ExoVasc® Personalised External Aortic Root Support (PEARS)

Project Status – 20 May 2019

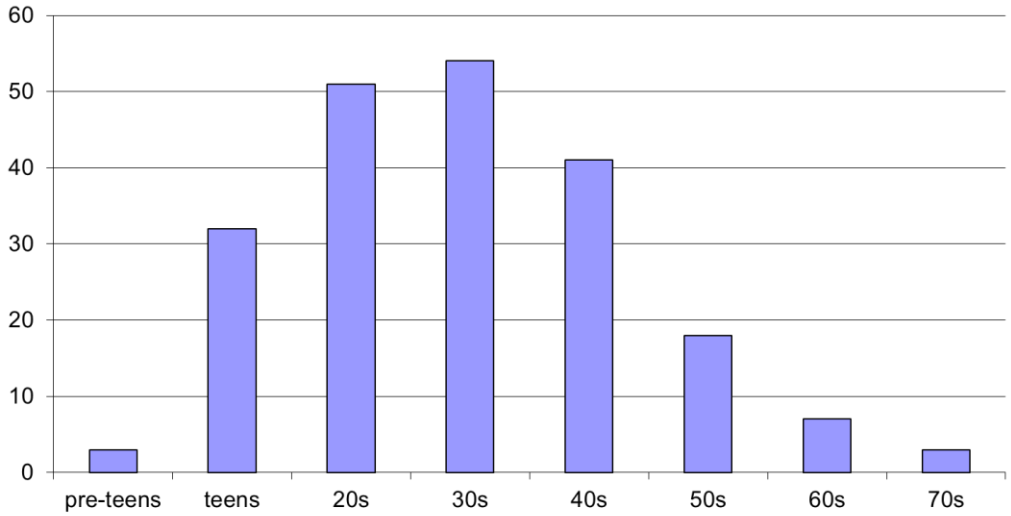
1. Patient Numbers & Demographics

As of 20 May 2019 we have treated 209 patients using Personalised External Aortic Root Support (PEARS) surgery and the ExoVasc® implant:

141 males + 68 females with a collective total of 657 post-operative patient years experience

- Patient 1 @ 15 years post-op
- 18 patients @ 10 years post-op
- 40 patients @ 5 years post-op

PEARS – Patients' ages



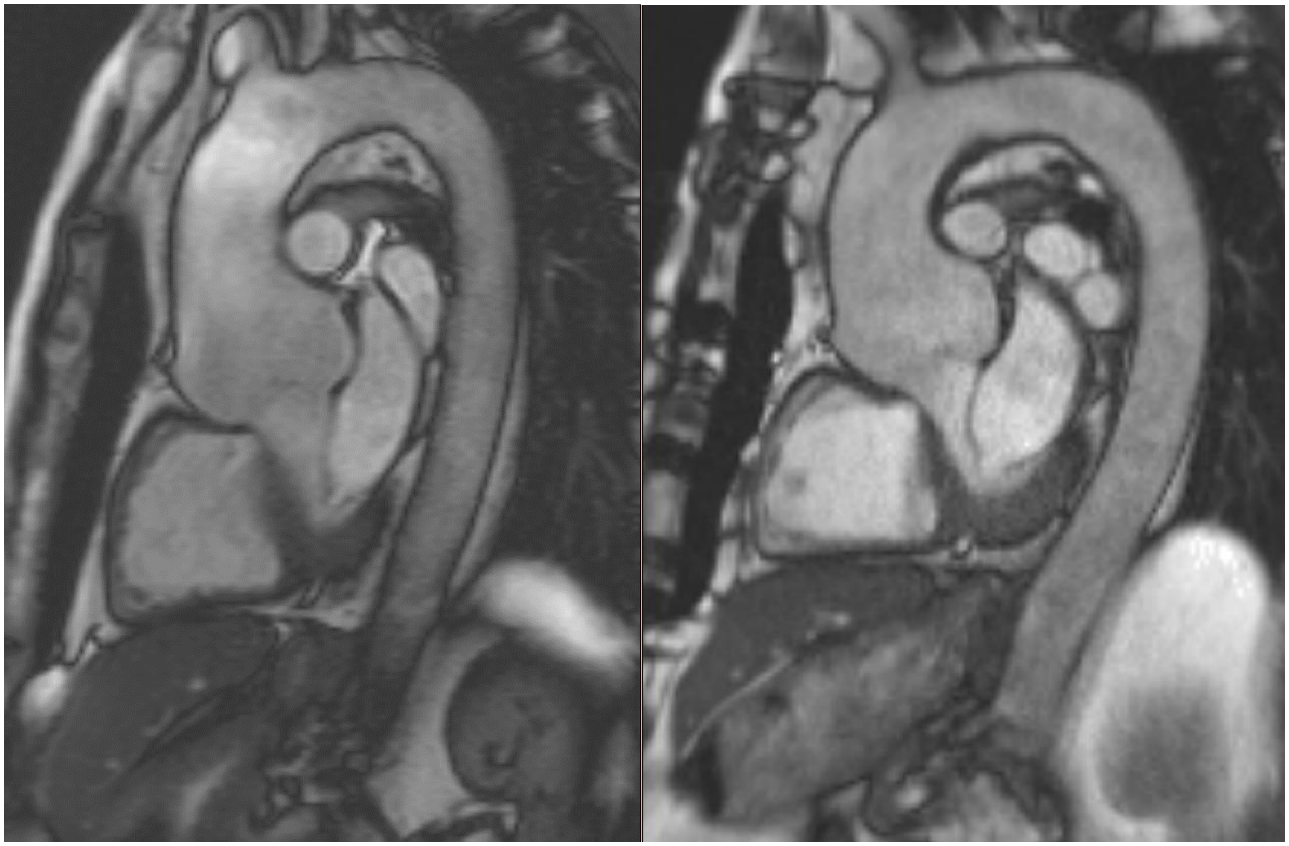
2. Disease types treated

PEARS surgery has been applied to aortic management associated with:

- Marfan syndrome - >135 (12 patients having concurrent mitral repair)
- Loeys-Dietz syndrome - 11
- Bicuspid Aortic Valve disease - >14 (4 bi-sinuate, bicuspid + 10 tri-sinuate fused bicuspid)
- Transposition of the great arteries repaired by a switch operation - 3
- Tetralogy of Fallot -1
- Aortic valve disease - Ross Procedure – 13 (including 2 Turner Syndrome)
- Idiopathic – >15
- ACTA2 - 2

3 Control of Aortic Dilation

Patients have been invited to have annual cardiac MRI. Patient 1 has been scanned annually. This (unchanging) image pair being typical: - pre-op and 15 years post op:



Patient 1: April 2004 (3 weeks pre-op) and January 2019 (15 years post-op)

This demonstrates stability of the aortic dimensions and morphology within the ExoVasc® implant over a significant time period.

4. Patency of coronary arteries through the ExoVasc® implant

Patient 1 had exercise induced angina in 2011 (7 years post PEARS surgery). A routine coronary angiogram carried out at the time showed smooth coronary lumens and widely patent coronary orifices where the coronary arteries pass through the soft, pliant textile of the ExoVasc® implant.

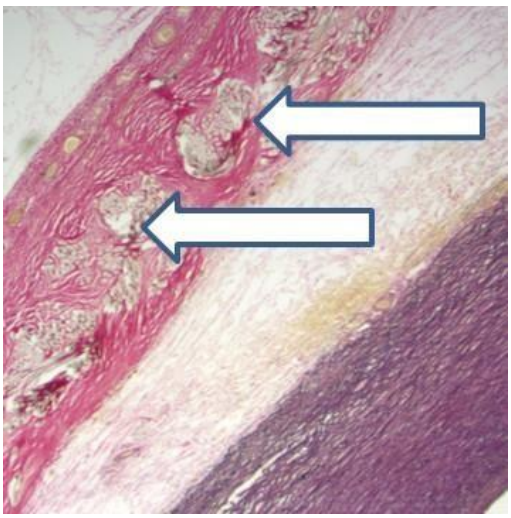
(see: https://exstent.com/wp-content/uploads/2017/04/icvts.ivs237.full_-1.pdf)

Patient 16 with Marfan syndrome and a bicuspid aortic valve died of a non-aorta related event some 4.5 years after PEARS surgery. As part of a post mortem examination, his aorta was examined. The coronary orifices and proximal coronary arteries were patent and appeared normal.

(see: https://exstent.com/wp-content/uploads/2017/04/Pepper-Goddard-RM-TT-ejcts-2014-1.pdf)

5 Incorporation of the ExoVasc® implant

Further histological inspection of patient 16's aorta also showed complete incorporation of the ExoVasc® implant into the adventitia, including neo-vascularisation.

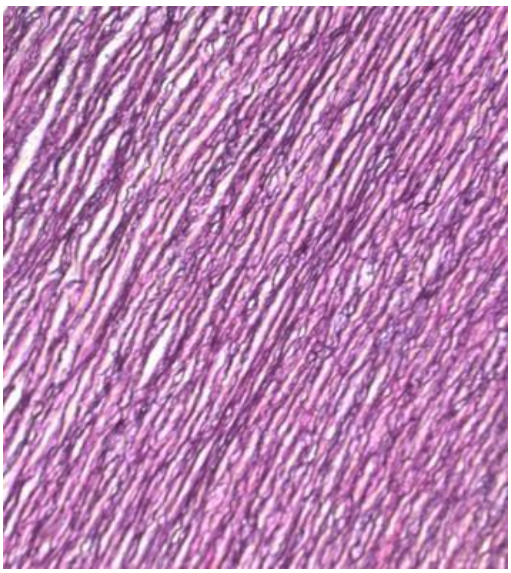


Neovascularisation (small yellow circles, top left of image) in the outer layers of the adventitia. The implanted textile (arrowed) is fully incorporated. (Note that the media has separated from the adventitia during sample preparation)

6. Repair of Media within the ExoVasc® implant

Not only does the PEARS ExoVasc® implant become incorporated into the adventitia, but the media within the implant recovers. While it remains fibrillin deficient, the media assumes a normal histological appearance. This is entirely consistent with the tensile load having been removed from the media and handled by the implant. The following images are taken from the paper by John Pepper and Martin Goddard:

(see: https://exstent.com/wp-content/uploads/2017/04/Pepper-Goddard-RM-TT-ejcts-20141.pdf)



Recovered media within PEARS ExoVasc® implant showing normal histology

7 Recovery of dilation-induced aortic regurgitation

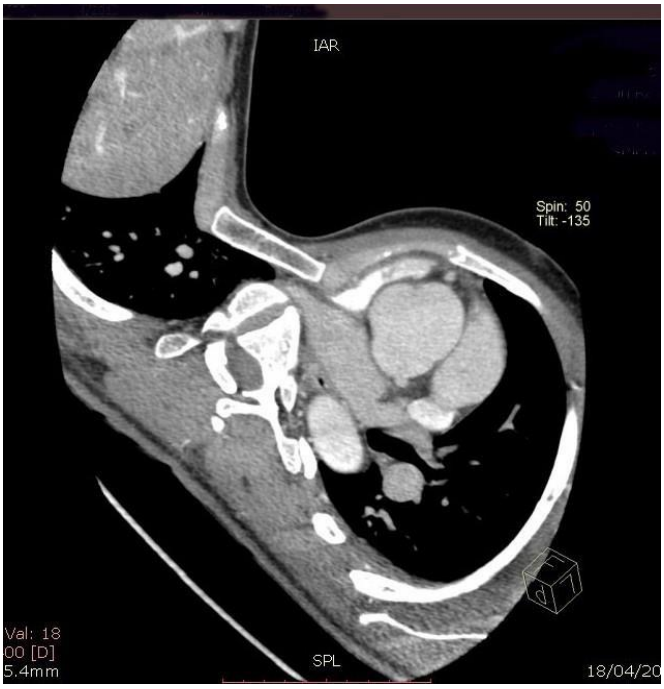
In order to provide security, in the event of 1 implant being unusable, Exstent Ltd supply 2 custom implants per patient. These are normally scaled on diameter at 100% and 95% to give the surgeon some additional choice. In 12+ cases, where some pre-operative AR was reported, the surgeon implanted the 95% ExoVasc® and subsequent Trans Oesophageal Echo./Trans Thoracic Echo examination reported reduction/eradication of the AR. Given the clinical requirement of dropping BP during the procedure (to better access the aortic root and effect the dissection down to the AVJ) fitting the 95% implant would seem a sensible step as it will reduce aortic diameter and thereby reduce tensile wall loading/risk of medial dissection.

If this reasonable clinical approach also improves coaptation of the aortic valve leaflets in a dilated aorta and recovers AR then this represents another positive benefit for the patient.

8. Intention to Treat - Surgical conversions & mortality

Of 214 patients intended for PEARS surgery, one was converted to VSRR (P86), one converted to a Florida Sleeve (P98), two converted to TRR (P119 & P191), one died perioperatively and a further patient (P112) died 7 months after surgery.

The patient who died perioperatively (P36) had a severe pectus (see below) which compromised access to the aorta. During the dissection of the aorta in preparation for the implantation, there was an operative injury to the left main coronary artery. Despite being swiftly put onto bypass (and later ECMO), the patient recovered slowly (72 hours) and then suffered an intra-cranial bleed from which he did not recover. The ExoVasc® support was not implanted in this patient.



Transaxial view of patient 36 - severe Pectus Excavatum

The second death was in patient P112 who had a history of aortic valve replacement and alcoholic cardiomyopathy that had been managed by implanting an ICD. This patient had a flow limiting lesion in their left circumflex artery prior to surgery. Postoperatively the patient developed cardiac failure due to an occluded circumflex coronary artery, which was managed by reoperation to adjust the ExoVasc support and application of a stent graft to the circumflex artery. Twelve days later the patient had a cardiac arrest and his ICD was reactivated. The patient died 6.5 months later of congestive heart failure.

9 Operation time
Surgical operation times for the PEARS procedure have been around 2 to 3 hours. This contrasts well with TRR and VSRR where patients might expect to be anaesthetised for between 4 and 7 hours.

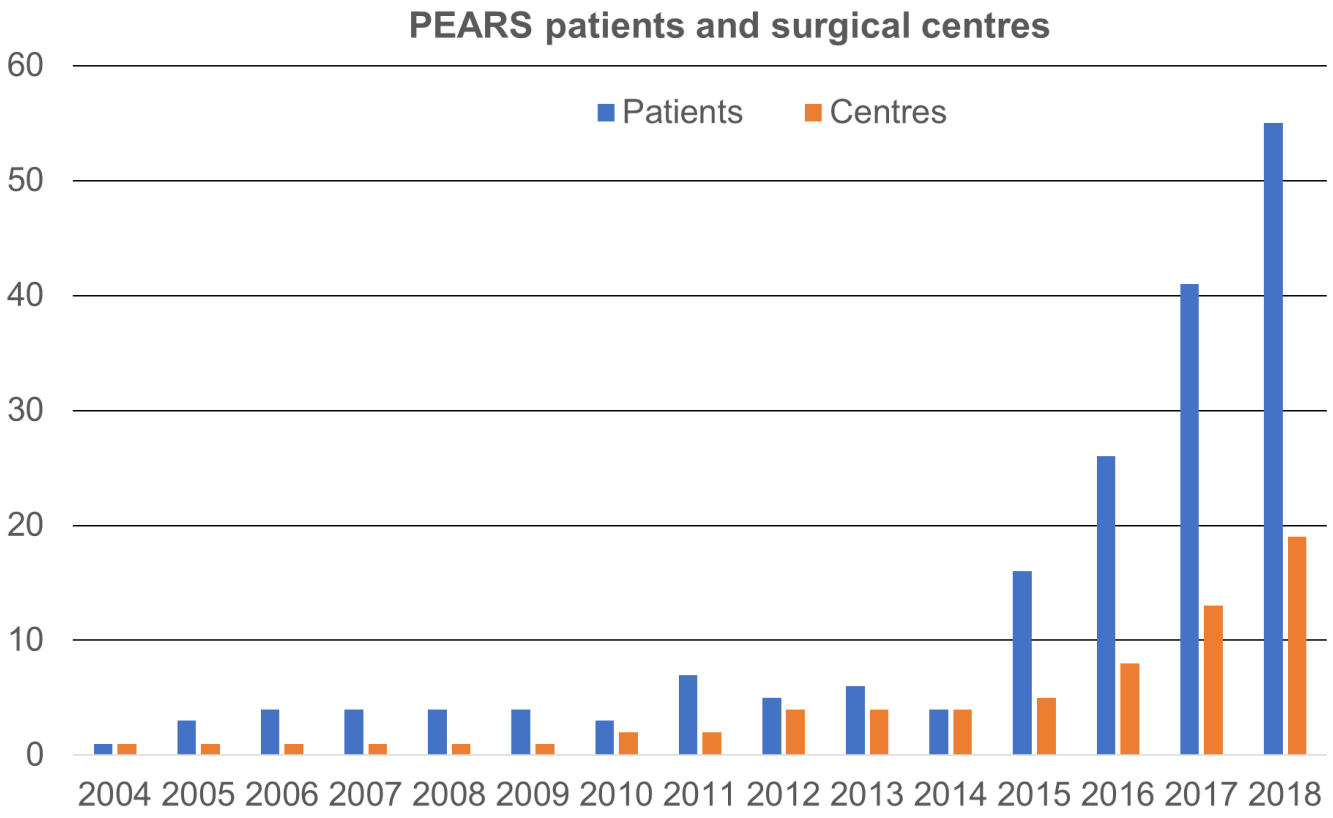
This shorter time in the operating room has a beneficial impact on overall procedure costs and should improve patient experience & recovery.

10. Cardio Pulmonary Bypass
PEARS surgery for patients with uncomplicated aortic anatomy is routinely carried out on a beating heart without cardiopulmonary bypass (CPB). In a small number of more complex cases, for example, in the Ross procedure and where anomalous coronary morphology or adhesions exist, CPB is used in parallel with a beating heart and at normal body temperature.

Apart from the reduction in procedure costs this represents, patient experience & recovery are both improved.

10. Parenthood
Four female Marfan patients (P3, P10 P42 & P51), having received an ExoVasc® implant, have subsequently had 5 uneventful pregnancies and deliveries of 5 infants without evidence of further aortic dilatation.

11. Patient take-up and clinical centres offering PEARS surgery
Patient take up is now accelerating with increased surgical centre numbers;



As of May 2019, there are 23 surgical centres offering PEARS surgery:

8 in the UK	2 in Ireland
1 in Belgium	1 in the Netherlands
6 in The Czech Republic	1 in New Zealand
3 in Australia	1 in Malaysia

Discussions are ongoing with prospective new surgical centres in Poland, Czech Republic, Slovakia, Switzerland, Australia and New Zealand

12. Formal Clinical Trial

After considerable time and effort was put into attempting to devise an appropriate Randomised Control Trial for PEARS, including extensive discussions with the UK's National Institute for Health Research (NIHR) and the Surgical Intervention Trial Unit at Oxford, the collective decision was that the patient numbers involved are too small to afford a useful level of statistical significance to any trial outcome, and it would be too difficult to find a reasonable and ethical strategy for the control group within the PICO that would be acceptable to patients.

13. Reference publications:

Copies of all the clinical papers on PEARS can be found at:

https://exstent.sharefile.com/d-s115d3b6953b485ca

T J Golesworthy
C Eng MEI MRSC

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