Effectiveness of personalized external aortic root support for prevention of aortic root dilatation in Marfan patients

Izgi; PEARS for prevention of aortic root dilatation

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Introduction

Aortic dissection leading to rupture is the main cause of mortality in Marfan syndrome patients (1). The risk of dissection progressively increases with increasing aortic root size (1,2). Current approaches for prevention of aortic dissection in Marfan patients have been centred on prevention of aortic root dilatation with drugs and prophylactic surgery to replace the aortic root (1,2). The drug therapy with beta blockers and angiotensin receptor blockers is aimed at slowing the rate of aortic dilatation. While the drugs might slow the rate of dilatation, the aorta still dilates and Marfan patients eventually undergo root replacement when a certain diameter threshold is reached.

Prophylactic replacement of the aortic root aims at replacing the vulnerable aortic root prone to dissection with a prosthetic graft. The techniques involve replacement of the aortic root and the aortic valve with a composite valve conduit (Bentall operation) and the valve sparing root replacement (VSRR) surgery (3). Bentall operation is now a straightforward technique with a low operative mortality; however it involves replacement of the aortic valve which is normal in most of the patients. This brings in the requirement of lifelong anticoagulation along with long term prosthetic valve related complications. The cumulative lifetime risk of prosthetic valve complications are substantial considering the younger ages at which Marfan patients have these operations. The VSRR techniques allow replacement of only the root with preservation of the native aortic valve. Therefore the risks associated with a prosthetic valve are eliminated; however there are other concerns with the VSRR. These techniques are technically more challenging with less standardization among centres. Apart from intraoperative challenges, there is a risk of significant aortic regurgitation and re-operation with VSRR (4). A recent multicentre study involving patients from centres with substantial expertise reported a 7% rate of significant aortic regurgitation at 1 year follow-up after VSRR in Marfan patients, suggesting that real life concerns about durability of these procedures are valid (5). Moreover, sparing of the aortic valve may not always be possible and there is probability of unanticipated intraoperative conversion to aortic valve replacement.

Personalized external aortic root support (PEARS) surgery has been developed as an alternative surgical method to prevent dilatation and dissection/rupture of the aortic root in Marfan patients (6,7). It involves surgical implantation of a bespoke mesh support around the aortic root and the ascending aorta. With three dimensional (3D) printing utilising the imaging data, the mesh is produced bespoke to each individual patient’s aortic root shape allowing perfect fitting. PEARS has been developed as a simpler surgical technique. Circulatory bypass is typically not needed during the surgery (8). The native aortic valve and the blood endothelium interface is preserved and therefore the prosthetic valve related complications of the Bentall procedure and technical challenges and the probable risk of aortic regurgitation of the VSRR approaches are potentially avoided. If PEARS is proven to be effective, these advantages may allow operating Marfan patients at even smaller aorta diameters. This might relieve the significant anxiety that Marfan patients are facing during the long duration of watchful monitoring until their aorta reaches the current size threshold recommended in the guidelines for aortic root replacement. The critical question is whether PEARS is really effective in preventing aortic root dilatation.

We have previously shown perioperative and procedural advantages of PEARS compared to root replacement (8) and the favourable clinical outcome of the patients during follow-up (9). We also showed in the preliminary reports of the technique that it keeps the aortic root size stable (10). The target in PEARS as a prophylactic surgery is to stabilize the aortic root and prevent its dilatation, as the size of the aortic root is currently regarded as the main factor determining the risk of dissection. The aim of the present study is to assess the medium to long term effectiveness of the PEARS on prevention of aortic root dilatation.
Methods:

Patients and the PEARs surgery

Following the conceptual and technical development period which is reported previously (6,7), PEARs surgery was first performed in 2004 following approval by the Royal Brompton Hospital Research and Ethics Committee (6). To date more than 100 patients with Marfan syndrome have undergone this surgery which is now offered by several other centers across the Europe. The present study involves prospective data from the series of the first 27 consecutive Marfan patients who had PEARs operation for prevention of proximal aorta dilatation and dissection between May 2004 and July 2012 during the evaluation phase of this new surgical technique at the Royal Brompton Hospital. These patients had close follow-up of their aorta size to monitor the effectiveness of PEARs.

All patients were diagnosed with Marfan syndrome according to Ghent criteria. They were recruited from the aortopathy clinic of the Hospital which has a well-established aortic surgery program with both the Bentall and the VSRR surgeries routinely being performed. Eligibility criteria for PEARs were an aortic root size of 40–55 mm and no or only mild aortic regurgitation (8). All Marfan patients satisfying the eligibility criteria were considered for the operation and none were declined on the basis of any pre-specified criteria. The patients were fully informed that PEARs is a novel approach for prevention of aortic root dilatation and dissection in Marfan syndrome in a detailed discussion with the operating surgeon (JP). They were also fully informed about the Bentall and VSRR options. All patients provided written informed consent for the PEARs surgery. Technical aspects of PEARs procedure has been published before (6,7,11) and a summary is provided in the Supplemental material I.

Study design

This was a prospective study aimed to test stability of the aortic root size at long term follow-up following PEARs surgery based on measurements by cardiovascular magnetic resonance (CMR) (Figure 2). The study was registered and approved as a clinical audit by the Quality and Safety Department of the Royal Brompton Hospital to assess the effectiveness of PEARs surgery for prevention of aortic root dilatation in Marfan patients. Three of all the 27 patients were excluded; in 2 of them the baseline and follow-up imaging was by computed tomography (CT) (metallic spinal roads causing significant artefacts in one patient and severe claustrophobia in the other patient precluded imaging by CMR) and the follow-up imaging studies for the third patient was not available since the patient was living abroad and his follow-up was not in our hospital. The remaining 24 patients had CMR examinations in our centre before the operation and at 6 and 12 months after the operation and wherever possible annually thereafter. In two of these 24 patients an increase in aortic root size was detected during the clinical follow-up due to identifiable causes of technical failures at the operation. One of these patients had cardiac arrest in the intensive care unit after the operation and the on-call surgery team took the decision to partly release the closing suture line of the external support after which the patient stabilised. The aortic root dilated at follow-up in this patient with partially released external support. In the second patient there was localised dilatation of the right coronary cusp of the aortic root in the region of right coronary ostia, the impression was that the opening for the coronary ostia was inadvertently cut large leaving this region not adequately supported (see discussion section and the images provided in the Supplemental material, section V). Pre-operative and follow-up aorta size comparison was repeated by both including and excluding these two patients.

Measurements of thoracic aorta size
CMR examinations were performed on 1.5 Tesla scanners (see Supplemental Material II for the imaging protocol). For aorta measurements a batch of 120 anonymised CMR studies was formed. This included the baseline and the latest CMR studies of all the 24 patients as well as randomly selected studies of the patients acquired at any time during their follow-up to dilute the batch in an attempt to minimize any possible measurement bias. A single operator (CI) measured the aorta size on these individual anonymised studies following a stringent predefined protocol (see Supplemental Material III for aorta measurement protocol). The following measurements were made: aortic annulus size, 3 diameters of the sinus of Valsalva measured at cusp to commissure (the largest and the mean of these 3 measurements used for comparison), ascending aorta diameter, aortic arch diameter and descending aorta diameter. Additionally, cross-sectional area measurements were taken at the sinus of Valsalva, ascending and the descending aorta to be able to detect any asymmetrical changes in size such as a localised bulging that might be difficult to catch with the diameter measurements. The presence and severity of aortic regurgitation was assessed visually on cine images and by flow mapping at the aortic root. Measurements from the pre-operative baseline studies were compared with those at the latest study in the follow-up by March 2016.

Another set of 30 anonymised studies from all the CMR studies of the patients were randomly selected for analysis of intra-observer variability. These 30 studies were duplicated and aorta measurements were repeatedly done blindly and in a random order to define the intra-observer variability and the limits of maximum change in aorta sizes attainable to measurement variability.

**Statistical analysis**

Summary statistics were recorded as mean and standard deviation for continuous variables and frequency and percentage for binary variables.

Initially, aortic measurements before the operation and at the latest follow-up were compared by paired t-test. The presence or absence of aortic regurgitation before and after the surgery as a binary variable was compared by the McNemar’s test. Secondly, we aimed to test whether any of the changes in aortic diameters and cross sectional areas during follow-up after the operation were significantly different from normal measurement variability. In the absence of a control group such an approach allowed a reasonable assessment of the effectiveness of PEARS for prevention of aortic root dilatation for two reasons: 1- the well-defined natural history of Marfan syndrome involves progressive dilatation of the aorta and 2- in practice any clinically significant change in aorta size at follow-up should exceed any changes attributable to measurement variability. Therefore, we calculated the mean intra-observer change for each of the aorta measurements and defined the measurement variability range as the absolute value of this change in either direction. Any changes in the aorta size from the preoperative to follow-up measurement where the 95% confidence interval was completely outside this measurement variability margins were significant, similar to an equivalence and non-inferiority analysis. All P-values are two tailed and a P-value of <0.05 was considered significant. All statistical analyses were performed by one of the authors (SN) using Stata 14 (StatCorp, College Station, TX, USA).

**Results**

The mean age of the 24 patients at the time of PEARS surgery was 33.1 +/- 13.3 years (range 16-58) and the mean of the largest aortic root diameter was 44.9 +/- 2.8 mm (range 41 - 52 mm). Eight of the patients were female and 16 patients were male. Mean duration to the latest follow-up study after the operation was 75.6 +/- 31.3 months (6.3 +/- 2.6 years) with 19 of the 24 patients (~80%) completing at least 5 years follow-up after the operation.
Comparison of pre-operative and follow-up aorta measurements is shown in Table 1 and Figure 2. There was no significant increase in the aorta size at the levels of the annulus, aortic root (sinus of Valsalva), ascending aorta and the arch. However the size of the descending aorta increased significantly at follow up as seen in the diameter and cross-sectional area measurements. There was no increase in the percentage of patients with mild aortic regurgitation and in none of the patients was there an increase in the severity of aortic regurgitation or more than only mild aortic regurgitation at follow-up.

Intra-observer measurement variability and the accepted maximum margins attributable to measurement variability that was used for comparing significance of changes in the aorta measurements are shown in Table 2. For measurements of aortic diameters at different levels, the maximum of the acceptable ranges for measurement variability was 1.2mm (for largest sinus of Valsalva diameter) suggesting robust reproducibility of aortic measurements.

Figure 3 shows comparison of changes in aortic diameters and cross sectional area measurements against the maximum acceptable margin of measurement variability. There was significant increase in the descending aorta diameter at follow-up and increase in aortic arch diameter could not be excluded. There was a tendency to a reduction in ascending aorta diameter however an increase could not be totally excluded. There was no significant increase in the size of the annulus and sinus of Valsalva; in fact there was a tendency for a smaller annulus and sinus of Valsalva at long term follow-up after PEARs surgery. The results were in keeping with a stable proximal aorta diameter (annulus, sinus of Valsalva and probably the ascending aorta) which are supported by the PEARs sleeve and an increase in the diameter of the distal aorta segments which were not supported by the sleeve (the descending aorta and probably the arch).

Apart from the comparison of the blinded measurements reported here, some details on the clinical follow-up of aorta diameters are worth noting. Throughout the follow-up of the patients, on the un-blinded side-by-side direct comparison of the pre- and post-operative MR studies for clinical use, there were again no clinically significant changes detected in the proximal aorta diameters except for the 2 outlier patients. Similarly, in the other 2 patients from the original cohort of 27 patients in whom the follow-up was done by CT, no significant changes in the aortic diameters were detected during follow-up. Two female patients each had an uneventful pregnancy after the PEARs operation without any significant changes in their aorta sizes (decision for pregnancy was at the discretion of the patients after full counselling covering risks of pregnancy in Marfan patients as usual).

Discussion

The results of this study show that in medium to long term follow-up, PEARs keeps the aortic root size stable and prevents dilatation in Marfan patients. At the same time it is seen that the unsupported segments, the aortic arch and the descending aorta, remain prone to dilatation over time and hence close follow-up is mandatory for the continued risk of type B dissection as is the case after Bentall and VSRR operations.

Prevention of aortic dissection is a major target in the care of Marfan patients. The risk increases with increased aortic root diameter and preventing aortic root dilatation is an essential goal. Drugs have long been used in an attempt for delaying aortic root dilatation. The initial enthusiasm with losartan has largely been blunted by the disappointing negative results of the recent Marfan Sartan and other trials which showed no effect of losartan on the rate of aortic dilatation (12,13). The effectiveness of beta blockers has not been tested in large clinical trials. Therefore the current strategy for prevention of
aortic root dissection depends mainly on aortic root replacement surgery. Bentall operation is now a very well-established technique with very low operative mortality. But replacing an essentially normal valve and leaving the patients with all the potential prosthetic valve related complications in the early years of life is a major drawback. Added to this is the requirement for lifelong anticoagulation if a mechanical valve is used. VSRR operations have been developed to address these issues; however they are technically more challenging. Excellent results in Marfan patients were reported from the centres that have pioneered the technique with very low operative mortality rates and good long term success (14). However it is difficult to estimate generalizability of these results to other centres (15). The issues related to VSRR are peri-operative risks, unintentional conversion to valve replacement and finally long term durability and risk of aortic regurgitation at follow-up. The recent multicentre registry by Coselli et al showed a substantial risk of significant aortic regurgitation at a rate of 7% at one year follow-up after VSRR in Marfan patients (5). It is of note that centres involved in this registry had years of experience in VSRR. The meta-analysis by Benedetto et al comparing Bentall and VSRR surgeries in Marfan patients also showed a considerable re-intervention rate of 1.3%/year after VSRR surgery in Marfan patients (3). It is interesting to note that in this meta-analysis the rate of prosthetic valve related complications was higher with Bentall and the re-intervention rate was higher with the VSRR as expected, but overall the composite valve related event rate in both groups were comparable and not significantly different. This points to an actual trade-off between a lower thromboembolic and a higher re-operation rate with VSRR.

The present study proved stabilisation of the aortic root size with PEARs in an attempt to prevent aortic dissection. Also, evidence from previous animal studies have proved homogenous and full incorporation of the PEARs sleeve to the aorta resulting in a true mesh/biological aortic wall composite with significantly increased tensile strength (16). Therefore we believe that by strengthening the aortic wall and by preventing root dilatation the risk of a root dissection will be minimized with PEARs and even if dissection occurs the external mesh will prevent a rupture. Since the aortic root is fully restrained within the personalized mesh fully incorporated to the aortic wall, it is expected that the stability of the aortic root size shown in this study will be maintained lifelong as the external support essentially leaves no room for further dilatation. The annulus is also fully restrained and the risk of aortic regurgitation will be minimal. There have been skepticism about extension of the the PEARs deep into aorticoventricular level but our results prove stability of annulus size after PEARs; surgical details of extending the external mesh to the annular level are also provided in the Supplemental Material IV.

It is obvious that absence of a control group is an important limitation of this study which is a common inherent limitation in many surgical studies. Nevertheless we believe that the stringent and blinded measurement protocol and comparison with what is best achievable (i.e., limits of measurement variability) provided robust data. Dilution of the actual sample of 24 pre and post studies also helped to limit measurement bias. It is worth noting that, as expected, the blinded measurements correctly identified the increased aorta size in the two patients in whom PEARs failed due to known technical issues. Similarly, blinded measurements of the aortic arch and the descending aorta showed what is biologically plausible an expected. Both of these segments were not covered and supported by the external sleeve and our analysis showed significant increase in size of the descending aorta. Progressive dilatation of the descending aorta is already well-known after root replacement in Marfan patients (17). Un-blinded side-by-side measurements for clinical follow-up performed by an experienced aortic imaging specialist (RHM) also demonstrated the stability of the aortic root size after PEARs. It might be questioned whether these patients would necessarily have aortic root dilatation if they had not PEARs surgery. While in the absence of a control group this would be a legitimate argument, it should be noted that all the patients referred for PEARs had clinically proven progressive aortic root dilatation before
they were considered for the operation. Also the follow-up duration of this study was substantial to expect a clinically detectable aortic root dilatation in a Marfan population. The first patient to have PEARs had an aortic root dilated from 44mm to 49mm over 12 years and remained stable at 49mm 12 years after having the PEARs operation (Figure 4).

Our results also show that adjusting the mesh around the coronary orifices is a critical step in PEARs surgery as the probable scenarios in the two patients with aortic root dilatation at follow-up were related to the coronary openings in the mesh sleeve (Supplement Material V). Accordingly, a large cut probably will leave part of the sinus unsupported and might lead to dilatation from the unsupported segment and on the other hand an insufficient opening will lead to impingement at the coronary orifice leading to myocardial ischaemia. We have incorporated the lessons learned from these two cases in the evolving experience with the PEARs surgery and the imaging data set is now vigorously studied in every detail for planning the location and size of the coronary openings as a critical step in all the patients. Coronary buttons are also a vulnerable aspect in root replacement surgeries and aneurysm or stenosis at button sites are rare but well-defined complications of both the Bentall and VSRR operations (18-20).

It must be emphasized that PEARs was not developed with an intention to compete with the already established Bentall and VSRR techniques. It was mainly to complement the available techniques and to expand the armamentarium and choices for prevention of aortic dissection for the Marfan patients to choose from depending on their preferences. A surgical approach that is durable as the Bentall procedure, limiting annular dilatation as the re-implantation variety of VSRR (David operation) and preserving the physiologic functionality of the aortic root by preserving the sinuses as the remodelling variety of VSRR (Yacoub operation) would be an ideal approach in Marfan patients. We believe that PEARs satisfies most of these expectations. It is a durable valve sparing technique preventing aortic root dilatation without any increased risk of aortic regurgitation. The mesh sleeve has a proximal hem similar to an annuloplasty ring which was sewn deep into the aorta-ventricular junction limiting any annular dilatation as proved by our results here. The tensile strength of the aortic wall is significantly increased. The shape of the aortic root and the sinuses are preserved therefore physiology is much better maintained and the excessive stress on the valve leaflets seen in re-implantation (21) and associated with aortic regurgitation is avoided. The physiological Windkessel function after PEARs is at least partially preserved (22); this is in contrast to the fully rigid tubular grafts without any elasticity used in conventional root replacement surgeries. Also, PEARs is different from the other sleeve techniques that utilize semi-rigid low-porosity grafts which are hand crafted to wrap the aorta (23,24). These semi-rigid grafts incorporate poorly to the aortic wall leading to regions of buckling and even gaps between the graft and the aortic wall as shown in histological and imaging studies (25,26). Finally, another hypothetical advantage of PEARs is worth mentioning. In one of the Marfan patients where an autopsy material was evaluated 4.5 years after PEARs (mortality unrelated to aortic pathology, see ref 27 for further details) it was seen that there was no elastolysis in the segments supported by the mesh and the aorta was of normal appearance; whereas the unsupported arch displayed fragmentation of the elastic lamellae typical of Marfan syndrome. Thus, PEARs not only stabilises and strengthens the aortic wall but potentially may remedy the aortic wall in Marfan syndrome. It is hypothesized that the aortic root dilatation in Marfan syndrome is an end result of the interplay between the underlying genetic defects and the hemodynamic load mediated by mechanotransduction signaling pathways (28). Hence a plausible explanation for this rather unexpected beneficial effect of PEARs might be blunting of this...
abnormal mechanotransduction signalling pathway associated with elastolysis in the strengthened aortic wall (26). This exciting observation from just a single patient merits further research.

**Conclusion**

PEARS keeps the aortic root size stable and prevents its dilatation in medium to long term follow-up and therefore appears as a viable option for prevention of aortic root dissection in Marfan patients.

**References**

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Study flow-chart for assessing aorta size at long term follow-up after the PEARs operation.
Figure 2

Comparison of pre-operative and follow-up sizes at different levels of the aorta. Dashed lines represent the sizes of the 2 outlier patients. The pre-operative and follow-up mean and 95% confidence interval plots are drawn with exclusion of the outliers. Diameter measurements are in mm and area measurements are in cm². SV: sinus of Valsalva.
Comparison of changes in aorta size at follow-up with the maximum acceptable margin of measurement variability. The margins for changes attributable to measurement variability are shown in thick dashed lines for each segment/measurement of the aorta and displayed against the plots showing pre-operative to follow-up mean change and 95% confidence intervals with the matching segments of the aorta depicted above. SV: sinus of Valsalva.
CMR images of the aortic root before the operation and at follow-up. The CMR images of the aortic root before the PEARs operation in 2004 (A) and at follow-up 12 years after the operation in 2016 (B) from a Marfan patient are seen. Note the thickened aortic root in B with the full incorporation of the external support to the aortic wall extending down to the level of the aortic annulus and fully restraining the aortic root. The maximum root size measured at the sinus of Valsalva was 49mm in 2004 and remained stable at 49mm 12 years after the operation.
### Tables

#### Table 1

<table>
<thead>
<tr>
<th>Aorta measurements</th>
<th>All Patients (N=24)</th>
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<th></th>
<th>Outliers excluded (N=22)</th>
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<tr>
<td></td>
<td>Pre-op</td>
<td>Follow-up</td>
<td>Change</td>
<td>Pre-op</td>
<td>Follow-up</td>
<td>Change</td>
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<td>Annulus</td>
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<td>28.4 (2.3)</td>
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<td>28.9 (2.3)</td>
<td>28.5 (2.4)</td>
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<td>45.4 (4.0)</td>
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<td>44.9 (2.9)</td>
<td>44.5 (3.0)</td>
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<td>43.9 (3.8)</td>
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<td>43.5 (2.4)</td>
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<td>SV Area</td>
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<td>16.5 (2.9)</td>
<td>0.11</td>
<td>16.3 (2.0)</td>
<td>15.9 (2.4)</td>
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<tr>
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<td>32.4 (3.5)</td>
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<td>32.4 (3.6)</td>
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<td>8.5 (1.8)</td>
<td>0.23</td>
<td>8.2 (1.7)</td>
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<td>Arch</td>
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<td>0.35</td>
<td>4.1 (0.9)</td>
<td>4.4 (1.0)</td>
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<td>Aortic regurgitation [n(%)]</td>
<td>8 (33)</td>
<td>7 (29)</td>
<td>-1 (-4%)</td>
<td>8 (36)</td>
<td>6 (27)</td>
<td>-2 (-9%)</td>
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**Comparison of pre-operative and follow-up aorta measurements.** Diameter measurements are in mm and area measurements are in cm$^2$. SV: sinus of Valsalva.
Table 2

<table>
<thead>
<tr>
<th>Aorta measurements</th>
<th>First measurement</th>
<th>Repeated measurement</th>
<th>Mean Change</th>
<th>95% CI</th>
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<tr>
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<td>SV maximum Diameter</td>
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<td>15.9 (2.8)</td>
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<td>0.30, 0.51</td>
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<td>Ascending Aorta Diameter</td>
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<td>32.6 (4.0)</td>
<td>0.70</td>
<td>0.44, 0.96</td>
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<td>Asc Aorta Area</td>
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<td>8.1 (2.0)</td>
<td>0.24</td>
<td>0.14, 0.34</td>
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<tr>
<td>Arch</td>
<td>23.3 (2.3)</td>
<td>23.8 (2.3)</td>
<td>0.47</td>
<td>0.25, 0.68</td>
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<td>0.29, 0.84</td>
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<tr>
<td>Descendig Aorta Area</td>
<td>4.1 (0.9)</td>
<td>4.2 (0.9)</td>
<td>0.15</td>
<td>0.10, 0.20</td>
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Intra-observer measurement variability. Intra-observer measurement variability was derived from blinded repeated measurements of 30 randomly selected studies. The mean change between the two measurements was taken as the maximum accepted margin attributable to measurement variability for each segment of the aorta. Diameter measurements are in mm and area measurements are in cm². SV: sinus of Valsalva.