

# Marfan Syndrome: Diagnosis And Workup Of Cardiac Manifestations

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## Abstract

### INTRODUCTION

The prevalence of classic Marfan Syndrome (MS) is about 5 per 100,000, without gender, racial, or ethnic predilection. Because of the great heterogeneity of the syndrome, the actual prevalence may be considerably greater, probably about 1 per 10,000. MS has an autosomal dominant inheritance with high penetrance. In about 25 to 30 percent of patients, the disorder occurs without a positive family history and appears to be due to a new mutation.

MS is associated with defects in the fibrillin-1 gene (FBN1) on chromosome 15, where 125 reported and unreported mutations (of several types) have been described. Nearly every genotyped family has a unique mutation in the fibrillin genes, with the most common single mutation identified in just four unrelated pedigrees. This intragenic heterogeneity and the large size of the gene have precluded the routine screening of mutations to establish the diagnosis of the MS.

### DIAGNOSIS

Cardiovascular system: Cardiovascular involvement is the most serious problem associated with Marfan syndrome.

Major cardiovascular system criteria are as follows:

- Dilation of the ascending aorta with or without regurgitation
- Dissection of the ascending aorta

Minor cardiovascular system criteria are as follows:

- Mitral valve prolapse with or without regurgitation
- Dilatation of main pulmonary artery in the absence of valvular or peripheral pulmonic stenosis

- Calcification of the mitral valve annulus in patients younger than 40 years
- Dilatation or dissection of the descending thoracic or abdominal aorta in patients younger than 50 years

For cardiovascular system involvement to be considered diagnostic criteria, only one of the major or minor criteria must be present.

### WORKUP

Molecular studies of the fibrillin gene can be obtained in cases in which Marfan syndrome is suggested. The role of molecular genetics testing in the sporadic case is minor. In general, the diagnosis is made on a clinical basis using the Berlin criteria.

Imaging of the skeletal system and ophthalmologic evaluation is suggested and is out of the scope this article.

### CARDIOVASCULAR SYSTEM.

The electrocardiogram represents the best initial screening test for cardiac dysfunction in MFS, as greater than 80% of the patients have cardiac dysfunction over the course of their lives. Common findings on ECG include T-wave inversions (mitral valve prolapse) and development of anterior electrical forces across the precordial leads (pectus excavatum or cardiomegaly with leftward heart shift).

Once the electrocardiogram shows abnormal findings in the patient with MFS the echocardiogram or MRI is usually the next modality used to elucidate any clinically significant structural abnormalities. Aortic root enlargement typically occurs near the sinuses of Valsalva, although the ascending aorta and more distal aspect of the aorta may be involved

(associated with a worse overall prognosis).

Once an echocardiogram or MRI is obtained, the patient's results can be compared with body size using nomograms appropriate for the patients' age. In patients with MFS, the risk of developing aortic regurgitation is directly related to the overall size of the aortic root. In patients with roots less than 40 mm in diameter, the risk of developing aortic regurgitation is remote; however, in patients with roots greater than 60 mm, the aortic regurgitation is almost always present. Mitral valve prolapse also may be detected via echocardiographic analysis

### **TREATMENT**

#### **MEDICAL MANAGEMENT OF AORTIC DILATION**

Asymptomatic patients with mild to moderate aortic root enlargement require medical therapy, serial imaging and aggressive blood pressure control. Beta-blocker therapy preferred. In older children and adults, goal is to keep resting heart rate less than 70 and heart rate after sub maximal exercise less than 100. Use of long-acting medications (optimal for compliance) or divided doses helps maximize benefit and minimize symptoms at peak blood level. Other antihypertensive agents including calcium antagonists and angiotension-converting enzyme inhibitors, or angiotension receptor blockage (ARBs) can be used if beta blockade is medically contra-indicated, poorly tolerated, or additional blood pressure control required. Serial imaging is recommended every six months until stability of aortic size is documented, with annual imaging thereafter. Persons with an established descending or abdominal aortic dilation or dissection require aggressive blood pressure control and frequent imaging to document stability/instability of aorta.

#### **SURGICAL MANAGEMENT OF AORTIC DILATION**

Prophylactic resection of dilated ascending aorta is done when a certain "size threshold" is reached. Determination of "size threshold" in Marfan syndrome needs to be considered in totality, for example a patient with a family history of dissection may need surgery when dilation is 4.5 to 5 cm. One cannot predict the natural history of an individual's aortic disease in the Marfan syndrome. The larger the aortic root, the higher the risk of aortic dissection. In general, when the aortic dimension is greater than or equal to 5 cm, prophylactic aortic root replacement is recommended. Surgery is considered when aorta is 4.5-5 cm. especially if valve-sparing procedure is to be an option. Other factors which may significantly influence timing of aortic surgery

include rate of growth greater than 0.5 cm per year, presence of significant aortic regurgitation (AR), or worsening AR over time and family history of dissection, especially if dissection occurred at aortic dimension less than or equal to 5 cm. Prophylactic aortic root replacement carries a risk of 1 to 2% operative mortality. Surgical options include composite valve graft, valve-sparing procedure and bio-prosthetic/tissue valve. Composite valve graft has excellent durability but carries the risks of anticoagulation, thromboembolism, and endocarditis. Valve-sparing procedures are available for most patients if the aortic valve is functioning normally. Risk of possible re-operation in future, as long-term durability of repair is not known. Beta-blocker should be continued after surgery indefinitely. After repair of ascending aorta, one must follow the distal aortic segments over time for late-onset aneurysm formation. Post-operative patients require endocarditis prophylaxis.

#### **ENDOVASCULAR STENT-GRAFTING OF THE AORTA**

Data on stent-grafts in patients with MFS or other related connective tissue diseases (RCTDs) is very limited. Therefore, there is insufficient information available to guide decisions regarding its safety and efficacy in these conditions. MFS and RCTDs remain a contraindication for stent-graft repair in all investigational device exemption protocols.

#### **MANAGEMENT OF AORTIC DILATION IN CHILDREN**

Beta-blockers are prescribed either at time of diagnosis or upon documentation of aortic enlargement. In children less than 5 years of age the goal is to keep resting heart rate less than 80 and heart rate after exercise less than 110. Careful monitoring of dose is necessary during rapid body growth. Reduced or divided dosing or substitution with a calcium channel blocker, ARB or ACE-I can be considered when complications due to aggravation of asthma or lethargy-induced interference with learning are associated with beta-blockers.

#### **SURGICAL MANAGEMENT FOR CHILDREN**

Both composite graft repair and the valve-sparing procedure have shown good results. Rapid rate of growth of the ascending aorta (>1 cm per year) is widely used as an indication for surgical intervention in the pediatric population. Other indicators include new aortic regurgitation or the need for mitral valve surgery in an individual with substantial aortic enlargement. Adolescents should use adult

criteria when assessing need for surgery.

### MANAGEMENT OF PREGNANT WOMEN

All pregnancies should be considered high risk and multi-disciplinary evaluation is required (cardiologist and high risk obstetrician). Risk of dissection is lower if the aortic root diameter is less than 4.0 cm. Beta-blockers should be continued during pregnancy and continued after delivery because of heightened risk of dissection post-partum. Echocardiograms are recommended during each trimester of pregnancy and once during the two months following pregnancy. If possible, surgical repair of significant aortic root dilation should be done pre-partum.

### ACTIVITY/LIFESTYLE MODIFICATIONS

Competitive and collision contact sports are contraindicated. Static (isometric) exercise contraindicated (avoid weight lifting, gymnastics and pull-ups). Certain dynamic (isokinetic) exercise at decreased level of intensity is permitted with individualized heart rate. Exercise should be individually determined with particular attention to variation in intensity, even in the same type of activity, among different people. Endocarditis prophylaxis is required for patients with valvular heart disease.

### EVALUATION OF FIRST DEGREE-RELATIVES

Screening of all first-degree relatives of people with Marfan syndrome, bicuspid aortic valve or familial thoracic aortic aneurysm and dissections is warranted because of genetic predilection for aortic root aneurysm.

### PROGNOSIS

Recent strides in the management of the cardiovascular

manifestations of MFS have led to a significant decrease in morbidity and mortality. Prior to the advent of pharmacologic and surgical therapy for aortic root and valvular disease, the life expectancy for patients with MFS was about two-thirds that of the healthy population. Aortic dissection and congestive heart failure due to aortic and mitral valvular anomalies accounted for over 90% of known causes of death. Patient longevity now approaches that of persons without Marfan syndrome, although cardiovascular compromise is still the most common cause of patient death, likely due to sudden death in the previously undiagnosed patient and new diagnosis in those whose disease process has progressed beyond the scope of medical or surgical cure

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