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CASE REPORT

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Histology of a Marfan aorta 4.5 years after personalized external aortic root support

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Abstract

In 2008, a 26-year old man had personalized external aortic root support (PEARS) with a macroporous mesh. He was the 16th of 46 patients to have this operation. He had a typical Marfan habitus. His mother died of this disease as did his brother, with an aortic dissection. The patient himself died suddenly 4.5 years after his PEARS operation. At autopsy, there was no blood in the pericardium. The coronary orifices and proximal arteries were normal. His bicuspid aortic valve was minimally regurgitant as it was prior to operation and remained throughout follow-up. Macroscopically the implanted mesh was embedded in the adventitia and not separable from the aortic wall. Microscopically it was fully incorporated with collagen fibres as has been seen in our animal studies. The unsupported aortic arch showed some focal fragmentation of elastic fibres and a mild increase in mucopolysaccharides consistent with Marfan syndrome. These appearances were not present in the supported aortic root, which had the histological appearance of a normal aorta. He was the first patient to die with an implant. The histological appearances suggest the possibility that the incorporated support of the aortic root allowed recovery of the microstructure of the media.

Keywords: Marfan syndrome • Aortic root aneurysm • Sudden death

INTRODUCTION

We report the first autopsy findings of a personalized external aortic root support (PEARS) operation, which confirm the incorporation of the mesh into the aortic adventitia as was shown in sheep [1].

CASE REPORT

Our patient had a typical Marfan phenotype with a characteristic habitus, pectus excavatum and a dislocated lens. His aortic root diameter was 42 mm at the level of coaptation of the leaflets when measured by magnetic resonance imaging (MRI) prior to operation in September 2008 (Fig. 1A and C). Echocardiography showed a functioning bicuspid aortic valve and dilated cardiomyopathy with mildly impaired left ventricular function: left ventricular end-diastolic (LVEDD) and left ventricular end-systolic dimensions (LVESD) were 5.4 and 3.8 cm, respectively. The left ventricular ejection fraction (LVEF) was 49%. The estimated pulmonary artery pressure was 34 mmHg. The mitral valve and left atrial dimensions were normal.

His mother had Marfan syndrome (MFS) and died aged 52. His brother died following acute aortic dissection aged 23 years. Prophylactic aortic root surgery was advised and the patient requested PEARS. In December 2008, aged 26, he was the 16th patient to have this operation. A model of his aorta was made by computer-assisted design and rapid prototyping, commonly known as 3D printing. A supporting sleeve from a soft and pliable macroporous mesh was manufactured on this (Fig. 1B). At operation (John Pepper), the ascending aorta was mobilized to the aortoventricular junction and the mesh, extending proximal to the coronary arteries, was tethered to the left ventricle (Fig. 1E).

Intraoperative echocardiography showed his LVEF and his right ventricular ejection fraction to be unchanged from baseline as was his mild aortic regurgitation. The LVEF was 51% on the 4th postoperative day. He made an uncomplicated recovery and left hospital on the 6th postoperative day taking Bisoprolol and Lisinopril. He returned to work after 8 weeks.

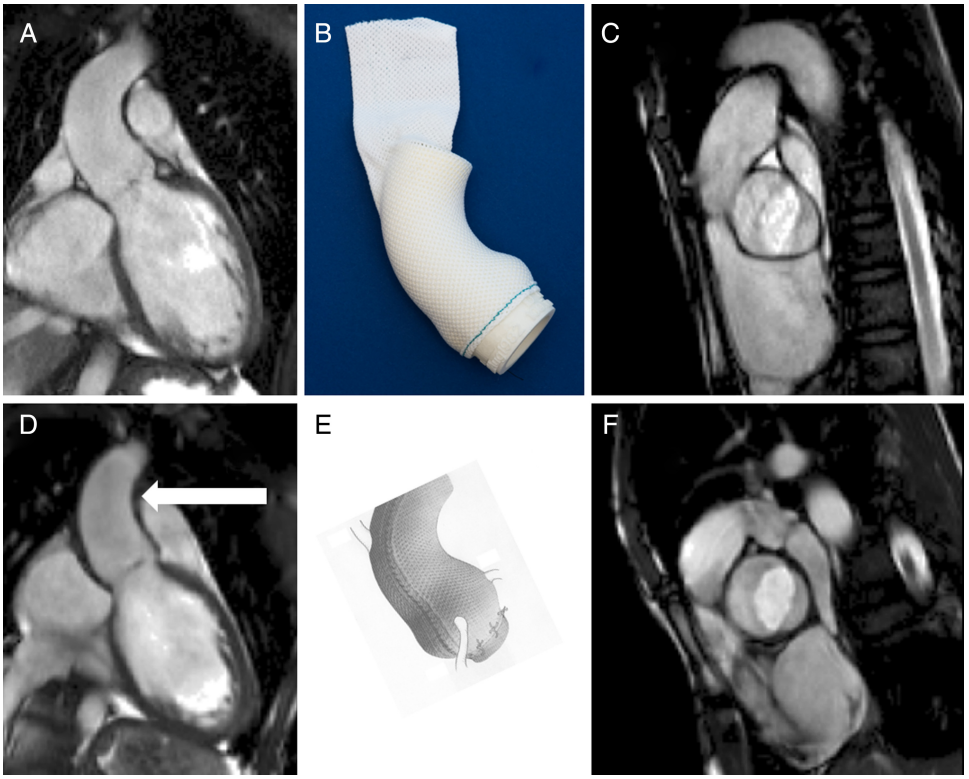

Figure 1: Diastolic frames selected from complete cine acquisition in the long axis of the left ventricle and the short axis of the aortic valve acquired before (**A** and **C**) and 11 months after PEARS (**D** and **F**). The LV is dilated in both studies and the aortic valve is bicuspid with only mild aortic regurgitation and no stenosis. The thickened aortic wall at the site of PEARS can be seen (arrow). The actual mesh support on the personalized former as used in this patient, derived by CAD modeling, is shown above (**B**) and a depiction of it in position is shown below (**E**). CAD: computer-aided design; PEARS: personalized external aortic root support; LV: left ventricle.

On 25 October 2009, he was sailing in cold sea water (5°C) when his dinghy capsized in strong winds. He was admitted to his regional hospital in cardiogenic shock. Troponin T measured on arrival was 0.37 ng/l (normal <0.1) and had returned to normal (0.09) 24 h later. The electrocardiogram showed ST depression in II, III, V4 and V5, which resolved after 24 h. Cardiac catheterization showed severe dilatation of the left ventricle with ballooning of the apex. The left ventricular end-diastolic pressure was 24 mmHg. The wall motion abnormality of the LV was not in a coronary distribution and selective coronary arteriography showed normal coronary ostia and unobstructed coronaries. Takotsubo syndrome (adrenaline-driven stress cardiomyopathy) was diagnosed. Left ventricular dimensions measured 5 days later after he had been transferred to the Royal Brompton Hospital were LVEDD 5.9 cm and LVESD 4.4 cm.

An MRI scan performed eight days after the acute event on 2 November 2009 showed a return to the preoperative appearances of a moderately dilated left ventricle with mild global impairment of systolic function: left ventricular end-diastolic volume 250 ml; left ventricular end-systolic volume 130 ml. There was no evidence of myocardial infarction or oedema. Comparison with before the operation (September 2008) showed that the aortic root dimensions were 42 and 41 mm (before and after) at the level of coaptation of the leaflets, and 35 mm at the sinotubular junction at both times (Fig.1A and D).

He rapidly improved, returned to work and was well when reviewed at 6 weeks and again 1 year later.

In May 2013, 4.5 years after his PEARS operation, he was found dead in bed. At autopsy, there were expected pericardial adhesions but no blood in the pericardium or mediastinum. The aortic arch and descending aorta appeared normal. The external aortic mesh was fully incorporated in the adventitia and could not be separated from it. There was no aortic dissection. There was no impingement on the coronary arteries or their orifices by the external support. There was good coaptation of the valve leaflets and, on testing with water, there was minimal leak in keeping with the mild degree of aortic regurgitation known to have been present through his bicuspid aortic valve.

The examining pathologist (Martin Goddard) found no reason to suspect that the mesh support had contributed to death. The mesh position was stable and it was fully incorporated by collagen (Fig. 2). A cross section from the unsupported arch of the aorta showed focal fragmentation of the elastic lamellae consistent with the MFS. In the supported portion, the aortic media was of normal appearance. Examination of the heart confirmed a dilated cardiomyopathy presumed to be related to MFS, as was the cause of death in his mother [2].

DISCUSSION

Elective root replacement in MFS has greatly improved life expectancy in affected patients. As a result, the threshold for intervention has reduced progressively over 30 years. Three forms of surgery are now available: total root replacement with a valved conduit, valve sparing root replacement (VSRR) and PEARS with a macroporous mesh sleeve, manufactured to the patient's own aortic dimensions [3].

PEARS is intended to prevent further expansion of root aneurysms and to preserve the architecture of the aortic valve support.

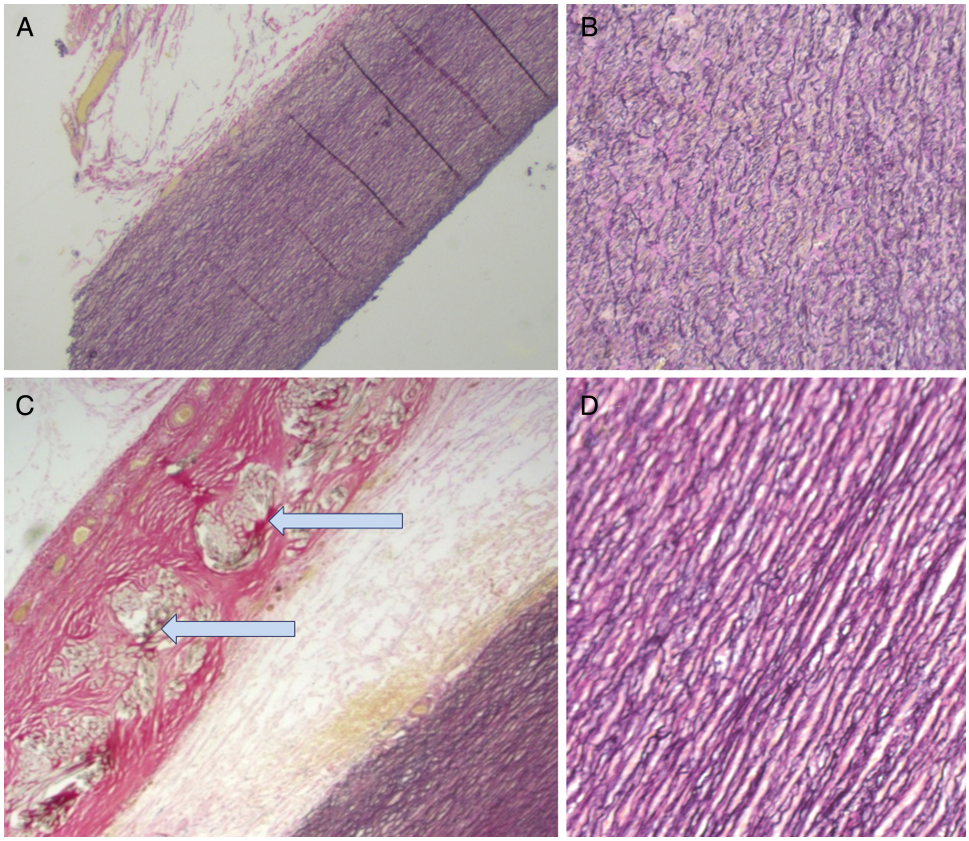

Figure 2: (**A**) Sections from the unsupported aortic arch shows focal fragmentation of elastic fibres and a mild increase in mucopolysaccharides (mag. ×2.5). There is no root in contrast to (**C**) and the adventitia is not clearly defined as it is in the ascending aorta. (**B**) A high-power view of the media of the unsupported aortic arch (mag. ×10). The appearances are of medial degeneration consistent with Marfan syndrome. (**C**) Section of the aortic root of a total thickness of 4.5 mm. Collagen fibres (red staining) pass through the interstices between the filaments of the root (blue arrows) embedding it in the adventitia. Foreign body-type giant cells and a few scattered chronic inflammatory cells are present (mag. ×2.5). (**D**) High-power view of the protected aortic root wall (mag. ×10). The underlying media shows well-preserved elastic lamellae with no fragmentation, loss or pooling of mucopolysaccharides. (N.B. There has been minor image size adjustment to create the montage).

This is a different concept from ablative root replacement [4]. The operation is intended to be prophylactic, performed at an earlier stage in the natural history of MFS. The patient's own aortic images are used to create a faithful copy of the aorta by computer-aided design, which is then made into a physical copy by '3D printing'. On this is made a macroporous fabric sleeve to be placed around the aorta, including the segment proximal to the coronary arteries, down to the aortoventricular junction.

The incorporation of the mesh in the outer layers of the aortic wall in this case is in accordance with the histological appearance previously shown by Cohen *et al.*, who used a limited *ad hoc* mesh support with a similar material in 102 patients from 1984 to 2003 [5]. Incorporation was also seen in the carotid artery of growing sheep [1]. The distensibilty and therefore the afterload are similar to that with any tube graft aortic replacement and so there is no additional stress on the left ventricle.

One might expect any degenerative changes to be worse in the root than in the arch but the protected aortic root in this patient had normal histology. This raises the intriguing possibility that the support enabled the aorta to heal by sparing it from the repetitive stress of systolic distension in an inelastic Marfan aorta, but we have no histology prior to PEARS on which to base a firm conclusion.

Because the aorta is not allowed to dilate further, the major factor predisposing to dissection is obviated and this is likely to diminish the risk of dissection. In the now less likely event of dissection, the strong root/aorta composite [1] would prevent intrapericardial rupture, the proximate cause of death in acute aortic dissection. It will also provide a technically more secure aortic wall than native Marfan aortic tissue if any further surgery were to be performed.

Although this is an isolated case report, it shows that the external supporting root strengthens the aortic wall by becoming fully incorporated. PEARS seeks to achieve the benefits of VSRR but, as a non-ablative procedure, it can be offered earlier. Because it preserves the size and configuration of the aortic root, PEARS optimizes the chance of maintaining aortic valve function.

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EDITORIAL COMMENT

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Re: Histology of a Marfan aorta 4.5 years after personalized external aortic root support

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Keywords: Aorta • Marfan Syndrome • Surgery

Life expectancy for patients with Marfan syndrome has increased significantly in recent decades and, today, it is almost superimposable with that of the general population [1]. There are multiple reasons for this increase but one of the major determinants has been the development in medical and surgical management. In fact, since the introduction of the Bentall-De Bono procedure in the 1970s, there has been an impressive increase in positive outcomes as well as in life expectancy. The continuing excellent results have led to a progressive decrease in the dimensions of the aortic diameter, for which prophylactic repair is recommended. However, the Bentall procedure is associated with a non-negligible incidence of prosthetic valve-related events, thus exposing patients to the constant risk of haemorrhage, thromboembolism and prosthetic valve endocarditis [2].

Aortic valve-sparing operations have been developed in order to reduce the incidence of these adverse events [3, 4]. The results achieved with these techniques have been excellent and lasting, as has been demonstrated in the long term, and, presently, at least in experienced centres, they represent the gold standard in the treatment of aortic root dilatation for Marfan patients.

The Personalized External Aortic Root Support (PEARS), at least theoretically, appears to be really fascinating. The possibility that the support spares the aortic wall from the repetitive stress of systo-diastolic distension, which leads to the healing of the aortic wall, is very attractive as documented by the present paper [5]. The results reported using this technique are really encouraging; no early mortality, no postoperative myocardial infarction or cerebrovascular events as well as no aortic, cerebral or aortic valve-related events at follow-up in a series of 30 patients [6].

On the other hand, some negative remodelling of the aortic wall has previously been reported, such as an intense fibrotic reaction at the level of the adventitia and periadventitia [7]. Moreover, a more or less intense inflammatory reaction is always present.

However, some hesitation can arise when the following considerations are taken into account:

- Leaving a native aorta, even though supported, means leaving a potential risk of dissection of the aortic wall, which can also occur in patients without any kind of connective tissue disorder and without histological alterations of the aortic wall.
- Fibrosis of the aortic wall leads to a loss of elasticity which, if associated with an inflammatory reaction and an increase of metalloproteinase activity, can increase the risk of dissection [8]. The authors have even speculated that if dissection occurs, the strong mesh/aorta composite would prevent intrapericardial rupture; the involvement of the arteries arising from the aorta cannot be avoided and neither can the frequent and consequent myocardial, cerebral and visceral malperfusion.
- I am not at all convinced that PEARS is a 'lesser procedure' as stated by the authors. Aortic root isolation is, at times, not easy even on an arrested heart, and it can be extremely challenging or impossible on a beating heart. Coronary injury, as reported by the same authors [6], as well as right and left atrial damage and, above all, damage to the right ventricle, which may be very fragile in Marfan patients, can always occur and can be life-threatening.
- Finally, we know that the lack of ventricular–aortic stabilization leads to further annular dilatation and recurrence or appearance of aortic regurgitation that are responsible of reoperation over time. Reaching the real ventricular–aortic junction on a beating