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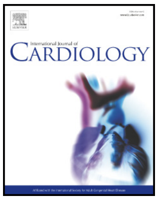

Effect of personalized external aortic root support on aortic root motion and distension in Marfan syndrome patients☆

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ABSTRACT

Objective: Personalized external aortic root support (PEARS) is a novel surgical approach with the aim of stabilizing the aortic root size and decreasing risk of dissection in Marfan syndrome patients. A bespoke polymer mesh tailored to each patient's individual aorta shape is produced by modeling and then surgically implanted. The aim of this study is to assess the mechanical effects of PEARS on the aortic root systolic downward motion (an important determinant of aortic wall stress), aortic root distension and on the left ventricle (LV).
Methods/results: A cohort of 27 Marfan patients had a prophylactic PEARS surgery between 2004 and 2012 with 24 having preoperative and follow-up cardiovascular magnetic resonance imaging studies. Systolic downward aortic root motion, aortic root distension, LV volumes/mass and mitral annular systolic excursion before the operation and in the latest follow-up were measured randomly and blinded. After a median follow-up of 50.5 (IQR 25.5–72) months following implantation of PEARS, systolic downward motion of aortic root was significantly decreased (12.6 ± 3.6 mm pre-operation vs 7.9 ± 2.9 mm latest follow-up, $p < 0.00001$). There was a tendency for a decrease in systolic aortic root distension but this was not significant (median 4.5% vs 2%, $p = 0.35$). There was no significant change in LV volumes, ejection fraction, mass and mitral annular systolic excursion in follow-up.
Conclusions: PEARS surgery decreases systolic downward aortic root motion which is an important determinant of longitudinal aortic wall stress. Aortic wall distension and Windkessel function are not significantly impaired in the follow-up after implantation of the mesh which is also supported by the lack of deterioration of LV volumes or mass.

1. Introduction

Acute aortic dissection is the most feared complication of Marfan syndrome [1,2]. Increased aortic wall stress is a major predisposing factor for dissection. According to the Laplace law, diameter of the aorta, aortic wall thickness and the luminal pressure are major determinants of aortic wall stress. These factors fully explain aortic wall stress in a circumferential direction [3,4]. Besides the circumferential wall stress, longitudinal wall stress, in the long axis of aorta, has also been proposed as a risk factor for dissection [4,5]. Indeed, longitudinal aortic wall stress has been shown to concentrate just above the sinotubular junction where most of the dissections occur as a transverse tear [5]. Other than the factors included in Laplace law, the systolic axial downward displacement of the aortic root also affects the longitudinal wall stress [6]. Marfan syndrome patients are rarely hypertensive and therefore high blood pressure does not seem to be a common predisposing factor for either circumferential or longitudinal increased wall stress [7]. This leaves the aortic root diameter, aortic wall thickness and systolic axial displacement of the aortic root as important factors associated with increased wall tension and risk of dissection in Marfan patients.

Personalized external aortic root support (PEARS) surgery is a novel surgical method for prevention of aortic root dilatation and dissection in Marfan patients [8]. A replica of the patient's aortic root and ascending aorta is constructed from the imaging data by computer modeling and then a bespoke porous medical grade fabric mesh sleeve is manufactured. The personalized external support fits intimately to patient's aorta shape, thanks to the exact modeling of the aorta by a computer aided design (Fig. 1). This mesh is then surgically implanted around the aorta extending from the annulus to the proximal aortic arch [9]. The aim of this procedure is to reinforce the aortic wall for prevention of dilatation. The

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☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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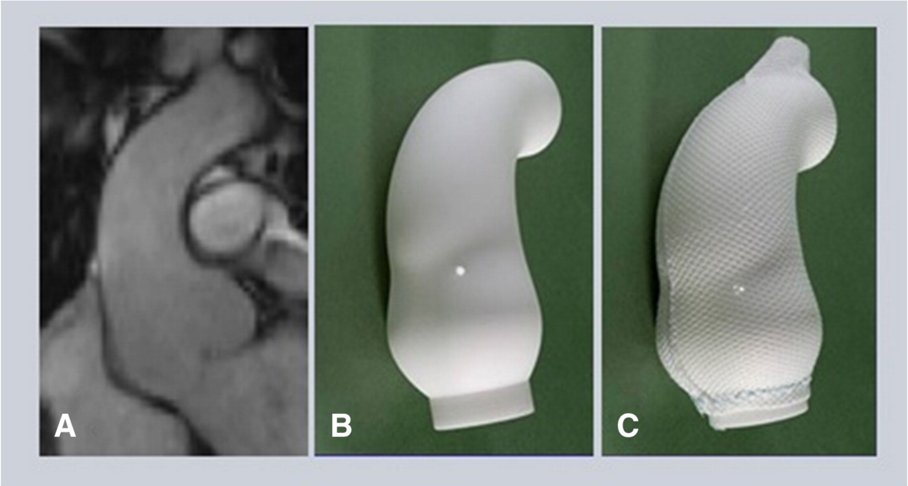

Fig. 1. Imaging data retrieved from the CMR study (A) is used to produce an exact model of each patient's aorta by using computer aided design and rapid prototyping (B) and then a bespoke porous, soft and pliable mesh is produced that is ready for implantation as seen mounted over the aorta model (C).

mesh is incorporated into the aortic wall and contributes to its thickness [10]. We have shown previously on follow-up studies that it holds the aortic shape and size stable, preventing any further increase in aortic dimensions [11,12]. Being incorporated in the aortic wall and extending from the aortic annulus up to the aortic arch, it may also stabilize the aorta in longitudinal direction and provide an additional benefit by limiting the axial downward motion of the aortic root in each systole.

The bespoke mesh sleeve used in PEARS surgery and the tubular Dacron grafts used in Bentall and valve sparing root replacement operations are made from the same basic polymer. However in contrast to the woven inelastic and stiff tubular grafts [13], the mesh used in PEARS is produced as a macroporous, soft and pliable fabric. It is well proven that decreased elasticity of the aortic wall is associated with increased afterload for the left ventricle with possible consequences of decrease in left ventricular ejection fraction, increase in left ventricular mass and possibly increased rates and severity of aortic regurgitation [14,15]. It is unknown whether the PEARS procedure is associated with any of these unwanted consequences.

In this study we investigated the effect of PEARS surgery on systolic downward motion of the aortic root. We also investigated the long term effects of implantation of the mesh on systolic distension of the aortic root with the possible consequences of impaired distensibility on left ventricular ejection fraction, left ventricular mass and aortic regurgitation.

2. Methods

2.1. Patients

To date 47 patients with Marfan syndrome have had prophylactic PEARS surgery for prevention of thoracic aorta dilatation and dissection. This novel surgical technique was developed and first implemented in the Royal Brompton Hospital under strict control of research ethics committee [2] and 27 patients had the operation at the Royal Brompton Hospital between the years 2004 and 2012. Criteria for the operation and clinical characteristics of the patients have been reported previously; briefly a suitable candidate for this preventive surgery would have an aortic root diameter of 40–45 mm and no or little aortic regurgitation [8]. In two of the patients the main imaging modality was computed tomography and in one patient clinical imaging was performed abroad before the patient had PEARS surgery in our center. The remaining 24 patients had cardiovascular magnetic resonance (CMR) examinations in our center before the operation and were followed up by CMR examinations after the operation at six months, 12 months and wherever possible annually thereafter. These patients formed the study group. The study was registered and approved as a clinical audit to assess the effectiveness of PEARS surgery by the Quality and Safety Department of the Royal Brompton Hospital.

2.2. CMR examinations and analysis of LV ejection fraction and mass

All CMR examinations were performed in a 1.5 T scanner (Siemens Avanto, Erlangen, Germany). Briefly, the basic CMR protocol performed in all the patients included localizers, multislice black-blood and bright-blood anatomic images, ventricular long axis and short axis cine images, short axis stack of aortic valve and root cine images [16]. All cine images were acquired with the balanced steady state free precession sequence with retrospective ECG gating to capture full cardiac cycle and at end-expiration.

Left ventricular volumes, ejection fraction and mass were calculated with dedicated software with exclusion of the papillary muscles from blood pool (CMRTools, Cardiovascular Imaging solutions, London, UK). The high reproducibility for these parameters with the software used in this study has been previously reported from our center [17]. Lateral mitral annular plane systolic excursion (MAPSE) was measured from the four chamber cine images by subtracting the distance from a reference point outside of the left ventricular apex to the lateral mitral annulus in end-diastole and end-systole. The measurements were performed blinded to patients' details. Left ventricular mass index was derived by dividing left ventricular mass by body surface area.

2.3. Assessment of aortic root motion, distension and aortic regurgitation

All the preoperative and the latest follow-up CMR study sessions were saved and anonymized in random order for analysis and comparison of aortic root motion, distension and aortic regurgitation.

Aortic root motion was defined as systolic downward motion of the annular plane as previously described [6]. For this measurement the left ventricular outflow tract cross-cut (LVOTxc) CMR cine images were used. This plane fully shows the annulus and the ascending aorta throughout systole and diastole and the systolic downward motion of the aortic root can be fully assessed. The plane of the aortic annulus was drawn at diastole and systole. In most cases these two planes were not parallel to each other due to the three dimensional motion of the aortic root. Therefore, for consistency we took the systolic downward motion of the aortic root as the length of a line drawn perpendicular to the mid-point of diastolic annulus plane to its intersection with the systolic annulus plane (Fig. 2).

For the assessment of aortic distension, from the same LVOTxc cine views the largest sinus-to-sinus measurement was taken at end-systole and end-diastole (Fig. 3). Aortic distension (also known as aortic strain) was then calculated as [(systolic diameter–diastolic diameter)/diastolic diameter] × 100 [3]. The region of the measurements in diastole and systole were not perfectly matching due to motion of the aortic root, therefore these distension measurements did not reflect the local distension properties of the aortic wall at a certain location but the overall distensibility and the Windkessell function of the aortic root.

Aortic regurgitation was visually assessed in the cine images of the left ventricular outflow tract and LVOTxc views.

2.4. Statistical methods

Data were recorded and analyzed in Microsoft Excel 2007 software (Microsoft, Washington, USA). Normally distributed continuous variables are expressed as the mean ± standard deviation and non-normally distributed variables as medians with interquartile ranges. Median and ranges were also provided for follow-up duration. Paired-*t* test was used to compare pre-operative and post-operative follow-up measurements except for the aortic distension parameter which was not normally distributed and assessed by the Wilcoxon signed-rank test. Box and whisker diagrams were used to show comparison of aortic root motion and distension before the surgical implantation of PEARS and in the follow-up. Intra-observer reproducibility of aortic root motion and distension were evaluated in a subgroup analysis of random 24 repeated measurements and expressed as mean and standard deviation of differences between repeated measurements. Likewise, inter-observer variability for aortic root motion was calculated in the same set of patients. All reported p values were two-sided. A p-value < 0.05 was considered as statistically significant for a single test and after Bonferroni correction for the multiple significance tests, the individual test significance level was set to <0.006.

3. Results

Mean CMR follow-up after surgery was 51.6 ± 26.4 months (median 50.5 months, range 8–101 and interquartile range 25.5–72 months). Mean systolic downward motion of the aortic root decreased significantly in the follow-up after PEARS surgery (12.6 ± 3.6 mm before operation vs. 7.9 ± 2.9 mm in the latest follow-up study, $p < 0.00001$) (Fig. 4). Aortic root downward motion was decreased in 21 of the total 24 patients (Fig. 5 and Movie I); unchanged in 1 and increased in 2 of the patients (increase was 2 mm in both of these two patients). Mean difference of repeated measurements of axial aortic root motion for assessment of intra-observer variability was 1.3 ± 0.9 mm and for inter-observer variability was 1.4 ± 1.0 mm.

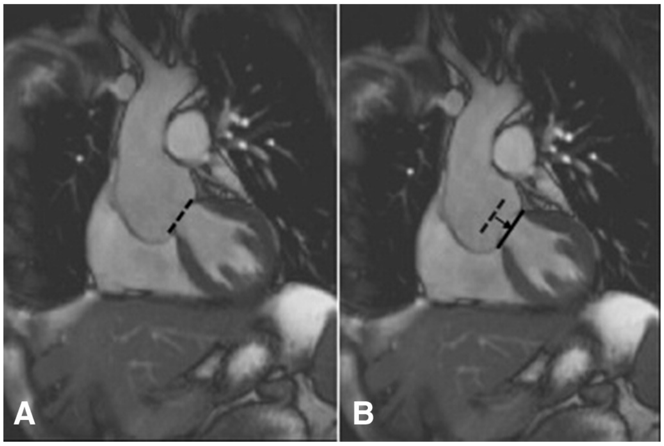

Fig. 2. Measurement of systolic downward aortic root motion. The plane of aortic annulus is shown as a dashed line at end-diastole (A) and as a solid line at end-systole (B). The end-diastolic plane was propagated to the end-systolic frame (B) and the downward motion was taken as the length of the line drawn perpendicular to the mid-point of end-diastolic annulus plane to its intersection with the end-systolic annulus plane (length of arrow in B).

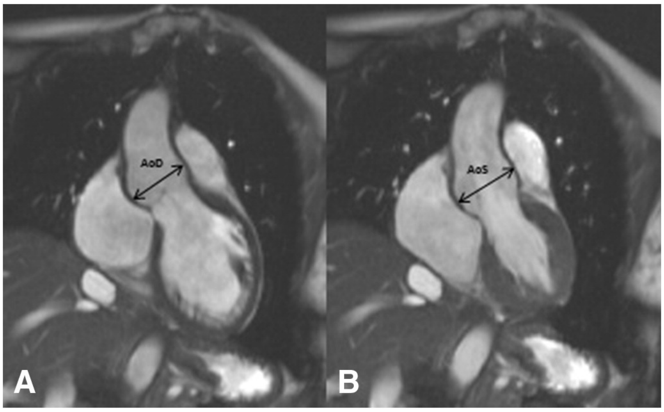

Fig. 3. Maximum aortic root diameter at end-diastole (AoD) and end-systole (AoS) were used to derive aortic root distension as [(AoS − AoD) / AoD] × 100.

There was a trend towards a mild decrease in aortic systolic distension but this was not statistically significant (median 4.5%, interquartile range 7% pre-operative vs median 2.0%, interquartile range 3.5% in follow-up, $p = 0.35$) (Fig. 6). Mean difference of repeated measurements for intra-observer variability was 1.3 ± 1.2%. Eight patients had mild aortic regurgitation before surgery; the remaining 16 patients had no aortic regurgitation. In the follow-up there was no increase in the severity of aortic regurgitation. Mild aortic regurgitation was observed in one patient who did not have it before surgery. In another patient mild aortic regurgitation that was present before surgery was not seen at follow-up. Overall there was no significant increase in number of patients with aortic regurgitation or in the severity of regurgitation that was present before surgery.

The changes in left ventricular volumes, ejection fraction, lateral MAPSE, mass and mass index are summarized in Table 1. There was no significant change in left ventricular volumes and ejection fraction

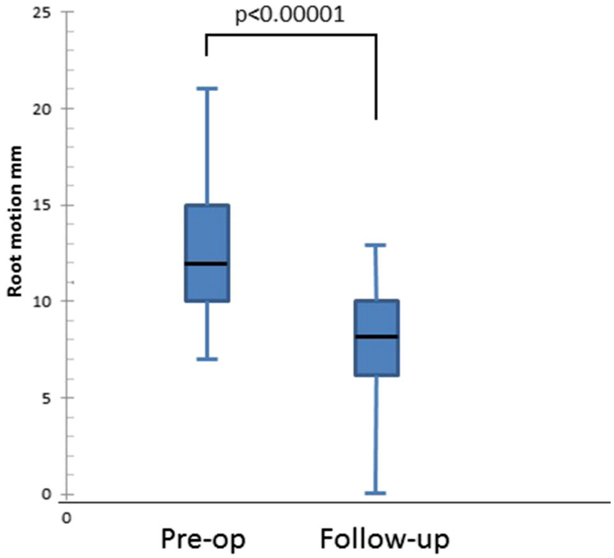

Fig. 4. Whisker box plots of systolic downward aortic root motion before and after PEARS surgery. Systolic downward aortic root motion decreased significantly in the follow-up after surgery.

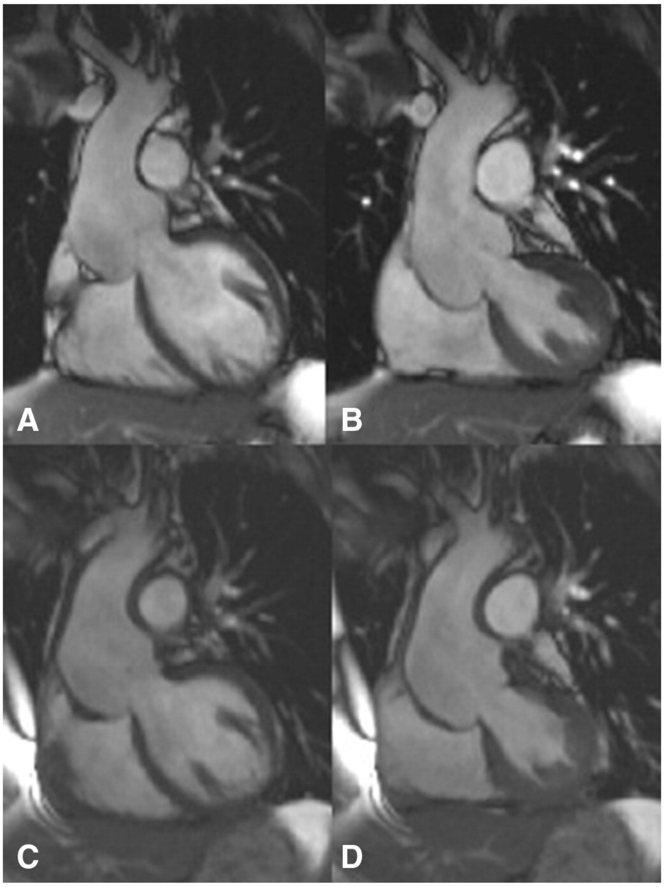

Fig. 5. Decrease in systolic downward aortic root motion after PEARS is shown in one of the patients. Systolic downward aortic root motion decreased from 15 mm before the operation (images A, end-diastole and B, end-systole) to 7 mm at the latest follow-up (C, end-diastole and D, end-systole) after PEARS. Note the increased aortic wall thickness with implantation of the mesh after PEARS surgery (C and D).

in follow-up after PEARS surgery. There was a trend towards a decrease in mass, mass index and MAPSE with individual p values for both of the comparisons below 0.05 but the significance was lost when correction for p value for multiple significance tests were applied.

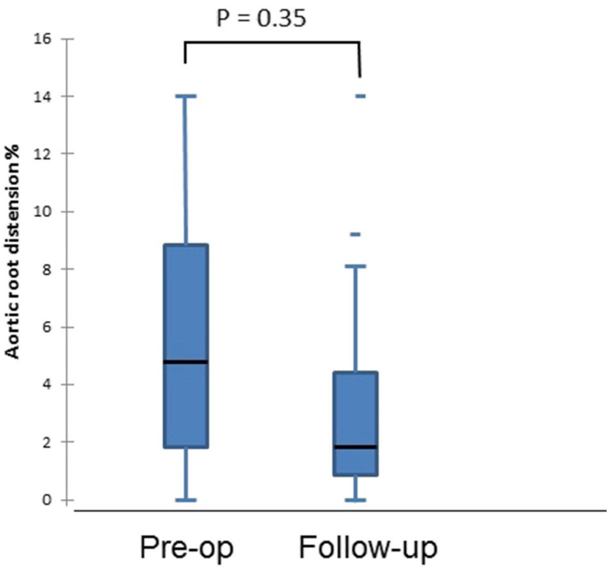

Fig. 6. Whisker box plots of aortic root distension before and after PEARS surgery. There was no significant change in distension of the aorta in the follow-up after PEARS.

Table 1
Left ventricular volumes, ejection fraction and mass before and during follow-up after PEARS surgery.

	Pre-op	Follow-up	p[*]
End-diastolic volume (ml)	182.8 ± 43.9	175.4 ± 41.8	0.232
End-systolic volume (ml)	67.5 ± 29.6	66.9 ± 28.6	0.874
Stroke volume (ml)	115.1 ± 19.7	108.8 ± 20.1	0.109
Ejection fraction (%)	64.3 ± 7.6	62.8 ± 9.4	0.342
MAPSE (mm)	12.3 ± 2.8	10.8 ± 1.9	0.029
Mass (g)	157.2 ± 25.3	149.6 ± 27.3	0.048
Mass index (g/m^2)	76.9 ± 11.2	73.2 ± 13.1	0.038

[*] Statistical significance was $p < 0.00625$ after adjustment of significance for multiple significance tests.

4. Discussion

4.1. Principal findings

In this study we have shown that following PEARS surgery:

1) the axial downward motion of the aortic root which is known to increase longitudinal aortic wall stress is significantly decreased,
2) aortic root distensibility properties are not significantly impaired and the Windkessel function is preserved,
3) there is no significant change/deterioration in left ventricular volumes, ejection fraction or mass,
4) there is no significant progression or new occurrence of aortic regurgitation.

4.2. Axial downward motion of aorta after PEARS and risk of dissection

The present study shows that the downward axial motion of the aortic root is significantly decreased after PEARS surgery. Histology of the artery after implantation of the mesh used in PEARS surgery was investigated in a sheep model [10] and also in the autopsy study of one of the patients who had sudden cardiac death (the death was not related to aortic pathology as the exostent and the aorta were found intact in the autopsy without any evidence of aortic dissection, but there were findings of dilated cardiomyopathy) [18]. Histologic evidence from both of these studies showed that the mesh is fully incorporated in the adventitia with collagen fibers filling the interstices of the macroporous mesh. Increase in collagen of the adventitia appears the most possible cause for limiting elongation of the aortic wall and downward axial motion of the root in systole. The axial downward motion has been shown to be an important determinant of the longitudinal tensile stress on aortic wall as discussed below. Therefore we believe that PEARS decreases longitudinal wall stress by limiting the aortic downward axial motion besides its favorable effect on prevention of increase in aortic root diameter.

Aortic dissection simply occurs when the tensile stress on its wall exceeds its strength [19]. Major directions of stress on the aortic wall are circumferential and longitudinal (i.e., along the long axis of aorta) [3,4]. The diameter of the aorta, blood pressure and wall thickness are the main determinants of circumferential wall stresses according to Laplace law [3,4,19]. This is the main reason why the diameter of the aorta, easily available by a variety of imaging techniques, has been used as a surrogate marker for aortic wall stress and the risk of dissection. This approach is supplemented by the extensive data in the literature linking increased aorta diameter to increased risk of dissection [19]. However most of the aortic dissections occur just above the sinotubular junction [7] with a transverse tear in the intima and cannot be explained simply by increased circumferential stress [4,5]. Tensile strength of the aortic wall is not homogenous and shows directional changes; most studies have consistently shown that the aortic wall is less strong in the longitudinal direction [20,21] with preferential rupture perpendicular to its long axis when stress is applied in both directions [22]. Moreover, Khanafer et al. studied tissue samples of human ascending aorta aneurysm and found that aneurysm diameter was more strongly correlated with increased longitudinal than circumferential wall stress [23]. All these findings suggest that longitudinal wall stress may be as important as circumferential stress in the pathogenesis of aortic dissection and may be the leading cause of a transverse tear along the long axis of the aorta.

Aorta diameter and blood pressure are also main determinants of longitudinal wall stress [4]. However, experiments by Beller et al. clearly showed that it is also significantly dictated by the elongation and stretch of the aorta due to systolic axial downward motion of the aortic root [4,6]. They showed in a finite element model of the ascending aorta that longitudinal wall stress is markedly increased with axial downward displacement of the aortic root [4,6]. In their model both circumferential and longitudinal wall stresses were concentrated in the outer curve of the ascending aorta a few centimeters above the sinotubular junction. Recently, Nathan et al. confirmed this finding and again showed that maximum aortic wall stress is localized just above the sinotubular junction in their finite element analysis of a realistic model derived from real aorta images acquired by computed tomography [24]. In the study by Beller et al., [6] just adding a ~9 mm systolic downward motion to their baseline model, the longitudinal stress increased by 50% reaching the degree of circumferential stress. Increasing that to 15 mm the longitudinal stress significantly exceeded the circumferential stress. Moreover, wall stress in a longitudinal direction induced by a 15 mm downward motion at normal (120 mm Hg) luminal pressure was almost comparable to circumferential stress at significantly increased (180 mm Hg) pressure. It is of note that a 15 mm downward axial motion was well within the range of root motion observed before exostent implantation in this study. Previous studies by Beller et al. showed that a reduced left ventricular ejection fraction decreases and aortic regurgitation increases aortic root motion [25]. There was no significant change in either of these parameters in the follow-up of patients after PEARS surgery therefore the decrease in aortic root motion was most probably due to incorporation of the mesh into the aortic wall after surgery.

The studies discussed above have consistently shown the importance of longitudinal wall stress and the impact of downward aortic root motion. However when assessing the risk of aortic dissection longitudinal wall stress is not specifically quoted and aortic root diameter is used as a surrogate index of aortic wall stress and the risk of dissection. Indeed root diameter is one of the most important determinants of both circumferential and longitudinal wall stress. Also assessment of axial downward motion necessitates true anatomic cine images which are mostly not available by computed tomography or echocardiography images. As used in the present study, CMR imaging provides cine images of the aorta in its long axis and along with accurate measurements of aorta diameter [16] can easily provide information on downward motion of the aortic root as a risk factor of increased longitudinal wall stress.

4.3. Aortic root distensibility after PEARS surgery

Aortic root strain (systolic percent change in aortic root diameter) was studied to assess aortic root distensibility properties in the follow-up after PEARS surgery in this study. We have found a trend for decreased distensibility after surgery but this was not statistically significant. As the aim of the bespoke mesh is to increase the tensile strength of the aorta, a decrease in distensibility is not unexpected. However, the results of the present study suggest that aortic compliance and the Windkessel function are at least partially preserved. The PEARS is from the same chemical material used in tubular Dacron grafts (polyethylene terephthalate). However, the PEARS is designed as a macroporous (0.7 mm pore size) medical-grade mesh fabric and as such is very soft and pliable. Moreover its bespoke design, allows a perfect fit to the aorta during surgical implantation without any risk of regional tensile disequilibrium. In contrast to the mesh sleeve used in PEARS surgery, woven tubular Dacron grafts used in Bentall and valve sparing root replacement operations are essentially non-compliant and highly stiff without any distensibility or Windkessel effect. Tremblay et al. showed that woven Dacron graft is the stiffest of all the graft materials used in aortic reconstruction with the stiffness ~25 times of the normal human aorta [13] and Bail et al. showed that patients with Dacron graft replacement of the aorta had a systolic change in diameter of only 0.7 mm [26].

In the sheep model of PEARS surgery, the mesh implanted to the normal carotid artery increased tensile strength ~5 times while increasing stiffness ~2 times compared to normal carotid artery segments not covered by the mesh [10]. In the present study we compared data before and after operation on patients with Marfan syndrome but it is well known that aortic distensibility properties are already impaired in Marfan patients [16]. As such, the comparison is not with normal aortas and our results suggest that the PEARS does not cause any further significant impairment of distensibility. In fact, stiffness significantly increases with increasing diameter of aorta [27] and hypothetically PEARS may prevent further deterioration of elasticity of the aorta by stabilizing the diameter helping the aorta to operate in the more physiological range of stress/strain curve with the added safety margin provided by the increased tensile strength [3].

Further support for preserved distensibility comes from our results that show no significant increase in left ventricular mass, decrease in ejection fraction or increase in aortic regurgitation in the follow-up after PEARS surgery. Significant left ventricular hypertrophy after replacement of the aorta with inelastic vascular prosthesis has long been known [28] and consistently proved experimentally [14]. Similarly, aortic root dilatation and stiffening have been shown to increase leaflet stress and reduce leaflet coaptation leading to aortic regurgitation despite normal leaflet structure [29]. Grotenhuis et al. showed that in patients with bicuspid aortic valves, a decrease in aortic elasticity was associated with left ventricular hypertrophy and increased severity of aortic regurgitation [15]. In another study they have shown in patients after the Ross procedure that decreased aorta distensibility was related to a decreased left ventricular ejection fraction [30]. None of these unfavorable effects were observed in this study of blinded pre and post PEARS surgery comparisons with substantial duration of follow-up. The observed trend for a mild decrease in MAPSE during follow-up may be related to intrinsic subclinical ventricular dysfunction often seen in Marfan syndrome patients [31]. An alternative explanation to this finding could be decreased aortic distensibility (increased stiffness) leading to increased hemodynamic load on the left ventricle, however no significant change in aortic distensibility after PEARS surgery was seen in this study.

Decreased elasticity of the proximal aorta may also have downstream effects leading to significantly increased wall stress in the descending thoracic aorta [32] and type B dissection [33,34] which are therefore hypothetically less likely with exostent implantation compared to inelastic graft replacement. A further benefit of PEARS might be smoother transition between the mesh covered portion of the aortic arch and the more distal aorta; this is in contrast to the abrupt change and mismatch of compliances at the anastomosis site after graft replacement [35].

4.4. Study limitations

There are some limitations of this study which are summarized as follows: 1 — Measurement of actual longitudinal wall stress directly from imaging data is not possible and hence we did not measure the longitudinal wall stress directly in this study but assessed one of its most important determinants that has been proven in previous models: the axial downward motion of the aortic root. 2 — We did not assess the cumulative effect of all the determinants on aortic wall stress after PEARS surgery, however we know from previous studies that implantation of exostent favorably affects the other factors effective on wall stress such as aorta diameter and wall thickness. 3 — The experiments and models on wall stress cited in this study were not necessarily representative of the aorta of Marfan syndrome patients. Nevertheless although the dominant factor in the pathophysiology of aorta dilatation and dissection is different in Marfan and age related/hypertensive aortic aneurysm/dissection, the same set of factors dictate wall stress. 4 — Since the CMR studies were a part of routine clinical assessment rather than research studies, blood pressure was not available for all the patients. Therefore we used percent diameter change to assess distensibility properties of the aortic root. The patients in our group however were not hypertensive and we believe that the percent change in diameter in the physiologic blood pressure range provided a reasonable estimate of distensibility. The finding of no change in left ventricular mass from blinded analysis further supports this. 5 — This was a pre- and post-PEARS surgery comparison study, as such the pre-surgery CMR measurements acted as the control for comparing with the post-PEARS surgery measurements. Hypothetically the ideal control group should be composed of sham operations which is far from being a realistic possibility for a surgery approved and applied in clinical practice. One might suggest that any operation involving the aortic root might lead to decreased root motion due to post surgery adhesions and fibrosis. However studies by Beller et al. have shown that this is not the case and aortic root motion not decreases; in fact increases after root replacement for aortic stenosis [36]. Also the findings of autopsy study of the patients who had sudden cardiac death showed that the PEARS mesh was fully incorporated in the adventitia and could not be separated from it which suggests that it is the external mesh attached to the adventitia which is limiting the motion of the aortic root in the longitudinal direction.

5. Conclusion

In conclusion, after PEARS surgery axial downward motion of the aortic root, a major determinant of longitudinal wall stress, is significantly decreased; aortic elastic properties and the Windkessel function are at least partially preserved and there is no significant deterioration in left ventricular mass and ejection fraction or increase in the incidence or severity of aortic regurgitation. These findings complement our previous observations that the bespoke mesh attaches firmly to the adventitia and increases the tensile strength of the arterial wall and PEARS surgery prevents dilatation of aortic root. All these findings provide further support on the effectiveness and safety of PEARS for prevention of aortic root dilatation and dissection in Marfan syndrome patients.

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Conflict of interest

The authors have no conflict of interest pertaining to this study.

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