ExoVasc® Personalised External Aortic Root Support (PEARS)

Project Status – 16 February 2021

1. Patient Numbers & Demographics

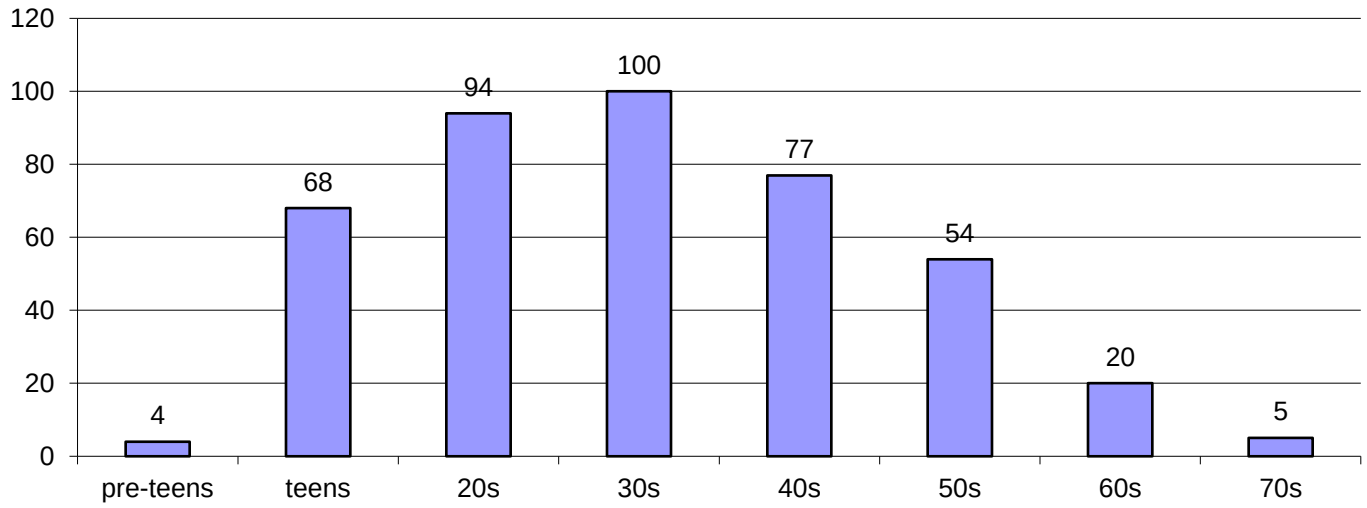
As of 16th February 2021, we have treated 422 patients using Personalised External Aortic Root Support (PEARS) surgery and the ExoVasc® implant:

292 males + 130 females with a collective total of 1199 post-operative patient years' experience

- Patient 1 @ 16 years post-op
- 22 patients @ 10 years post-op
- 62 patients @ 5 years post-op

PEARS – Patients' ages

The age range of patients treated is from 3 to 75 with the following age distribution:



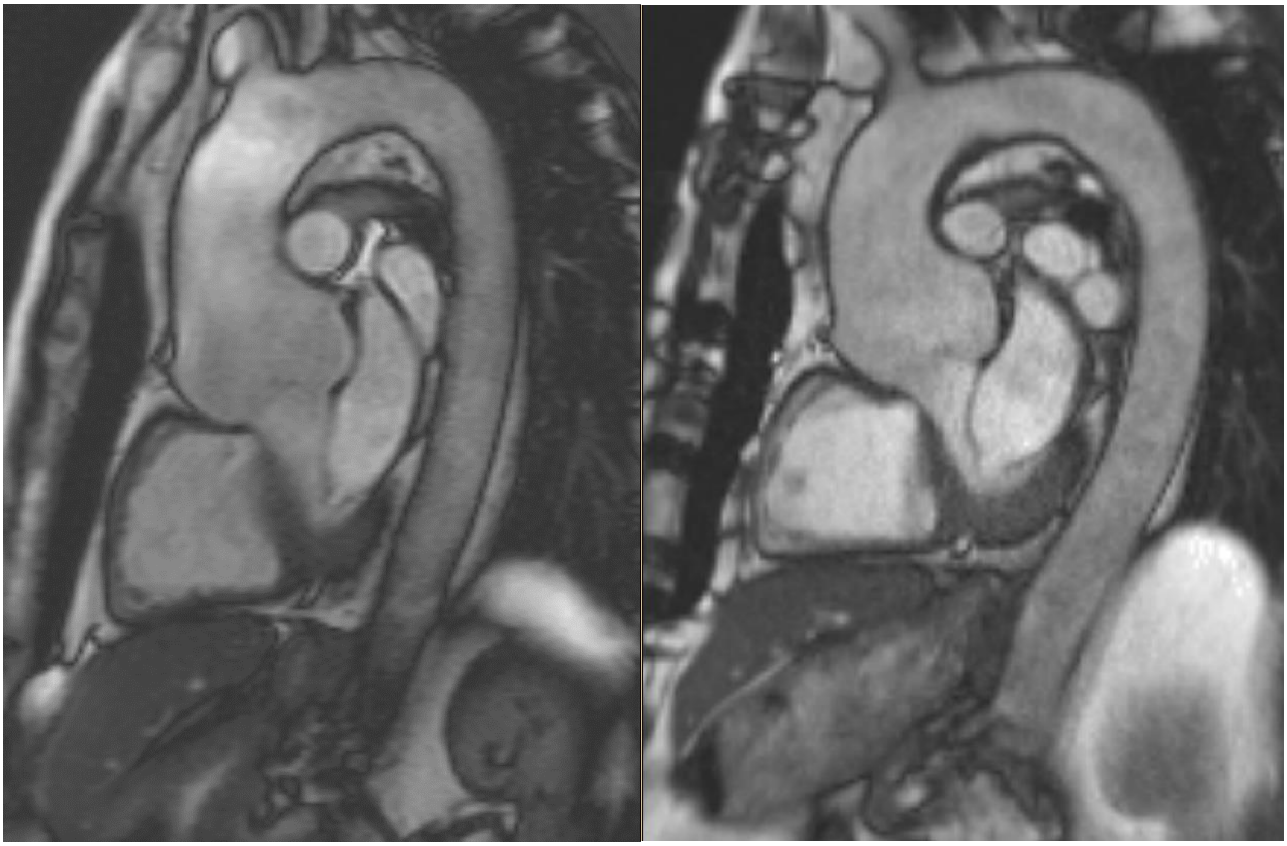
2. Disease types treated

PEARS surgery has been applied to aortic management associated with the following established conditions:

- Marfan syndrome – 224 (14 patients having concurrent mitral repair)
- Loeys-Dietz syndrome - 28 (1 patient having concurrent mitral repair)
- Idiopathic aortic dilation/other – 59 (inc. Turner's Syndrome, SMAD3, MYBCP3, NOS & FAAP)
- Bicuspid Aortic Valve disease - 52 (1 patient having concurrent mitral repair)
- Transposition of the great arteries repaired by a switch operation - 5
- Tetralogy of Fallot -1
- ACTA2 mutation – 3
- Aortic valve disease treated by the Ross Procedure – 35 (1 patient having concurrent mitral repair)
- Post free-standing root Ross operation autograft dilation – 6
- Case Report Form yet to be received – 15

3. Control of Aortic Dilation

Patients have been invited to have annual cardiac MRI and none have shown any sign of further dilatation. Patient 1 has been scanned annually with the following (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.

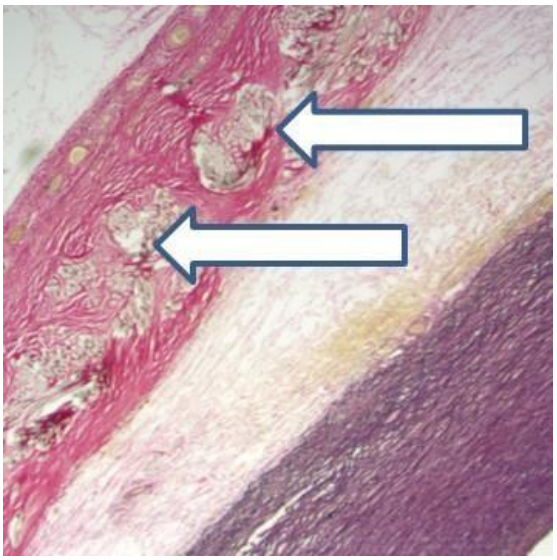
(see: https://exstent.com/wp-content/uploads/2017/04/icvts.ivs237.full_-1.pdf)

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 postmortem examination, his aorta was inspected and 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.

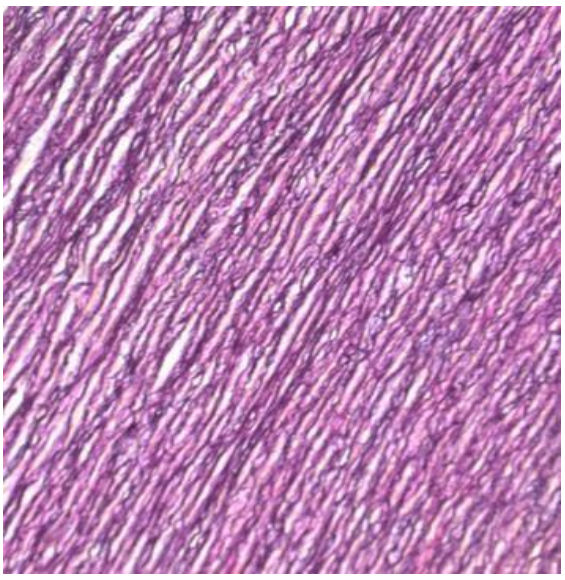


Neo-vascularisation (small yellow circles, top left of image) in the outer layers of the adventitia. The implanted textile (arrowed) is fully incorporated. (Note that the media has separated from the adventitia during sample preparation)

6. Repair of the 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 (in Marfan syndrome patients), the media assumes a normal histological appearance. This is entirely consistent with the repetitive tensile load having been removed from the media and handled by the implant.

(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

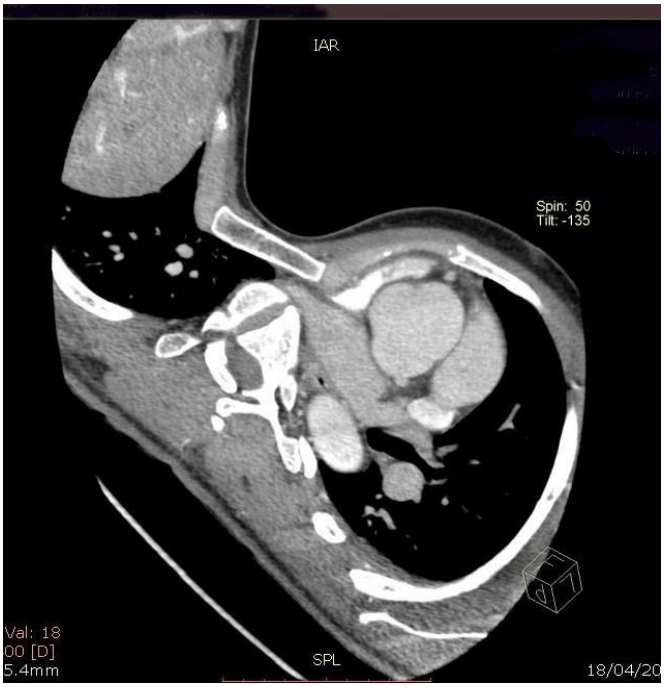
In order to provide security, Exstent supply 2 custom-made implants per patient. These are normally scaled on diameter at 100% and 95% to give the surgeon some additional choice. In at least 68% of cases, where some pre-operative AR was reported, subsequent Trans Oesophageal Echo./Trans Thoracic Echo ultrasound examination reported reduction or 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 and 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 430 patients intended for PEARS surgery, three were converted to VSRR, one converted to a Florida Sleeve, three converted to TRR, one died perioperatively and a further patient died 7 months after surgery.

The patient who died perioperatively (number 36) 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 and after 72 hours suffered an intra-cranial bleed from which he did not recover. The ExoVasc® support was not implanted in this patient. This represents a < 0.25% peri-operative mortality rate



Trans-axial view of Patient 36 with severe Pectus Excavatum

The second death 7 months after surgery was in a patient 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. Subsequent surgical access

Surgical evidence from 5 patients undergoing surgery subsequent to their PEARS surgery, suggests that the textile/living tissue composite that is created around the PEARS implant some months post PEARS surgery, is amenable to normal surgical cutting techniques and should present no barrier to follow-up surgery on the aorta.

11. Cardio Pulmonary Bypass

PEARS surgery for patients with uncomplicated aortic anatomy is routinely carried out on a beating heart without cardiopulmonary bypass (CPB) in approximately 79% of cases.

In a small number of more complex aortic cases, for example, in cases of concomitant mitral valve repair or where anomalous coronary morphology or adhesions exist, CPB is used in parallel with a beating heart at normal body temperature.
In complex PEARS surgery, eg PEARS reinforced free-standing root Ross procedures, CPB and body cooling are used.

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

12. Parenthood

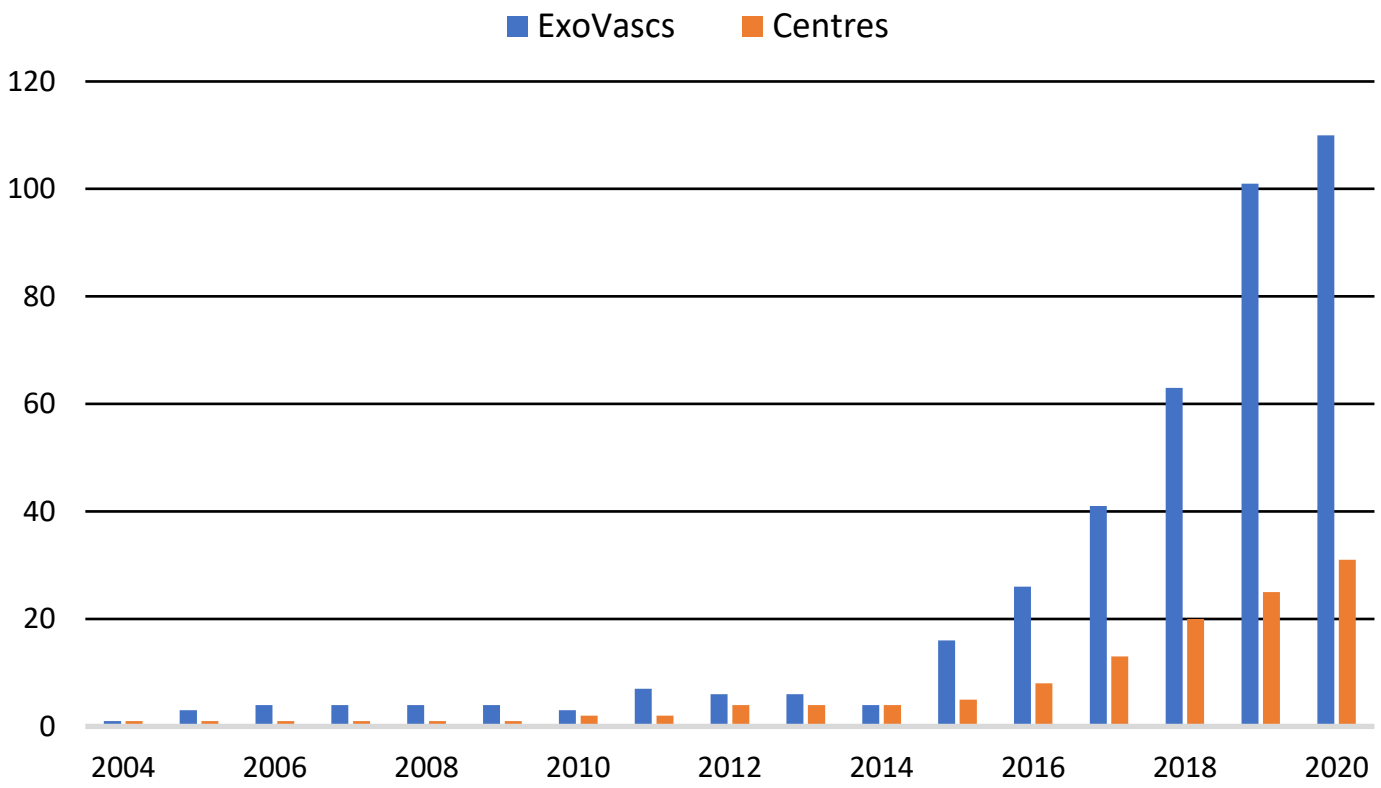
We know of ten female patients (9 MFS + 1 LDS) who have received an ExoVasc® implant and have subsequently had eleven successful pregnancies without evidence of further aortic dilatation. One of these patients had her (off-pump) PEARS surgery during her 2nd trimester. Both mother and child are doing well.

13. Procedure growth and clinical centres offering PEARS surgery

As of December 2020, there are 31 surgical centres offering PEARS surgery:

7 in the UK	2 in Ireland	1 in Belgium
2 in the Netherlands	8 in The Czech Republic	2 in New Zealand
3 in Australia	1 in Malaysia	1 in Poland
3 in Slovakia	1 in Greece	

In the last 5 years, patient take up has accelerated along with the increase in surgical centres;



Increase in PEARS surgical centres and patient numbers.

14. 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 and the Surgical Intervention Trial Unit at Oxford, the collective decision was that the patient numbers requiring this type of aortic surgery 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.

This subject is discussed further by Tom Treasure et al here: https://exstent.sharefile.com/d-sef4ba0a87c1646fdbfda3991d8e29ba0

and by Christoph Nienaber et al here: https://exstent.sharefile.com/d-s3397f67410504321a2a089665db47669

15. Reference publications:

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

https://exstent.sharefile.com/d-s6974127ec5014244a8ebef551669ab28

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