External aortic root support for Marfan syndrome: early clinical results in the first 20 recipients with a bespoke implant

John Pepper[1] • KM John Chan[1] • Jemyrr Gavino[1] • Tal Golesworthy[2] • Raad Mohiaddin[1] • Tom Treasure[3]

[1] Royal Brompton Hospital, London SW3 6NP, UK

[2] Exstent Ltd, Theocsbury House, Tewkesbury, Gloucestershire, England, UK

[3] Clinical Operational Research Unit, UCL (Department of Mathematics), 4 Taviton Street, London WC1H 0BT, UK

Correspondence to: Tom Treasure. E-mail: tom.treasure@gmail.com

DECLARATIONS

Competing interests
TG is a shareholder and director of Exstent Limited, which holds the intellectual property in the External Aortic Root Support project. TG was the originator of the concept and the first recipient of the treatment. No other authors had any competing interests

Funding
The External Aortic Root Support (EARS) project has been funded, to date, by Exstent Limited, a private limited liability company registered in the UK in July 2002

Ethical approval
All of these operations were performed with approval of

Summary

Objectives Fatal aortic dissection occurs at young age in Marfan syndrome. Prevention relies on elective replacement of the aortic root. The placement of an external aortic root support, tailored to the anatomy of the individual patient has been proposed as a feasible alternative.

Design, setting and main outcome measures External aortic root support was offered to patients with Marfan syndrome with aortic root diameter of 40–55 mm and without aortic regurgitation. By computer-aided design, a model of the individual patient's aorta was created from cardiac magnetic resonance images and a bespoke external aortic support was manufactured. Comparative measurements were made of the ascending aorta at the level of closure of the aortic valve cusps from magnetic resonance imaging studies taken preoperatively, at first follow-up, and at most recent follow-up. For patients having aortic root surgery at the same institution, in the same time frame as the first 10 patients, clinical data were retrieved on Marfan and other patients having aortic root replacement to serve as a reference data.

Results Twenty patients were operated upon from May 2004 to October 2009, 13 men and 7 women, median age 33 years. All 20 patients are alive and well at the time of last follow-up. Preoperative aortic diameters were 40–54 mm. All postoperative images were satisfactory with an overall reduction in aortic root dimensions. The surgery took half the time of other aortic root surgery. Cardiopulmonary bypass was used only in the first patient, myocardial ischemia was not required in any patient, and no postoperative anticoagulation is mandated.

Conclusions The primary objective of this surgery was fully achieved in 19 of the 20 patients, reinforcing the ascending aorta while leaving the native aortic valve intact and conserving the blood/endothelium interface.

Introduction

Dissection of the ascending aorta is the commonest cause of death for people with Marfan syndrome, said to affect as many as 70%, often in their 20s or 30s, if this hazard is not pre-empted by surgery. Contemporary population data are not available as known Marfan syndrome families are routinely

the Brompton Hospital Research Ethics Committee under research governance

Guarantor
TT

Contributorship
JP performed all the operations; RM has been responsible for all imaging, its development and its interpretation; TG and TT developed the concept from its inception; KMJC and JG extracted and collected data; TT performed the data analysis and displays, and wrote the first draft. All authors have read and approved the final version of the manuscript

Acknowledgements
Michael Lamperth and Warren Thornton, Imperial College developed the CAD modelling software

Reviewer
David Anderson

screened. If aortic dissection occurs it is almost always fatal but the patient may be saved by prompt and expert surgery, however, registry data for aortic dissection show that 21% of Marfan patients presenting with aortic dissection die of the dissection.[1] The dilatation of the aortic root which typically precedes dissection is a consequence of the genetic inability to make normal fibrillin. In the normal aorta the fibrillin permits expansion and recoil of the aortic wall. Some of the force of left ventricular ejection is taken up in the aorta and, after aortic valve closure, the aortic wall returns this energy. This is the origin of the dicrotic notch in the aortic pressure trace, evidence of a second pressure wave. In the absence of normal fibrillin the aorta dilates and thins, and the media is prone to dissect. Dissection characteristically results in severe aortic valve regurgitation, loss of perfusion of arterial branches, and/or rupture into the pericardium.

The mainstay of current management is preemptive replacement of the whole of the ascending aorta, with re-implantation of the coronary arteries and (most commonly) replacement of the aortic valve. The first reported operation was performed by HH Bentall at Hammersmith Hospital in the 1960s.[2] Over the subsequent 20 years the operation was refined.[3] Off-the-shelf composite tube-and-valve prostheses became available and provide a very reliable mechanical replacement. In contemporary practice elective surgery can be offered with a leading centre reporting no perioperative deaths (30 days) in 235 elective operations.[4] However, replacement of the aortic valve is an inherent part of the modern Bentall operation and if this is with a mechanical valve the patient is committed to lifelong anticoagulation. The implications for active lives, travel, sport and childbearing are considerable as is the cumulative hazard of thromboembolism from the mechanical valve. Valve-sparing operations have been devised and iteratively modified most notably by Tirone David[5] and Magdi Yacoub.[6] These operations remain exacting to perform and prone to failure. Bioprosthetic replacement is a less technically exacting means of reducing thromboembolic risk but at the price of likely eventual valve failure with the need for re-operation. The options have recently been reviewed.[7]

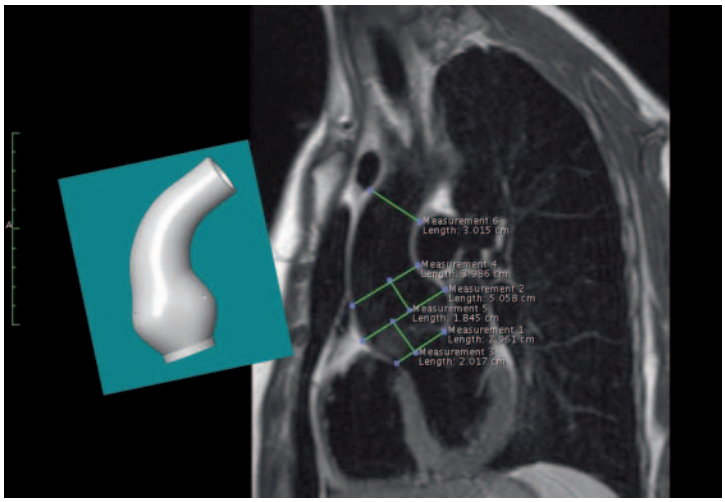
However well-refined and expert are the surgical techniques, these operations are a major undertaking. Cardiopulmonary bypass with full heparinisation is essential with all its attendant risks. There are, in addition, specific hazards of air and/or particulate embolism in aortic surgery. These hazards are not captured by reports of 30-day mortality. Surgery is, therefore, deferred as long as it seems safe to wait. Accurate prediction of the timing of dissection is impossible but a family history of dissection at young age is important and, while dissection can occur before the aorta has dilated massively, the absolute size and the rate of change are generally regarded as indicative. A typical approach is to monitor aortic root dimensions on a regular basis, usually by annual echocardiography. In order to refine and make more objective that decision, a method of plotting the individual patient's aortic root diameter against a nomogram was devised, based on the 95% prediction interval of aortic dimensions for Marfan aortas in patients of the same sex and height.[8,9] While this made the decision easier to discuss explicitly it did little to relieve the anxiety of patients and clearly, for some, added to the burden of apprehension.

An alternative to replacement by wrapping the aorta at various aortic sites and for various pathologies was reported by Robiscek and Thubrikar.[10] This approach has largely been abandoned because of several patterns of failure. The development of a bespoke external aortic root support (EARS)[11,12] offered an opportunity to radically re-think the process of care for Marfan patients. Because the EARS operation can be performed without cardiopulmonary bypass, without entering the circulation, and without interfering with the valve in any way, this procedure offers the opportunity of truly preemptive management. If, as anticipated, the external support can hold the whole of this aortic segment at a size where the risk of dissection is low risk, it may obviate, or greatly postpone, the need for more radical and ablative surgery. We report here the early clinical outcomes in the first 20 patients operated upon. To provide some context for the clinical data reported, we present similar data for two comparator groups, namely Marfan patients and non-Marfan patients that had aortic root surgery.

Methods

A prospective study was approved by the Hospital Research Ethics Committee. External aortic root

Figure 1
An MRI scan of a patient with Marfan syndrome orientated so that the aorta is seen along its long axis. Some of the dimensions used to make model are shown and the model is superimposed



support was offered to patients with Marfan syndrome with aortic root diameter of 40–55 mm and without clinically important aortic regurgitation. Following a prespecified protocol of imaging and computer-aided design, a model of the individual patient's aorta was created in thermoplastic and a bespoke external aortic support was manufactured.

Production of the bespoke external support

The exact dimensions of the individual patient's aorta are taken from magnetic resonance images and processed using a dedicated computer-aided design (CAD) routine. These measurements are used to produce a 3D reconstruction of the patient's aorta from the aorto ventricular junction to beyond the brachiocephalic artery. The X,Y and Z coordinates of the reconstructed aorta are exported to a rapid prototyping (RP) machine and a model of the patient's aorta made in thermoplastic (Figure 1). The thermoplastic model is the former upon which the external support, with a vertical seam, is manufactured from a medical grade polymer mesh. Technical details are already published.[13] In brief, the aorta is dissected away from adjacent structures, specifically the pulmonary artery. The surgical dissection is taken below the coronary arteries as far as the ventriculo-aortic junction to which it is secured by sutures. The support is passed behind the aorta and sutured up the front. It is secured around the brachiocephalic artery at the distal end (Figure 2). No cutting or sewing of the fragile Marfan aortic tissue is required.

Patient characteristics and operative details

For all EARS patients the age, gender, date of birth, date and operative times, date of discharge and aortic measurements are kept on a prospective database (Table 1). The Royal Brompton Hospital Clinical Database was searched for all operations with the operative site recorded as <ascending aorta> that took place in the period May 2004 to March 2007 inclusive (the calendar months of the first 10 EARS operations). A case-by-case review of the operative details was made for patients who had operations replacing all the native ascending aortic tissue including the aortic sinuses (of Valsalva) and had re-implantation of the coronary arteries. This has become the generally accepted minimum requirement of a pre-emptive operation in the Marfan syndrome. Data retrieved included age, gender, operative time, cross-clamp time, bypass time, the occurence of arrythmias and whether warfarin was mandated following surgery to provide comparative information for conventional extirpative surgery for Marfan and other aortic root pathology (Table 2).

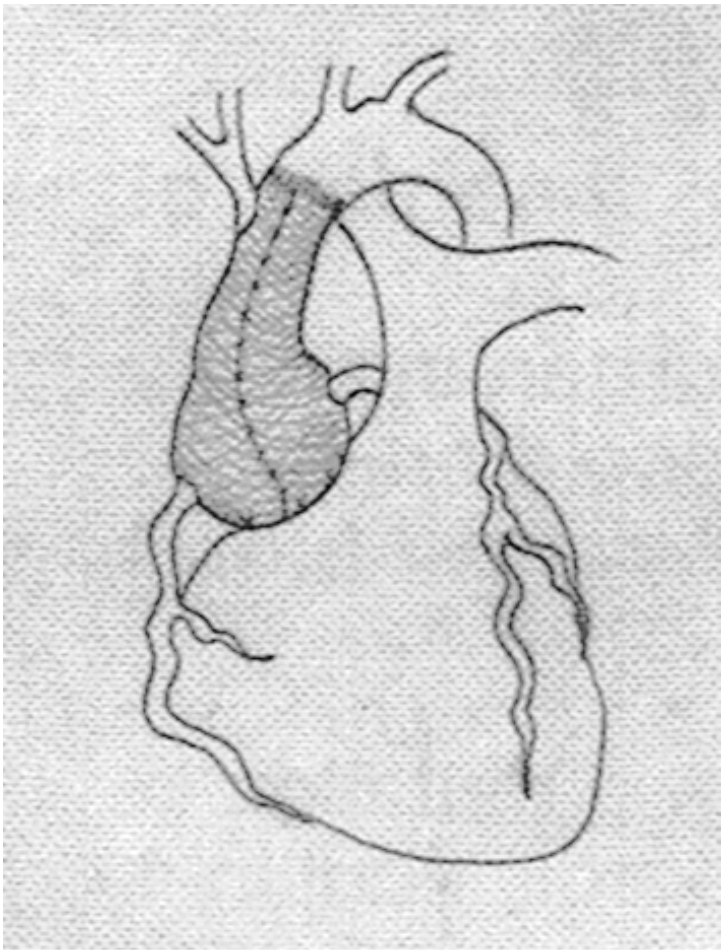
Results

Patients were considered as candidates for this surgery if the aortic sinus diameter was 40–55 mm and there was no more than trivial regurgitation. No patients were excluded for any other technical reason. All 20 consecutive patients meeting these criteria were offered this surgery.

Surgical outcomes and operative details

The first 20 patients (13 men, seven women) underwent EARS from May 2004 to October 2009. There have been no deaths and the operation was completed exactly as planned in 19/20 while the 20th patient had partial release of the external support. In no patient was there a need to convert to root replacement or other form of surgery. Cardiopulmonary bypass was used for 20 minutes in the first patient only.

Figure 2
Artist's impression of the external aortic root support in position



The age, operative time and length of stay are summarized in Table 1.

In two patients there were technical problems. In patient 18 there were anatomical anomalies in the coronary arteries. The right coronary was non-dominant and, as can occur with this anatomy, the left main coronary artery had effectively no length and the bifurcation to left anterior descending and circumflex branches was at the aortic wall. Further imaging clarified the anatomy and the operation was completed as planned the following week.

In patient 20 there was a postoperative cardiac arrest with ventricular fibrillation. The circulation was restored after removing the anterior closing suture on the aortic root support. The likely explanation is that the location of one the coronary origins had been misinterpreted on the MRI scan. The patient made a normal recovery thereafter and left hospital at eight days. The aorta in this patient is only partially supported and will be monitored. Completion of the EARS, if required, should not be technically difficult.

The preoperative aortic root measurements are shown along with the first and latest postoperative measurements in Figure 3.

Comparison groups

In the calendar months May 2004 to March 2007, 94 patients had operations coded to the site <ascending aorta>. Of these, 10 had undergone one to three previous operations and a further 56 had operations that did not involve total replacement of the ascending aorta. These were excluded from further analysis.

This left 28 patients who underwent total replacement of the ascending aorta including the aortic sinuses of whom seven had Marfan syndrome and 21 had other pathology. Of the seven Marfan patients, five had valve sparing operations and two had composite root replacement. Of the 21 non-Marfan patients, 13 had composite

Table 1
Demographic, perioperative and follow-up data on 20 patients having external aortic root support surgery for Marfan syndrome

	Median	*IQR*	*Range*
Age at operation (years)	33	26–39	16–58
Aortic diameter (mm)	47	43–48	40–54
Operation time (minutes)	148	136–163	125–415
Length of stay (days)	6	5–7	3–16
Follow-up interval (months)	20	10–39	0–67
Change in aortic diameter (mm) (*n*=16)	–1	–2–+1	–6–+3

Table 2
Comparison data on 28 consecutive patients (seven Marfan, 21 with other pathologies)

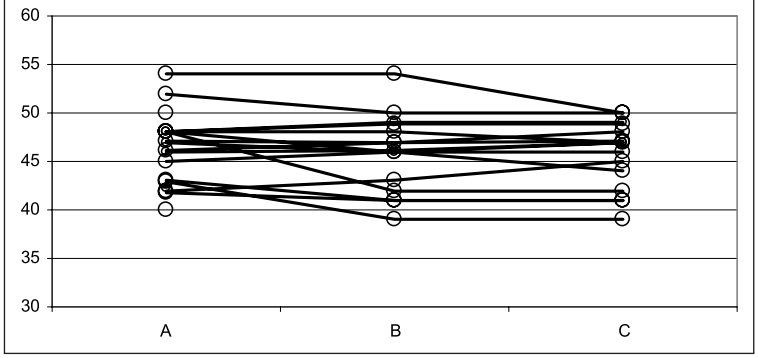
Group	*Marfan root (n=7)*	*Other root (n=21)*
Man:Woman	6:1	17:4
Age (median and range)	32(17–60)	57(19–80)
Operation time (minutes)	374(240–493)	340(165–562)
Bypass time (minutes)	149(139–323)	210(118–275)
Cross-clamp time (minutes)	106(100–243)	143(97–195)
Deaths in hospital	0	2
Arrhythmia	5	10
Postoperative days in hospital (median and range)	8(4–119)	8(1–57)
Warfarin mandated by a mechanical valve	3	7

root replacement (modern Bentall) operations, four had homograft root replacement, two had valve sparing root replacements and two had Ross procedures.

The patients with non-Marfan pathology were on average about twice the age of the non-EARS Marfan patients. The Marfan patients undergoing EARS (10) and root replacement operations (7) were similar in age and sex ratio to the non-EARS Marfan patients. Median and ranges of procedure times for the three groups are given in Table 2. For the 28 root replacement operations, whether for Marfan or other pathology, procedure times were broadly similar and can be summarized by interquartile range (IQR) as follows: operative time IQR 290–435 minutes; cardiopulmonary bypass IQR 149–227 minutes; myocardial ischaemia (with cold hyperkalaemic protection) IQR 106–168 minutes.

The EARS patients had shorter operation times and were spared any cardiopulmonary bypass (after the first) and any myocardial ischaemia (Table 1).

Figure 3
Dimensions of the ascending aorta at the level of closure of the aortic valve cusps before operation (A) at the first postoperative scan (B) and most recent MRI scan. We know from a meticulous study of these dimensions that on read–reread measurements of duplicate scans, presented in random sequence, commonly had differences of up to 4–5 mm. What we are seeing is a tendency for EARS to reduce the diameter of the Marfan aorta which remains stable thereafter. The longest follow-up scan is five years after surgery[12]



Discussion

The purpose of aortic root surgery in Marfan syndrome is to pre-empt the risk of dilatation and dissection thus saving the patient from aortic regurgitation and death due to aortic dissection. Successful placement of external aortic support in 19 of 20 patients has been completely achieved, and partially achieved in the 20th with the option still open of completing the aortic root support at any time.

It should be remembered that the aorta distal to the support is unprotected by this form of aortic external root support, a limitation shared by all forms of Bentall root replacement and its valve-sparing variants. However, a number of the problems associated with root replacement with a composite graft are avoided by EARS. The magnitude of surgery is greatly reduced and the hazards associated with cardiopulmonary bypass, myocardial ischaemia, and the neurological risks associated with air or particulate embolization, and use of circulatory arrest, are all obviated.

The consecutive series of seven Marfan patients contemporaneous with the first 10 EARS patients were of similar age and pathology. They had a considerable operative, bypass and myocardial ischaemic time, all of which are avoided by EARS. In

that regard, they are similar to the 21 non-Marfan patients undergoing aortic root surgery. The EARS Marfan patients also retain their native valve, without any interference to its support or movement, and their endothelium/blood interface is conserved.

There are remaining concerns. One is that the aorta might still dissect within the supported segment. It should be recalled that aortic dissection is strongly related to the aortic size and hence the triggers for replacement are based on increased aortic dimension and the rate of increase.[8,9,14] We contend that holding the aorta at smaller size will reduce that risk. We also believe that the risk of fatal rupture into the pericardium is likely to be prevented. Any further need for surgery is likely to be facilitated by this support. We envisage that the thin, soft and flexible material of the support will be incorporated in the aortic adventitia and provide an external layer which can be cut and more safely sewn than the pathological aorta found in Marfan syndrome which is notoriously treacherous.

Another concern has been safeguarding the coronary orifices and indeed in two of the 20 patients the exact location and anatomy of the coronary arteries caused some perioperative problems, incompletely resolved in one. Impingement on the coronary arteries, once the support is correctly positioned seems to us unlikely; the edge is soft and flexible and cut at the time of surgery to form a flange rather than a hard edge. It should be recalled that the coronary orifices are the Achilles' heel of the Bentall operation.[3] The suture line of the coronary button is necessarily in to Marfan aortic tissue and the avoidance of any suture line at this site seems to us an advantage.

We cannot predict eventual outcome from such an early and limited experience. However, the support is made of a very well tried and tested material known to be stable in the circulation for very many years. Once accurately placed and incorporated around the aorta, it is improbable that it will rupture; it is soft, flexible and porous so it is very unlikely that it will migrate. Sparing the patient anticoagulation is a considerable advantage and this less ablative surgery can be justified at an earlier time, thus reducing years of anxiety while undergoing repeated echo measurements.

References

1 Januzzi JL, Marayati F, Mehta RH, *et al*. Comparison of aortic dissection in patients with and without Marfan's syndrome (results from the International Registry of Aortic Dissection) 1. *Am J Cardiol* 2004;**94**:400–2

2 Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. *Thorax* 1968;**23**:338–9

3 Treasure T. The evolution of aortic root surgery for Marfan syndrome. *Interact Cardiovasc Thorac Surg* 2010;**10**:353–5

4 Gott VL, Cameron DE, Alejo DE, *et al*. Aortic root replacement in 271 Marfan patients: a 24-year experience. *Ann Thorac Surg* 2002;**73**:438–43

5 David TE, Feindel CM, Bos J. Repair of the aortic valve in patients with aortic insufficiency and aortic root aneurysm. *J Thorac Cardiovasc Surg* 1995;**109**:345–51

6 Yacoub MH, Gehle P, Chandrasekaran V, Birks EJ, Child A, Radley-Smith R. Late results of a valve-preserving operation in patients with aneurysms of the ascending aorta and root. *J Thorac Cardiovasc Surg* 1998;**115**:1080–90

7 Kirsch ME, Ooka T, Zannis K, Deux JF, Loisance DY. Bioprosthetic replacement of the ascending thoracic aorta: what are the options? *Eur J Cardiothorac Surg* 2009;**35**:77–82

8 Treasure T, Chow T, Gallivan S. Replacement of the aortic root in Marfan's syndrome. *N Engl J Med* 1999;**341**:1473–4

9 Treasure T, Reynolds C, Valencia O, Child A, Gallivan S. The timing of aortic root replacement in the Marfan syndrome: computer aided decision support. In: Enker J, ed. *Cardiac Surgery and Concomitant Disease*. Darmstadt: Springer; 1999. p. 91–8

10 Robicsek F, Thubrikar MJ. Conservative operation in the management of annular dilatation and ascending aortic aneurysm. *Ann Thorac Surg* 1994;**57**:1672–4

11 Golesworthy T, Lamperth M, Mohiaddin R, Pepper J, Thornton W, Treasure T. The Tailor of Gloucester: a jacket for the Marfan's aorta. *Lancet* 2004;**364**:1582

12 Golesworthy T, Treasure T, Lamperth M, Pepper J. Reducing fear and the risk of death in Marfan syndrome: a Chaucerian pilgrimage. *Br J Cardiol* 2006;**13**:267–72

13 Pepper JR, Golesworthy T, Utley M, *et al*. Manufacturing and placing a bespoke support for the Marfan aortic root: description of the method and technical results and status at one year for the first ten patients. *Interact Cardiovasc Thorac Surg* 2010;**10**:360–5

14 Treasure T. Elective replacement of the aortic root in Marfan's syndrome. *Br Heart J* 1993;**69**:101–3