural ectasia). "Minor criteria" included features that were not only common in the general population but can occur together in people either by chance or as part of conditions often confused with Marfan syndrome, such as some types of Ehlers-Danlos syndrome and MASS phenotype. The Ghent criteria are summarized in Table 1.

Concerns have emerged about the Ghent criteria because some of the phenotypic features necessitate imaging studies that are not otherwise indicated clinically (eg, computed tomography or magnetic resonance imaging for dural ectasia and protrusio acetabuli). The clinical criteria that are likely to emerge in the near future will focus more on the presence or absence of ectopia lentis, aortic root dilatation, and a family history of confirmed Marfan syndrome.

Molecular Genetic Criteria

The likelihood of finding a pathological mutation in *FBN1* in a patient with classic Marfan syndrome according to the Ghent criteria is ≈95%.[7] Mutations in regulatory sequences well outside the coding region will be missed by current methods used in clinical molecular diagnostic laboratories. This is quite good performance in terms of sensitivity, however. The problem lies in specificity; numerous disorders that are often clinically difficult to distinguish from Marfan syndrome, such as familial ectopia lentis, MASS phenotype, and familial aortic aneurysm, also may have mutations in *FBN1*. Thus, for the patient being evaluated for the first time,

Table 1. Ghent Criteria for Marfan Syndrome Diagnosis

Organ System	Major Criteria	Minor Criteria
Family history	Primary relative with Marfan criteria	None
	FBN1 mutation present	
	Haplotype around *FBN1* with unequivocally diagnosed Marfan syndrome in family	
Skeletal	Four of the following:	Pectus excavatum (moderate severity)
	Pectus carinatum	Joint hypermobility
	Pectus excavatum, needing surgery	Arched palate
	Reduced upper segment–to–lower segment ratio or arm span–to–height ratio >1.05	Facial features (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
	Wrist and thumb signs	
	Scoliosis >20°	
	<170° extension of elbows	
	Pes planus (medial displacement of medial malleolus)	
	Protrusio acetabuli	
Ocular	Ectopic lentis	Flat cornea
		Increased axial length of globe
		Hypoplastic iris
Cardiovascular	Dilatation of the ascending aorta	Mitral valve prolapse
	Ascending aortic dissection	Pulmonary artery dilatation
		Mitral annular calcification (<40 y)
		Dilatation or dissection of the descending thoracic aorta or abdominal aorta (<50 y)
Pulmonary	None	Spontaneous pneumothorax
		Apical blebs
Skin/integument	None	Striae atrophicae without weight gain, pregnancy, or stress
		Recurrent incisional herniae
Dura	Lumbosacral dural ectasia	None

who has some but not enough features for a clinical diagnosis and no or an uncertain family history, molecular analysis is of minimal help. The real benefit of DNA analysis arises when a pathological mutation is known in a family, and relatives at risk can be screened, presymptomatically or prenatally, to determine whether they need to be monitored clinically or if they can be reassured that they have not inherited the mutation.

Cardiovascular Features of Marfan Syndrome

Cardiac disease is a predominant feature of Marfan syndrome and includes proximal ascending aortic dilatation, dilatation 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 (Figures 1 and 2).[3,10] Forty years ago, average life expectancy in Marfan syndrome was reduced by approximately one third.[11] In those days before effective surgical approaches to proximal ascending aortic disease, up to 90% of deaths in Marfan syndrome were due to acute aortic dissection or chronic aortic regurgitation.[11] By the mid-1990s, however, Marfan syndrome patients managed with the medical therapy and timely surgical intervention described in this review had a markedly improved life expectancy.[12,13] A thorough understanding of the pathogenesis, natural history, and effective medical intervention of aortic disease in Marfan syn-

drome is therefore critical for all cardiovascular practitioners. Additionally, approaches to therapy are evolving, and the prospects for improved morbidity and mortality provide considerable hope to patients and their relatives. Finally, findings about the cardiovascular diagnosis and management of Marfan syndrome are applicable to patients with aortic disease due to other causes.[14,15]

Pathophysiology of Aortic Dilatation and Aneurysm Formation

The earliest recognition of the tissue abnormalities underlying aortic dilatation in Marfan syndrome was that of degeneration of the medial layer, with fragmentation, disarray, and loss of elastic lamina and replacement by basophilic-staining proteoglycan[16] (Figure 3). The lacunar appearance of regions of degeneration and the paucity of cells led to the term coined by Erdheim, *cystic medial necrosis*, which is often thought incorrectly to be pathognomonic of Marfan syndrome. Medial degeneration is nonspecific and occurs in other aortic diseases and hypertension. Furthermore, the media develops neither cysts nor overt necrosis; rather, the histopathology is indicative of an ongoing injury and repair process.[16] Electron microscopy in humans and mouse Marfan syndrome models demonstrates disarray throughout the extracellular matrix, with shrunken smooth muscle cell fibers, thickened basement membranes, abnormalities of collagen fiber structure, and
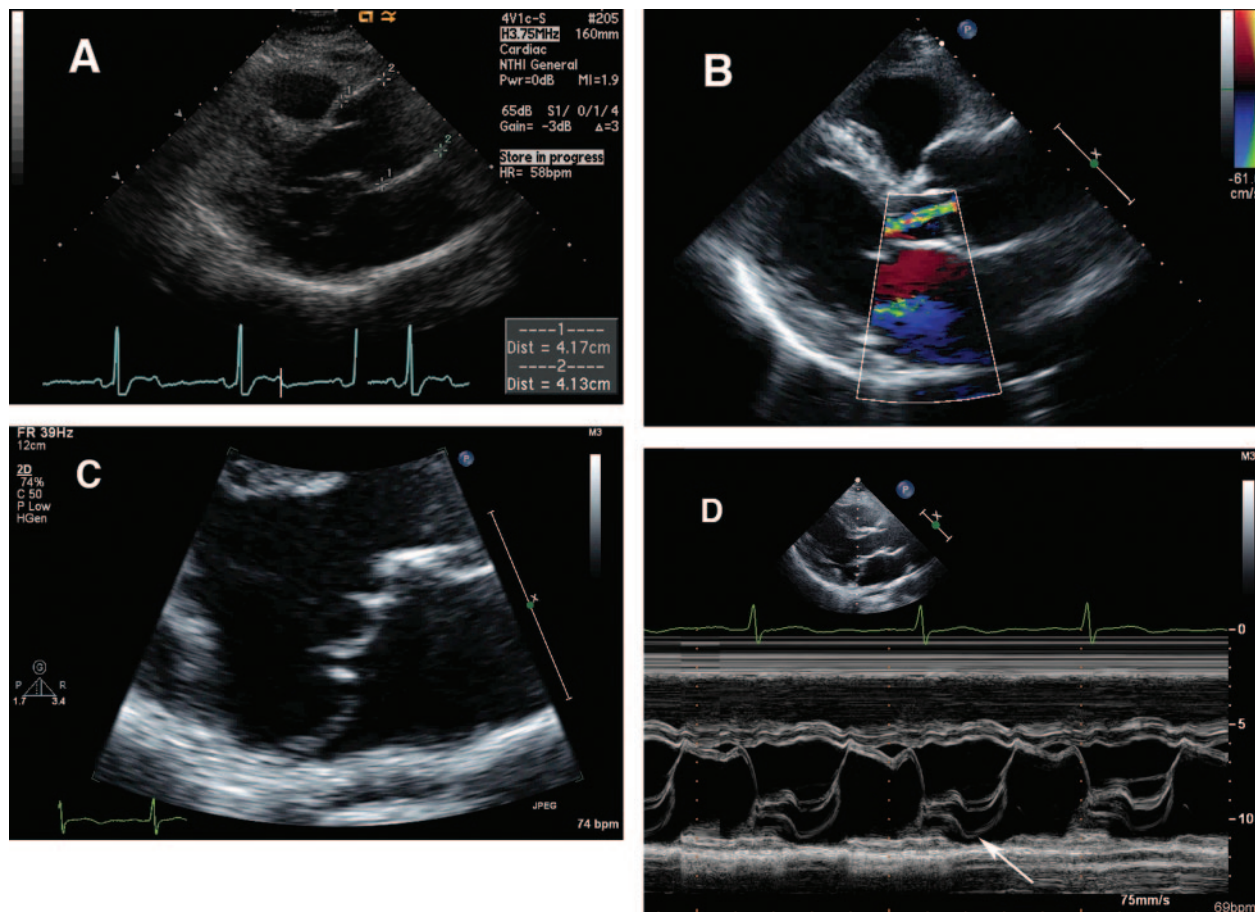
Figure 1. A, Two-dimensional echo image in the parasternal long axis demonstrates dilation of the aortic root in a Marfan syndrome patient. B, Color Doppler echo shows mild regurgitation through an otherwise normal aortic valve, which results from the dilatation of the root. C, Marfan Syndrome patient with moderate mitral valve prolapse, demonstrated in 2-dimensional echo images. D, Classic M-mode demonstration of prolapse of the posterior mitral valve leaflet (arrow).

progressive fragmentation and loss of elastic lamellae.[17,18] The process is associated with signs of ongoing inflammation and matrix metalloproteinase activation.[19,20]

The genetic basis of Marfan syndrome is mutations in the gene encoding fibrillin-1 (*FBN1*) at chromosomal locus 15q21.1.[21] This protein is an essential component of microfibrils that are major structural and regulatory components in the extracellular matrix.[22,23] Fibrillin-1 microfibrils support cellular adhesion in the extracellular matrix via interaction with integrins.[24] More than 1000 mutations in *FBN1* have been identified in people with classic Marfan syndrome and other disorders.[4,25] Most mutations are missense in that they are single-nucleotide changes that result in substitution of an amino acid, occur within 1 of 46 tandem repeated epidermal growth factor–like domains, and result in enhanced proteolytic degradation of fibrillin-1.[26–28] Because patients have 1 normal and 1 abnormal *FBN1* allele, the original concept of molecular pathogenesis in Marfan syndrome was a classic "dominant-negative" effect—mutant fibrillin-1 proteins interacted with the normal protein monomers from the nonmutated *FBN1* allele, with the result that all microfibrils were abnormal. Intrinsic to this model, the function of microfibrils was viewed as primarily structural, and abnormalities in microfibrillar structure "weakened" the extracellular matrix.

This facile explanation for the progressive dilatation seen in the proximal aorta and the histopathology of medial degeneration has proven to be largely incorrect. "Weak connective tissue" never provided an explanation for overgrowth of tubular bones, osteopenia, reduced mass of skeletal muscle and adiposity, and craniofacial abnormalities.[15]

More recent understanding of the regulatory functions of microfibrils in the extracellular matrix suggests an alternative pathogenesis of Marfan syndrome aortic disease. Dietz and colleagues,[15,29] in elegant experiments using mouse models for Marfan syndrome, showed that many of the pulmonary, cardiovascular, skeletal, and skeletal muscle features of Marfan syndrome are due to abnormal levels of activation of TGF-β, which is a potent stimulator of inflammation, fibrosis, and activation of certain matrix metalloproteinases, especially matrix metalloproteinases 2 and 9. TGF-β is secreted as a large latent complex (TGF-β+latency-associated peptide+latent TGF-β binding protein), which is sequestered by the extracellular matrix.[30] Fibrillin-1 shares homology with latent TGF-β binding proteins, and the TGF-β latent complex specifically binds to fibrillin-1 domains.[31] Matrix sequestration is critical to the regulated activation of TGF-β, and perturbation of this fibrillin-1 function contributes to the pathogenesis of Marfan syndrome.[32] Excess TGF-β activa-
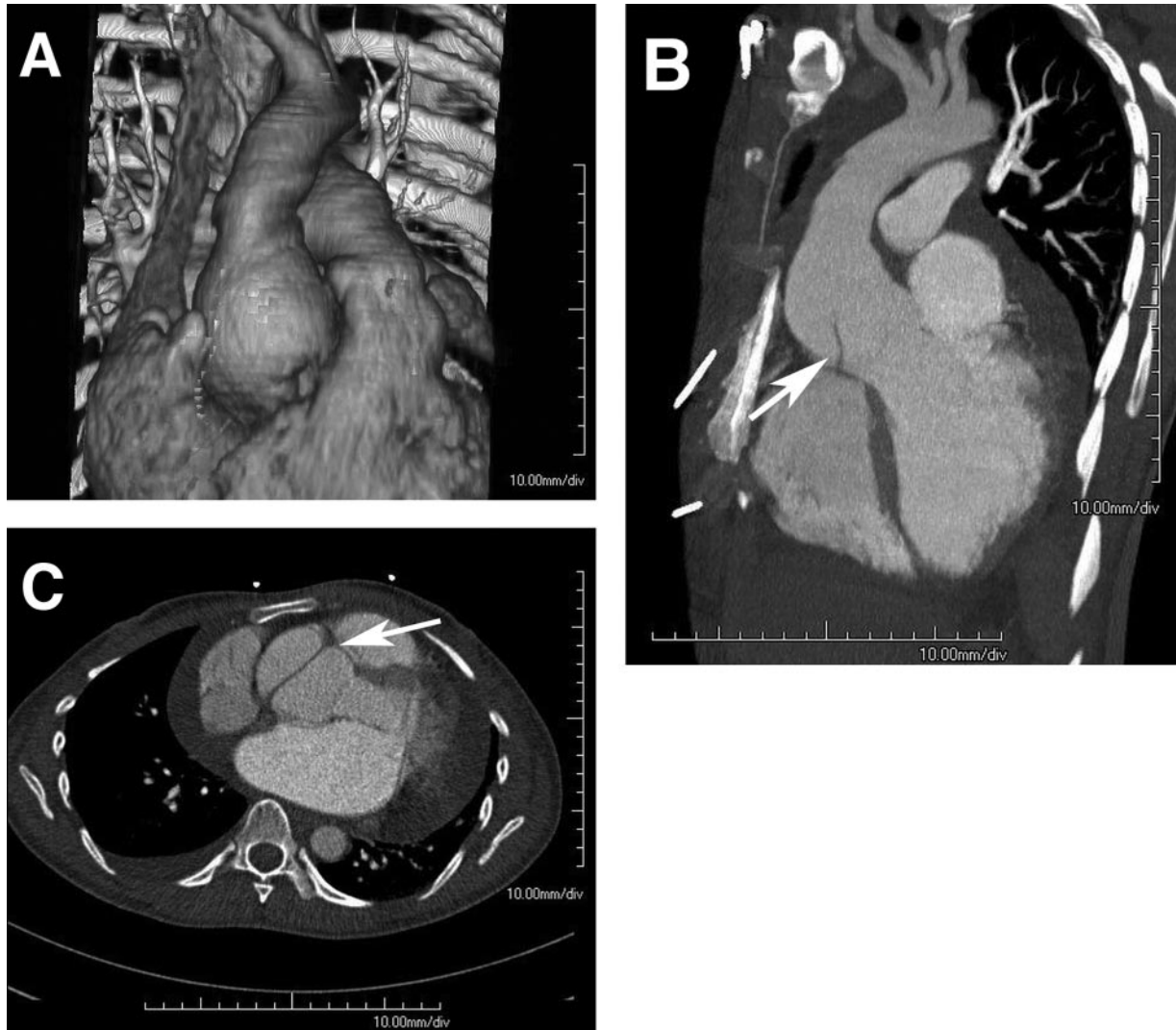
Figure 2. A, A volume-rendered computed tomographic angiography image demonstrates the dilatation of the proximal aortic root and ascending aorta. B and C, Computed tomographic imaging demonstrates evidence of acute type A dissection (arrows). Image courtesy of William Boone, MD.

tion in tissues correlates with failure of lung septation, development of a myxomatous mitral valve, and aortic root dilatation in mice into which a human mutation that causes Marfan syndrome was introduced.[33]

This combination of structural microfibril matrix abnormalities, dysregulation of matrix homeostasis mediated by excess TGF-β, and abnormal cell-matrix interactions is responsible for the phenotypic features of the Marfan syndrome aorta.[5] Ongoing destruction of the elastic and collagen lamellae and medial degeneration result in progressive dilatation of proximal aortic segments, as well as a predisposition to aortic dissection from the loss of appropriate medial layer support. Loss of elasticity in the media also results in progressively increased aortic stiffness and decreased distensibility.[34,35]

Hemodynamic Contribution to Aortic Dilatation

Superimposed on underlying Marfan syndrome tissue abnormalities are the normal hemodynamic stressors on the proximal aorta throughout the cardiac cycle.[36] These include outwardly directed forces of wall strain, twisting forces of torsion, intrinsic wall stress (related to aortic diameter and wall thickness), and endothelial shear forces[36] (Figure 4). Normal hemodynamic stressors are accentuated further by pressure and volume overload states of underlying diseases, such as hypertension and aortic regurgitation. Hemodynamic stress itself causes damage to underlying aortic tissue, regardless of underlying tissue abnormalities. Even in normal aortic tissues, mechanotransduction of hemodynamic stress results in activation of endothelial and medial growth factors and secondary messengers.[37] In Marfan syndrome, mechanotransduction of hemodynamic stress further exacerbates the tissue-related activation of vascular smooth muscle cells, matrix metalloproteinases, and TGF-β. The intrinsic tissue abnormalities of the Marfan aortic root—wall thinning, aortic dilatation, and loss of distensibility—increase wall stress further and augment hemodynamic stress. This vicious cycle leads to ever-progressive aortic dilatation, a cycle augmented by the development of aortic regurgitation once the commissures are sufficiently stretched (Figure 5). The dilation of the
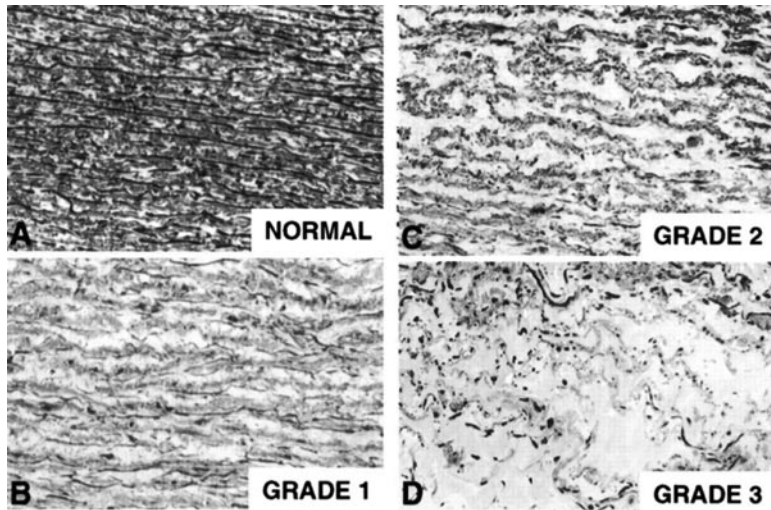
Figure 3. Progressive levels of histologic degeneration of the aortic tissue seen in Marfan syndrome. Reproduced, with permission of the publisher, from Niwa K, Perloff JK, Bhuta SM, Laks H, Drinkwater DC, Child JS, Miner PD. Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. *Circulation.* 2001;103:393–400. Copyright © 2001, the American Heart Association.

aorta ultimately reaches levels that predispose to aortic dissection and rupture and the potential demise of the Marfan syndrome patient. Attempts to break this cycle via medical management are essential to slow progression of aortic disease, delay the need for surgery, and reduce the incidence of catastrophic events.

Clinical Risk Factors for Morbidity and Mortality

Patients with Marfan syndrome are at risk for catastrophic aortic complications and mortality, and several indices are associated with increased risk. First among these is the absolute size of the proximal aorta.[38,39] Aortic size >5.0 cm is strongly predictive of elevated risk of aortic dissection and rupture,[12] and surgical intervention at that stage is key. The "normal" diameter of the aorta is directly proportional to body size throughout normal growth and into adulthood[40] (Figure 5). Given their above-average stature and therefore elevated body surface area, growing individuals with Marfan syndrome should have their aortic measurements indexed to body surface area.[41] This can be expressed as an aortic size ratio based on gender- and body size–related norms[40,42] or expressed in relationship to the aortic size population normal distribution, as a *Z* score (Figure 6). When considered in these terms, patients with Marfan syndrome with proximal aortic ratios of >1.3 or *Z* scores >3 are at particular risk.[43] However, certain Marfan syndrome patients present interesting nuances. For example, adiposity is often reduced in young patients; the body surface area calculated from standard nomograms will underestimate the expected diameters of the proximal aorta and result in a higher *Z* score. Alternatively, adults tend to accumulate central adiposity in adulthood, which will increase the calculated body surface area and reduce the apparent degree of aortic dilatation. Adults who gain weight after skeletal maturity will appear to have an improved aortic *Z* score. In such instances, focus on the absolute diameter and its change is appropriate. In addition, the existing "aortic growth curves" are separated into children and young adults; interestingly, the curves do not overlap accurately. This poses problems for the clinician managing patients who transition from adolescence to adulthood. Additionally, a common question is whether
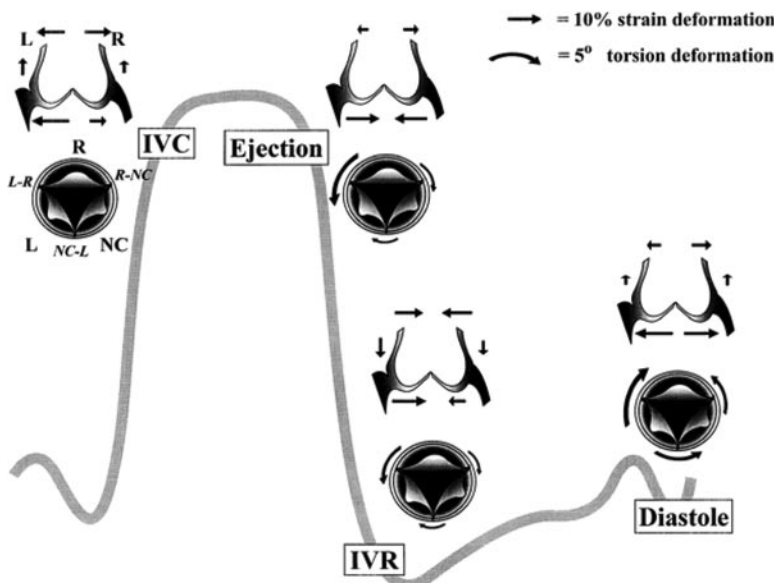

Figure 4. Complex hemodynamic stressors characterize the cardiac cycle in the proximal aorta. Reproduced, with permission from the publisher, from Dagum et al.[36] Copyright © 1999, the American Heart Association.
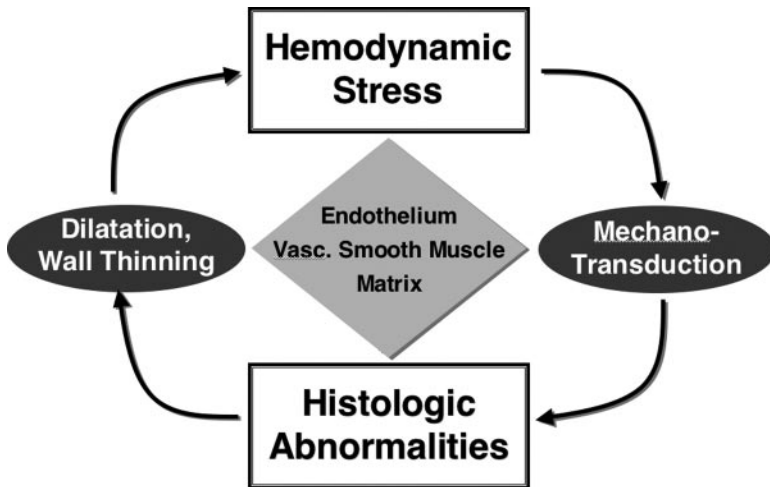
Figure 5. Interactions between combined hemodynamic stressors and underlying histologic abnormalities result in a spiral of progressive degeneration and dilatation of aortic tissue.

tall adults deserve to have larger aortic diameters, even beyond the diameters considered to be normal. The only study that addresses this issue directly suggested that the normal aortic root diameter actually plateaus, and someone 210 cm tall is not justified in having an aortic root dimension of 44 mm.[44] However, this question requires additional investigation.

In addition to absolute aortic dimensions, the rate of change in size of the proximal aortic root over time is important. Even at relatively normal absolute aortic dimensions, a rapid increase in aortic size (>0.5 cm/y) portends an increased risk of dissection. Additionally, a family history of early aortic complications is strongly predictive of decreased event-free survival.[13] Finally, diminished aortic compliance measured echocardiographically or by other means is also a strong predictor of progressive aortic dilatation and poor prognosis in Marfan syndrome patients, although this is rarely measured on a routine clinical basis. Patients with Marfan syndrome can die from other cardiovascular complications, especially severe mitral regurgitation (especially in children with a severe phenotype) and dysrhythmia.[45]

Medical Management of Marfan Aortic Disease

Use of β-adrenergic blockade to reduce hemodynamic stress on the proximal aorta in Marfan syndrome was first suggested in 1971, on the basis of findings in malignant hypertension that reduction in the rate of increase in aortic pressure over time (dP/dt) was more effective at lowering risk of aortic dissection than could be explained by reduction of blood pressure alone.[46] Subsequent small studies of β-blockade in animal models of aortic disease and in uncontrolled studies of Marfan syndrome had varying results.[47,48]

The first randomized open-label trial of β-blockade in Marfan syndrome patients was reported in the 1990s.[49] In this study, 32 Marfan syndrome patients with modest aortic
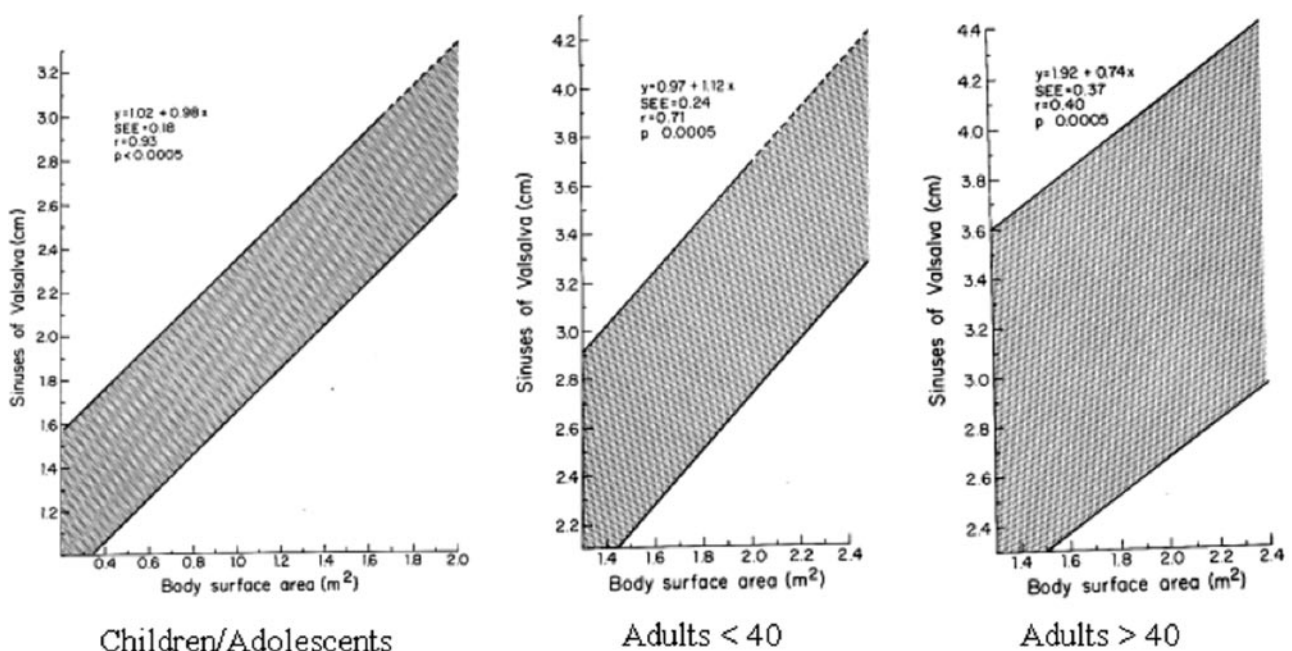

Figure 6. Age-related normative values for aortic root size in children and adults. Reproduced, with permission of the publisher, from Roman et al.[40] Copyright © 1989, Elsevier.

dilatation but without underlying aortic valve disease were randomly assigned to propranolol and compared with 38 similar untreated Marfan syndrome control patients. Propranolol dose was optimized by titration to a heart rate of <100 bpm during submaximal exercise (running up and down 2 flights of stairs) and increase of systolic ejection interval of 30%. Aortic size and rate of change were followed over time with M-mode and 2-dimensional echocardiography.[40] This group of predominantly young Marfan syndrome patients (mean age, 15.4 years) was followed prospectively for 10.7 years in the treatment arm.[49] At entry, absolute aortic diameters differed between control and treatment groups (30.2 versus 34.6 mm, respectively), but no difference was found in the aortic ratio (1.3 versus 1.4). Over a decade, the rate of growth of the proximal aortic segment in the treatment group (0.023/y) was significantly lower than that seen in controls (0.084/y; $P<0.001$). No effect of initial aortic diameter was observed on the rates of change in aortic diameter over time in either group.[49] Overall event-free survival was not significantly different between groups at the end of study, but event rates in the treated group were significantly lower during intermediate years of follow-up. Adverse side effects in this young population were minimal and generally well tolerated. To date, this remains the largest randomized trial of β-adrenergic blockade in the Marfan syndrome population.

Most subsequent studies confirmed a decrement in aortic dilatation rate, but only 1 has been able to suggest a mortality benefit.[50,51] This recent retrospective study compared 77 children younger than 12 years who had been started on β-blockade by their physicians with 78 other children with Marfan syndrome who had not been treated. The mean aortic diameter at the sinuses of Valsalva was slightly larger in the treated patients than in the controls (29.7 versus 27.3 mm; $P=0.03$). Over a period of >3 years, the absolute aortic diameters were similar in the 2 groups because the rate of dilatation in the treated patients was less than in those who did not receive β-blocker (0.16 mm/y). Another study, with important methodological weaknesses, concluded that β-blockade had no positive benefit.[52] This retrospective study compared 29 Marfan syndrome patients younger than 18 years started on β-blockade when aortic dilatation was documented with 34 patients who were never treated.[52] All of the treated patients were followed at 1 institution while the majority of the untreated group was managed at a separate hospital. The dose of β-blockade was advanced to 25 mg daily in children and 50 mg daily in adolescents; these target doses were considerably less than the optimal doses used in the other studies cited previously. After an average of ≈6 years, both the absolute mean aortic root diameters and the aortic root mean Z scores did not differ between the groups.[52]

The presumption has been that β-blocker therapy reduces the exposure of weakened, histologically abnormal tissues to destructive hemodynamic stressors, both inotropic and chronotropic, and thereby slows the progression of aortic dilatation. However, other hypotheses for the beneficial effect of β-blockade, such as a direct effect on the extracellular matrix, have never been explored satisfactorily. Both short-term and long-term β-blockade improves aortic stiffness index and

elasticity in patients with modest dilatation or less,[53,54] a benefit not observed in patients with marked dilatation.[35]

Other drugs that have been investigated include calcium channel antagonists with negative inotropic activity and angiotensin-converting enzyme (ACE) inhibitors. In a prospective study, verapamil demonstrated a mild reduction in aortic growth rates.[51] In another study, Marfan patients treated with ACE inhibition had reduced aortic growth rate and a lower event rate compared with those treated with β-adrenergic blocker therapy over a 3-year period.[55] This study, however, was nonrandomized, treating physicians had a choice of β-blocker or enalapril, leading to a potential for confounding by indication, and the doses of drugs were not optimized by any consistent criteria. Patients with perceived lower risk could have preferentially chosen treatment with the ACE inhibitor, whereas high-risk patients would more likely be steered toward β-blockade as "standard of care." The presence of significantly lower aortic distensibility and higher stiffness index in the β-blocker group suggests that such a differential therapy choice did exist.[55] Other studies of ACE inhibitor therapy on aortic compliance demonstrated a heterogeneous effect, with minimal impact on the ascending segments of the aorta.[56]

Experimental Medical Therapy

Most of the phenotypic features in a mouse model carrying a mutation known to cause human Marfan syndrome are due to increased activity of TGF-β. This cytokine signals through the SMAD cascade,[57] and increased levels of SMAD2, documented by histochemistry, are present in the mitral valve and aortic wall in affected animals.[33,58] Treatment of affected mice with antibodies against TGF-β prevent the development of myxomatous mitral valve disease and aortic aneurysms. A similar beneficial effect occurred on treatment with losartan, a drug that blocks angiotensin II type 1 receptors. Angiotensin II promotes cellular proliferation and fibrosis and suppresses apoptosis when binding to its type 1 receptor, whereas binding to its type 2 receptor has opposite effects. The effects of stimulation of the type 1 receptor are mediated, at least in part, by TGF-β. Blocking the type 1 receptor interferes with processes that are detrimental to tissue in mice (and by extension, humans) with Marfan syndrome while not affecting signaling through type 2 receptors that leads to beneficial effects. An ACE inhibitor, on the other hand, reduces angiotensin II levels and thereby signaling through both receptors.

Treatment of affected mice with losartan prenatally and continuing until 10 months of age resulted in preservation of proximal aortic elastic fiber histology and overall aortic diameter comparable to that of wild-type mice.[58] In contrast, mice with the same mutation treated with propranolol had disruption of elastic lamellae and dilated aortic roots comparable to affected mice treated with placebo.[58] When therapy with losartan was initiated at 2 months of postnatal age, which is comparable to adolescence in humans, the histological abnormalities and dilatation were reversed. Although propranolol therapy was associated with a reduction in aortic growth rate, this effect was significantly less than that seen with losartan.[58] These results in this mouse model of Marfan syndrome suggest that treatment with angiotensin receptor

blockers potentially both targets the underlying tissue pathology and reduces hemodynamic stressors. Eighteen children with severe Marfan syndrome and moderate-to-severe aortic root dilatation were treated with angiotensin receptor blockade (most with losartan, 1.4 mg/kg per day) in addition to β-adrenergic blockade. Most showed a significant reduction in the rate of change of the diameters of the aortic root and the sinotubular junction over a mean of 2 years of observation.[58a] The benefits of such therapy have not yet been demonstrated in human Marfan syndrome. A multicenter trial of losartan versus atenolol in children and young adults with Marfan syndrome was initiated in early 2007 to address this vital question.[59,60]

Current Recommendations for Medical Management

Although future therapy directed at the fibrillin-1 gene or the TGF-β axis may ultimately prove most effective at preventing the aortic complications of Marfan syndrome, β-blocker therapy currently remains the "standard of care."[3] All Marfan syndrome patients who can tolerate β-blockade should be treated, regardless of the presence or absence of aortic dilatation. Dosage should be titrated to maximum effect, typically to a resting heart rate of <60 bpm if blood pressure will allow. Atenolol administered twice daily is currently the drug of choice of many practitioners because it has long half-life and is relatively cardioselective, with fewer central nervous system and other side effects.[3] In those individuals who develop side effects and therefore cannot tolerate β-blockade, verapamil can be considered a second-line therapy.[51] Patients who have need of additional medications to control blood pressure, especially those with chronic dissections, might be treated with an angiotensin receptor blocker in addition to β-blockade. Patients who choose to initiate losartan, without clear indications in advance of controlled trials in humans documenting its effectiveness, should continue β-blockade in addition.

Effects of pharmacological therapy should be monitored closely during the initiation phase to ensure that heart rate goals and blood pressure management are optimal. Subsequent to that, more infrequent outpatient follow-up is acceptable, with semiannual history and physical examinations to monitor for changes in disease status. As children grow, an increase in medication dose is usually required. Routine monitoring of proximal aortic size and rate of growth is essential in all patients, usually with echocardiography on an annual basis. As the size of the aortic root approaches 4.5 cm or if an accelerated rate of growth (>0.5 cm/y) is noted, more frequent assessments are indicated. Because the most prominent dilatation of the Marfan aorta is located proximally, transthoracic echocardiography is typically adequate for visualization and measurement of the aortic root, proximal ascending aorta, and arch. In those cases in which echo is technically inadequate, cardiac magnetic resonance or computed tomography of the thoracic aorta is indicated.

As in the general population, management of acute dissection of the ascending aorta (type A) in the Marfan syndrome is a surgical emergency. Unfortunately, in the emergency medicine setting, severe chest pain in a young person often does not prompt evaluation for dissection. For the patient who has not been diagnosed with Marfan syndrome, a tall, asthenic habitus, anterior chest deformity, or a family history of aortic dissection or sudden death should suggest the possibility of aortic dissection.

Type B dissection, typically with the initial tear in the proximal descending thoracic aorta, accounts for ≈10% of acute dissection in Marfan syndrome. Once diagnosed, the initial management can employ standard medical approaches, unless pain is intractable, limb or organ ischemia is evident, the aortic diameter exceeds 5 cm, or rapid expansion of the aortic dimension is occurring. In these cases, strong consideration of open surgical intervention should be given. After the first several months, patients with a chronic type B dissection should be managed with β-adrenergic blockade, additional antihypertensive medication if needed, and computed tomographic or magnetic resonance imaging at intervals dictated by symptoms, diameter, and rate of change of diameter. Strong consideration for surgical repair should be given when the diameter exceeds 5 to 6 cm. In our experience, many patients with Marfan syndrome have been followed for a decade or more with stable type B dissection. Experience with intravascular aortic stenting for acute or chronic type B dissection is limited,[61,62] and some patients require open repair in the intermediate term.[63] Some experts recommend against the use of stent grafts in the descending thoracic and abdominal aorta in Marfan syndrome, except in the case of false aneurysms in previously operated patients in which the stent can be anchored into existing synthetic grafts.[64] Currently in the United States, patients with Marfan syndrome and other connective tissue disorders are excluded by the US Food and Drug Administration from trials of stent grafting in the thoracic and abdominal aorta.

Other Management Issues in Marfan Syndrome

Sudden unexpected deaths of several prominent athletes with undiagnosed or unsuspected Marfan syndrome highlight issues surrounding physical exertion and exercise. Questions about physical activity are frequently raised in the day-to-day management of Marfan syndrome patients. Because of their tall stature, children with Marfan syndrome may be encouraged to participate in certain sports that are potentially hazardous. Therefore, both pediatric and adult cardiovascular practitioners must be aware of the current recommendations for exercise.[65]

In general, physical activities can be roughly divided into aerobic (dynamic) exercise, in which changes in muscle length are high and muscular contractions have small force, and isometric (static) exercise, in which change in muscle length is minimal but muscular contractions involve large amounts of force.[66] Strenuous static exercise, such as weight lifting, is contraindicated in Marfan syndrome because of the marked increases in peripheral blood pressure and proximal aortic wall stress during these activities.[67] Although dynamic exercise is also associated with increases in cardiac output and systolic blood pressure, an associated decrease has been observed in peripheral vascular resistance and diastolic blood pressure. An increase occurs in proximal aortic wall stress, which is usually lower than with isometric exercise.[66] Modest levels of dynamic/aerobic activity are therefore likely to be safe in most Marfan patients and might be encouraged, when

Table 2. Recommendations for Athletic Activity in Marfan Syndrome

Patient Description	Recommendation
(a) No aortic root dilatation (<40 mm; *Z* score <2)	IA, IIA: Low and moderate static activity
(b) Moderate mitral regurgitation or less	Low dynamic activity
(c) No family history of dissection or sudden death	
(a) Aortic root dilatation (≥40 mm; *Z* score ≥2)	IA: Low dynamic activity
(b) Moderate to severe mitral regurgitation or more	
(c) Prior root reconstruction, chronic dissection	
(d) Family history of dissection or sudden death	
Any degree of aortic root dilatation	Avoid bodily impact sports

Adapted from Maron et al.[65]

appropriate, to promote overall cardiovascular conditioning and psychological health.[3] Activity levels should be maintained at ≈50% of aerobic maximum, with maximal heart rates in the range of 100 to 110 bpm for children and <100 bpm for adults (if optimal β-blockade is assumed).[66]

Highly competitive aerobic sports, associated with significant increases in cardiac output and aortic dP/dt sustained over prolonged periods of time, are contraindicated in Marfan syndrome.[66,68] Bodily collisions (as in contact sports) and marked changes in ambient air pressure (as in scuba diving or sudden changes in altitude in nonpressurized aircraft) should be avoided.[68] The former can cause aortic and other arterial trauma, and the latter can predispose to pneumothorax. Decisions about activity regulation should also be made in light of the estimated severity of underlying disease, including whether or not a particularly malignant family history of Marfan aortic complications is present, as well as the overall size and growth rate of the proximal aortic root. In this way, individualized recommendations can be presented. In such a clinically variable disease, "absolute" advice is problematic, but recommendations from the National Marfan Foundation (www.marfan.org) and recent guidelines from the American Heart Association/American College of Cardiology task forces can serve as useful templates (Table 2).[68]

Women with Marfan syndrome have 2 concerns when considering reproduction. The first is the 50/50 chance of having a child affected by this autosomal dominant condition. The second is the risk of pregnancy on the maternal heart and cardiovascular system. The baseline hemodynamic stress on the proximal aortic root is accentuated by pregnancy-related increases in cardiac output, heart rate, stroke volume, and circulating volume, particularly during the later stages of pregnancy. It is not surprising, therefore, that a majority of the aortic complications in pregnant Marfan syndrome patients have been described in the third trimester of pregnancy.[69] Interestingly, the risk of aortic rupture and dissection extends beyond the prepartum and peripartum time periods, with up to one fifth of complications occurring ≥2 days after

uneventful delivery.[69] Risk of aortic complications during pregnancy is directly related to the degree of baseline aortic enlargement of the aortic root, with few complications occurring in those with aortic root diameters <4.2 cm.[70,71] The most common aortic complication in those with minimal root dilatation is type B dissection. An absolute risk of type A dissection in a pregnant woman with an aortic root diameter >4.0 cm is difficult to quantify but is clearly increased.[70,72] Although the rate of increase in aortic diameter of most pregnant women with Marfan syndrome is no different than that in age-matched nonpregnant women with Marfan syndrome,[73] some studies suggested that those individuals in whom significant aortic dilatation occurs are at higher risk for aortic dissection.[72] When the maternal aorta has a normal or minimally dilated caliber, with appropriate counseling, most couples consider the maternal risk of pregnancy acceptable.[71]

In those Marfan syndrome patients who choose to become pregnant, close monitoring during pregnancy by both a high-risk obstetrician and a cardiologist familiar with Marfan syndrome is recommended.[3] Prophylactic treatment with β-blockers can blunt increases in heart rate and dP/dt from mid-trimester on, albeit with small risks of fetal intrauterine growth restriction, hyperbilirubinemia, and hyperglycemia.[69] Angiotensin receptor blockade is contraindicated in women attempting to conceive and during pregnancy. Periodic echocardiographic assessment of aortic root size is recommended to identify those at high risk for complications. Labor and delivery by the vaginal route are likely safe, with appropriate regional anesthesia and positioning to reduce fluctuations of venous return and pulse pressure during delivery.[69] In those patients with aortic root diameters much >4.0 cm, consideration can be given to prophylactic root repair with sparing of the native aortic valve, as described subsequently. Composite graft repair with a mechanical valve is problematic with pregnancy because of the need for long-term warfarin therapy, which can be teratogenic. The type of anesthesia and mode of delivery should place the least possible hemodynamic stress on the maternal aorta. In some cases a cesarean section may be indicated, but it carries the risk of rapid shifts in blood volume. Epidural anesthesia should take into account the likelihood of dural ectasia and lumbosacral meningoceles.[74]

Management of Mitral Valve Prolapse and Mitral Regurgitation

In addition to aortic dilatation, laxity of the mitral valve apparatus is common in Marfan syndrome, resulting in the presence of mitral valve prolapse in between 50% and 80% of cases.[3,75] This prevalence is far higher than that of isolated mitral valve prolapse in the general public (2.4%) and is associated with differing morphology and histology of the mitral apparatus.[75] A recent surgical series demonstrated longer and thinner leaflets in Marfan syndrome patients, with less hypercellularity and more common anterior and bileaflet prolapse than in patients with isolated forms of "classic" mitral valve prolapse pathology.[76] Graded increase of TGF-β activity in the mitral valves of heterozygotic and homozygotic fibrillin-1–deficient mice is associated with progressively worse mitral valve prolapse and abnormal mitral

anatomy compared with wild-type mice.[33] This pathogenesis, however, differs from isolated forms of mitral valve prolapse, which have been traced to multiple, unrelated genetic loci.[75]

Marfan syndrome patients with mitral valve prolapse present with variable degrees of mitral regurgitation, with up to 12% to 13% having moderate or severe mitral regurgitation.[3] Although the associated left ventricular volume overload and systolic function may be associated with sudden cardiac death, this is uncommon below the age of 50 years.[45] Surgical repair of the severely regurgitant mitral valve is possible in Marfan syndrome patients and has been associated with a high event-free survival at 10 years.[76]

Management of Dysrhythmia

ECG abnormalities, including prolonged atrioventricular conduction time and ST-segment abnormalities, are common in Marfan syndrome.[77] Ventricular repolarization abnormalities (prolongation of the QT interval and the presence of U waves) in Marfan syndrome are associated with a higher prevalence of ventricular dysrhythmias compared with controls.[77] In a recent prospective series of 70 Marfan syndrome patients, ventricular dysrhythmias were seen in 21% of patients, with sudden cardiac death attributed to primary arrhythmia in 4%.[45] Prolongation of QT interval and ventricular arrhythmias were more common in those patients with significant diastolic left ventricular dilatation.[45] Further study is warranted to define appropriate interventions in these patients, although treatment with β-blockade may have a favorable impact.

Timing of Aortic Surgical Intervention in Marfan Syndrome

Timing of surgical intervention in Marfan syndrome is a matter of utmost importance to prevent the morbidity and mortality associated with ascending aortic dissection. The risk of type A dissection is proportional to the overall size of the proximal aorta, in Marfan patients as well as in other causes of noninflammatory proximal aortic aneurysms.[39,41,43,78] Mortality and event rates (aortic dissection, need for surgical intervention) are significantly higher in adults with Marfan syndrome when the absolute aortic root dimension is >5.0 cm,[78] has an aortic ratio >3,[43] or has an aortic size index of ≥4.25 cm/m².[41] Rate of aortic dilatation is an additional risk factor for dissection or death; change in aortic ratio of >5% per year portends a poor outcome.[43] A family history of aortic dissection is another predictor of risk. Accordingly, replacement of the aortic root and ascending aorta in Marfan syndrome with a composite graft (valved conduit) is recommended when the greatest diameter of the proximal aorta reaches 5.0 cm in adults.[12,79] When the rate of change of aortic diameter is rapid[43] or when the patient has had relatives suffer aortic dissection,[13] elective surgery should be considered at a maximal diameter of 4.5 cm.[80,81] Criteria for children are less well defined. Fortunately, children with Marfan syndrome rarely need to have aortic root repair, and dissection under the age of 12 is uncommon. Delaying surgery to avoid a valve–patient mismatch later in life must be balanced against the risk of dissection. Typically, surgery should be considered if the aortic ratio is >3.

Current options for elective surgical repair of the Marfan aortic root are diverse with acceptable risk. Composite graft replacement of root and aortic valve has excellent short- and long-term outcomes.[82] This has been supplemented by newer valve-sparing techniques, including Yacoub remodeling and David reimplantation techniques.[83] Although differences can be seen in long-term freedom from aortic regurgitation between the 2 valve-sparing techniques, with the reimplantation approach being more favorable, mortality outcomes of either are excellent.[83,84] A registry of patients who have an aortic valve-sparing procedure is collecting data from an international consortium of surgeons, and additional outcome data will emerge in the next few years. More detailed discussions of surgical options can be found elsewhere.[83] Elective surgical repair or replacement of the proximal aorta in Marfan syndrome carries with it a very low morbidity and mortality (1.5% 30-day mortality, even lower in centers with the most experience),[12] very comparable to surgery performed in non-Marfan aortic replacements. Emergency aortic replacement, on the other hand, is associated with markedly increased 30-day mortality in Marfan syndrome (11.7%).[12] Thus, the goal of the primary practitioner or cardiovascular specialist in ongoing management is careful timing of elective surgical intervention to avoid the high morbidity and mortality associated with aortic dissection and emergency surgery.

Heart Transplantation

In patients with Marfan syndrome who have end-stage heart failure for whatever reason (most commonly, severe valvular regurgitation or primary cardiomyopathy), orthotopic transplantation is an effective approach.[85]

Postoperative Medical Management

The aorta distal to the ascending aortic conduit is susceptible to dilatation and dissection, and therefore routine imaging of the entire aorta is recommended.[86] Earlier reports of distal arterial complications, especially of branch vessels, may overstate the actual risks in Marfan syndrome because some patients with mutations in TGF-β receptors, who are particularly susceptible to dissections of branch vessels, were likely included.[6,7] Long-term maintenance on β-blockade and exercise restrictions should also be considered.

Summary

As recently as 40 years ago, people with Marfan syndrome faced a virtually hopeless situation on account of chronic mitral and aortic regurgitation, heart failure, and acute and chronic aortic dissection. Life span was reduced by at least one third, with many patients succumbing in the second and third decades.[11] Today, cardiovascular manifestations of Marfan syndrome remain among the central issues in diagnosis and management, but it is incumbent on the physicians who encounter these patients to stress the prophylactic monitoring and therapies that now can result in a nearly normal life expectancy. Regular monitoring of valvular function and aortic diameter, early initiation of long-term β-adrenergic blockade and elective repair of a moderately regurgitant mitral valve or of a moderately dilated aortic root while preserving the native aortic valve are standards of care.

Additionally, insights into the pathogenesis of clinical problems hold considerable promise for more effective, and even curative, medical therapies.

Disclosures

None.

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KEY WORDS: aorta ■ genetics ■ mitral valve ■ Marfan syndrome

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