REVIEW

Marfan's syndrome and the heart

Alan Graham Stuart, Andrew Williams

Arch Dis Child 2007;92:351–356. doi: 10.1136/adc.2006.097469

In recent years, there have been many advances in the treatment of cardiac disease in children with Marfan's syndrome. Early diagnosis, meticulous echocardiographic follow-up and multidisciplinary assessment are essential. Medical treatment with β -blockers is probably helpful in most children with aortic root dilatation. Research on TGF β signalling and the potential treatment role of TGF β antagonists may lead to exciting new treatments, but the results of clinical trials are awaited. In managing the cardiovascular complications of Marfan's syndrome, the paediatrician has to walk a difficult path. On the one hand, restrictive lifestyle advice and drugs may need to be prescribed, often in the context of a family history of major surgery or even sudden death. On the other hand, it is essential to encourage the often asymptomatic child to develop and mature as normally as possible.

is present in many other tissues including lung, dura mater, skin, tendons, ciliary zonules of the lens, myocardium, heart valves and periosteum. Abnormalities in these fibrillin-containing tissues are found in most patients with Marfan's syndrome.

In 1991, mutations in the fibrillin-1 gene (15q21.1) were found to cause Marfan's syndrome.⁵ For many years, this was thought to be the only cause of the Marfan phenotype. In 2005, however, it was reported that mutations in transforming growth factor β (TGF β) receptors 1 and 2 on chromosome 3 caused a vascular phenotype similar to that seen in Marfan's syndrome.⁶ TGF β cytokines have a major role in tissue development and cellular regulation.⁷ A full description of the advances in understanding of genotype-phenotype correlations is beyond the scope of this paper, but excellent up-to-date reviews are available.^{8–10} In summary, it seems that there is a regulatory relationship between extracellular microfibrils and TGF β signalling. An abnormality in either can lead to the development of the Marfan phenotype.

Marfan's syndrome was first described in 1896 by the French paediatrician, Professor Antoine Marfan.¹ He described a 5-year-old girl, Gabrielle, who had the typical phenotype we now associate with this condition. In 1912, Salle described mitral valve abnormalities and heart dilatation in an infant with heart failure, but it was not until 1943 that the typical cardiac abnormalities (aortic dilatation and dissection) were linked to the Marfan phenotype.² Cardiovascular disease accounts for >90% of premature deaths in patients with Marfan's syndrome.³ Over the past few years, there have been important advances in the understanding of the development of Marfan's syndrome, and this has led to the investigation of new therapeutic targets. The incidence, pathophysiology, diagnosis and treatment of the cardiovascular abnormalities that occur in Marfan's syndrome are reviewed in this paper. In particular, the diagnosis and treatment of cardiovascular complications in children with Marfan's syndrome is emphasised.

INCIDENCE AND AETIOLOGY

Marfan's syndrome is an autosomal dominant disorder of connective tissue, which has both high penetrance and variable severity. The incidence of Marfan's syndrome is around 2–3 per 10 000 individuals.⁴ In 25% of individuals there is no family history, which suggests that the condition has presented de novo.

Marfan's syndrome is caused by an abnormality of fibrillin, a 350-kD glycoprotein, which is the main structural component of microfibrils. Microfibrils provide a supporting scaffold for the deposition of elastin throughout the body. Fibrillin

CLINICAL FEATURES

Multiple organ systems are affected, including the skeleton, eyes, heart, lungs and blood vessels. There are several excellent descriptions of the typical features in both adults and children.^{11–13} Marfan's syndrome is diagnosed using the Ghent nosology (table 1), which combines clinical and genetic factors.¹⁴

Marfan's syndrome may be suspected on antenatal ultrasound,¹⁵ but the diagnosis is often not made until late childhood or in adulthood. In the young child, it can be difficult to make a definitive diagnosis. Children often have an evolving phenotype and may need to be followed up for several years before the diagnosis can be confirmed or refuted.¹⁶ All possible cases should be regularly assessed by echocardiography, optometry and skeletal survey as the child grows. A complete family history and assessment of other family members also gives clues to the diagnosis. The American Academy of Paediatrics has produced detailed recommendations for the follow-up of children with Marfan's syndrome, which takes this difficulty into account.¹⁷

"Neonatal" Marfan's syndrome is a severe form of Marfan's syndrome often associated with a deletion in the exon 24–32 region of the fibrillin 1 gene (fig 1). This rare condition differs from the more usual infantile Marfan's syndrome in the

See end of article for authors' affiliations

Correspondence to: Dr A G Stuart, Congenital Heart Centre, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol BS2 8BJ, UK; agstuart@blueyonder.co.uk

Accepted 19 October 2006

Abbreviation: TGF β , transforming growth factor β

Table 1 Ghent diagnostic criteria for Marfan's syndrome. Major Criteria needed in two organ systems and minor criterion in a third system

System	Major criteria	Minor criteria
Family history	Independent diagnosis in parent, child or sibling	None
Genetics	Mutation FBN1	None
Cardiovascular	Aortic root dilatation, dissection of ascending aorta	Mitral valve prolapse, calcification of the mitral valve (<40 years), dilatation of the pulmonary artery, dilatation/dissection of descending aorta 2 needed of the following: flat cornea elongated globe myopia
Ocular	Ectopia lentis	For the skeletal system to be involved 2–3 major, or 1 major and 2 minor signs should be present: moderate pectus excavatum, high arched palate, typical facial features, joint hypermobility
Skeletal	At least 4 of the following: pectus excavatum needing surgery, pectus carinatum, pes planus, positive wrist or thumb sign, scoliosis >20° or spondylolisthesis, armspan-height ratio >1.05, protrusio acetabulae, diminished extension elbows (<170°)	Spontaneous pneumothorax, apical bulla Striae, recurrent or incisional herniae
Pulmonary		
Skin		
Central nervous system	Lumbosacral dural ectasia	

Lumbosacral dural ectasia and protrusio acetabulae are diagnosed using magnetic resonance imaging or a computed tomography scan.

severity of the cardiac and pulmonary manifestations.¹⁸ Infants with the “neonatal” form often have severe mitral and tricuspid regurgitation in addition to aortic root dilatation. Similarly, the usual arachnodactyly and tall stature may be accompanied by ectopia lentis, very loose skin “as if two sizes too big”, emphysema and joint contractures. The cardiovascular features often require surgical intervention in infancy and this may be complicated by scoliosis and pulmonary hypertension. The long-term prognosis is very poor, usually because of progressive valve dysfunction or lung abnormalities.^{18–19}

Recently, an important Marfan-like syndrome has been described: the Loeys Dietz syndrome.²⁰ This is associated with aggressive aortic vascular disease and can be distinguished by the presence of hypertelorism, low-set ears and a bifid uvula or cleft palate. This condition is associated with abnormalities of TGFBR1 and TGFBR2. In comparison with Marfan's syndrome, there is a much higher risk of dissection at a young age, at smaller vessel dimensions and in non-aortic vessels. Genotyping can be used to guide treatment, and most patients tolerate cardiac surgery well.²¹ Other Marfan-like syndromes do exist,²² and this emphasises the importance of regular follow-up and assessment (using the Ghent criteria) of all possible cases of Marfan's syndrome.

CARDIOVASCULAR ABNORMALITIES

Virtually all adults with Marfan's syndrome have an abnormal cardiovascular system. In early childhood, however, the features may be mild and easily missed. The most common cardiovascular abnormalities are dilatation of the aorta and mitral regurgitation (table 2). Most children with Marfan's syndrome have aortic root dilatation. The reported frequency of other valve abnormalities depends to some extent on the rigour of the method of assessment. Moreover, some abnormalities (eg, mitral regurgitation and prolapse) can be intermittent and vary from mild to severe at different times in the same patient. Children with valvular complications are at increased risk of infective endocarditis. Recommendations for antibiotic prophylaxis are changing, but good dental hygiene and early treatment of skin sepsis remain vital. A dilated pulmonary artery is a minor criterion used in diagnosis, but this is of relatively little importance in the paediatric Marfan's population.

Cardiac arrhythmias are an under-recognised cause of morbidity in both children and adults. A link between Marfan's syndrome and Wolff-Parkinson-White syndrome has been postulated, and atrial fibrillation has been reported in children and adults.^{39–40} Minor ECG abnormalities may be

Figure 1 Chest x ray showing scoliosis, mitral valve replacement and cardiomegaly. (A) Chest x ray of a 9-month-old girl with neonatal Marfan's syndrome; (B) the same child aged 4 years old. She had undergone a tricuspid valve repair and mitral valve replacement (note the prosthetic valve ring) and the heart size is smaller. However, the scoliosis has increased. She died from respiratory failure 9 months later.

Table 2 Cardiovascular manifestations of Marfan's syndrome^{11 13 23–38}

Lesion/feature	Symptoms	Frequency	Complications	Comments
Aortic root dilatation	None	60–80% ^{11 28 30 31 37}	Aortic dissection	Dissection rare in children <10 years old
Pulmonary artery dilatation	None	76% ³⁵	Dissection rare	Diagnostic feature in those <40 years old
Mitral regurgitation/prolapse/annular calcification	Palpitations	52–68% ²⁹	Arrhythmias	Regurgitation may be intermittent
	Chest pain dyspnoea		Endocarditis	
Descending aorta dilatation	None		Ventricular dysfunction	
Endothelial dysfunction/abnormal aorta elasticity	None	80–100% ^{32 36}	Aortic dissection	Rare in childhood
			Increased vascular stiffness	May contribute to dissection risk
Tricuspid valve prolapse	None unless severe	4% ³⁰	May progress requiring repair	Severe disease uncommon except in infantile type
Left ventricular dysfunction	Dyspnoea	36% in infantile type ³⁷ Up to 100%	Diastolic. May be progressive to systolic dysfunction	May occur despite normal valves
	Reduced exercise tolerance	Severity varies ^{26 27}		
Arrhythmias	Palpitations	Up to 20–30% ^{23–25}	May cause sudden death	Associated with ventricular dilatation
	Collapse			
Coronary artery aneurysm	Chest pain	<1% ³⁴	Only described in adults	
Atrial septal defect	Myocardial infarction	4% ³⁸	May need surgical repair	More common than in normal population
	None			

present in up to 50% of children with Marfan's syndrome.²³ In addition, ventricular arrhythmias may occur and can lead to sudden death.^{24 25 41} This is not surprising given the extensive fibrillin network that extends throughout the myocardium.²⁶ For the same reason, paradoxical septal motion is common. There is also an important subgroup that has marked left ventricular dysfunction unrelated to valve regurgitation.^{27 42}

ASSESSMENT OF CARDIOVASCULAR SYNDROME

Echocardiography is the mainstay of assessment of children with Marfan's syndrome. Table 3 shows a protocol for cardiovascular assessment. Detailed echocardiographic assessment should include a full study of left ventricular function, aortic root dimensions and intracardiac valves. Structural lesions should be excluded—in particular, atrial septal defect. Each unit should have a standardised protocol for measurement of the aortic root to allow reproducible sequential measurements, which can be plotted against the body surface area (fig 2).⁴³ Normal values are available for aortic root dimensions in children and adults.⁴³ These nomograms have been criticised as they do not reflect the normal aortic root dimensions in tall, slim children in whom Marfan's syndrome has been excluded. Rozendaal *et al*⁴⁴ suggested that an adjusted nomogram derived from tall children without Marfan's

syndrome be used to take this into account. The same group devised a discrimination score that showed that the rate of aortic root growth in children and adolescents with Marfan's syndrome differs from the normal population with a sensitivity and specificity of 84% and 73%, respectively.⁴⁵ Perhaps the most important factor is the need for each echocardiography unit to develop a standardised measurement technique that allows reproducible measurements to be recorded sequentially in comparison to somatic growth. This allows discrimination between normal aortic growth and progressive dilatation and also enables implementation of the appropriate treatment (fig 3).

The pattern of root dilatation should also be noted as diffuse dilatation, with loss of the sinotubular junction is associated with an increased risk of dissection.⁴⁶ In some children it is not possible to fully assess the aorta owing to a poor acoustic window. This may be exacerbated by marked scoliosis. In such a situation, MRI scanning should be used. This has the benefit of allowing an assessment of the lumbar dura. Dural ectasia is present in 40% of children and in >90% of adults with Marfan's syndrome.^{47 48}

The frequency of cardiovascular assessment will depend on the age of the child, the underlying cardiovascular abnormalities and treatment. In general, most children should be assessed every 6–12 months^{12 17}. This may need to be more frequent when starting treatment or if there is a rapid growth phase.

TREATMENT OF CARDIOVASCULAR SYNDROME

General advice

Most authorities advise children and adolescents with Marfan's syndrome to avoid isometric exercise and competitive or contact sports,^{4 49} because of the small risk of aortic dissection on exercise.^{4 50 51} Unfortunately, this advice can occasionally lead to complete avoidance of recreational exercise. Regular exercise has many psychosocial and general health benefits.⁵² Moreover, although studies on Marfan's syndrome have not been performed, regular exercise is known to attenuate poor vascular compliance in conditions such as diabetes and hypertension.^{53 54} Consequently, children with Marfan's syndrome should be

Figure 2 Echocardiographic measurement of aortic root. The aortic root should be measured at the sinus of Valsalva (1), sinotubular junction (2) and ascending aorta (3). Measurements should be plotted against normal values. LA, left atrium; LV, left ventricle.

Figure 3 Sample aortic root growth plot. This shows an idealised graph of sinus of Valsalva measurements plotted over a 6-year period in a child with Marfan's syndrome from a family with a history of aortic dissection. The shaded area represents the normal range.³¹ Point A is when β -blocker therapy was started. At point B the child was referred for aortic root replacement.

encouraged to remain active, and a specific aerobic exercise prescription may be beneficial. Similarly, adherence to a healthy "Mediterranean diet" and avoidance of obesity and cigarette smoking should be recommended, as this may prevent exacerbation of the increased vascular stiffness that occurs in the Marfan aorta.^{55–57}

Owing to its autosomal dominant inheritance, relatives are also at risk from Marfan's syndrome and should be offered medical assessment. Genetic counselling for would-be parents explaining the 50% risk to their child and the potential complications during pregnancy, especially increasing aortic root dilatation, should also be discussed.

The diagnosis of Marfan's syndrome itself, with its increased mortality and morbidity also raises psychosocial issues, and the early involvement of clinical psychologists and support groups such as The Marfan Association UK can help in many cases.

Risk stratification

Risk stratification in children is difficult. In adults, excessive aortic root dilatation (>1.7 mm/year), increased aortic stiffness, aortic root diameter >55 mm^{58, 59} and dilatation at the aortic sinotubular junction⁴⁶ are important risk factors for dissection. A family history of aortic dissection is one of the most important risk factors. The absence of lens dislocation has been reported as a risk factor for aortic dissection, although this may simply reflect delay in diagnosis and treatment.⁵⁸

Medical treatment

There are no large, randomised controlled trials of medical treatment in Marfan's syndrome. Despite this, four categories of drugs have been used to delay or prevent aortic root dilatation: β -blockers, calcium antagonists, angiotensin converting enzyme inhibitors and, most recently, angiotensin-receptor blockers.

β -Blockers

Many small studies have concluded that β -blockade is successful in slowing aortic root growth and improving survival in some children and adults with Marfan's syndrome.^{60–63} Multiple protective mechanisms have been proposed, including a reduction in inotropy, chronotropy and change in aortic pressure over time (dP/dT).⁴ Other studies have suggested that β -blockade may lead to a paradoxical increase in vascular

Table 3 Protocol for cardiovascular assessment of Marfan's syndrome

Clinical assessment	Comment
Weight/height	Allows calculation of body surface area for aortic root nomogram
Auscultation	Ejection click is common if aortic root dilated, mid-systolic click may be present in valve prolapse. Murmurs usually associated with valve regurgitation
Blood pressure	If on β -blocker, calcium antagonist or ACE inhibitor/receptor blocker
Electrocardiogram	12-lead ECG at each visit. Consider ambulatory or event monitor if palpitations
Echocardiogram	Full study every 6–12 months during childhood. Measure LV dimensions and function, pulmonary valve diameter, aortic root diameter. Plot aortic root against body surface area nomogram.

ACE, angiotensin-converting enzyme; ECG electrocardiography; LV, left ventricular.

stiffness in some patients.⁶⁴ In the only randomised trial of β -blockade, 32 adolescents and young adults were treated with high-dose propranolol for 10 years.⁶⁰ In comparison with the control group, fewer patients (5 v 9) reached the clinical end points of aortic regurgitation or dissection, cardiac surgery or death. In addition, there was a slower rate of aortic dilatation in the control group. This study suggested that propranolol was ineffective in patients with increased body weight or aortic dilatation >40 mm, implying that early onset of treatment with an adequate dose is probably important. Interestingly, there were two sudden deaths (without dissection) in the control group, suggesting that propranolol may have an additional protective effect against lethal arrhythmias.

Calcium antagonists

In patients who cannot tolerate β -blockers, calcium antagonists have been suggested as a substitute as they are negative inotropes and also have a vasodilator effect. Rossi-Foulkes *et al*⁶¹ published a small series of 44 children on medical treatment (β -blockers or calcium antagonists) and found that the medicated group had a slower aortic growth rate. However, only six children were taking calcium antagonists. No other studies have been published.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors cause systemic vasodilatation and reduce aortic stiffness.⁶⁵ They can also prevent aortic dissection associated with cystic medial necrosis in an animal model.⁶⁶ In a recent study, Yetman *et al*⁶² compared the effect of enalapril and β -blockade in 58 patients with Marfan's syndrome. Over a 3-year period, enalapril was associated with a smaller increase in aortic root diameter and fewer clinical end points than β -blockade, although the β -blocker dosage may have been suboptimal.

Angiotensin receptor blockade

The most exciting advance in the study of Marfan's syndrome in recent years has been the appreciation that enhanced signalling of TGF β is an integral link in the pathogenesis of the disorder. Losartan, an angiotensin 11 type 1 receptor blocker used in the treatment of hypertension and heart failure, is a TGF β antagonist. In a seminal study by Habashi *et al*,⁶⁷ the administration of losartan to a mouse model of Marfan's syndrome prevented the development of aortic aneurysm and partially reversed the other somatic features. A randomised trial coordinated by the US National Heart, Lung and Blood Institute is now in progress to establish whether this will be effective in humans.

Cardiac surgery

Few children with Marfan's syndrome require cardiac surgery before reaching the teenage years. In the neonatal form, surgery may be necessary to repair or replace the mitral or tricuspid valves and to replace the aortic root.⁶⁸ Outside of infancy, tricuspid valve surgery is rarely necessary, and mitral valve repair or replacement is uncommon in childhood. Tsang *et al*⁶⁸ reported only seven children referred over a 7-year period to a large cardiac surgical centre. Of these, three had the infantile form of the syndrome, two required mitral valve replacements (aged 2 and 7 years, one of whom also underwent tricuspid valve repair) and one aortic root replacement (aged 2 years). The four older children all required aortic root surgery (aged 15, 17 and 18 years).

The traditional form of elective aortic root replacement is the composite (Bentall) graft.⁶⁹ This involves the resection of the aneurysmal portion of the ascending aorta and replacement with a prosthetic valve incorporated in a Dacron tube. More recent alternatives include using a valve-sparing procedure or novel exostent technique. The valve-sparing procedure involves resecting the ascending aorta and replacing it with a sculpted Dacron tube, which sits above the native aortic valve.^{70–71} This has the major advantage of avoiding the need for anticoagulation. Although the aortic valve leaflets are abnormal in patients with Marfan's syndrome, the data on adults suggest that survival is similar to the composite graft, and valve-related complications are lower.⁷² Preliminary results in children suggest that the valve-sparing technique has excellent short-term results, but this is dependent on the precise valve-sparing method used.⁷³ The exostent is a new concept, which involves creating a three-dimensional model of the dilated aorta and producing a computer-designed stent, which is placed on the outside of the dilated root.⁷⁴ This avoids the need for bypass surgery, but prevents any form of growth, thus cannot be used in a young child. Long-term data are awaited. The final option is the use of a human donor aorta (homograft). This has the advantage of avoiding anticoagulation but is complicated by the shortage of homografts and the poor longevity of the graft in young patients.^{75–76}

Perhaps the most important decision is the timing of aortic root surgery. The ideal time to replace the root is "one or two months before it dissects".⁷⁷ Although aortic dissection is rare in childhood, the success of elective replacement (>95% survival) is much lower than if emergency surgery is needed. In adults, it is usually recommended that the root be replaced when the sinus of Valsalva measures 5 cm, although this figure is reduced if there are additional risk factors such as a strong family history of dissection.^{4–78} In older children, most authors recommend root replacement at 5 cm, when enlargement is >1 cm/year or if there is progressive aortic regurgitation.²⁸

Authors' affiliations

Alan Graham Stuart, Congenital Heart Centre, Bristol, UK

Andrew Williams, Sir Geraint Evans Wales Heart Research Institute, Cardiff, UK

Competing interests: AGS is a Medical Advisor to the Marfan Association UK.

REFERENCES

- Marfan AB. Un cas de deformation congenitale des quatre membres, plus prononce aux extremités, caracterise par l'allongement des os avec un certain degre d'amincissement. *Bull Mem Soc Med Hop (Paris)* 1896;**13**:220–6.
- Salle V. Ueber einen fall von angeborner abnormen Grosse der Extremitäten mit einen an Akromegalia erinnernden Symptomenkomplex. *Jahrb Kinderheilk* 1912;**75**:540–50.
- Pyeritz RE. The Marfan syndrome. *Annu Rev Med* 2000;**51**:481–510.
- Judge DP, Dietz HC. Marfan's syndrome. *Lancet* 2005;**366**:1965–76.
- Dietz HC, Pyeritz RE, Hall BD, *et al*. The Marfan syndrome locus: confirmation of assignment to chromosome 15 and identification of tightly linked markers at 15q15–q21.3. *Genomics* 1991;**9**:355–61.
- Loeys BL, Chen J, Neptune ER, *et al*. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005;**37**:275–81.
- Ramirez F, Rifkin DB. Cell signaling events: a view from the matrix. *Matrix Biol* 2003;**22**:101–7.
- Boileau C, Jondeau G, Mizuguchi T, *et al*. Molecular genetics of Marfan syndrome. *Curr Opin Cardiol* 2005;**20**:194–200.
- Dietz HC, Loeys B, Carta L, *et al*. Recent progress towards a molecular understanding of Marfan syndrome. *Am J Med Genet C Semin Med Genet* 2005;**139**:4–9.
- Robinson PN, Arteaga-Solis E, Baldock C, *et al*. The molecular genetics of Marfan syndrome and related disorders. *J Med Genet* 2006;**43**:769–87.
- Stuart AG, Wilson DG. Marfan syndrome: is early diagnosis useful? *Curr Paediatr* 1998;**8**:121–5.
- Dean JC. Management of Marfan syndrome. *Heart* 2002;**88**:97–103.
- Godfrey M. The Marfan syndrome. In: Beighton P, eds. *McKusick's heritable disorders of connective tissue*. St Louis: Mosby, 1993:51–135.
- DePaeye A, Devereux RB, Dietz H, *et al*. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;**62**:417–26.
- Koenigsberg M, Factor S, Cho S, *et al*. Fetal Marfan syndrome: prenatal ultrasound diagnosis with pathological confirmation of skeletal and aortic lesions. *Prenat Diagn* 1981;**1**:241–7.
- Lipscomb KJ, Clayton-Smith J, Harris R. Evolving phenotype of Marfan's syndrome. *Arch Dis Child* 1997;**76**:41–6.
- Anonymous. American Academy of Pediatrics - Committee on genetics. Health supervision for children with Marfan syndrome. *Pediatrics* 1996;**98**:978–82.
- Hennekam RC. Severe infantile Marfan syndrome versus neonatal Marfan syndrome. *Am J Med Genet A* 2005;**139**:1.
- ter Heide H, Schrander-Stumpel CT, Pals G, *et al*. Neonatal Marfan syndrome: clinical report and review of the literature. *Clin Dysmorphol* 2005;**14**:81–4.
- Loeys BL, Chen J, Neptune ER, *et al*. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005;**37**:275–81.
- Loeys BL, Schwarze U, Holm T, *et al*. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *New Engl J Med* 2006;**355**:788–98.
- Pannu H, Fadulu VT, Chang J, *et al*. Mutations in transforming growth factor-[beta] receptor type II cause familial thoracic aortic aneurysms and dissections. *Circulation* 2005;**112**:513–20.
- Tsai-Goodman B, Wilson DG, Davies S, *et al*. ECG abnormalities in children with Marfan syndrome: is QT dispersion a useful measurement of arrhythmogenicity? *Cardiol Young* 2001;**11**(Suppl 1):309.
- Chen S, Fagan LF, Nouri S, *et al*. Ventricular dysrhythmias in children with Marfan's syndrome. *Am J Dis Child* 1985;**139**:273–6.
- Savolainen A, Kupari M, Toivonen L, *et al*. Abnormal ambulatory electrocardiographic findings in patients with the Marfan syndrome. *J Intern Med* 1997;**241**:221–6.
- Robinson TF, Cohen-Gould L, Remily RM, *et al*. Extracellular structures in heart muscle. *Adv Myocardiol* 1985;**5**:243–55.
- Savolainen A, Nisula L, Keto P, *et al*. Left ventricular function in children with the Marfan syndrome. *Eur Heart J* 1994;**15**:625–30.
- Cattaneo SM, Bethea BT, Alejo DE, *et al*. Surgery for aortic root aneurysm in children: a 21-year experience in 50 patients. *Ann Thorac Surg* 2004;**77**:168–76.
- Hirata K, Triposkiadis F, Sparks E, *et al*. The Marfan syndrome: cardiovascular physical findings and diagnostic correlates. *Am Heart J* 1991;**123**:743–51.
- Pyeritz R, Wappel MA. Mitral valve dysfunction in the marfan syndrome. Clinical and echocardiographic study of prevalence and naturel history. *Am J Med* 1983;**74**:797–807.
- Geva T, Hegesh J, Frand M. The clinical course and echocardiographic features of Marfan's syndrome in childhood. *Am J Dis Child* 1987;**141**:1179–82.
- Groenink M, Mulder BJ. Severe cardiovascular features of marfan syndrome in childhood: just another manifestation or a specific entity? *Int J Cardiovasc Imaging* 2004;**20**:269–70.
- Wilson DG, Bellamy MF, Ramsey MW, *et al*. Endothelial function in Marfan syndrome: selective impairment of flow-mediated vasodilation. *Circulation* 1999;**99**:909–15.
- Meijboom LJ, Timmermans J, van Tintelen JP, *et al*. Evaluation of left ventricular dimensions and function in Marfan's syndrome without significant valvular regurgitation. *Am J Cardiol* 2005;**95**:795–7.
- Imakita M, Yutani C, Ishibashi-Ueda H, *et al*. Chronic dissecting aneurysm of the isolated coronary artery with hemorrhagic myocardial infarction: a rare complication of cardiac operation in a female with Marfan's syndrome. *Heart Vessels* 1990;**5**:243–6.
- Nollen GJ, Van Schijndel KE, Timmermans J, *et al*. Pulmonary artery root dilatation in Marfan syndrome: quantitative assessment of an unknown criterion. *Heart* 2002;**87**:470–1.
- Hirata K, Triposkiadis F, Sparks E, *et al*. The Marfan syndrome: abnormal elastic properties. *J Am Coll Cardiol* 1991;**18**:57–63.
- Morse RP, Rockenmacher S, Pyeritz R, *et al*. Diagnosis and management of infantile Marfan syndrome. *Pediatrics* 1990;**86**:888–95.
- Radford DJ, Izukawa T. Atrial fibrillation in children. *Pediatrics* 1977;**59**:250–6.
- Johnson CD. The Wolff-Parkinson-White syndrome associated with Marfan's syndrome. *Bol Asoc Med P R* 1989;**81**:361–4.
- Yetman AT, Bornemeier RA, McCrindle BW. Long-term outcome in patients with Marfan syndrome: is aortic dissection the only cause of sudden death? *J Am Coll Cardiol* 2003;**41**:329–32.

- 42 **De Backer JF**, Devos D, Segers P, *et al*. Primary impairment of left ventricular function in Marfan syndrome. *Int J Cardiol* 2006;**112**:353–8.
- 43 **Roman MJ**, Devereux RB, Kramer-Fox R, *et al*. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol* 1989;**64**:507–12.
- 44 **Rozendaal L**, Groenink M, Naeff MS, *et al*. Marfan syndrome in children and adolescents: an adjusted nomogram for screening aortic root dilatation. *Heart* 1998;**79**:69–72.
- 45 **Groenink M**, Rozendaal L, Naeff MS, *et al*. Marfan syndrome in children and adolescents: predictive and prognostic value of aortic root growth for screening for aortic complications. *Heart* 1998;**80**:163–9.
- 46 **Roman MJ**, Rosen SE, Kramer-Fox R, *et al*. Prognostic significance of the pattern of aortic root dilatation in the Marfan syndrome. *J Am Coll Cardiol* 1993;**22**:1470–6.
- 47 **Knirsch W**, Kurtz C, Haffner N, *et al*. Dural ectasia in children with Marfan syndrome: a prospective, multicenter, patient-control study. *Am J Med Genet A* 2006;**140**:775–81.
- 48 **Oosterhof T**, Groenink M, Hulsmans FJ, *et al*. Quantitative assessment of dural ectasia as a marker for Marfan syndrome. *Radiology* 2001;**220**:514–18.
- 49 **Maron BJ**, Ackerman MJ, Nishimura RA, *et al*. Task Force 4: HCM and other cardiomyopathies, mitral valve prolapse, myocarditis, and Marfan syndrome. *J Am Coll Cardiol* 2005;**45**:1340–5.
- 50 **Corrado D**, Basso C, Rizzoli G, *et al*. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol* 2002;**42**:1959–63.
- 51 **Hirth A**, Reybrouck T, Bjarnason-Wehrens B, *et al*. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: a consensus document. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:293–9.
- 52 **Fletcher GF**, Balady G, Blair SN, *et al*. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation* 1996;**94**:857–62.
- 53 **Moriguchi J**, Itoh H, Harada S, *et al*. Low frequency regular exercise improves flow-mediated dilatation of subjects with mild hypertension. *Hypertens Res* 2005;**28**:315–21.
- 54 **Mason NJ**, Jenkins AJ, Best JD, *et al*. Exercise frequency and arterial compliance in non-diabetic and type 1 diabetic individuals. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:598–603.
- 55 **Raitakari OT**, Ronnema T, Jarvisalo MJ, *et al*. Endothelial function in healthy 11-year-old children after dietary intervention with onset in infancy: the Special Turku Coronary Risk Factor Intervention Project for children (STRIP). *Circulation* 2005;**112**:3786–94.
- 56 **Cuevas AM**, Germain AM. Diet and endothelial function. *Biol Res* 2004;**37**:225–30.
- 57 **Adams JN**, Brooks M, Redpath TW, *et al*. Aortic distensibility and stiffness index measured by magnetic resonance imaging in patients with Marfan's syndrome. *Br Heart J* 1995;**73**:265–9.
- 58 **Groenink M**, Lohuis TA, Tijssen JG, *et al*. Survival and complication free survival in Marfan's syndrome: implications of current guidelines. *Heart* 1999;**82**:499–504.
- 59 **Nollen GJ**, Groenink M, Tijssen JG, *et al*. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. *Eur Heart J* 2004;**25**:1146–52.
- 60 **Shores J**, Berger KR, Murphy EA, *et al*. Progression of aortic dilatation and the benefit of long-term B-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;**330**:1335–41.
- 61 **Rossi-Foulkes R**, Roman MJ, Rosen SE, *et al*. Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. *Am J Cardiol* 1999;**83**:1364–8.
- 62 **Yetman AT**, Bornemeier RA, McCrindle BW. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. *Am J Cardiol* 2005;**95**:1125–7.
- 63 **Salim MA**, Alpert BS, Ward JC, *et al*. Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. *Am J Cardiol* 1994;**74**:629–33.
- 64 **Haouzi A**, Berglund H, Pelikan PCD, *et al*. Heterogeneous aortic response to acute B-adrenergic blockade in Marfan syndrome. *Am J Cardiol* 1997;**133**:60–3.
- 65 **Lacourciere Y**, Beliveau R, Conter HS, *et al*. Effects of perindopril on elastic and structural properties of large arteries in essential hypertension. *Can J Cardiol* 2004;**20**:795–9.
- 66 **Nagashima H**, Uto K, Sakomura Y, *et al*. An angiotensin-converting enzyme inhibitor, not an angiotensin II type-1 receptor blocker, prevents beta-aminopropionitrile monofumarate-induced aortic dissection in rats. *J Vasc Surg* 2002;**36**:818–23.
- 67 **Habashi JP**, Judge DP, Holm TM, *et al*. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006;**312**:117–21.
- 68 **Tsang VT**, Pawade A, Karl TR, *et al*. Surgical management of Marfan syndrome in children. *J Card Surg* 1994;**9**:50–4.
- 69 **Bentall H**, De Bono A. A technique for complete replacement of the ascending aorta. *Thorax* 1968;**23**:338–9.
- 70 **Birks EJ**, Webb C, Child A, *et al*. Early and long-term results of a valve-sparing operation for Marfan syndrome. *Circulation* 1999;**100**(Suppl):II29–35.
- 71 **Patel ND**, Williams JA, Barreiro CJ, *et al*. Valve-sparing aortic root replacement: early experience with the De Paulis Valsalva graft in 51 patients. *Ann Thorac Surg* 2006;**82**:548–53.
- 72 **de Oliveira NC**, David TE, Ivanov J, *et al*. Results of surgery for aortic root aneurysm in patients with Marfan syndrome. *J Thorac Cardiovasc Surg* 2003;**125**:789–96.
- 73 **Vricella LA**, Williams JA, Ravekes WJ, *et al*. Early experience with valve-sparing aortic root replacement in children. *Ann Thorac Surg* 2005;**80**:1622–6.
- 74 **Golesworthy T**, Lamperth M, Mohiaddin R, *et al*. The Tailor of Gloucester: a jacket for the Marfan's aorta. *Lancet* 2004;**364**:1582.
- 75 **Shaddy RE**, Hawkins JA. Immunology and failure of valved allografts in children. *Ann Thorac Surg* 2002;**74**:1271–5.
- 76 **Stark J**. The use of valved conduits in pediatric cardiac surgery. *Pediatr Cardiol* 1998;**19**:282–8.
- 77 **Treasure T**. Cardiovascular surgery for Marfan syndrome. *Heart* 2000;**84**:674–8.
- 78 **Lemaire SA**, Carter SA, Volguina IV, *et al*. Spectrum of aortic operations in 300 patients with confirmed or suspected Marfan syndrome. *Ann Thorac Surg* 2006;**81**:2063–78.
- 79 **Fast JH**, Boers GH, Meijers-Jacobs S, *et al*. Cardiovascular abnormalities in Marfan syndrome. *Ned Tijdschr Geneesk* 1992;**136**:1259–63.