

doi:10.1093/eurheartj/ehaa596

PEARS procedure and the difficulty to provide evidence for its benefits

Personalised External Aortic Root Support (PEARS) in patients with a dilated aortic root and ascending aorta was established some time ago although is still not fully recognised by the cardiovascular community.¹

The ExoVasc[®] Personalised External Aortic Root Support (PEARS) is a computer designed, custom-made implant to match individual aortic root morphology. It was first introduced in 2004 as a conservative surgical approach for Marfan patients with asymptomatic aortic dilation.^{2–4} The concept and production of a personalized device was the

result of research and development between 2000 and 2004 when the first operation was performed.^{2,5}

Computer-aided design based on three-dimensional re-construction of magnetic resonance/computer tomographic (MR/CT) images, a dedicated manufacturing method, and a refined surgical technique

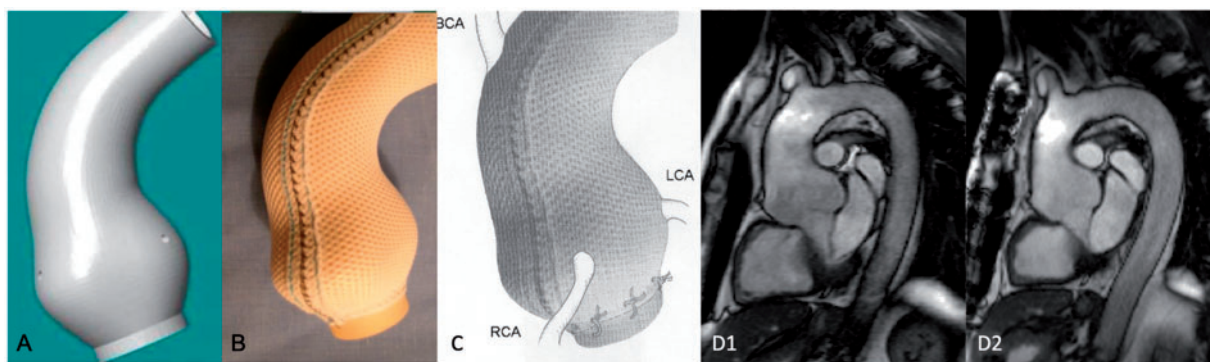


Figure 1 (A) Model created with measurements from MRI. (B) Replica of the aorta in thermoplastic, from three-dimensional printing and the soft macroporous mesh sleeve. (C) Relationship between support and the aortoventricular junction, the coronary, and brachiocephalic arteries. (D) Before (D1) and 12 years (D2) magnetic resonance (MR) scans with complete conservation of the aortic root architecture.

have all essentially remained consistent since inception without the need for iterative improvement, different from valve-sparing root replacement (VSRR) and total root replacement (TRR). In 2011, PEARS underwent health technology appraisal by the Interventional Procedures Advisory Committee (IPAC) of the (British) National Institute of Health and Care Excellence (NICE) with approval for selected patients.⁶ Figure 1 summarizes the concept of PEARS from manufacturing to clinical practice.

According to an internal audit in April 2020, PEARS had spread through a few centres across Europe, Australia, and New Zealand, and applied to 321 cases in 29 centres including 184 patients with Marfan syndrome, 27 with bicuspidity, 21 with idiopathic aortopathy, and 19 with Loey-Dietz syndrome. The concept has also been extended for support of pulmonary autograft in the setting of a Ross operation in 29 patients. The interim analysis revealed a peri-operative mortality of 0.3%, and a short operation time as most PEARS surgeries were carried out off-pump. Surveillance data over 16 years show no late complications with regards to the index PEARS procedure.¹⁷ Despite such a robust track record the operation has not really been accepted widely as a pre-emptive intervention to avoid later complications, despite widespread documentation of success over 16 years. Obviously, PEARS is able to prevent further expansion of a mildly dilated aortic root/ascending aorta, further dilation of the aortic annulus and expansion of the sinotubular junction with no later valve incompetence or aortic dissection.⁸ Surveillance in general has been very reassuring.

At a recent meeting with a fellow cardiologist, I explained PEARS in detail and how it could be used as pre-emptive surgery in preventing expansion of the aortic root. I discussed this technology, now available for selected patients after careful screening, and tried to portray this innovation as a meaningful addition to the armamentarium of operations for patients with proximal aortopathy. Despite all success stories and compelling argument for pre-emptive surgery at relatively low risk, our discussion quickly ran dry when it came to randomized data to prove the benefit of a new concept over standard treatment!

Certainly, there is no answer as there is no randomized data. However, the question itself revealed the underlying dilemma when advocating PEARS as a useful and beneficial intervention for asymptomatic patients. Moreover, it became clear that the medical community has a fixation on results of randomized controlled trials (RCT) to

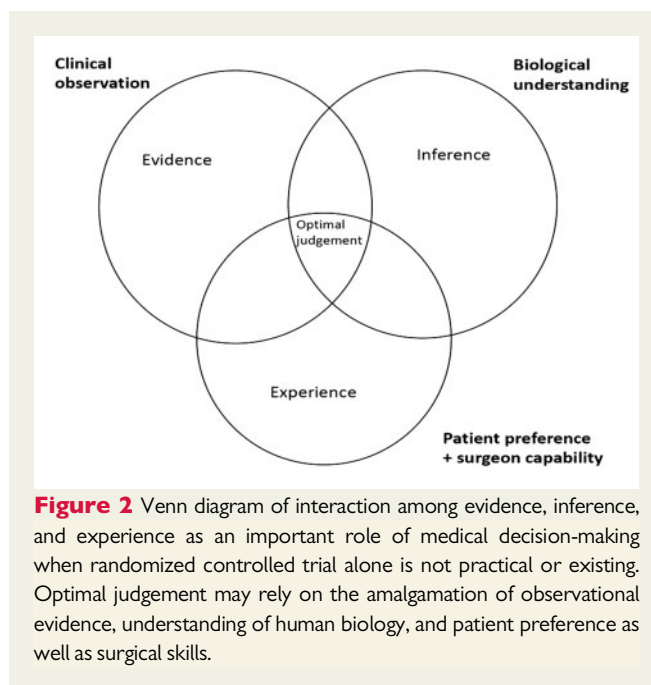


Figure 2 Venn diagram of interaction among evidence, inference, and experience as an important role of medical decision-making when randomized controlled trial alone is not practical or existing. Optimal judgement may rely on the amalgamation of observational evidence, understanding of human biology, and patient preference as well as surgical skills.

establish a new method in a traditional environment. But are RCTs the correct tool to evaluate pre-emptive surgery in a carefully selected patient cohort who has already shown benefit from it?⁹ Let's just imagine a RCT of PEARS against a standard treatment to prevent dilation of the ascending aorta or the aortic root.

First, the only accepted preventive action today is a pharmacological intervention using either beta-blockers or angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) to slow the process of aortic dilation in Marfan patients with minimal success. If you accept this as a pre-emptive intervention, a head to head comparison of patients with proximal aortopathy under preventive pharmaceutical therapy vs. another group under the same medication with additional PEARS would be a way to design a RCT.¹⁰ Of course, central elements of randomization such as blinding would not be possible due to the nature of such a trial and sham surgery involving thoracotomy will probably not be ethically viable.^{11–13} Most researchers agree that sham surgery may be considered only if conditions of scientific

necessity, minimal risk, and valid informed consent are all present which however, is unlikely in such a scenario.¹⁴

Second, another potential scenario could be a comparison between PEARS and other surgical approaches, e.g., aortic root replacement or repair involving valve preservation. However, this would mean that pre-emptive PEARS which ideally is invoked at a root diameter of 40–45 mm is compared with a different surgical approach usually recommended after reaching a critical threshold of 50 mm in Marfan aortopathy.¹⁵ This dilemma implies that both the demographic and anatomic profile of patients qualifying for either of the two operations would be different. A procedure probably most usefully applied early in the process of progressive dilation (such as PEARS) would be compared to an established operation intended for later in the dilation process, i.e., when reaching a critical threshold for replacement surgery (such as the David and Yacoub procedures). In other words, it would be comparing PEARS with apples, certainly not scientifically sound for randomization. Moreover, the nature of the operations is different, with PEARS being a relatively short procedure not requiring cardiac arrest, cardiac pulmonary bypass, or body cooling under normal conditions, whereas David or Yacoub operations take longer, require a different kind of expertise and certainly cardio-pulmonary bypass and hypothermic arrest over a lengthy period of time.¹⁶

Finally, while different conditions would not allow randomization the discussion on endpoints in comparing totally different surgical strategies would be futile and problematic with regards to suitable outcome measures.¹⁰ It would just not be rational to compare surgical strategies currently indicated for different reasons. Moreover, considering the relatively low prevalence of aortic dilation, any kind of RCT in this setting is likely to be underpowered and take a long time to complete recruitment and follow-up.

So, is it fair to challenge the success story of PEARS by requesting results obtained by RCT? Looking back into the history of clinical medicine, evidence supporting surgical procedures has usually been based on observational studies.¹⁷ Reflection over two decades reveals that less than half of surgical treatment recommendations could be addressed by a RCT¹⁰ including both Yacoub and David procedures. All surgical RCTs are conceptually hindered by factors including surgeons' preferences, operative expertise, sources of funding, referral pattern and selection bias. A Venn diagram (Figure 2) shows how inference interplays with evidence and expertise, all essential components of successful surgery.

In addition, an important element of a RCT is the existence of equipoise,¹⁸ a situation with no evidence that one strategy is superior or inferior to another. In the case of PEARS there is no such comparator, neither surgically nor pharmacologically that could serve as a control

group. One could advocate a comparison of PEARS with nothing or medication, which may however raise ethical questions considering that PEARS is already proven to be safe and efficacious in halting dilation of the aortic root/ascending aorta never shown by any other technology or pharmacology. With this in mind, the element of equipoise is essentially non-existent, without mentioning medico-legal concerns and surgeons' preferences. Moreover, ideally equipoise should not only exist in the medical community but also in patient groups.¹⁸ Other issues, such as blinding and sham interventions, fail to apply in a comparative trial with PEARS, even when comparing it to VSRR with another level of complexity. As already outlined, the indication for aortic replacement surgery is an advanced stage of aortopathy whereas PEARS is best applied in the early stage of aortopathy in asymptomatic patients. Once again, the fundamental basis for RCT is just not present.

Considering all of the above, the basis for any kind of RCT involving PEARS is absent and any comparative RCT is therefore futile. While we believe that there is neither a conceptual scenario for a comparative trial, nor justification for it, a way out of this dilemma remains a compulsory registry¹⁹ documenting every case from all centres practising PEARS. An external body should monitor this compulsory registry and demand complete data submission. Interested surgeons or centres should be given the chance to train a dedicate surgeon in centres with significant patient numbers.²⁰ By using a uniform data collection scheme and by submitting patients to the same aftercare and follow-up, sufficient data will be provided over time to evaluate PEARS even without any RCTs.

If we consider treating patients as our first priority, or even putting ourselves in the position of a patient with aortic dilation, would we really choose no intervention or a pharmaceutical intervention only? Do we believe that a dilated aorta, continuing to dilate, is going to stop dilating miraculously without intervention? And how does PEARS look when compared with existing surgical options at a stage of advanced dilation, i.e., TRR and VSRR?

Surely, we owe it to patients to consider not only conventional but also low-risk innovative procedures now available for selected patients. Finally, patients need to know about such innovative options; with an increasing number of informed patients presenting, the ethical risk of not considering innovative treatment may eventually extend to a credibility risk for the Cardiologist concerned, or even for the entire cardiovascular community.

Conflict of interest: none declared.

References

References are available as supplementary material at *European Heart Journal* online.



Christoph A. Nienaber MD, PhD
Corresponding author
Cardiology and Aortic Centre,
Royal Brompton & Harefield Hospital NHS
Foundation Trust, London SW3 6NP, UK
Department of Cardiology,
National Heart and Lung Institute,
Faculty of Medicine, Imperial College London, UK
Email: c.nienaber@bht.nhs.uk



Sabine Ernst MD, PhD
Department of Cardiology, National
Heart & Lung Institute,
Faculty of Medicine,
Imperial College London, UK
Cardiology Department,
Royal Brompton & Harefield Hospital
NHS Foundation Trust London SW3 6NP, UK



Xun Yuan MBBS MMed
Cardiology and Aortic Centre,
Royal Brompton & Harefield Hospital NHS
Foundation Trust, London SW3 6NP, UK
Department of Cardiology,
National Heart and Lung Institute,
Faculty of Medicine,
Imperial College London, UK

References online

Title: PEARS procedure and the difficulty to provide evidence for its benefits

References:

1. Izgi C, Newsome S, Alpendurada F, Nyktari E, Boutsikou M, Pepper J, Treasure T, Mohiaddin R. External Aortic Root Support to Prevent Aortic Dilatation in Patients With Marfan Syndrome. *J Am Coll Cardiol* 2018;**72**(10):1095-1105.
2. 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**(9445):1582.
3. Pepper J, John Chan K, Gavino J, Golesworthy T, Mohiaddin R, Treasure T. External aortic root support for Marfan syndrome: early clinical results in the first 20 recipients with a bespoke implant. *J R Soc Med* 2010;**103**(9):370-5.
4. Treasure T, Pepper J. A call for expressions of interest in a comparative study of the options for pre-emptive aortic root surgery for people with Marfan syndrome. *European Journal of Cardio-Thoracic Surgery* 2013;**44**:588.
5. Treasure T, Golesworthy T, Pepper J, Ruiz F, Gallivan S. Prophylactic surgery of the aortic root in Marfan Syndrome: reconsideration of the decision making process in the era of customised external aortic root support. *J Vasc Endovasc Surg* 2011;**18**:215-23.
6. Treasure T, Pepper J, Golesworthy T, Mohiaddin R, Anderson RH. External aortic root support: NICE guidance. *Heart* 2012;**98**(1):65-68.
7. Treasure T, Takkenberg JJ, Golesworthy T, Rega F, Petrou M, Rosendahl U, Mohiaddin R, Rubens M, Thornton W, Lees B. Personalised external aortic root support (PEARS) in Marfan syndrome: analysis of 1–9 year outcomes by intention-to-treat in a cohort of the first 30 consecutive patients to receive a novel tissue and valve-conserving procedure, compared with the published results of aortic root replacement. *Heart* 2014;**100**(12):969-975.
8. Izgi C, Nyktari E, Alpendurada F, Bruengger AS, Pepper J, Treasure T, Mohiaddin R. Effect of personalized external aortic root support on aortic root motion and distension in Marfan syndrome patients. *International journal of cardiology* 2015;**197**:154-160.
9. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *Bmj* 2002;**324**(7351):1448-1451.
10. Solomon MJ, McLeod RS. Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery* 1995;**118**(3):459-467.
11. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet* 2002;**359**(9307):696-700.
12. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood pressure* 1992;**1**(2):113-119.
13. Polgar S, Mohamed S. Evidence-Based Evaluation of the Ethics of Sham Surgery for Parkinson's Disease. *Journal of Parkinson's disease* 2019(Preprint):1-10.
14. Niemansburg SL, van Delden JJ, Dhert WJ, Bredenoord AL. Reconsidering the ethics of sham interventions in an era of emerging technologies. *Surgery* 2015;**157**(4):801-10.
15. Treasure T. CardioPulse: options for pre-emptive aortic root surgery for people with Marfan syndrome. *Eur Heart J* 2013;**34**(26):1947-9.
16. Treasure T, Pepper JR. Aortic root surgery in Marfan syndrome. *Heart* 2011;**97**(12):951-2.
17. Howes N, Chagla L, Thorpe M, McCulloch P. Surgical practice is evidence based. *British Journal of Surgery* 1997;**84**(9):1220-1223.

18. Lilford RJ, Jackson J. Equipoise and the ethics of randomization. *Journal of the Royal Society of Medicine* 1995;**88**(10):552.
19. O'Gara PT, Sundt TM, Acker MA, David TE, Michler RE, Borger MA, Ailawadi G, Thourani VH, Gillinov AM, Damiano RJ, Mack MJ, Lee R, Rose EA, Gardner TJ, Miller MA, Weisel RD, Gelijns AC. The Cardiothoracic Surgical Trials Network: Implications for clinical practice. *J Thorac Cardiovasc Surg* 2017;**154**(6):1938-1956.
20. Bashir M, Harky A, Fok M, Shaw M, Hickey GL, Grant SW, Uppal R, Oo A. Acute type A aortic dissection in the United Kingdom: Surgeon volume-outcome relation. *J Thorac Cardiovasc Surg* 2017;**154**(2):398-406 e1.