Marfan Syndrome - 2009.

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Cardiac and circulatory abnormalities

The most important complications of Marfan are those affecting the heart and major blood vessels; some are potentially life-threatening. About 90% of Marfan patients will develop cardiac complications.

- **Aortic enlargement.** This is the most serious potential complication of Marfan syndrome. Because of the abnormalities of the patient's fibrillin, the walls of the aorta (the large blood vessel that carries blood away from the heart) are weaker than normal and tend to stretch and bulge out of shape. This stretching increases the likelihood of an aortic dissection, which is a tear or separation between the layers of tissue that make up the aorta. An aortic dissection usually causes severe pain in the abdomen, back, or chest, depending on the section of the aorta that is affected. Rupture of the aorta is a medical emergency requiring immediate surgery and medication.
- **Aortic regurgitation.** A weakened and enlarged aorta may allow some blood to leak back into the heart during each heartbeat; this condition is called aortic regurgitation. Aortic regurgitation occasionally causes shortness of breath during normal activity. In serious cases, it causes the left ventricle of the heart to enlarge and may eventually lead to heart failure.
- **Mitral valve prolapse** Between 75 and 85% of Marfan patients have loose or "floppy" mitral valves, which are the valves that separate the chambers of the heart. When these valves do not cover the opening between the chambers completely, the condition is called mitral valve prolapse. Complications of mitral valve prolapse include heart murmurs and arrhytymias. In rare cases, mitral valve prolapse can cause sudden death. Delayed repolarization, especially when combined with mitral valve prolapse, is associated with occurrence of ventricular dysrhythmia. Serious ventricular dysrhythmia can occur in children with

Marfan's syndrome with or without substantial valve disease, and the dysrhythmia appears to progress with age.

- **Infective endocarditis.** Infective endocarditis is an infection of the endothelium, the tissue that lines the heart. In patients with Marfan, it is the abnormal mitral valve that is most likely to become infected.
- **Counseling for pregnancy** (**von Kodolitsch Y, Robinson PN. Marfan syndrome: an update of genetics, medical and surgical management. *Heart*. Jun 2007;93(6): 755-60**.
  - Fifty percent risk for transmitting a pathogenic mutation to offspring
  - High-risk pregnancy with aortic root diameter of more than 40 mm or previous cardiovascular surgery or severe heart disease
  - Prepartum aortic root replacement with diameters of more than 40 mm
  - Serial echocardiography until 3 months postpartum
- Beta-blockers
  - Beta-adrenergic receptor antagonists have gained acceptance as potential agents for delaying aortic expansion and for delaying the progression to rupture or dissection.
  - The rate of surgical interventions has substantially declined during the past decade of beta-blockade use.
  - Beta-blocker therapy retards aortic growth in children and adolescents with Marfan syndrome.
  - A recent study concluded that data are not sufficient to recommend or discourage the use of beta-blockers in children with congestive heart failure **[Best Evidence] Frobel AK, Hulpke-Wette M, Schmidt KG, Laer S. Beta-blockers for congestive heart failure in children. *Cochrane Database Syst Rev*. Jan 21 2009;CD007037**
  - Calcium antagonist therapy also retards aortic growth, but a recommended dose has not been established.
  - The optimal age to begin beta-blockade therapy has not been determined. Some investigators begin therapy during infancy, but others wait until the aortic diameter

exceeds the 95th percentile or a rapid rate of dilation is observed.
    - In asymptomatic patients, the elastic properties of the aortic root appear to have a heterogeneous response after long-term treatment with atenolol.
    - The stiffness index and distensibility are most likely to be useful when the baseline end-diastolic aortic root diameter is more than 40 mm.
    - More experience is needed to determine the optimal dose of beta-blockers to minimize growth of the aortic root.
- ACE inhibitors (**Williams A, Davies S, Stuart AG, Wilson DG, Fraser AG. Medical treatment of Marfan syndrome: a time for change. *Heart*. Apr 2008;94(4):414-21)(Pyeritz RE. Marfan syndrome: 30 years of research equals 30 years of additional life expectancy. *Heart*. Mar 2009;95(3): 173-5**.)
    - ACE inhibitors reduce central arterial pressure and conduit arterial stiffness and may be useful in Marfan syndrome. This approach received support by a short-term, nonrandomized study comparing enalapril with beta blockade in which stiffness and rate of dilatation improved with the ACE inhibitors.[31]
    - Another study of patients with Marfan syndrome maintained on beta blockade examined the impact of adding an ACE inhibitor, perindopril, compared with placebo. Over a 24-week period, those receiving the ACE inhibitor had a reduction in aortic stiffness and less absolute change in aortic root dimensions (**Ahimastos AA, Aggarwal A, D'Orsa KM, et al. Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. *JAMA*. Oct 3 2007;298(13):1539-47**.)
- Matrix metalloproteinases (MMPs)
    - Syndromes that resemble Marfan syndrome, especially in the potential for aneurysm and dissection, were found to be due to mutations in genes encoding *TGF β* receptors.
    - The potential importance of MMPs was stimulated by studies of non-Marfan syndrome abdominal aortic aneurysm in humans and thoracic aortic aneurysm in

mice engineered to have Marfan syndrome, in both of which levels of MMP-2 and MMP-9 were raised.
    - Doxycycline administration to a mouse model of Marfan syndrome suppressed MMPs and improved aortic wall architecture and stiffness compared with atenolol.
    - Marfan's syndrome Conduction disturbances and ventricular arrhythmias have rarely been described in this syndrome. Keidar et al described a case report a patient with symptomatic heart block, prolonged atrial-His interval and ventricular arrhythmia in whom a permanent ventricular pacemaker has been implanted, is described. **Keidar S et al; Heart block in Marfan's syndrome Angiology.1981 Jun;32(6):398-401**
- Other therapy
    - Anticoagulant medications such as warfarin are needed after artificial heart-valve placement.
    - Intravenous antibiotic therapy is required during cardiac and noncardiac procedures to prevent bacterial endocarditis.
    - Progesterone and estrogen therapy have been used to induce puberty and reduce the patient's ultimate height if hormonal treatment is begun before puberty, but no conclusive data are yet available to show whether this therapy reduces scoliosis.
- Future therapeutic strategy
    - The discovery that *TGFβ* antagonism can rescue aortic aneurysm in C1039G/+ mice prompted the idea to test the efficacy of losartan, a widely used angiotensin II type I receptor (AT1) antagonist, because of its antihypertensive properties and ability to counteract TGFβ in animal models of chronic renal disease and cardiomyopathy.
    - Thus, TGFβ antagonism is a general strategy against aneurysm progression in patients with Marfan syndrome and other disorders of the TGFβ-signaling network.
- Genetic counseling
    - Affected individuals can transmit the condition to 50% of their offspring.
    - The recurrence risk is 50% if one parent is affected. The recurrence risk is small if neither parent is affected.

- During counseling, the variability of the disease should be emphasized because an affected child may be more or less affected than the parent.

Surgical Care

- Indications for prophylactic surgery of the aortic root in adults (at least one criterion)(**von Kodolitsch Y, Robinson PN. Marfan syndrome: an update of genetics, medical and surgical management. *Heart*. Jun 2007;93(6):755-60**.
  - Aortic root diameter of more than 55 mm (50 mm according to some authors) and aortic root diameter of more than 50 mm (45–50 mm according to some authors) in patients with high risk for aortic complications
    - Family history for aortic dissection
    - Growth of the aortic root of more than 10 mm/y
    - Dilatation of the aortic sinus involving the ascending aorta
    - More than mild aortic regurgitation
    - Severe mitral regurgitation
    - Before major noncardiovascular surgery
    - Women planning pregnancy
  - Aortic ratio of more than 1.5
  - Ratio of the diameters of the aortic root and the descending aorta of more than 2
- Indications for prophylactic surgery of the aortic root in children
  - If possible, surgery should be delayed until adolescence
  - Aortic root diameters with similar thresholds as in adults
  - Aortic root diameters outside the upper confidence interval deviate upward from the perused centile on follow-up echocardiograms
- Cardiovascular surgery
  - Cardiovascular surgery can substantially prolong survival. Prophylactic and emergency cardiovascular surgery is needed for treatment of aortic and mitral regurgitation, aortic aneurysm, and aortic dissection. Emergency surgical replacement of the aortic root is indicated for survivors of acute proximal aortic dissection.
  - The ascending aorta is usually replaced when the aorta exceeds 55-60 mm in diameter. Composite valve-graft replacement is performed, in which the dilated aortic segment is replaced by a prosthetic valve sewn into a

tube graft with reimplantation of the coronary ostia (modified Bentall procedure). Composite valve-graft replacement of the aortic root has low rates of morbidity and mortality, produces excellent long-term results, and is currently the treatment of choice for proximal dissection or clinically significant annuloaortic ectasia in patients with Marfan syndrome.

- An aortic valve–sparing procedure is evolving for patients with an aortic aneurysm and favorable characteristics of the aortic valve and annulus. The advantages of this procedure include the avoidance of anticoagulation and a lowered risk of thromboembolism and endocarditis. The aortic valve–sparing procedure is still controversial because of concerns that it poses a risk of progressive valvular degeneration and annular dilation. Additional long-term data are required before routine use of this procedure can be recommended