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CONGENITAL HEART DISEASE

Diagnosis and treatment of Marfan syndrome: an update

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> But in no regard was he more peculiar than in his personal appearance. He was singularly tall and thin. He stooped much. His limbs were long and emaciated. His forehead was broad and low.
>
> "A Tale of the Ragged Mountains", Edgar Allan Poe, 1844

Marfan syndrome (MFS) is a connective tissue disease inherited in an autosomal dominant fashion and associated with a decreased life expectancy. Skeletal features as well as a particular facial appearance are some of its most memorable features and are thought by some to be described as early as 1844 in popular literature.[w1] Its earliest description in the medical literature is believed to be by Antoine-Bernard Marfan in 1896, giving the condition its name. Clinically, aortic dilatation and dissection are the most important and life threatening manifestations, but cardiac, ocular, skeletal, and neurological involvement may also impose a considerable burden. In order to facilitate diagnosis and research, expert committees published and consecutively refined a number of consensus documents: The 'Berlin Nosology' of 1986, the 'Ghent Nosology' of 1996, and more recently the 'Revised Ghent Nosology' of 2010. Milestones of therapy were the use of β-blockers to slow progression of aortic dilation[1] and the introduction of prophylactic aortic root replacement to avoid dissection.[2] Since the discovery of the condition's autosomal dominant inheritance (1931), the abnormalities of the fibrillin-1 protein (1990), and identification of pathogenic mutations in the *FBN-1* gene (1991), our pathophysiological understanding has come a long way.

In this article we aim to highlight some of the more recent developments in the diagnosis and treatment of MFS in adults.

DIAGNOSIS

Owing to the multi-systemic nature of the disease, establishing the diagnosis of MFS is like piecing together a puzzle. Because aortic and cardiac complications are of foremost importance, often the cardiologist will be at the centre of the diagnostic efforts. For a sound evaluation he or she will have to look far beyond just heart and vessels, coordinating a multi-modality and multi-specialist approach (figure 1).

Current and historical nosologies attempt to standardise the spectrum and thus the definition of the disease for both clinical and scientific use. With the main goal of identifying patients at risk for an increased morbidity and mortality, the criteria have been changed and refined over time. In the most current 'Revised Ghent Nosology' of 2010,[3] aortic dilatation/dissection and ectopia lentis (luxation of the lens) were given more weight, while other less specific criteria were made less influential. Also genetic testing has gained a more prominent role. Aortic dilatation is defined by the use of a z-score (Z), which is equivalent to the number of standard deviations the actual aortic root diameter differs from the mean of a group of healthy controls. In the absence of a family history of MFS the diagnosis can be made: (1) in the case of Z≥2 (or dissection) and the presence of ectopia lentis; (2) in the case of Z≥2 (or dissection) and the presence of 7 or more points of a systemic score; and (3) in the case of Z≥2 (or dissection) and a probably causal FBN1 mutation. Finally, the occurrence of ectopia lentis together with an FBN1 mutation known to be associated with aortic dilatation (4) is sufficient to make the diagnosis. Together with a family history, ectopia lentis or Z≥2 or a systemic score ≥7 are sufficient to make the diagnosis in adults (box 1).

Evaluation of ~~further~~ systemic involvement is done by working through a systemic score checklist where theoretically a maximum of 20 points can be reached (box 2). The nosology goes into great detail on how to evaluate each item.

A number of related disease entities with significantly different clinical courses and management exist. MASS phenotype (MASS: ~~Mitral valve prolapse, Aortic enlargement, Skin and Skeletal findings~~), ectopia lentis syndrome (ELS), Loeys-Dietz syndrome, and Shprintzen-Goldberg-Syndrome are just a few of those that have to be differentiated. The nosology takes care to separate these from MFS through the use of additional clinical criteria, biological testing, and finally the results of genetic testing (table 1).

Imaging

Transthoracic echocardiography (TTE) is the primary imaging tool in the diagnosis of MFS; transoesophageal echocardiography may be used in emergency situations when dissection is suspected. The aortic root is best visualised in a parasternal long axis view. The maximum diameter of the aortic annulus, sinus of Valsalva, and ST junction should be visualised and measured. The diameter of the annulus is usually measured in mid systole. It is a virtual structure defined by the connection of the lowest insertion points of the semilunar cusps. Aortic root measurements should be done parallel to the plane of the aortic valve and perpendicular

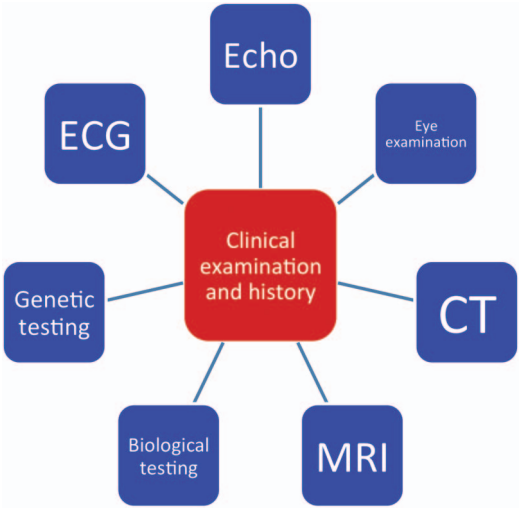

Figure 1 Multiple modalities and methods have to be used for the diagnosis and follow-up of Marfan syndrome patients. Echo, echocardiography.

to the axis of blood flow in end-diastole. Depending on the intended use (diagnosis with z-score calculation or follow-up), leading edge as well as inner edge measurements may be necessary. The largest correctly measured root diameter obtained from at least three transthoracic images should be reported.

Box 1 The revised Ghent criteria for the diagnosis of Marfan syndrome and related conditions[3]

In the absence of family history:
1. Ao (Z≥2) AND EL=MFS*
2. Ao (Z≥2) AND FBN1=MFS
3. Ao (Z≥2) AND Syst (≥7pts)=MFS*
4. EL AND FBN1 with known Ao=MFS

EL with or without Syst AND with an FBN1 not known with Ao or no FBN1=ELS

Ao (Z<2) AND Syst (≥5 with at least one skeletal feature) without EL=MASS

MVP AND Ao (Z<2) AND Syst (<5) without EL=MVPS

In the presence of family history:
5. EL AND FH of MFS (as defined above)=MFS
6. Syst (≥7 patients) AND FH of MFS (as defined above)=MFS*
7. Ao (Z≥2 above 20 years old, ≥3 below 20 years) + FH of MFS (as defined above)=MFS*

*Caveat: without discriminating features of SGS, LDS or vEDS AND after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated.

Ao, aortic diameter at the sinuses of Valsalva above indicated z-score or aortic root dissection; EL, ectopia lentis; ELS, ectopia lentis syndrome; FBN1, fibrillin-1 mutation (as defined in table 1); FBN1 not known with Ao, FBN1 mutation that has not previously been associated aortic root aneurysm/dissection; FBN1 with known Ao, FBN1 mutation that has been identified in an individual with aortic aneurysm; FH, ????; LDS, Loeys-Dietz syndrome; MASS, myopia, mitral valve prolapse, borderline (Z<2) aortic root dilatation, striae, skeletal findings phenotype; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; SGS, Shprintzen-Goldberg syndrome; Syst, systemic score; vEDS, ?????; Z, z-score.

In addition to TTE, MRI is a key technique in the diagnosis and management of MFS. It allows detailed assessment of the aortic root and the heart (valvular regurgitation, ventricular dimensions and function) when echocardiography may be hindered by chest deformities. Also, it allows regular imaging of the whole aorta without the need for radiation exposure. Finally, many of the systemic manifestations (dural ectasia, scoliosis, chest deformities, protrusio acetabula) can be easily visualised, though not with the same coil. Current European guidelines recommend MRI or CT imaging of the entire aorta for all Marfan patients upon making the diagnosis. It has been emphasised that measurements of the aorta in MRI or CT images should be done in a double oblique technique (figures 2 and 3) to avoid skewed images that may easily lead to false results. Concerning the possible lines of measurements of the aortic root (cusp-to-commissure vs cusp-to-cusp, figure 4) there is a lack of standardisation. With MRI some authors have found diastolic non-contrast enhanced cusp-to-commissure measurements correspond closely with inner edge echocardiography measurements.[w2]

In clinical practice identification of the exact aortic dimensions at the level of the root using contrast enhanced MRI can be quite challenging due to motion blurring. A recent study with MFS patients compared contrast enhanced MRI of the aortic root with non-contrast (ECG triggered) imaging as well as echocardiography. Non-contrast MRI images as opposed to contrast images allowed clearer delineation of the aortic root dimensions with significantly better intra- and inter-observer agreement, but with a greater offset (mean difference 3.4 mm) when compared with echocardiographic measurements.[w3] Other groups have shown good correlation of non-contrast MRI measurements with the gold standard of ECG gated CT scans. In this respect it appears that non-contrast images may be the better choice for serial measurements typical for MFS follow-up (figure 5). However, because it is well recognised that contrast enhanced MRI is superior in demonstrating dissection flaps, a combination of MRI sequences for a full assessment of vessel pathologies should be used.[w4]

With aortic involvement beyond the sinus of Valsalva becoming more relevant, it has been postulated that distal aortic diameters may not be useful for the prediction of dissection or rupture.[w5] In the search for better parameters of the involvement of the whole vessel the assessment of aortic volume by means of contrast enhanced MRI has been studied. In a small pilot study with 22 MFS patients and a follow-up of 3 years, aortic volume (annulus to bifurcation) was well reproducible and showed a superior effect size compared with that of distal diameter assessment.[w6] It remains to be seen whether this parameter will gain any importance in clinical management or research.

Diffuse peripheral arterial aneurysms are well known features of other connective tissue disorders

Box 2 Scoring of systemic features according to the revised Ghent nosology[3]

Scoring of systemic features

- 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)
- Pneumothorax—2
- Dural ectasia—2
- Protrusio acetabuli—2
- Reduced US/LS 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 (all types)—1

Maximum total: 20 points; score ≥ indicates systemic involvement; US/LS, upper segment/lower segment ratio.

such as the Loeys-Dietz syndrome (genes: *TGFBR1*, *TGFBR2*) and Ehlers-Danlos syndrome of the vascular type (gene: *COL3A1*). They have traditionally not been associated with MFS, but the results of two recent studies suggest otherwise. In a retrospective analysis of about 140 MFS patients (all with FBN1 mutations) who had undergone routine thoraco-abdominal CT or MRI as part of their follow-up, about one third had incidental findings of peripheral vascular aneurysms. Fifty-five per cent of the peripheral aneurysms were deemed to require intervention.[4] A prospective series using Doppler ultrasound systematically examined the supra-aortic trunks, the arteries of the upper and lower extremities, the aorto-iliac arteries, and the visceral branches of the abdominal aorta in 21 consecutive MFS patients. Of the 15 adults, 10 (67%) had peripheral vascular arterial aneurysms and two patients underwent semi-urgent repair.[5]

Table 1 Features of some of the most important differential diagnoses of Marfan syndrome

Differential diagnosis	Gene	Discriminating features
Loeys-Dietz syndrome	*TGFBR1/2*	Bifid uvula/cleft palate, arterial tortuosity, hypertelorism, diffuse aortic and arterial aneurysms, craniosynostosis, clubfoot, cervical spine instability, thin and velvety skin, easy bruising
Shprintzen-Goldberg syndrome	*FBN1* and others	Craniosynostosis, mental retardation
Congenital contractural arachnodactyly	*FBN2*	Crumpled ears, contractures
Weill-Marchesani syndrome	*FBN1*, *ADAMTS10*	Microspherophakia, brachydactyly, joint stiffness
Ectopia lentis syndrome	*FBN1*, *LTBP2*, *ADMTSL4*	Lack of aortic root dilatation
Homocystinuria	*CBS*	Thrombosis, mental retardation
Familial thoracic aortic aneurysm syndrome	*TGFBR1/2*, *ACTA2*	Lack of marfanoid skeletal features, levido reticularis, iris flocculi
Ehlers-Danlos syndromes (vascular, valvular, kyphoscoliotic type)	*COL3A1*, *COL1A2*, *PLOD1*	Middle sized artery aneurysm, severe valvular insufficiency, translucent skin, dystrophic scars, facial characteristics

Modified from the revised Ghent nosology.[3]

Suspicion of MFS in primary care

Making the correct diagnosis of MFS in a patient may eventually have great impact on morbidity and mortality. However, suspicion of the disease—either by the patient or his physicians—is the key to referral. In this respect the revised nosology may be unnecessarily complex for the primary care setting, while also lacking clear recommendations on whom to refer to a specialised centre. Sheikhzadeh *et al*[6] aimed to develop a simplified model to identify patients with possible MFS who require definite workup. Of 329 consecutive patients thoroughly evaluated for MFS, 208 were randomly assigned to a derivation group. Using multivariate logistic regression, 14 clinical variables—all generally easily available without any imaging modalities—were analysed for their association with a positive MFS diagnosis. Seven of these variables were included in a simple prediction score and receiver operating characteristic (ROC) analysis was used to define cut-off points. Interestingly, body height—commonly associated with MFS—was not predictive and excluded from the final model. Patients with low, moderate, and high probability were identified as having MFS in 12%, 42%, and 92% of the cases, respectively. Validation of the score in the remaining 121 patients showed good agreement (box 3).

While having limited utility to strictly exclude MFS, the score may nevertheless guide decision making for a further (eventually expensive and time consuming) workup in the absence of specialised imaging modalities or expertise.

Appraisal of the new nosology

Comparison studies between old and new nosology found the new nosology easier to apply in many cases. Both showed in general a good agreement in patient classification, but some patients were reclassified to alternative diagnoses such as ELS and MASS phenotype.[w7 w8] It is important to note that these patients may still be diagnosed as having MFS later on if the aortic diameter enlarges to fulfil current criteria.

The introduction of the z-scores, however, has been criticised for several reasons. The most widely used formula for the calculation of the z-score of an individual patient aorta has been proposed by Roman *et al*.[7] Using body surface area (BSA) and age, a normal leading edge echocardiographic aortic root diameter can be calculated, and in a second step the number of standard deviations (z-score) that the actual measurement differs from the normal value is derived. The validity of these calculations or nomograms has been the matter of ongoing debate. The formula has been derived from the measurements of only 135 adults and assumes a linear relationship between BSA and

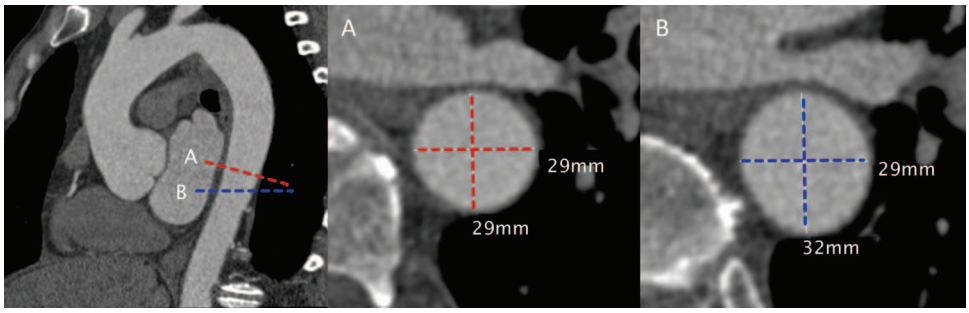

Figure 2 Simply measuring aortic diameters in transversal slices (B) may introduce a significant error when the vessel axis is not perfectly aligned with the longitudinal body axis. This will result in overestimation of maximal vessel diameters as compared to the double oblique measurement (A).

aortic diameter. Above the greatest diameter in the dataset the linear relationship was extrapolated. More recent studies with healthy controls questioned the linearity in certain BSA ranges and suggested that an absolute threshold of aortic root diameters exists.[w9] [w10] Using the formula of Roman *et al* in patients with high BSA values might falsely reject the MFS diagnosis[8] due to overestimation of normal sizes above a certain BSA (figure 6). Also, with the increasing incidence of overweight patients, the use of BSA to calculate normal aortic root sizes is questionable.

In a recent study by Devereux *et al*,[9] echocardiographic (leading edge) measurements of the aortic root of 1207 healthy subjects were analysed. Aortic root diameters were found to be larger in men and increased with body size and age. From these data, two new equations for the calculation of z-scores were proposed.[9] A subsequent validation study with old and new z-score equations (2674 aortic root measurements of 260 patients) found the new Devereux equation (using height rather than BSA) to be especially robust (box 4).[w11]

The recently published Dutch national MFS guidelines have incorporated these considerations and recommend the use an absolute threshold of 40 mm in adults, in addition to the use of classic nomograms at lower diameters.[w12] We suggest that, especially in patients with a large BSA, use of one of the newer z-scores should be considered and an absolute aortic root diameter >40 mm should always raise the suspicion of a pathologic enlargement. While hard to quantify, the 'classic pear-shaped' ~~a~~ aspect of the aortic root can also be taken into account when making the diagnosis.

Genetic testing

Currently genetic testing is not mandatory according to the revised nosology as the diagnosis can often be made by phenotype alone. Genetic testing in these patients may thus be considered unnecessary by some. On the other hand, it may be tempting to simply draw blood and test for an FBN1 mutation in all patients referred for evaluation of MFS without resorting to systemic scoring. In our view none of these strategies seems advisable. Some phenotypes may only be identified as MFS with the genetic information available, while in other cases a classic Marfan phenotype may not show an FBN1 mutation. Furthermore, there are carriers of FBN1 mutations who do not fulfil current criteria but may be at risk of developing an MFS phenotype later on. Finally, a number of patients with MFS phenotype will turn out to have a TGFBR1/2 mutation, thus classifying them as Loeys-Dietz syndrome patients mandating a different clinical management. In a recent study, genotype information from sequencing of the *FBN1* and *TGFBR1/2* genes

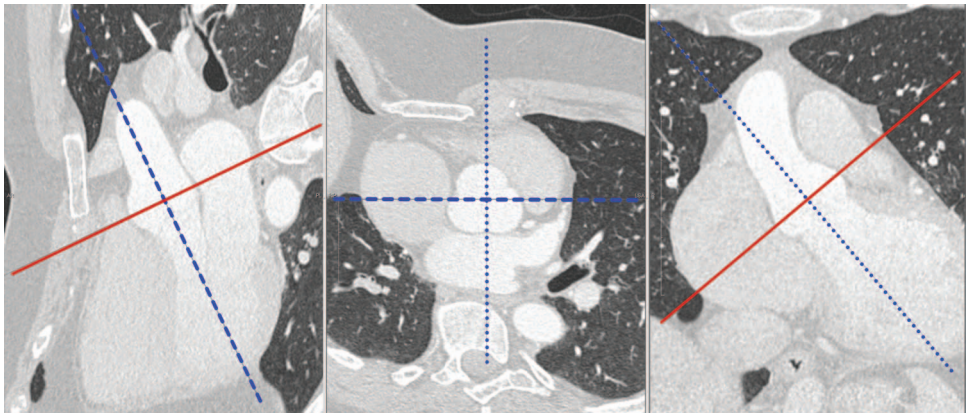

Figure 3 Example of double oblique measurements. After three dimensional reconstruction of CT data, two orthogonal planes (left and right images) are adjusted to go through the axis of the structure to be measured (in this case the aortic root). A third plane (middle image) orthogonal to the first and second is used to measure an exact cross section of the structure of interest. All segments of the aorta should be measured in this fashion in order to avoid skewed slices and false results.

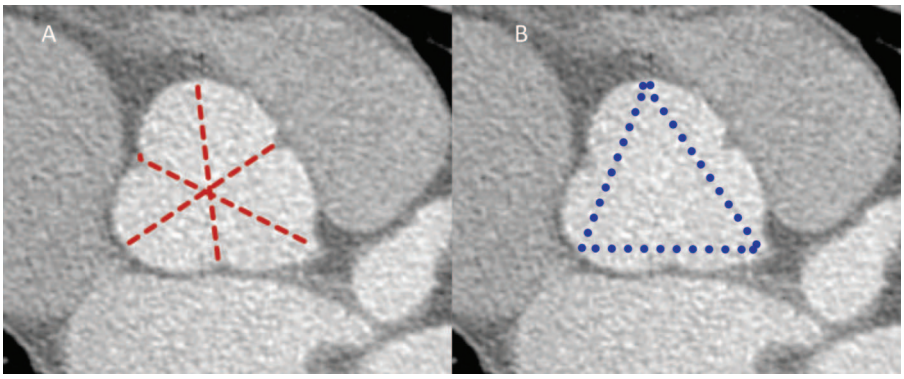

Figure 4 Example of aortic root measurements in CT images. Cusp-to-commissure measurements (A) may give slightly different diameters than those measured from cusp-to-cusp (B). The method used for measurement should be stated in the imaging report.

resulted in changes of the final diagnosis in 11% of patients.[10] We recommend testing phenotype positive patients as it helps to validate the clinical diagnosis, exclude alternative diagnoses, and facilitates the diagnosis in the patients' offspring.

The threshold to test patients with only limited systemic involvement remains controversial. It has been suggested that features in at least two or three organ systems with one major criterion (according to the older 1996 Ghent nosology) have to be present to make an FBN1 mutation reasonably probable.[11]

With the increasing relevance of genetic testing in many diseases a need has arisen for faster, broader, and cheaper analyses. Lately resequencing arrays in the form of 'gene chips', combining a number of genes relevant in aortic disease, have been proposed as a fast alternative to conventional capillary sequencing, allowing costs to be reduced by up to 50%. However, currently small heterogous insertions and deletions may be missed in some cases and necessitate follow-up investigations.[w13] Individual whole genome sequencing has been proposed as another alternative to identify gene mutations.[w14] While this approach provides the most comprehensive collection of individual genetic variations, it obviously raises some tough ethical questions.

MANAGEMENT

Aortic dissections and rupture are the main causes of reduced life expectancy of MFS patients. Earlier recognition of the disease, better imaging techniques as well as medical and surgical therapies have contributed to increasing survival by 30 years within the last 30 years.[w15] The revised Ghent nosology is the first to contain recommendations on follow-up, and medical and surgical treatment.[3] Other sources of recommendations are the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines on thoracic aortic disease[w16] and the European Society of Cardiology (ESC) guidelines on grown-up congenital heart disease.[12]

FOLLOW-UP

Yearly transthoracic echocardiograms are recommended in all patients to monitor progression of aortic dilatation, which is mainly found in the aortic root. ~~A yearly TTE examination is recommended for follow-up in stable patients with normal dimensions beyond the aortic root~~. Diameters close to surgical thresholds or rapid progression mandate more frequent imaging. MRI or CT should be performed every 5 years in patients with normal aortic dimensions beyond the aortic root, and yearly in patients with involvement of more distal parts.[12] American guidelines call for a second TTE 6 months after making the diagnosis to assess the rate of change and decide on further imaging intervals.[w16] A double oblique technique (figures 2 and 3) should be used for diagnosis and follow-up to avoid erroneous measurements. Annual ophthalmological evaluation is deemed essential to avoid ocular complications such as ectopia lentis, retinal detachment or glaucoma.

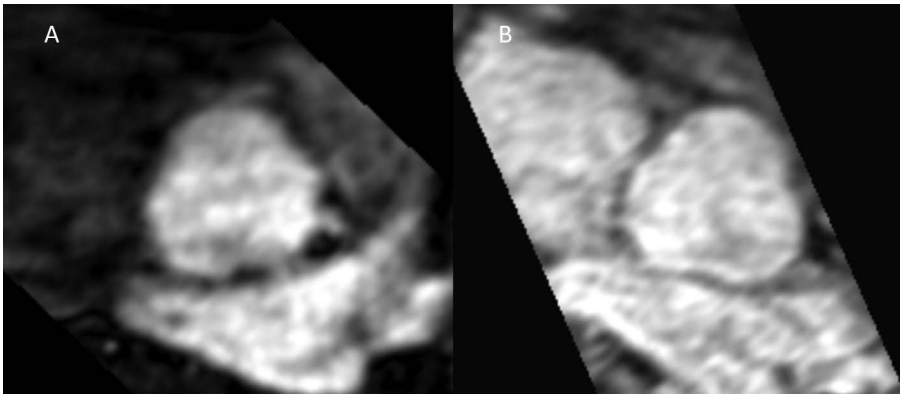

Figure 5 MRI of the aortic root. With contrast enhanced imaging (A) there is a considerable amount of motion blurring. Non-contrast ECG gated imaging (B) may allow a clearer delineation of root dimensions.

Box 3 Clinical variables of a simple prediction score[6] for the pre-test probability of MFS. All variables are usually easily available through clinical examination and history taking

- Family history of Marfan syndrome
- Previous thoracic aortic surgery
- Pectus excavatum
- Wrist and thumb sign
- History of pneumothorax
- Striae
- Ectopia lentis

MEDICAL MANAGEMENT

The theory behind β-blocker therapy in MFS is that a reduction of heart rate, blood pressure, and amplitude will reduce aortic stress and thus dilatation.[w17] β-blockers have been shown to reduce progression of aortic root size. Their effect on the rate of aortic dissections, elective valve surgery, root surgery or mortality remains unclear.[3] Initiation of β-blockade is currently recommended in all MFS patients regardless of aortic size. Other classes of antihypertensive medications are only recommended if β-blockers are not tolerated or are contraindicated, and if these other medications have also shown some effect on aortic root dilatation.

Our understanding of the pathophysiology of aortopathy in MFS has changed considerably since the introduction of β-blocker therapy. Fibrillin 1—once thought be mainly involved as a structural extracellular matrix protein—has been found to be an important regulator of transforming growth factor β (TGF-β), with the abnormal protein resulting in excessive TGF-β activation. Since the mechanotransduction complex of smooth muscle cells (SMCs) also binds to fibrillin-containing microfibrils at the periphery of elastic fibres, FBN1 mutations are also suspected of disrupting SMC contraction. Descriptions of the involved pathways have been published in great detail.[w18] ~~Angiotensin 1 receptor blockers~~ (ARBs) reduce levels of total and active TGF-β and decrease its signalling. Angiotensin 2 receptor activation, however, remains uninhibited and is thought to have an anti-inflammatory and antiproliferative effect.[w19] In an MFS mouse model the ARB losartan almost completely inhibited further aortic growth and histological changes of the elastic fibres in the aortic wall.[14] The first encouraging results from an observational pilot study in 17 paediatric MFS patients[15] received much attention and led to the initiation of a number of clinical trials.

In 2013 the results from a prospective, randomised, open label, multicentre trial on the effect of losartan on aortic dilatation in 233 adult MFS patients were published. Patients with and without prophylactic aortic surgery were randomised to receive either losartan or no additional medication along with their current therapy. Because 38% of the included patients had already received aortic root replacement, the group with a native aortic root consisted of only 145 patients. After a mean follow-up of 3.1±0.4 years, unoperated patients on losartan showed a significantly lower rate of aortic root dilatation than unoperated controls (0.77 ±1.36 mm vs 1.35±1.55 mm, p=0.014). This positive effect could not be shown for segments distal to the aortic root. In previously operated patients the aortic arch dilatation rate was significantly lower in the losartan group when compared with the control group (0.50±1.26 mm vs 1.01 ±1.31 mm, p=0.033). There were no differences in clinical endpoints (dissections, surgery, death). The latter finding is not surprising, however, as much larger studies with longer follow-up would be required to study such endpoints. Since more than two thirds of patients in both groups were also taking β-blockers the effect of ARB monotherapy could not be assessed. Of note, the authors showed that the positive effect on the aortic root was independent of the systemic blood pressure, which supports the concept of a specific molecular

Box 4 A new z-score normalised for height by Devereux *et al.*[9]

Mean predicted aortic root (AR) (cm) for length=1.519+(age×0.010)+(~~H~~×0.010) – (sex×0.247)
Z=(measured diameter—predicted AR)/SD with an SD of 0.215 cm
Sex: male=1, female=2.

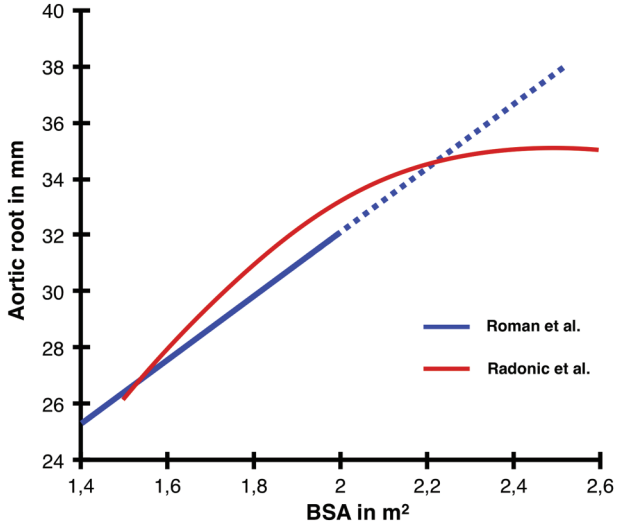

Figure 6 Normal aortic root diameters for different body surface areas (BSA). The nomograms by Roman *et al*[7] assumed a linear relationship between diameters and BSA (blue line). Diameters at higher BSA were simply extrapolated (dotted line). More recently, the measurements by Radonic *et al*[8] suggested a curved relationship with no patients reaching 38 mm or more (red line). Modified from Roman *et al*[7] and Radonic *et al*.[8]

Box 5 Current recommendations for invasive management based on the current revised Ghent nosology (Ghent)[3] and/or the current European Society of Cardiology (ESC) guidelines[12]

Recommendations for invasive management

Dissections

- Type A dissection: Emergency surgery (Ghent)
- Type B dissection: Medical management. Possible indications for surgery: intractable pain, limb or organ ischaemia, an aortic diameter exceeding 5.5 cm, or a rapid increase in the aortic diameter (Ghent)

Prophylactic surgery

- Patients should undergo surgery when aortic root maximal diameter is:

>50 mm (Ghent, ESC)

46–50 mm with family history of dissection or progressive dilation >2 mm/year or severe aortic regurgitation (AR) or mitral regurgitation (MR) or desire of pregnancy (Ghent, ESC)

- In small individuals, the use of an indexed diameter adjusted for body surface area of 2.75 cm/m^2 should probably be used for operative decision making (ESC)
- Patients should be considered for surgery when other parts of the aorta >50 mm or when dilation is progressive (ESC)

Endovascular therapy

- Endovascular stent grafting of the descending thoracic aorta in patients with Marfan syndrome is not recommended unless the risk of conventional open surgical repair is deemed prohibitive (Ghent, ESC)

effect of losartan.[16] Further studies will be needed before definite recommendations regarding the use of ARBs in MFS can be provided.

INVASIVE MANAGEMENT

Earlier recommendations[w20] advised prophylactic surgery with aortic root diameters of 45 mm in all MFS patients. More recently it has been shown that a steep (fourfold) increase in the risk of an event (death/dissection) exists at 50 mm. The event rate was 1.33% with diameters of 50–54 mm and only 0.3% with diameters of 45–49 mm. Event rates at diameters <50 mm were even lower when pregnant patients or those with neonatal MFS were excluded.[w21] Current guidelines now recommend a threshold of 50 mm. A family history of early dissection, a rapid progression of dilatation (2 mm or 5 mm, respectively), significant aortic or mitral valve disease, and a desire for pregnancy reduce this to 45 mm (box 5).

In our experience the criterion of rapid progression is especially vulnerable to error. We advise to always analyse current and older imaging data in a standardised manner (figures 2–4) to exclude flaws from skewed measuring planes or suboptimal image quality.

Both the ACCF/AHA and the ESC guidelines suggest alternative indexed thresholds for shorter patients. The revised Ghent nosology suggests a threshold for the descending aorta of 55 mm.

Surgery

The composite graft (Bentall procedure) with a mechanical valve connected to an aortic prosthesis used to be the gold standard for surgery of the dilated aortic root. With MFS patients being quite young at their first operation the necessity for life-long anticoagulation was increasingly criticised. In attempts to preserve the aortic valve and restore function by aortic root repair, valve sparing operations were developed. The David's procedure with sparing of the valve, root replacement by a prosthesis, and reimplantation of the coronary arteries has since become the standard in many centres whenever there is a morphologically normal aortic valve and aortic root dilatation is the reason for regurgitation.

In an earlier series on use of the David procedure in 59 MFS patients, up to 20% of reoperations after 10 years were described,[w22] raising concern about the durability of the repair. In a meta-analysis published by Benedetto *et al*[17] in 2011, valve sparing root replacement (VSRR, 413 patients) was compared with total root replacement (TRR, 972 patients). In this study the re-intervention rate in VSRR was found to be only 1.3%/year. This rate was even lower in the TRR group (0.3%/year). On the other hand, the rate of thromboembolic events was higher in the TRR group (0.7%/year vs 0.3%/year). Finally, in a recent publication by David *et al*[w23] on their results of VSRR in a mixed population of 296 patients (only 36% MFS), the freedom from reoperation was 97.8% at 10 and 15 years, and the freedom from moderate to severe aortic regurgitation was 92.9% and 89.4% at 10 and 15 years, respectively. Of note, the presence of MFS appeared to lower the risk of aortic regurgitation, but these patients were significantly younger. Group differences in the retrospective trials, strict patient selection, and finally improvement of surgical technique over time may have contributed to these positive results.

Endovascular management

With prophylactic or emergency operations of the dilated aortic root, more MFS patients survive until they eventually experience complications at sites distal to the aortic root. The distal aorta has been reported to be the site of a first event (dissection or prophylactic operation) in up to 18% of MFS patients.[w24] Endovascular treatment has emerged as an effective treatment of descending aortic aneurysms and type B aortic dissections in non-Marfan patients. But there has been some concern, primarily based on pathophysiologic considerations and sparse reports, that this approach may not be suitable for MFS patients. Definitive data are lacking. Not surprisingly, current guidelines recommend

against routine endovascular stenting of the descending aorta in MFS patients and prefer open surgery if possible.

A systematic review has now compiled the results of 54 MFS patients who underwent endovascular stent grafting due to aortic dissection. Periprocedural mortality was low (1.9%) compared to published data on patients without MFS. However, the incidence of periprocedural endoleaks was about 2–3 times higher (21.6%) than published incidences in meta-analyses and registry data of non-MFS patients. The problem of endoleaks seemed to persist at an average follow up of 2.5 years, and the need for re-interventions or surgical conversions was high. Finally, a high mortality rate of 12% at follow-up was found, leading to the conclusion that the overall results were less than optimal.[18] Due to the lack of comparative studies with conservative medical therapy or open surgical repair, this study is not able to give advice on the optimal strategy to pursue. The alarming results shown here support the notion that endovascular treatment should only be performed after very careful patient evaluation on an individual basis.

LIFESTYLE RESTRICTIONS

Static physical exercise—especially involving Valsalva manoeuvres—is associated with a pronounced increase in systemic blood pressure[w25] and aortic wall stress.[w26] Clinically, case series suggest an association between weight lifting and aortic dissections[w27] in predisposed patients. Current guidelines advise against exercise to exhaustion and contact sports, as well as any activities involving Valsalva manoeuvres in MFS patients.

MANAGEMENT OF PREGNANCY

Due to an increased risk of cardiovascular complications, pregnant women with MFS should be followed closely. In a recent study by Donnelly *et al*[19] a pregnancy was associated with an increase of aortic root diameters by a mean of 3 mm. After delivery the progression rate decreased but stayed elevated, leading to an increased rate of prophylactic root surgery. One hundred and ninety-nine pregnancies in MFS women with root diameters <45 mm were followed. While an increase in other cardiovascular complications was noted, no aortic dissections or deaths occurred.

According to current recommendations, an aortic root diameter >45 mm before a planned pregnancy is an indication for prophylactic surgery. In pregnant women with these diameters a caesarean section should be the preferred mode of delivery.

PREDICTING THE COURSE OF DISEASE

Surveillance of aortic diameters and assessment of the rate of progression are currently the mainstay of risk prediction. In this regard rapid progression mandates earlier prophylactic surgery.[12] MFS patients are also at risk for valvular and myocardial involvement as well as arrhythmia. Recently a number of attempts have been made to identify further markers of disease severity and prognosis.

A bicuspid aortic valve (BAV) is a common abnormality in the general population, with a prevalence between 0.5–1.3%.[w28 w29] The condition is associated with valvular dysfunction as well as aortic dilatation and dissection. In this respect the presence of both BAV and MFS may influence progression of aortic dilatation. Results of a recent study by Nistri *et al*[w30] suggest a higher prevalence of BAV in patients with MFS (4.7%), as well as a more severe involvement of the aorta with a higher percentage of aneurysms requiring surgical interventions.

Parameters of arterial stiffness predict clinical events in a number of cardiovascular conditions. Augmentation index—a parameter of arterial stiffness non-invasively acquired by applanation tonometry—has been shown to independently predict progression of aortic root disease. During a mean follow-up of 22±16 months, lower values of augmentation indices and pulse wave velocity (PWV) were associated with a more stable course of disease.[w31] With velocity encoded MRI, regional sampling of aortic stiffness through PWV assessment is possible. In a recent study regional PWV was found to be increased in MFS patients in almost all aortic segments as compared to healthy volunteers. After a follow-up of 2 years the sensitivity of increased regional PWV for the prediction of intraluminal growth was ≤33% while the specificity was ≥78%, suggesting only a complimentary prognostic value.[w32]

An increased TGF-β activation plays a crucial role in the pathophysiology of aortopathy in MFS. In a recent study including 99 MFS patients prospectively followed for 38 months, TGF-β was proposed as a prognostic biomarker in MFS. Not only were TGF-β values significantly increased as compared to healthy controls, but they correlated with larger aortic diameters and a faster aortic root growth rate. Patients with TGF-β values above a cut-off of 140 pg/mL had a 6.5 times higher risk of reaching the composite endpoint of aortic dissection and prophylactic aortic root surgery.[20]

Although aortic dilatation is the most evident cardiovascular manifestation of MFS, involvement of the myocardium with ventricular dilatation, decreased left ventricular function, and sudden cardiac death have been described.[w33] In a prospective cohort study (n=77), parameters of transthoracic echocardiography, 12 lead resting ECG, signal averaged ECG, Holter ECG, and N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations were analysed for their value in predicting sudden cardiac death, ventricular tachycardia, ventricular fibrillation, and arrhythmogenic syncope during a follow-up of 2.3 years. Upon multivariate Cox analysis, NT-proBNP emerged as the only independent predictor of the composite endpoint (HR 2.34).[w34]

SUMMARY

MFS is a connective tissue disease that is associated with decreased life expectancy mainly because of aortic complications. Early diagnosis, medical

Diagnosis and treatment of Marfan syndrome: key points

Diagnosis
- Diagnosis is currently based on the revised Ghent nosology of 2010.
- It requires a comprehensive clinical examination as well as multiple imaging modalities.
- Genetic testing may help to make the diagnosis and exclude ~~important~~ other disease entities.
- The use of z-scores may overestimate normal values, especially with increased weight or height.

Imaging
- Serial imaging of the aorta by annual transthoracic echocardiography enables the aortic root to be monitored.
- MRI and CT are important to visualise the entire aorta at regular intervals.
- Double oblique measurements are essential for an exact assessment.

Medical management
- Early medical treatment has the goal of delaying the progression of aortic dilatation.
- Currently β-blocker treatment is still considered the gold standard.
- The first prospective randomised trial of losartan treatment showed encouraging results.

Surgery
- Prophylactic surgery has greatly improved outcomes of the disease.
- Valve sparing root surgery is currently considered the standard of choice.
- Endovascular treatment has shown suboptimal results and is not routinely recommended.

Prognosis
- TGF-β values and measurement of aortic stiffness may help to estimate the risk of progression.

treatment to delay the progression of aortic dilatation or possibly halt the pathologic process in the aortic wall, as well as timely elective surgery are the key measures to improve the outcome of this disease.

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The revised Ghent nosology tried to simplify the diagnosis and at the same time improve its accuracy. It puts more weight on genetic testing. This approach appears more feasible now, with next generation sequencing making testing faster and more affordable. Nevertheless, controversial issues remain such as the use of z-scores for the definition of aortic dilatation.

Current standards of imaging modalities have improved the precision of aortic dimension measurements and the follow-up of its potential progression.

While β-blockers with their solely haemodynamic effects still represent the standard medical therapy, ARBs may directly interfere with the pathologic process in the vessel wall. Results from the first randomised trial appear to support this concept.

Surgical therapy has improved, but the optimal timing of intervention remains a matter of controversy. Current guidelines recommend surgery when root diameter exceeds 50 mm. Intervention should, however, be considered with a diameter of 45 mm when certain risk factors are present.

Further progress—particularly with regard to medical treatment, genetic aspects and prognostic markers—can be expected in the near future.

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