The distal aorta in the Marfan syndrome

B.J.M. Mulder

Prolonged survival of patients with Marfan syndrome after aortic root replacement has led to an increased number of patients with aortic complications beyond the root. Elective replacement of the aortic root removes the most important predilection site for aneurysms, but the distal aorta remains at risk. Predictors for aortic growth and adverse events in the distal aorta include aortic diameter, aortic distensibility, previous aortic root replacement, hypertension and aortic regurgitation. After aortic dissection, the initial false lumen diameter is an independent predictor for late aneurysm formation. Although there are a few reports of short-term success after endovascular stent grafting of the descending thoracic aorta, stent grafting in patients with Marfan syndrome is not recommended unless intervention is clearly indicated and the risk of conventional open surgical repair is deemed prohibitive. Optimal long-term outcome demands lifelong radiographic follow-up and medical treatment with β -blocker therapy. After aortic dissection rigorous antihypertensive medication is of utmost importance. Losartan, an angiotensin II type I receptor antagonist, might offer the first potential for primary prevention of clinical manifestations in Marfan syndrome, but the results of clinical trials have to be awaited. (*Neth Heart J* 2008;16:382-6.)

Keywords: Marfan syndrome, distal aorta, aortic growth, aortic aneurysm, aortic dissection therapy, intervention

B.J.M. Mulder

Department of Cardiology, Academic Medical Center
Amsterdam, the Netherlands

Correspondence to: B.J.M. Mulder
Department of Cardiology, Academic Medical Center,
PO Box 226600, 1100 DD Amsterdam, the Netherlands
E-mail: b.j.mulder@amc.uva.nl

The leading cause of premature death in patients with Marfan syndrome is aortic dissection due to progressive dilation of the aorta. The abnormal fibrillin protein which results from the genetic defect that causes the disease gives rise to pathology of the aortic wall, especially of the proximal aorta. Elective repair of the aortic root has greatly improved survival of patients with Marfan syndrome. It has been recommended to replace the aortic root before the aortic diameter exceeds 50 to 55 mm.¹⁻³ Adherence to these guidelines may lead to a substantial reduction of type A dissections in Marfan syndrome.^{4,5} Measurement of aortic diameters have, therefore, become a strongly recommended strategy of management (figures 1 and 2). Asymmetric dilation of the aortic root may go unnoticed as in the majority of Marfan patients the largest aortic diameter (from left to right coronary cusp) might not be detected with the standard echocardiography measurements in the long-axis view (right to noncoronary cusp).⁶

Distal aortic diameters

Prolonged survival after aortic root replacement has led to an increase in the number of patients with aortic complications beyond the root.⁷ Pathology of the aorta distal from the root remains a cause of concern. After surgery, many patients need second operations for aneurysms or dissections distal from the aortic root (figure 3).^{8,9} In fact, the Marfan syndrome may affect any vessel in which elastin fibres are an important structural component of its wall. This applies to the entire aorta, although elastin is found in diminishing quantities from its proximal to its distal part.¹⁰

In a European survey of all aortic events observed during follow-up, almost one out of three occurred in the distal aorta.¹¹ In 18% of these patients the distal aorta was the site of first complications. In a study by Finkbohner et al., the first aortic event occurred in the distal aorta in 16% of the patients.¹²

Elective replacement of the aortic root removes the most important predilection site for aneurysms, but the distal aorta remains at risk. In the European survey, the rate of events involving the distal aorta increased after elective aortic root surgery. Diameters

Figure 1. Long-axis echocardiography showing a dilated aortic root in a patient with Marfan syndrome.

of the distal aorta were greater in patients who had than in those who had not undergone aortic root surgery.¹¹ A clarification of this finding may be that patients who undergo elective surgery are patients with a more advanced stage of the disease. Another explanation is that intervention at the level of the root has an impact on the more distal aorta, as a result of haemodynamic factors, altered wall mechanics, or because of clamping of the aorta during the operation.

Figure 3. MR angiogram showing dilation of the abdominal aorta after previous aortic root replacement in a patient with Marfan syndrome.

Figure 2. MR imaging of a dilated aortic root in a patient with Marfan syndrome.

Predictors for aneurismal formation

It is widely known that an increased diameter of the proximal aorta is the strongest predictor of adverse outcome. Similarly, in the distal aorta, increased diameters have been shown to be associated with a higher risk of aortic events.¹¹ In addition, Nollen et al. have demonstrated that a reduced distensibility of the descending thoracic aorta is a predictor of progressive dilation of the descending thoracic aorta.¹³ A decrease of one $10^{-3} \text{ mmHg}^{-1}$ was associated with a fourfold increase of risk independently of aortic diameter. None of the patients with a thoracic distensibility $>3.10^{-3} \text{ mmHg}^{-1}$ had progressive descending thoracic aortic dilation.

No differences in the elasticity of the distal aorta were found between patients with and without previous elective aortic root surgery.¹⁴

Natural aortic growth rate and aneurismal formation have been studied in both children and adults with Marfan syndrome.¹⁵⁻²⁰ Rapid aortic growth may occur in a small subset of patients and has been shown to be a risk factor for aortic dissection. Initial aortic diameter, a distensibility $<3.10^{-3} \text{ mmHg}^{-1}$ in the thoracic descending aorta, previous aortic root replacement, hypertension and aortic regurgitation have all been identified as predictors for rapid aortic growth.^{21,22} In a study of 23 female patients with Marfan syndrome and 33 pregnancies, pregnancy appeared to have a small but significant influence on long-term aortic growth in women with an aortic root diameter $\geq 4.0 \text{ cm}$.²³

Aortic dissection

Patients who survive an acute aortic dissection remain at lifelong risk for aortic aneurysm formation, aortic

Figure 4. MR imaging of a type B dissection.

rupture extension or recurrence of aortic dissection (figure 4). This applies both for patients with unrepaired type B dissection and for patients with repaired type A dissection. After successful repair of acute type A dissection, patients often have persistent dissection of the distal aortic segments, anatomically equivalent to a type B dissection.

After aortic dissection, patients with Marfan syndrome are at increased risk for the development of late aneurysms compared with patients without Marfan syndrome.²⁴

Late survival and the rate of distal aortic dilation after discharge from the hospital have been shown to be similar for patients with all types of aortic dissection and modes of therapy.²⁵ A similar rate of aortic dilation among various types of surgery can be at least partly explained by the fact that the false lumen remains commonly patent after ascending aortic surgery for type A dissection.

In a study of 168 survivors of type A dissection, aortic diameter, elevated systolic blood pressure and presence of a patent false lumen were independent risk factors for aortic growth.²⁶ Song et al. found the initial false lumen diameter at the upper thoracic aortic to be the most powerful independent predictor of late aneurismal change in patients with type A or type B dissections.²⁴

A large false lumen probably reflects high false lumen pressure, which may play a critical role in dilating the false lumen itself and generating an aortic aneurysm.

Intervention: surgery or stenting?

The onset of aortic enlargement after aortic dissection is unpredictable. Therefore, careful monitoring and regular imaging of the entire aorta is essential for optimal timing of surgery or percutaneous intervention. During the last decades, remarkable advances have been made in endovascular stent-grafting repair. However, in patients with Marfan syndrome, there is limited information regarding the impact of persistent radial forces of a stent graft in the abnormal and weak aorta. Although there are few reports of short-term success after endovascular stent grafting of the descending thoracic aorta, stent grafting in patients with Marfan syndrome is not recommended unless intervention is clearly indicated and the risk of conventional open surgical repair is deemed prohibitive.²⁷ To date, presence of Marfan syndrome has been a strict exclusion criterion in all thoracic aortic stent-graft trials. Furthermore, these patients are usually young, and because the current long-term durability of available stent grafts is unknown, stent grafting is not prudent and should be avoided. In experienced centres, open thoraco-abdominal aortic replacement can be achieved safely in such patients, with low morbidity and mortality.²⁸ The optimal timing of surgery for a thoracic aortic aneurysm in patients with Marfan syndrome is uncertain. Indications for surgery include rapid aneurysm expansion and an aortic diameter greater than 50 mm.

Medical treatment

Current available data indicate that modification of surgical techniques cannot improve most factors associated with the degree of aortic enlargement. Thus, optimal long-term outcome demands lifelong radiographic follow-up. Moreover, the importance of rigorous antihypertensive medical treatment, aiming at a systolic blood pressure less than 120 mmHg, has been stressed by several experts.²⁶ Beta-blocker therapy may be protective, independent of its effects on blood pressure, by reducing the impulse of left ventricular ejection.^{29,30}

There are indicators that losartan, an angiotensin II type 1 receptor antagonist and a drug widely used to treat arterial hypertension in humans, offers the first potential for primary prevention of clinical manifestations in Marfan syndrome. It was originally believed that Marfan syndrome results exclusively from the production of abnormal fibrillin-1 that leads to structurally weaker connective tissue when incorporated into the extracellular matrix. This effect seemed to explain many of the clinical features of Marfan syndrome, including aortic root dilatation and acute aortic dissection. Recent molecular studies, mostly based on genetically defined mouse models of Marfan syndrome, have challenged

Figure 5. MR angiogram of a patient with entire aortic replacement.

this paradigm.³¹ These studies established the critical contribution of fibrillin-1 haploinsufficiency and dysregulated transforming growth factor-beta signalling to disease progression. It seems that many manifestations of Marfan syndrome are less related to a primary structural deficiency of the tissues than to altered morphogenetic and homeostatic programmes that are induced by altered transforming growth factor-beta signalling. Most important, transforming growth factor-beta antagonism, through transforming growth factor-beta neutralising antibodies or losartan, has been shown to prevent and possibly reverse aortic root dilatation, mitral valve prolapse, lung disease, and skeletal muscle dysfunction in a mouse model of Marfan syndrome.³²

In the Netherlands, a large nationwide randomised study has recently been started to investigate the effect of losartan on aortic growth (www.comparestudy.nl).

Lifelong follow-up

Because of the advances in medical and surgical therapy, the life expectancy of patients with Marfan syndrome has improved substantially. Patients surviving multiple and complex re-operations have become a real challenge for cardiologists and surgeons and for aortic imaging with CMR or CT studies (figures 5 and 6).³³⁻³⁵ Lifelong and regular follow-up of these patients requires involvement of trained specialists with ample expertise in a tertiary referral centre. ■

References

- 1 Therrien J, Gatzoulis M, Graham T, Bink-Boelkens M, Connelly M, Niwa K, et al. CCS Consensus Conference 2001 update: Recommendations for the management of adults with congenital heart disease – Part II. *Can J Cardiol* 2001;17:1029-50.

Figure 6. MR angiogram showing aneurismal dilation of reimplanted islands in the descending aortic graft.

- 2 Nollen GJ, Groenink M, Van der Wall EE, Mulder BJM. Marfan syndrome: Current insights in diagnosis and management of cardiovascular complications. *Cardiol Young* 2002;12:320-7.
- 3 Nollen GJ, Mulder BJM. What's new in Marfan syndrome? *Int J Cardiol* 2004;97(suppl 1):103-8.
- 4 Groenink M, Lohuis TAJ, Tijssen JPG, Naef MSJ, Hennekam RCM, Van der Wall EE, et al. Survival and complication free survival in Marfan's syndrome: implications of current guidelines. *Heart* 1999;82:499-504.
- 5 Engelfriet PM, Tijssen JGP, Kaemmerer H, Gatzoulis MA, Boersma E, Oechslin E, et al. Adherence to guidelines in the clinical care for adults with congenital heart disease. The Euro Heart Survey on adult congenital heart disease. *Eur Heart J* 2006;27:737-45.
- 6 Meijboom LJ, Groenink M, Van der Wall EE, Romkes H, Stoker J, Mulder BJM. Aortic root asymmetry in Marfan patients; evaluation by magnetic resonance imaging and comparison with standard echocardiography. *Int J Cardiac Imag* 2000;16:161-8.
- 7 Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilén U, et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. *Eur Heart J* 2005;26:2325-3.

- 8 Carrel T, Beyeler L, Schnyder A, Zurmühle P, Berdat P, Schmidli J, et al. Reoperations and late adverse outcome in Marfan patients following cardiovascular surgery. *Eur J Cardiothorac Surg* 2004;**25**: 671-5.
- 9 Van der Velde ET, Vriend JWJ, Mannens MMAM, Uiterwaal CSPM, Brand R, Mulder BJM. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: Rationale, design, and first results. *Eur J Epidemiol* 2005;**20**:549-57.
- 10 Halloran BG, Davis VA, McManus BM, Lynch TG, Baxter BT. Localization of aortic disease is associated with intrinsic differences in aortic structure. *J Surg Res* 1995;**59**:17-22.
- 11 Engelfriet PM, Boersma E, Tijssen JGP, Bouma BJ, Mulder BJM. Beyond the root: dilatation of the distal aorta in the Marfan's syndrome. *Heart* 2006;**92**:1238-3.
- 12 Finkbohner R, Johnston D, Crawford ES, Coselli J, Milewicz DM. Marfan syndrome. Long term survival and complications after aortic aneurysm repair. *Circulation* 1995;**91**:728-33.
- 13 Nollen GJ, Groenink M, Tijssen JGP, Van der Wall EE, Mulder BJM. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. *Eur Heart J* 2004;**25**: 1146-52.
- 14 Nollen GJ, Meijboom LJ, Groenink M, Timmermans J, Barentsz JO, Merchant N, et al. Comparison of aortic elasticity in patients with the Marfan syndrome with and without aortic root replacement. *Am J Cardiol* 2003;**91**:637-40.
- 15 Meijboom LJ, Timmermans J, Zwinderman AH, Engelfriet PM, Mulder BJM. Aortic root growth in men and women with the Marfan's syndrome. *Am J Cardiol* 2005;**96**:1441-4.
- 16 Groenink M, Rozendaal L, Naeff MSJ, Hennekam RCM, Hart AAM, Van der Wall EE, et al. Diagnostic and prognostic value of aortic root growth in children and adolescents with Marfan syndrome. *Heart* 1998;**80**:163-9.
- 17 Rozendaal L, Groenink M, Naeff MSJ, Hennekam RCM, Hart AAM, Van der Wall EE, et al. Marfan syndrome in children and adolescents: an adjusted nomogram for screening aortic root dilation. *Heart* 1998;**79**:69-72.
- 18 Van Karnebeek CDM, Naeff MSJ, Mulder BJM, Hennekam ECM, Offringa M. Natural history of cardiovascular manifestations in Marfan syndrome. *Arch Dis Child* 2001;**84**:129-37.
- 19 Oosterhof T, Groenink M, Hulsmans F, Van der Wall EE, Hennekam RCM, Smit R, et al. Quantitative assessment of dural ectasia as a marker for Marfan syndrome. *Radiology* 2001;**220**: 514-8.
- 20 Nollen GJ, Van Schijndel KE, Timmermans J, Groenink M, Barentsz JO, Van der Wall EE, et al. Pulmonary artery root dilatation in Marfan syndrome: Quantitative assessment of an unknown criterion. *Heart* 2002;**87**:470-1.
- 21 Lazarevic AM, Nakatani S, Okita Y, Marinkovic J, Takeda Y, Hirooka K, et al. Determinants of rapid progression of aortic root dilatation and complications in Marfan syndrome. *Int J Cardiol* 2006;**106**:177-82.
- 22 Legget ME, Unger TA, O'Sullivan CK, Zwink TR, Bennett RL, Byers PH, et al. Aortic root complications in Marfan's syndrome: identification of a lower risk group. *Heart* 1996;**75**:389-95.
- 23 Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJM. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J* 2005;**26**:914-20.
- 24 Song JM, Kim SD, Kim JH, Kim MJ, Kang DH, Seo JB, et al. Long- term predictors of descending aorta aneurismal change in patients with aortic dissection. *J Am Coll Cardiol* 2007;**50**:799-804.
- 25 Doroghazi RM, Slater EE, DeSanctis RW, Buckley MJ, Austen WG, Rosenthal S. Long term survival of patients with treated aortic dissection. *J Am Coll Cardiol* 1984;**3**:1026-34.
- 26 Zierer A, Voeller RK, Hill KE, Kouchoukos NT, Damiano RJ, Moon MR. Aortic enlargement and late reoperation after repair of acute type A aortic dissection. *Ann Thorac Surg* 2007;**84**:479-87.
- 27 Svensson LG, Kouchoukos NT, Craig Miller D, Bavaria JE, Coselli JS, Curi MA, et al. Wheatley III Expert Consensus Document on the Treatment of Descending Thoracic Aortic Disease Using Endovascular Stent-Grafts. *Ann Thorac Surg* 2008;**85**(suppl):S1-41.
- 28 Coselli JS, LeMaire SA. Current status of thoracoabdominal aortic aneurysm repair in Marfan syndrome. *J Card Surg* 1997;**12**:167-72.
- 29 Meijboom LJ, Westerhof BE, Nollen GJ, Spaan JAE, De Mol BAJM, Jacobs MJHM, et al. Beta-blocking therapy in patients with Marfan syndrome and entire aortic replacement. *Eur J Cardio Thor Surg* 2004;**26**:901-6.
- 30 Engelfriet P, Mulder BJM. Is there benefit of β -blocking agents in the treatment of patients with the Marfan syndrome? *Int J Cardiol* 2007;**114**:300-2.
- 31 Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006;**312**:117-21.
- 32 Matt P, Habashi J, Carrel T, Cameron DE, Van Eyk JE, Dietz HC. Recent advances in understanding Marfan syndrome: should we now treat surgical patients with losartan? *J Thorac Cardiovasc Surg* 2008;**135**:389-94.
- 33 Aalberts JJ, van den Berg MP, Bergman JE, du Marchie Sarvaas GJ, Post JG, van Unen H, et al. The many faces of aggressive aortic pathology: Loeys-Dietz syndrome. *Neth Heart J* 2008;**16**:299-304.
- 34 Symersky P, Vriend JWJ, Spijkerboer AM, Mulder BJM, Legemate DA, De Mol BAJM. Endovascular treatment of a bleeding aortic aneurysm after descending aortic aneurysm repair with island re-implantation. *J Thorac Cardiovasc Surg* 2005;**130**:576-7.
- 35 Vriend JWJ, Meijboom LJ, Nollen GJ, Jonkers RE, De Mol BAJM, Mulder BJM. Compression of the left main bronchus and pulmonary artery after entire aortic replacement with dacron arterial grafts. *Ann Thorac Surg* 2004;**78**:E54-E55.