Anatomical and functional evaluation of the cardiovascular system in Marfan syndrome
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Chapter
Summary

Adapted from: What is new in the Marfan syndrome?

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Introduction

The Marfan syndrome is an autosomal dominant disorder of connective tissue, caused by mutations in the *FBN1* gene on chromosome 15q21 encoding a large glycoprotein called fibrillin-1, a main component of extracellular microfibrils found in a wide range of tissues. The Marfan syndrome is characterised by highly variable clinical manifestations in primarily skeletal, ocular and cardiovascular organ systems. Prevalence has been estimated at 2-3 per 10,000 and about 25-30% of cases represent new mutations. Prognosis is mainly determined by progressive dilatation of the aorta, potentially leading to aortic dissection and death at young age. Prophylactic surgery and treatment with b-adrenergic blocking agents have improved life expectancy substantially, from 47 years in 1972 to 61 years in 1995. Early identification of patients with Marfan syndrome is therefore of considerable importance.

Genetics

Marfan syndrome is the result of mutation in the *FBN1* gene (Figure 1). More than 500 mutations have been identified and almost all are unique to an affected individual or family. *FBN1* consists of 65 exons, with almost every domain of fibrillin-1 being encoded by an individual exon. The locations of the mutation are spread throughout the *FBN1* gene. The majority of mutations are missense mutations (about two-thirds of all *FBN1* mutations) that alter a single amino acid out of the 2,871 amino acids that constitute the protein. Most of these missense mutations occur in EGF-like domains and are predicted to disrupt calcium binding and/or the secondary structure of the domain. About 20% of all reported mutations cause a frameshift with a downstream premature termination codon and approximately 12% of all mutations found to date are splice site mutations.

Genotype-phenotype correlations in the Marfan syndrome have been complicated by the large number of unique mutations reported, as well as by clinical heterogeneity among individuals with the same mutation. At present it is still not possible to find a mutation

![Figure 1 Schematic representation of the domain organization of fibrillin-1](image-url)
in approximately 20% of the patients with a definite diagnosis of Marfan syndrome\textsuperscript{15}. Moreover, mutations in the \textit{FBN1} gene have also been found in patients with other fibrillinopathies. Some associations have emerged, however. Skipping of exons 24-32 correlates with the most severe, neonatal forms of Marfan syndrome\textsuperscript{16,17,18}. Mutations that change a cysteine residue or a residue that is crucial for calcium binding in one of the cbEGF-like domains usually cause classic Marfan syndrome\textsuperscript{19,20}. A significant subset of mutations located in exons 59–65 (the last seven exons of \textit{FBN1}) seem to be associated with mild phenotypes\textsuperscript{21}.

In Chapter 8, we investigated whether type or location of the \textit{FBN1} was associated with aortic stiffness assessed by magnetic resonance (MR) imaging. Thirty novel \textit{FBN1} mutations were detected. There was no association between \textit{FBN1} genotype and aortic stiffness. This is similar to other known poor genotype-phenotype associations in patients with Marfan syndrome. The study provides further evidence that type or location of the \textit{FBN1} mutation do not influence phenotypic severity; other modifiers of phenotypic expression must be implicated, which is subject for further studies. Hutchinson et al. suggested that differences in normal \textit{FBN1} expression could contribute to the clinical variability seen in families with Marfan syndrome, and should be considered as a potential modifier of phenotype\textsuperscript{22}.

Until recently, three models of the pathophysiology of Marfan syndrome have been proposed. Initially, a dominant negative model of pathophysiology was hypothesized, in which the mutant fibrillin monomer disrupts assembly of normal fibrillin-1 into microfibrils or is itself misincorporated into the microfibrils\textsuperscript{23}. The level of mutant protein modulates the severity of the disease. Two other models are disturbance of tissue homeostasis of elastic fibers, and increased susceptibility of fibrillin to proteolysis\textsuperscript{24,25}.

Recently in a study by Neptune et al. a fourth model of pathophysiology has been proposed\textsuperscript{26}. It was shown that mice deficient in fibrillin-1 had marked dysregulation of transforming growth factor-\(\beta\) (TGF-\(\beta\)) activation and signaling, resulting in apoptosis in the developing lung. Perinatal antagonism of TGF-\(\beta\) attenuated apoptosis and rescued alveolar septation \textit{in vivo}.

This pathogenetic mechanism might also underlie other manifestations of Marfan syndrome, including myxomatous changes of valve leaflets and bone overgrowth. If this model could be confirmed in humans, some pathologies might become amenable to perinatal treatment.
Table 1. Diagnostic Criteria for Marfan's Syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>Independent diagnosis in parent, child, sibling</td>
<td>None</td>
</tr>
<tr>
<td>Genetics</td>
<td>Mutation FBN1</td>
<td>None</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Aortic root dilation</td>
<td>Mitral valvar prolapse</td>
</tr>
<tr>
<td></td>
<td>Dissection of ascending aorta</td>
<td>Calcification of the mitral valve( &lt; 40 yrs.)</td>
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<tr>
<td></td>
<td></td>
<td>Dilation pulmonary trunk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dilation/dissection of descending aorta</td>
</tr>
<tr>
<td>Ocular</td>
<td>Ectopic lens</td>
<td>(4 needed):</td>
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<tr>
<td></td>
<td></td>
<td>Flat cornea</td>
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<tr>
<td></td>
<td></td>
<td>Myopia</td>
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<td></td>
<td></td>
<td>Elongated globe</td>
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<td></td>
<td></td>
<td>(2 needed):</td>
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<td></td>
<td></td>
<td>Moderate pectus excavatum</td>
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<tr>
<td></td>
<td></td>
<td>High narrowly arched palate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Typical face</td>
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<td></td>
<td></td>
<td>Joint hypermobility</td>
</tr>
<tr>
<td>Skeletal</td>
<td>(4 needed):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pectus excavatum needing surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pectus carinatum</td>
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<tr>
<td></td>
<td>Pes planus</td>
<td></td>
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<tr>
<td></td>
<td>Wrist and thumb sign</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scoliosis &gt; 20 ° or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spondylolisthesis</td>
<td></td>
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<tr>
<td></td>
<td>Arm span-height ratio &gt; 1.05</td>
<td></td>
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<tr>
<td></td>
<td>Protrusio acetabulae (xray, MRI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diminished extension elbows (&lt; 170 °)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td>Spontaneous pneumothorax</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>Apical bulla</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Lumbosacral dural ectasia (CT or MRI)</td>
<td>Unexplained stretch marks (striae)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent or incisional hemiae</td>
</tr>
</tbody>
</table>

Because of the intragenic heterogeneity molecular genetic screening is hampered to a considerable extent, and diagnosis is still based mainly on clinical major and minor features, as defined by a multidisciplinary council of experts in the field, known as the Ghent nosology\(^{13}\) (Table 1).

In the Ghent nosology, dural ectasia was added to the major criteria for Marfan syndrome. In a recent study, quantitative criteria for dural ectasia were established using MR imaging\(^{27}\). Dural sac - vertebral body ratio was calculated at all lumbosacral levels from L1 through S1. A dural sac - vertebral body ratio at L3 > 0.47 or at S1 > 0.57 could identify Marfan syndrome with 95% sensitivity and 98% specificity. No other major criterion reaches the sensitivity and specificity of dural ectasia for Marfan syndrome.

Cardiovascular manifestations
The most common cardiovascular manifestations of Marfan syndrome include mitral valve prolapse and regurgitation, but aortic dilatation, especially of the aortic root, is the most common cause of morbidity and mortality. Dilatation of the sinus of Valsalva is
found in 60-80% of adults with Marfan syndrome. Elastic fibers, composed of elastin deposited in microfibrils, are relatively more prevalent in the ascending aorta than in any other region of the arterial tree. This biochemical feature, coupled with the repetitive stress of left ventricular ejection, probably accounts for aortic dilatation usually occurring primarily in the aortic root. The rate of dilatation is heterogeneous and unpredictable. Beta-blockers have been shown to reduce the rate of aortic dilatation and to improve survival in patients with Marfan syndrome during a follow-up of more than 10 years. Echocardiography in the parasternal long-axis view is mostly used for measurement of the aortic root. MR imaging is particularly useful for imaging of the entire aorta, for patients with dysformed chest wall and asymmetrically aortic roots.

A relatively unknown cardiovascular manifestation of Marfan syndrome is dilatation of the main pulmonary artery (Chapter 2). Normal values for the pulmonary artery root have been established recently. Of 50 patients with Marfan syndrome, MR imaging showed in 37 (74%) patients an enlarged pulmonary artery root above the upper limit of normal, 34.8 mm. Dilatation of the pulmonary artery was more prominent in the root than in the distal main pulmonary artery, similar to the dilatation process in the aortic root in patients with Marfan syndrome. There was a good correlation between pulmonary and aortic root diameter, indicating that pulmonary root dilatation seems to increase with progressive involvement of the cardiovascular system. Until now, pulmonary artery aneurysm and dissection are rare, but they may become of more clinical relevance in the near future because of increased longevity in patients with Marfan syndrome.

In Chapter 3, we reported about measurement of dimensions of the pulmonary artery using a simple spin echo (SE) MR imaging-technique (Axial SE-MRI). We compared these data with contrast enhanced MR-angiography (CE-MRA) and found approximately equal values with both techniques. We concluded that SE-MRI is a simple and reliable method to measure pulmonary artery dimensions in patients with Marfan syndrome, which could very well be used for follow-up. Besides, a slight asymmetry in the pulmonary artery root was detected.

Although not included in the diagnostic criteria for Marfan syndrome, it has been speculated that a fibrillin defect in the myocardium may predispose patients with Marfan syndrome to LV dilatation and reduced LV function. Recently, in a study of 36 patients with Marfan syndrome without significant valvular regurgitation, LV dimensions were found within the normal range. No abnormal change in LV dimension was observed during an average follow-up period of 10.8 years. Mean ejection fraction was 60±4% (range 50% to 69%) and there was no change in ejection fraction over time. The authors
concluded that LV dilatation and dysfunction do not occur in most patients with Marfan syndrome in the absence of important valvular regurgitation.

Aortic stiffness
The risk of aortic dissection rises appreciably with increasing aortic size, but it may occur at any point in the course of the disease\textsuperscript{36,39}. As an additional potential predictor for aortic dissection noninvasive aortic stiffness has been investigated in patients with Marfan syndrome\textsuperscript{40,41,42}.

![Figure 2](attachment:image)

Three-dimensional MR imaging of the entire aorta. Levels for distensibility measurements are indicated with solid lines. Flow wave velocity between these levels was calculated.

Groenink et al. demonstrated decreased aortic elasticity (=increased aortic stiffness) determined by measurement of local distensibility and flow wave velocity with MR imaging in non-operated patients with Marfan syndrome\textsuperscript{41} (Figure 2).

After aortic root replacement, both patients presenting with dissection at the time of the operation and electively operated patients with Marfan syndrome deserve intensive attention because aneurysms and dissection of the aorta may develop distal to the site of the graft\textsuperscript{7,43}.

In a population of 117 patients with Marfan syndrome no significant differences in aortic elasticity could be demonstrated between 39 patients with and 78 without aortic root replacement (Chapter 5)\textsuperscript{44}. This agrees with the observation of Finkbohner et al. that the incidence of surgery for aneurysm or dissection in the thoracoabdominal aorta is similar (16\%) in electively operated and non-operated patients with Marfan during a follow-up period of 25 years\textsuperscript{42}. Patients after elective aortic root replacement are probably not at
higher risk for aortic complications in the residual aorta than non-operated patients\textsuperscript{44}.

In \textit{Chapter 6}, we investigated the heterogeneous response to $\beta$-blockade in patients with Marfan syndrome by means of a non-invasive assessed aortic pressure-area curve. This new noninvasive method to derive aortic pressure-area curves showed that most patients with Marfan syndrome had a similar pressure-area curve to control subjects with similar blood pressures. Five patients on $\beta$-blockade showed a transition point in the pressure-area curve, which could play a crucial role in the heterogeneous response to $\beta$-blocking therapy in Marfan patients. We concluded that patients with a transition at low blood pressures may not benefit from $\beta$-blocking agents.

The prognostic significance of aortic stiffness was investigated in a prospective follow-up study of 78 non-operated patients with Marfan syndrome (\textit{Chapter 7}). During a 6-year follow-up, 4 (5\%) of 78 patients developed an aortic dissection (1 type A, 2 type B, and 1 infra-renal dissection). Twenty (26\%) of the 78 patients had progressive aortic root dilatation (mean aortic diameter increase $>1$ mm/year). There were 5 (6\%) patients with progressive descending thoracic aortic dilatation and 6 (7\%) with progressive abdominal aortic dilatation. Multivariate analysis revealed that local distensibility was an independent predictor of progressive thoracic descending aortic dilatation. For progressive aortic root and abdominal aortic dilatation local initial diameter appeared to be the major predictor. This means, that for optimal risk assessment and monitoring of patients with Marfan syndrome, both aortic stiffness and diameter should be assessed.

\textbf{Aortic surgery}

Until recently, composite replacement of the aortic valve and ascending aorta was the standard operation for aortic root aneurysm in patients with Marfan syndrome. Over the past 30 years, composite valve graft has become a low risk operation and a very durable one for these patients. In a recent report by Gott and associates on the results of aortic root replacement in 675 patients with Marfan syndrome, the operative mortality was 1.5\% for elective operations and 11.7 \% for emergency operations\textsuperscript{45}. Five and 10-year survival after aortic root replacement was 84\% and 75\%, respectively\textsuperscript{45}.

Aortic root replacement in patients with Marfan syndrome has been associated with a considerable higher risk of redissection and recurrent aneurysm than in patients with another etiology of aortic disease\textsuperscript{46}. Presence of dissection, either acute or chronic, at the time of first operation is a significant predictor of subsequent repeat aortic operation\textsuperscript{42}. Other risk factors for reoperation are hypertension and smoking\textsuperscript{42}.

For those patients wishing to avoid anticoagulation therapy two types of valve-sparing
operations have been introduced in the early 1990s: reimplantation of the aortic root (David's procedure), and remodelling of the aortic root (Yacoub's procedure)\textsuperscript{47,48}. Either type of valve-sparing aortic root replacement appears to be safe, reproducible, and associated with reasonable 5- to 10-years results for selected patients, at least in institutions with cardiac surgeons who have considerable personal experience with this procedure\textsuperscript{49}. Survival was excellent in a recent report from the Toronto group, although 25% of the patients had severe aortic regurgitation 10 years after valve-sparing aortic root replacement\textsuperscript{50}. The long-term results of valve-sparing aortic root replacement, and the overall incidence of all valve-related and aorta-related complications in large numbers of patients with Marfan syndrome are still unknown.

A relatively unknown postoperative complication, both after aortic valve-sparing operations and after composite aortic valve replacement is coronary ostial aneurysm\textsuperscript{51} (Chapter 4) (Figure 3). In a series of 40 patients with Marfan syndrome who underwent MR imaging 3 months to 19 years after elective aortic root surgery 27 (43%) patients had coronary ostial aneurysms. Coronary ostial aneurysms were more frequently seen in patients \( \leq 35 \) years of age at operation versus those \( > 35 \) years of age. Time after operation, did not influence the prevalence of coronary ostial aneurysms. Therefore, it seems likely that coronary ostial aneurysms are not progressive and develop due to perioperative stretch of the weakened wall of the coronary ostium. Follow-up studies, however, are needed to confirm this.

Over the past 30 years improvement of diagnostic modalities and aggressive medical and surgical therapy, have resulted in considerable improvement of life expectancy of patients with Marfan syndrome.
References


