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## Personalized external aortic root support: a review of the current status

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### Summary

Personalized external aortic root support (PEARS) is an emerging technology. It is a pre-emptive operation to halt aortic root expansion and maintain aortic valve function in Marfan syndrome and is also applicable to aortic root aneurysms of other aetiologies. To fully evaluate PEARS, awareness of all those who advise these patients is necessary to ensure that patients are fully informed of the alternative operations, to carefully build experience, to ensure safety and quality and to monitor outcomes. Herein, we present a summary of published methods and outcomes and the arrangements in place for fuller evaluation.

**Keywords:** Marfan syndrome • Aortic root aneurysm • Personalized external aortic root support

### INTRODUCTION

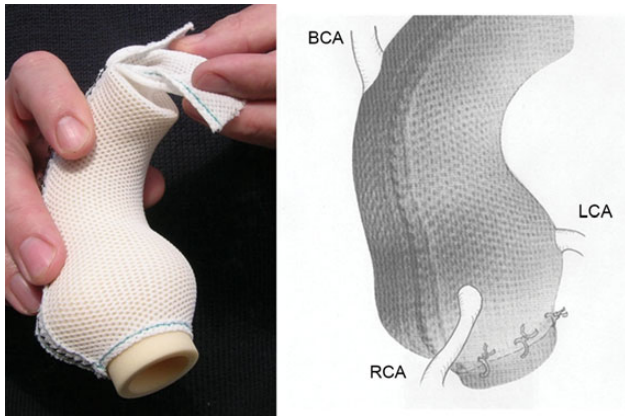
Personalized external aortic root support (PEARS) is a procedure in which a 3D copy of the patient's aorta is made by computer-aided design. Using that as a former, a mesh sleeve of the same shape and size is made to fit that patient's aorta [1] (Fig. 1). PEARS might appropriately be considered as a niche innovation still under evaluation in an observational phase. More than 60 patients have had this surgery in a 12-year period. Operations have been performed in six centres and follow-up is more than 260 patient-years.

We here summarize our work in progress for the consideration of colleagues who encounter the clinical scenario of people in whom the Marfan phenotypic morphology is expressed and aortic root dimensions are increasing [2]. The possibility of a pre-emptive operation might be considered for other congenitally determined root aneurysms, some of which are included in our experience [3]. The aorta may not yet be at a size at which root replacement is mandatory by established criteria, but may nevertheless be a cause for serious future concern [4]. PEARS may be considered for these patients because it spares the aortic valve, conserves the architecture of the aortic valve support, but presents no obstacle to further surgery. One might argue that 'no bridges are burnt' by this conservative surgery. Indeed, it is possible in our view that PEARS may prove, for a good number of these patients, a definitive means to hold the sinuses at a size and shape that allow the aortic valve to remain competent [5, 6] (Fig. 2). In the two cases where we have been able to examine the aorta years after the mesh has become

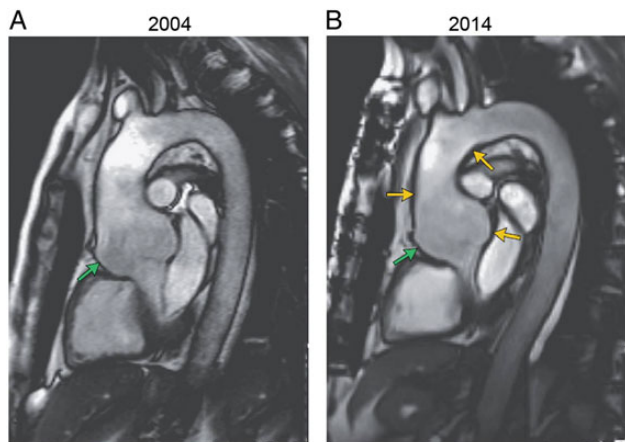
incorporated, the macroscopic and histological appearances make acute aortic dissection originating in the root seem much less likely than it would otherwise have been (Figs 3 and 4).

### SUMMARY OF THE TECHNICAL ASPECTS

The innovative features of PEARS include the use of computer-aided design and rapid prototyping (also known as 3D printing) to make a model of the individual's ascending aorta on which the supporting mesh is manufactured [1] (Fig. 1). The inventor of PEARS is an engineer with no prior awareness of 'wrapping' techniques, so PEARS is not an iterative modification of earlier techniques but revisits the idea of external support applying more recently available technology. The requirements of a pre-emptive operation were thought through from first principles in collaboration with a cardiac anatomist and design engineers [8, 9]. As surgeons we (Tom Treasure, John Pepper) revisited the concept of 'support' rather than excision of the Marfan aorta [10]. The individualized approach, using a custom-made mesh support (ExoVasc<sup>®</sup>, Exstent Limited, Tewkesbury, UK), had from the outset a distinctly different approach to 'wrapping' of the aorta using a vascular graft material which it should be remembered was designed for a quite different purpose which requires it to have some physical stiffness [11, 12]. PEARS is better envisaged as intimately fitting hosiery; a soft stocking made to fit rather than being 'wrapped' around the leg. The sinuses of Valsalva create a complex 3D shape which would require much cutting and gusseting to match accurately; this is overcome by making the snug fit part of



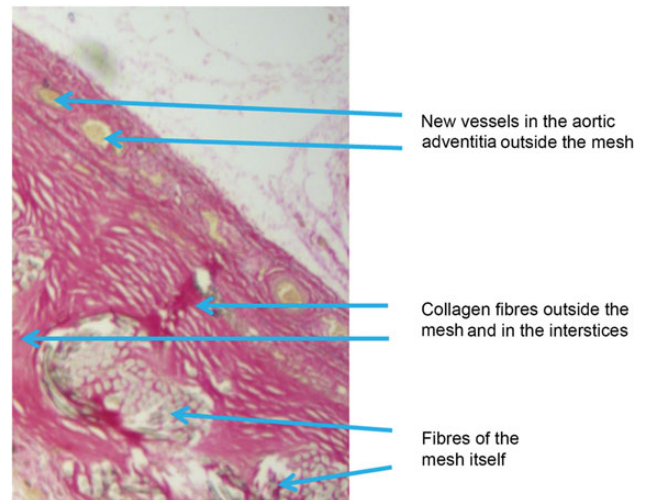
**Figure 1:** On the left is the mesh sleeve on a former made by computer-aided design and rapid prototyping (3D printing). The porosity of the mesh can be seen and its soft and pliant texture in the fingers is evident. On the right is a composite illustration to show the relationship between the brachiocephalic trunks and the right and left coronary arteries. BCA: brachiocephalic artery; LCA: left coronary artery; RCA: right coronary artery.



**Figure 2:** A pseudo-axial view of the aorta in a patient with Marfan syndrome (A) before and (B) 10 years after implantation of a PEARS. Reproduced with permission from the *New Engl J Med* [6]. PEARS: personal external aortic root support. The green arrows indicate the point of maximum cross sectional diameter at the level of apposition of the aortic leaflets, unchanged after 10 years. The yellow arrows indicate discernible thickening due to incorporation of the mesh.

a manufacturing process. A support of the right shape is then presented to the surgeon ready to apply (Fig. 1). It is customary to prepare more than one copy. An undersized 95% support is a useful means of restoring the aortic root to a slightly smaller size which, as has been shown by Plonek *et al.* [13], can correct aortic valvular regurgitation.

The chemical composition of the synthetic medical grade thread shares biocompatibility with tried and tested materials, but differs in that the PEARS implant has a soft macroporous mesh structure rather than the rigid format used for vascular grafts. A similar mesh fabric has previously been shown to be fully incorporated in the human aorta, and the fabric itself appears from the previous experience of others to remain stable indefinitely [14, 15]. In a meticulous analysis of 'blind' read--reread measurements made in multiple sequential images, we have confirmed that the aortic root retains its shape and size over several years and it is likely to then remain stable [16].

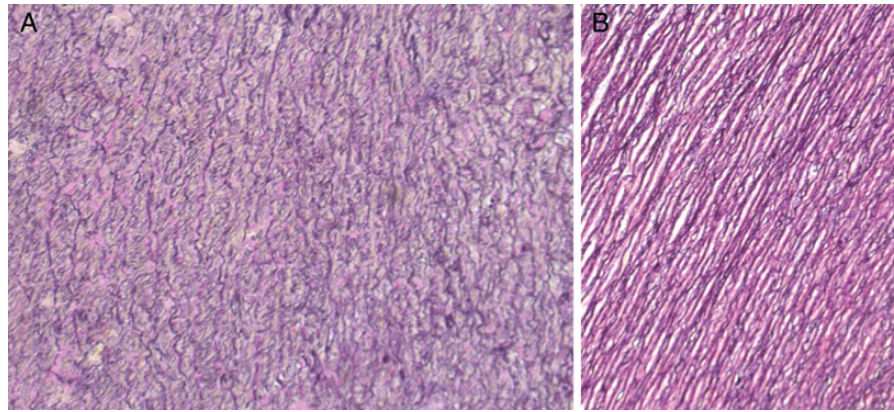


**Figure 3:** The incorporation of the mesh in the adventitia with collagen fibres growing through the interstices and new vessel formation in the adventitia. Original photograph supplied by Prof. Martin Goddard, Papworth Hospital, University of Cambridge [7].

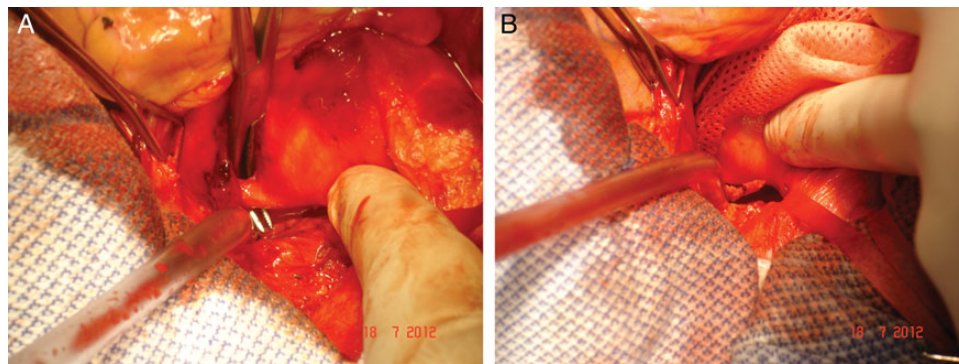
## ADVERSE EVENTS

Detailed clinical results have been reported in the first 30 patients who had completed at least 1-year follow-up and are now, on average, 7 years after operation [3]. This experience includes the following single instances of specific adverse events, based on review of all operated patients in our experience with PEARS, with data collected on an intention-to-treat basis.

- (i) There has been one death with an implant in place, more than 4 years after a successful surgery in a man of 26 years of age. Death appeared to be unrelated to the PEARS procedure or the implant itself. He died in his sleep probably due to arrhythmia. His mother also had Marfan syndrome and arrhythmia related to it. The aorta and aortic valve were independently judged to be intact by a cardiac pathologist. To our considerable surprise, the autopsy findings were of normalization of the histology of the aortic media. The pathologist's interpretation was that the relief of beat-by-beat aortic wall stress, afforded by the fully incorporated mesh, may have allowed restoration of healthy collagen [7]. This is in line with restoration of function in other collagen-containing tissues treated with splinting or support (Fig. 4).
- (ii) There has been only one reoperation. Following PEARS surgery in 2009 in a 44-year old woman, the mesh suture line was partially released after reopening of the sternotomy in the intensive care unit for hypotension. No explanation was found. The aorta was monitored closely and while the root remained stable in general, there was expansion of the unsupported non-coronary sinus resulting in aortic valve regurgitation. At reoperation after 6 years, the supported aorta was robust and could be safely cut and sewn. The operating surgeon (Ulrich Rosendahl) thought that spontaneous dissection of her aorta was probably precluded by the robustness of the mesh/aorta composite wall. This 'natural experiment' confirms earlier findings in the use of an equivalent mesh in the 1980s and 1990s [15].
- (iii) There has been one perioperative death related to left main stem coronary injury in a patient with severe pectus excavatum. No mesh support was implanted. The focus of surgery



**Figure 4:** The histology of the media in the unsupported arch (A) compared with normal histology within the mesh supported area (B). The appearance commonly called 'medial necrosis' is not seen within the mesh and yet that is where one would expect to see it at its most severe. Original photographs supplied by Prof. Martin Goddard, Papworth Hospital, University of Cambridge [7].



**Figure 5:** The dissector is passed proximal to the left coronary artery (A) and the tongue of the mesh support passed beneath it. (B) The mesh is then anchored to the aortoventricular junction. Original photographs from Mario Petrou [1]. The continuity of the mesh is restored by suturing the incision made to include the coronary artery.

was limited to the recovery of the myocardium. The cause of death 5 days after the surgery was a cerebral bleed related to cardiac support at a time when the left ventricular function was improving. This serves as a stark reminder that no aortic root surgery can be regarded as 'safe'.

## REDUCTION IN SURGICAL COMPLEXITY AND THE BURDEN OF CARE

PEARS provides an engineered solution based on the measurement of the individual patient's images. It, therefore, avoids the need for *ad hoc* tailoring. This moves the surgery nearer to the principle of 'workmanship of certainty' where the hazard is reduced by making the measurements and judgements ahead of time [17] and away from the 'workmanship of risk' where minor errors of judgement and technique may compromise the whole objective of valve-sparing surgery. This analysis of a spectrum of types of workmanship is from the late David Pye of the Royal College of Art in London [18] and was alluded to by Tirone David in his AATS presidential address [19].

The operation does not require interruption of the coronary blood flow because there is no need for the heart to be arrested or the aorta to be opened. Cardiopulmonary bypass is not usually required, but a degree of controlled hypotension facilitates dissection of the aorta, particularly proximal to the left coronary artery

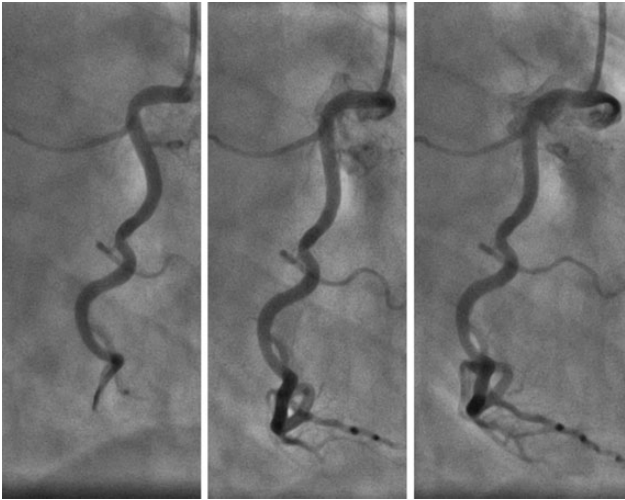
(Fig. 5). There being no randomized patients, this analysis of peri-operative burden of care required an innovative study design including statistical minimization to achieve the best possible comparative analysis [20]. In this analysis of the first 20 PEARS patients, compared with matched patients having root replacement, operation time was half, blood loss a quarter and transfusion and cardiopulmonary bypass were largely avoided. Although these are well tolerated in young patients [21], they have inherent risks and there is merit in avoiding them [22].

## FREQUENTLY ASKED QUESTIONS

In the course of presenting our results, discussants and reviewers have raised concern about potential dangers. There have been recurring themes and so we will address these frequently asked questions here.

### Wraps migrate

The commonest concern is an extrapolation from the complication occasionally seen after the aorta has been wrapped with stiff, low porosity vascular graft material [11] after which surgeons have encountered cases of graft migration and impingement on the coronary orifices. This has never happened to date with PEARS



**Figure 6:** A coronary angiogram was performed in the first patient 7 years after implantation of PEARS [24]. The passage of the catheter in to the coronary artery and back flow into the aorta is unimpeded and appears usual for coronary angiography. PEARS: personalised external aortic root support.

and after nearly 12 years' experience, we think we may have enough accumulated experience to think that this complication is unlikely to occur. The mesh is fully incorporated with natural growth of adventitial collagen; new blood vessels grow through and around the 0.7 mm pores in the soft mesh [7, 15, 23] (Fig. 3). The mesh cannot move independently of the aortic wall once that incorporation has taken place and seems to form a new composite structure. Because the knitted mesh of the support is extremely soft and pliant it is unlikely to do any harm because it does not present a hard edge to the coronary artery. In 2 patients, coronary angiograms have been performed (at 1 and 7 years) and the orifices were widely patent and the take-off from the aorta was completely normal [24] (Fig. 6).

### The aorta is known to become thinner after wrapping

Another fear has been that there would be thinning of the aorta as reported in 2 patients within *ad hoc* Dacron wraps [25]. In fact, we have seen the opposite effect. The incorporation of the mesh in the aortic adventitia causes an overall moderate increase in thickness of the aorta, just discernible on magnetic resonance imaging [6]. This effect has been seen histologically in historical human use of a similar mesh [14, 15] and in sheep experiments [23]. The thickening appears to be due to new connective tissue, generated in response to the mesh [7] (Figs 3 and 4).

### The aorta is still there and may dissect

There was a fear that dissection could still occur within the supported aorta but to date that has not happened in any patient with PEARS. The histological changes seem to us to make that less and less likely (Figs 3 and 4).

Increase in size is the biggest risk for dissection; PEARS holds the aorta with no further enlargement, so the principal calculable risk is obviated [16]. At the point where the intimal tear is characteristically seen, the aortic wall stress is ameliorated [26]. Drug trials of losartan

have thus far failed to halt the progression of root dilatation [27]. PEARS appears to consistently achieve this effect. Marfan syndrome remains the major indication for PEARS, but our experience includes other aortic root pathologies, as yet in small numbers.

## CLINICAL FOLLOW-UP

There have now been more than 60 operations with a median follow-up of 6 years (range up to 12 years) and 260 patient-years of follow-up. With the exception of the patients itemized above, all patients are free from aortic or aortic valve adverse events. Details were provided in previous publications [3].

## EVALUATION OF NEW TECHNOLOGIES

How surgical devices should be evaluated has been the subject of expert discussion [28–30]. Determined efforts were made by us to design a randomized controlled trial (RCT) [31–33]. After much expert consideration with trial methodologists, including those in the National Institute for Health Research which oversees research in the British National Health Service, an RCT was deemed impossible for two reasons. One was the challenge of finding either surgeons or patients in true equipoise since there are such clear differences in the potential consequences of PEARS, the modern Bentall composite root replacement and valve-sparing root replacement [5, 34–36]. The other is the rarity of the disease and therefore in the number of individual patients who are at a point in their lives when they face the choice of which operation to have. With an increasing number of patients and the passage of time, PEARS appears to be at the point in its development when observational studies may prove to be sufficient evidence as is now the case for both Bentall's and David's operations [35]. As far as we know, there have been no randomized trial of either operation, and probably for similar reasons. Compared with no surgery, either of the existing prophylactic operations meets the criteria for acceptance of observational evidence alone [37, 38]. Any comparison between them involves acceptance or avoidance of lifelong anticoagulation [21], so a position of 'equipoise' is unlikely to be attained because that is not likely to be a 'toss-of-a-coin' decision. PEARS is more comparable with David's operation, but it would require surgeons experienced in valve-sparing root replacement to see PEARS as having sufficient equivalence to permit random assignment.

Our current policy is to cautiously extend the use of PEARS with surgeons who wish to adopt this technique and who are interested in the use of custom-made devices in their own selected patients. A process of proctoring is in place for those who want to share in the evaluation of this promising approach to genetically determined aortic root aneurysms. The operation has undergone Health Technology Appraisal under the auspices of NICE in England [39]. It is a candidate for Commissioning through Evaluation [40] and is out to patient and public consultation with the statement 'Given the potential high value of this intervention, the clinical panel recommended that the commissioning team develop a proposal for Commissioning through Evaluation or a public value trial.' (<https://www.engage.england.nhs.uk/consultation/spec-services-clinical-commissioning>).

**Conflict of interest:** none declared.

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