Predictive value for paravalvular regurgitation of 3-dimensional anatomic aortic annulus shape assessed by multidetector computed tomography post-transcatheter aortic valve replacement

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Aims
Paravalvular regurgitation (PAR) remains a serious complication after trans-catheter aortic valve replacement (TAVR). Multidetector computed tomography (MDCT)-based measurements of the aortic basal virtual ring (BVR) are considered the gold standard for trans-catheter heart valve (THV) sizing. However, the real anatomic aortic annulus is a 3-dimensional structure. To compare measurement of 3D-anatomic annulus with BVR and secondly to assess independent predictive parameters that may impact on PAR+ mild post-TAVR (PAR+).

Methods and results
MDCT was performed in 92 patients before and after balloon or self-expandable TAVR. 3D-AA shape was obtained point by point following the semilunar attachment of aortic cusps (Osirix-MD 2.8.2). 3D-oversizing index (nominal THV area/3D-AA area² × 100) was calculated as well as 2D-oversizing index using BVR area instead of 3D-AA area. PAR was quantified by planimetry of vena-contracta in transthoracic echocardiography short-axis view. Valvular calcium volume and annulus calcium area were measured using Hounsfield-intensity detection. ROC curves and logistic regression for PAR+ were performed. BVR area overall underestimated 3D-AA area by 19+9% (P, 0.001), significantly more in PAR+ (26 ± 7%) vs. PAR (−) (17 ± 9%, P < 0.001). 3D-oversizing index had greater predictive value for PAR > mild (area under the curve, AUC = 0.88) with 88% sensitivitvity (Se) and 82% specificity (Sp) than 2D-oversizing index (AUC = 0.68) with 84% Se, but only 41% Sp (P < 0.0001). Also, valvular calcium volume and annulus calcium area were less predictors for PAR > mild (AUC = 0.68, respectively, AUC = 0.75, P = 0.002). In a multivariate analysis, only 3D-oversizing index showed an independent value for PAR > mild (OR = 18.6, P < 0.001).

Conclusion
Basal ring CT measurement significantly underestimated the real 3D-anatomic aortic annulus area. This may impact on THV sizing and PAR incidence. 3D-oversizing index is the most predictive factor for PAR > mild.

Keywords
trans-catheter aortic valve replacement • aortic stenosis • aortic annulus • 3D MDCT • paravalvular aortic regurgitation

Introduction
Understanding the aortic root anatomy has become pivotal in the setting of TAVR to choose the appropriate trans-catheter valve (THV) size and minimize post-TAVR paravalvular aortic regurgitation (PAR). On this issue, computed tomography (MDCT) is largely used because of its higher reproducibility as well as its spatial resolution for measurement of the basal ring annulus. However, despite decreased incidence of PAR by adequate THV sizing using MDCT,1
this is still the most frequent complication of TAVR and is independently related to poor prognosis. Among the factors that underlie PAR, the ratio of deployed THV to the native annulus is the most predictive.

The basal ring is defined as the ring crossing the three insertion points of each cusp. However, it is a virtual approximation of the anatomic aortic annulus, which displays a fibrotic 3-dimensional ‘crown-like’ structure, corresponding to the landing zone of THV where anchoring and good contact must be achieved (Figures 1 and 2).

Therefore, anatomic annulus 3-dimensional analysis may be of paramount importance with regard to THV sizing and PAR incidence.

Objectives

The primary goal of this study was to compare measurement of 3-dimensional anatomic annulus with conventional cross-sectional virtual basal ring. Second aim was to assess relevant independent predictive parameters including both geometrical aortic annulus parameters and aortic valve calcium distribution that may impact on PAR post-TAVR with potential application on sizing strategy.

Methods

Population

A total of 100 consecutive patients with symptomatic severe aortic stenosis (AS) not eligible for surgery or at high operative risk underwent TAVR between January 2011 and December 2014. Patients with bicuspid valve and patients with THV malposition or valve in valve procedure were not included. Complete data of MDCT and TTE pre- and post-TAVR were achieved in 92 patients.

Informed consent was obtained from each patient prior to the investigation as required by local Ethics Committee.

Multidetector computed tomography

Prior to TAVR, an enhanced MDCT was performed in all patients. Otherwise, all patients underwent a MDCT after the TAVR.

All examinations were performed using Philips Brilliance 64 and 256-slice MDCT scanners (Philips Medical). Standard technical parameters were used: 100 kV tube voltage, 600–800 mAs intensity without modulation, and temporal resolution 125–165 ms. Retrospective ECG gating was performed. Contrast enhancement was achieved with 50–60 mL of Iomeprol 400 mg/mL (Iomeron®).

The mean total DLP was 1323 ± 292 mGy cm for both CT pre- and post-TAVR.

The thickness of reconstructed images was 0.45–0.67 mm. All data were transferred to an offline post-processing dedicated workstation (EBW; Philips Medical and OsiriX-MD, version 2.8.2, Pixmeo, Geneva, Switzerland).

Images were reconstructed in systolic phase in 76 patients (82%); however, the more stable cardiac phase was chosen, to limit heart motion artefacts.

Data from 15 randomly selected patients were compared in both systolic and diastolic phases.
Basal ring measurement

The virtual basal ring plane was obtained by orthogonal multiplanar mode, as follows: two orthogonal planes of aortic long axis bisect the middle of the cusps, and then the aortic annulus was obtained by moving the third perpendicular transverse plane to the three lowest insertion points of the cusps, also called the nadirs as previously described.8

The basal ring annulus area was then manually traced with a calliper, including the three nadirs cusp insertions.

3-Dimensional anatomic annulus measurement

3D-anatomic annulus was obtained point by point following aortic cusps insertion using a curvilinear multiplanar mode on an offline workstation (OsiriX-MD v.2.8.2 64-bit). On average, 25 points covered the entire anatomic annulus circumference from the nadir to the commissures of each aortic cusp. We obtained a 3D shape similar to a crown-like ring, superimposed on the aortic longitudinal orthogonal plans.

The curvilinear view represents three unroll semilunar cusp insertion mimicking the native anatomic annulus festooned shape (Figure 3). The planar projection of the 3D anatomic annulus was assessed on a transverse cross-sectional plane, and area was traced manually with a calliper.

The difference between the projected 3D-AA area and BVR area was defined as: delta index = (3D-anatomic annulus area/basal ring area) − 1) × 100.

Mean time used for calculation of aortic annulus by 2D method was 1–2 min and 2–3 min for 3D method.

Prior TAVR prosthesis indexes

Nominal THV area represents the theoretical area of a fully expanded prosthesis.

Prior oversizing indexes5,9 were calculated using the ratio of nominal THV area to both 3D anatomic annulus area and basal ring area:

3D-oversizing index = (nominal THV area/3D − AA area − 1) × 100
2D-oversizing index = (nominal THV area/basal ring area − 1) × 100

Post-TAVR prosthesis indexes

A MDCT was performed in all patients post-TAVR, to measure ‘in situ’ THV area in a transverse plane using orthogonal multiplanar mode. The external prostheses area was traced manually at the level of the annulus. Thus, we defined cover indexes as the ratio of in situ THV area to either 3D-anatomic annulus area or basal ring area, as follows:

3D-Cover index = (in situ THV area/3D − AA area − 1) × 100
2D-Cover index = (in situ THV area/basal ring area − 1) × 100

Echocardiography

A complete two-dimensional, colour, pulsed, and continuous wave Doppler echocardiographic examination was performed post-TAVR at discharge. (Philips IE33, Best, the Netherlands).

TTE Short axis was performed to detect the number and the severity of the paravalvular leak. PAR was quantified by planimetry of vena contracta at the origin of the regurgitation jet, traced manually with a caliper using zoom mode after adequate alignment to prostheses short-axis plane. To detect the strict origin of the PAR jet, a multi-level short-axis plane was performed with biplane-colour mode, using a 3D echo probe (XS-1 Pure Wave microbeamforming Philips Medical). The longitudinal THV view plane is fixed, and the transvers short-axis plane scans the full height of the prostheses.

Figure 3  MDCT 3D anatomic annulus, represented in three orthogonal planes, modelled point by point following the three semilunar aortic cusps insertion, using a curvilinear multiplanar mode. The 3D anatomic annulus (in green) crown-like shaped is superimposed on the three planes (A and B). (C) 3D anatomic annulus projected area in cross-sectional plane (mauve plan) at the level of commissures. (D) MDCT curvilinear view of anatomic annulus similar to unrolled festoon native annulus (see Figure 1). Calcium annulus area (mm²) was automatically contoured based on detection of high-density region (an empiric cut-off of >900 HU). (E) Transverse plan at the level of basal virtual ring (red circle) compared with the projected 3D-AA area (green circle).
PAR was quantified as follows: absent (including trivial leaks), mild <0.10 cm², moderate 0.10–0.30 cm², and severe >0.30 cm² according to current recommendation of Valve Academic Research Consortium (VARC II) criteria. All echo examinations post-TAVR were analysed blind to CT measurements and performed by two experienced echo readers. Echo data were saved as images or cine-loops. Intra- and interobserver reproducibility was analysed for PAR as qualitative variable and classed as none or traces, mild or >mild (agreement coefficient = 0.91 and 0.88, respectively).

**Aortic valve calcium quantification**

Calcium appositions were automatically contoured based on an automatic detection of high-density region (an empiric cut-off of >900 HU). Valve calcium volume (mm³) of the aortic valve was measured automatically after defining a region of interest including the aortic valve from annulus to commissures. Calcium annular apposition (mm²) was analysed on the unrolled festoon-like annulus, obtained by curvilinear multiplanar representation (Figure 3D).

**TAVR procedures and device positioning**

The procedure was performed under general anaesthesia. Both self-expandable prostheses CoreValve (Medtronic, Inc., Minneapolis, MN, USA) size 26, 29, or 31 mm and Balloon-Expandable prostheses Edwards SAPIEN or SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) size 23, 26, or 29 mm were implanted. Balloon valvuloplasty was performed with a balloon of 20–26 mm in diameter during simultaneous rapid pacing before placing the device. No post dilatation was performed. The access was trans-femoral when possible or trans-apical, and the device was deployed under fluoroscopic guidance.

Post-TAVR CT was used in three-chamber view to determine device positioning according to the depth of the stent below annular margin at aortic-mitral continuity.

The size of the valve was chosen according to the MDCT basal ring area, following current recommendations.

**Statistical analysis**

For continuous variables compared across independent groups, a non-parametric Mann–Whitney U test was used, and for qualitative variables, a Fisher F test was used.

Paired data were assessed using a paired t-test for normally distributed variable and a Wilcoxon signed rank test for non-normally distributed variables.

Inter- and intra-observer agreements retrieved from a random sample of 20 patients were evaluated for 2D and 3D measurements by calculating intra-class correlation coefficients (ICCs), and an ICC >0.8 was considered to indicate excellent agreement.

Receiver-operating characteristic (ROC) curves were generated using post-TAVR PAR > mild as the event. Additional analysis was done for PAR > mild as the event.

Areas under the curve were compared for different CT measures derived from traditional aortic basal ring (2D-oversizing index), 3D-anatomic aortic annulus CT measures (3D-oversizing index), and the valve calcium volume.

Specific cut-offs were defined using these curves on the basis of the highest sum of the sensitivity and specificity for the prediction of PAR > mild.

Baseline variable and procedural factors related to PAR post-TAVR were evaluated in a multivariable logistic regression model for PAR > mild.

2D and 3D CT aortic annular measures were compared in systole and diastole in 15 randomly selected patients.

A P-value of <0.05 was considered statistically significant.

Statistical analysis was performed with XLSTAT2013 soft (©Addinsoft, Paris, France).

**Results**

**Population**

Baseline clinical, procedural, and echocardiographic characteristics before TAVR are shown in Table 1.

Ninety-two patients (82 ± 6 years old) (51 females) were included with severe symptomatic aortic valve stenosis mean calculated aortic valve area of 0.61 ± 0.15 cm² and a mean gradient of 48.2 ± 13.6 mmHg. The mean calculated logistic EuroSCORE of the study population was 19.7 ± 8.3 and STS score 25.7 ± 11. Eighty-one per cent of the patients were New York Heart Association functional class III or IV.

**TAVR procedures**

Trans-apical access was used in 21 patients and trans-femoral in the rest of patients.

Per-operative mortality was 3%, due to right ventricular failure, other to device migration and another to brain haemorrhage.
Sixty-two patients each received prostheses, either Edward SAPIEN or SAPIEN XT, of which 32 patients had prostheses of 23 mm, 27 patients of 26 mm, and 3 patients with 29 mm.

CoreValve was implanted in 30 patients of which 17 with 26 mm and 13 with 29 mm.

There was no difference for the depth of implantation or LVOT-aorta angle between PAR+ and PAR− group (P = 0.26, respectively, P = 0.22).

**Multidetector computed tomographic measurements of the aortic anatomic annulus and basal ring**

Intra-observer variability was $1.25 \pm 13.58 \text{ mm}^2$ for 3D-annulus area ($\text{ICC} = 0.98$) and $1.19 \pm 15.83 \text{ mm}^2$ for 2D-annulus area ($\text{ICC} = 0.95$). Inter-observer variability was $2.33 \pm 17.3 \text{ mm}^2$ for 3D-annulus area ($\text{ICC} = 0.94$) and $2.38 \pm 16.1 \text{ mm}^2$ for 2D-annulus area ($\text{ICC} = 0.95$).

Basal ring area underestimated by $19 \pm 9\%$ the real 3D-anatomic annulus projected area (392 $\pm$ 63 vs. 467 $\pm$ 80 mm$^2$, $P < 0.001$). However, this difference reached 26 $\pm$ 7% in PAR(+) group (404 $\pm$ 62 vs. 509 $\pm$ 71 mm$^2$) and 17 $\pm$ 9% in PAR(−) group (387 $\pm$ 63 vs. 451 $\pm$ 78 mm$^2$, $P < 0.001$).

The mean absolute difference between 3D-AA and BVR was $63 \pm 36 \text{ mm}^2$ for PAR(−) and $105 \pm 25 \text{ mm}^2$ for PAR(+) group ($P < 0.001$). There was no effect of pre-procedural AR on delta index (coefficient of determination, $R^2 = 0.010$).

Additional data according to PAR grade for Computed Tomographic and Echocardiographic prior and post-TAVR are shown in Table 2.

**Paravalvular aortic regurgitations**

Post-procedural PAR more than mild was observed in 25 patients with planimetry of PAR vena-contracta at $22.4 \pm 6 \text{ mm}^2$ and 18

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**Table 1** Baseline clinical and echocardiographic characteristics before TAVR

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 92)</th>
<th>PAR− (n = 67)</th>
<th>PAR+ (n = 25)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>82 $\pm$ 6</td>
<td>82 $\pm$ 6</td>
<td>83 $\pm$ 5</td>
<td>0.544</td>
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<td>Female, n (%)</td>
<td>51 (55.4)</td>
<td>37 (55.2)</td>
<td>13 (52)</td>
<td>0.876</td>
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<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.8 $\pm$ 5.7</td>
<td>28.4 $\pm$ 6.2</td>
<td>26.1 $\pm$ 4.02</td>
<td>0.153</td>
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<tr>
<td>Body surface area (m$^2$)</td>
<td>1.75 $\pm$ 0.29</td>
<td>1.75 $\pm$ 0.31</td>
<td>1.77 $\pm$ 0.22</td>
<td>0.982</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>20 (21.7)</td>
<td>17 (25)</td>
<td>4 (16)</td>
<td>0.129</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>39 (42.3)</td>
<td>31 (46.2)</td>
<td>8 (32)</td>
<td>0.794</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>7 (7.6)</td>
<td>5 (7.4)</td>
<td>2 (8)</td>
<td>0.750</td>
</tr>
<tr>
<td>Pulmonary disease, n (%)</td>
<td>47 (51)</td>
<td>37 (55.2)</td>
<td>10 (40)</td>
<td>0.968</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>56 (60.8)</td>
<td>37 (55.2)</td>
<td>19 (76)</td>
<td>0.453</td>
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<tr>
<td>Cerebral disease, n (%)</td>
<td>15 (16.3)</td>
<td>11 (16.4)</td>
<td>4 (16)</td>
<td>0.946</td>
</tr>
<tr>
<td>Renal MDRD (mL/min)</td>
<td>55.7 $\pm$ 18</td>
<td>56.8 $\pm$ 19</td>
<td>54.8 $\pm$ 18</td>
<td>0.836</td>
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<tr>
<td>Log EuroSCORE</td>
<td>19.7 $\pm$ 8.3</td>
<td>19.2 $\pm$ 8.2</td>
<td>21.1 $\pm$ 8.3</td>
<td>0.305</td>
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<tr>
<td>STS score</td>
<td>25.7 $\pm$ 11</td>
<td>24.9 $\pm$ 10.1</td>
<td>28 $\pm$ 13.2</td>
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**Echocardiographic characteristics**

<table>
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<th>PAR− (n = 67)</th>
<th>PAR+ (n = 25)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Aortic peak pressure gradient (mmHg)</td>
<td>74.1 $\pm$ 21.2</td>
<td>75.5 $\pm$ 21.8</td>
<td>70.6 $\pm$ 19.6</td>
<td>0.358</td>
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<tr>
<td>Mean aortic pressure gradient (mmHg)</td>
<td>48.3 $\pm$ 13.6</td>
<td>48.9 $\pm$ 13.1</td>
<td>46.4 $\pm$ 15.1</td>
<td>0.427</td>
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<tr>
<td>Aortic valve area (cm$^2$)</td>
<td>0.61 $\pm$ 0.15</td>
<td>0.60 $\pm$ 0.15</td>
<td>0.64 $\pm$ 0.16</td>
<td>0.316</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>52.8 $\pm$ 15.3</td>
<td>52.7 $\pm$ 15.5</td>
<td>53.2 $\pm$ 15.1</td>
<td>0.968</td>
</tr>
<tr>
<td>Pulmonary pressure (mmHg)</td>
<td>44.1 $\pm$ 9.7</td>
<td>44.1 $\pm$ 9.5</td>
<td>44.2 $\pm$ 10.4</td>
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**Procedural characteristics**

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<th>PAR+ (n = 25)</th>
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</thead>
<tbody>
<tr>
<td>Edwards Sapien valve</td>
<td>62</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
<td>Trans-femoral</td>
<td>41</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Trans-apical</td>
<td>21</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Valve size: 23 mm</td>
<td>32</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Valve size: 26 mm</td>
<td>27</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Valve size: 29 mm</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>CoreValve</td>
<td>30</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Valve size: 26 mm</td>
<td>17</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Valve size: 29 mm</td>
<td>13</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Data are expressed as mean $\pm$ SD or as number (percentage). P-value between PAR+ and PAR−.

BMI, body mass index; CABG, coronary artery bypass grafting; MDRD, glomerular filtration rate; STS, Society of Thoracic Surgeons; PAR+, paravalvular regurgitation more than mild; PAR−, paravalvular regurgitation less than or equal to mild.

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Predictive value for paravalvular regurgitation of 3D-anatomic aortic annulus
patients with mild PAR (8.9 ± 2.3 mm²) while 49 patients had no (or traces of) regurgitation (1 ± 1.7 mm²).

**Prior TAVR indexes**

2D-oversizing index was positive in all groups. It was +23 ± 13% per all and significantly higher in PAR (−) group +25 ± 13% vs. +18 ± 10% in PAR (+) group (P = 0.009).

3D-oversizing index had a positive value (+8 ± 11%) in PAR (−) group and a negative one −7 ± 7% in PAR (+) group (P < 0.001).

**Post-TAVR indexes**

In situ THV area post-TAVR was found to be +13 ± 11% greater than the basal ring area (2D-cover index) for PAR (−) group and +2 ± 7% in PAR (+) group (P < 0.001).

However, considering the 3D-anatomic annulus area, the 3D-cover index was −3 ± 8% for PAR (−) vs. −19 ± 5% in PAR (+) group (P < 0.001).

**ROC curves evaluating predictive value for post-TAVR PAR > mild**

Areas under the curves and specific cut-offs generated by ROC curves are shown in Table 3 (Figure 4).

The 3D-oversizing index had a significantly greater discriminatory value (area under the curve, AUC = 0.88) for PAR > mild than the same based on the conventional basal virtual ring area (AUC = 0.68) (P < 0.0001).

A negative 3D-oversizing index had 88% sensitivity and 82% specificity with 65% positive predictive value and 95% negative predictive value for occurrence of PAR > mild post-TAVR. In comparison, a 2D-oversizing index less than the cut-off +25% had 84% sensitivity, but only 41% specificity and 36% positive predictive value (P < 0.001) for PAR > mild.

A cut-off of +21% difference between 3D-AA and BVR had 82% Se and 73% Sp (AUC = 0.82) for PAR > mild.

The annulus calcium area had significantly higher discriminatory value (AUC 0.75, 0.66–0.85) than valvular calcium volume (AUC = 0.68) (P = 0.034); however, it was significantly less predictive than 3D-oversizing index AUC = 0.88 (P = 0.002).

**CT assessment of calcification**

Valve calcium volume was approximately two-fold increased in PAR (+) group (388 ± 558 mm³) vs. PAR (−) group (195 ± 220 mm³, P = 0.009).

Mean annulus calcium area was 23 ± 32 mm² for PAR (−) group vs. 57 ± 91 mm² for PAR (+) group (P = 0.004).

**Univariable and multivariable logistic regression model for PAR**

Logistic regression model for PAR is shown in Table 4.

There was no significant difference between the trans-femoral (n = 71) and apical (n = 21) groups concerning the occurrence of PAR (P = 0.47). Also, there was no significant interaction between the type of prosthesis, sex, or aces site and PAR (+). In a univariable analysis, 3D-oversizing index had a significant OR = 33, P < 0.0001 for PAR (+), delta index OR = 4.76, P < 0.0001, as well 2D-oversizing index OR = 2.9, (P = 0.044) and valve calcium volume (OR = 1.2, P = 0.056).

However, only 3D-oversizing index (OR = 18.6, P = 0.005) and delta index (OR = 2.91, P = 0.023) have shown an independent predictive value of PAR (>mild) in multivariable logistic regression model and also post-TAVR 3D-cover index (OR = 5.8, P < 0.0001).

**Variation of 2D and 3D measurements throughout the cardiac cycle**

While 2D annulus displayed significant variations with larger BVR area in systole (P = 0.001) and increased Dmax/Dmin ratio in diastole (P = 0.001) (Table 5), no significant differences were found for 3D annulus.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Computed tomographic and echocardiographic data pre- and post-TAVR according to PAR grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 92)</td>
</tr>
<tr>
<td>3D anatomic annulus area (mm²)</td>
<td>467 ± 80⁷</td>
</tr>
<tr>
<td>3D-cover index (%)</td>
<td>−7 ± 10⁷</td>
</tr>
<tr>
<td>3D-oversizing index (%)</td>
<td>+4 ± 12⁷</td>
</tr>
<tr>
<td>Delta (%)</td>
<td>19 ± 9³</td>
</tr>
<tr>
<td>Basal ring area (mm²)</td>
<td>392 ± 6³</td>
</tr>
<tr>
<td>2D-cover index (%)</td>
<td>+10 ± 11³</td>
</tr>
<tr>
<td>2D-oversizing index (%)</td>
<td>+23 ± 13³</td>
</tr>
<tr>
<td>THV in situ area (mm²)</td>
<td>429 ± 64</td>
</tr>
<tr>
<td>Valve calcium volume (mm³)</td>
<td>248 ± 354³</td>
</tr>
<tr>
<td>Annuclus calcium area (mm²)</td>
<td>23 ± 13³</td>
</tr>
<tr>
<td>Vena-contracta PAR planimetry (mm²)</td>
<td>8.4 ± 9.8³</td>
</tr>
</tbody>
</table>

Values are mean ± SD. P-value vs. PAR > mild. 3D-cover index: (in situ THV external area/3D anatomic annulus area − 1) × 100. 2D-cover index: (in situ THV external area/basal ring area − 1) × 100. 3D-oversizing index: (nominal THV area/3D anatomic annulus area − 1) × 100. Delta: (3D anatomic annulus area/basal ring area − 1) × 100. THV, trans-catheter aortic valve replacement; THV, trans-catheter heart valve; PAR, paravalvular aortic regurgitation.

*P < 0.001; ¹P < 0.05 vs. PAR > mild.
Discussion

Virtual basal ring: a weak approximation of the real anatomic aortic annulus

Our study is the first to focus on the real anatomic annulus 3D modelled point by point following the semilunar cusp insertions to aortic wall. We must keep in mind that the virtual basal ring currently used for prosthesis sizing is only an approximation of the real anatomic annulus since it includes the muscular septum as well as the membranous structures (namely the anterior mitral leaflet and the membranous septum) in addition to the three nadirs of the cusps (see Figure 5A). Hence, more than half of the circumference of the basal virtual ring represents a thin membranous structure mobile during the cardiac cycle that may not assure a tight contact with the prosthesis. The combined movement of anterior leaflet and membranous septum is centripetal in diastole, reducing the anterior–posterior diameter (see Figure 5B) inducing a more ovoid shape of the 2D-annulus.

Actually, the real 3D anatomic aortic annulus is a flexible but quite inextensible fibrous structure, represented by bands of dense connective tissue, like collagen, which belongs to the fibrous skeleton of the heart.

Consequently, the prostheses do not deploy ‘in situ’ more than the 3D anatomic annulus; otherwise, there is a high risk of annulus rupture.

Table 3  Receiver-operating characteristic curve analysis for calcium, 3D and 2D CT indexes with post-TAVR paravalvular regurgitation > mild as the outcome measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>P-value</th>
<th>Cut-off</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-oversizing index</td>
<td>0.88 (0.81–0.94)</td>
<td>–</td>
<td>0%</td>
<td>88</td>
<td>82</td>
<td>65</td>
<td>95</td>
</tr>
<tr>
<td>2D-oversizing index</td>
<td>0.68 (0.56–0.78)</td>
<td>0.0001</td>
<td>25%</td>
<td>84</td>
<td>41</td>
<td>36</td>
<td>93</td>
</tr>
<tr>
<td>Delta (3D AAA/BVR)</td>
<td>0.82 (0.73–0.91)</td>
<td>0.2</td>
<td>21%</td>
<td>84</td>
<td>73</td>
<td>54</td>
<td>92</td>
</tr>
<tr>
<td>Annulus calcium area</td>
<td>0.75 (0.66–0.85)</td>
<td>0.047</td>
<td>14 mm²</td>
<td>87</td>
<td>61</td>
<td>45</td>
<td>93</td>
</tr>
<tr>
<td>Valve calcium volume</td>
<td>0.68 (0.56–0.79)</td>
<td>0.002</td>
<td>150 mm³</td>
<td>84</td>
<td>55</td>
<td>41</td>
<td>90</td>
</tr>
</tbody>
</table>

Cut-offs were defined on the basis of the highest sum of the sensitivity (Se) and specificity (Sp) for the prediction of PAR > mild. P-value of ROC curves analysis vs. 3D-oversizing index ROC curve.

PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

Table 4  Logistic regression model for post-TAVR paravalvular regurgitation > mild

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI) univariable</th>
<th>P-value</th>
<th>OR (95% CI) multivariable</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-oversizing (&lt;cut-off)</td>
<td>33 (8.6–130.7)</td>
<td>&lt;0.0001</td>
<td>18.6 (4.5–76.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2D-oversizing (&lt;cut-off)</td>
<td>2.9 (1.03–8.1)</td>
<td>0.044</td>
<td>Dropped</td>
<td>–</td>
</tr>
<tr>
<td>Delta (per 10%)</td>
<td>4.76 (2.7–10.2)</td>
<td>&lt;0.0001</td>
<td>2.91 (1.15–7.3)</td>
<td>0.023</td>
</tr>
<tr>
<td>Valve calcium volume per 100 mm³</td>
<td>1.19 (0.99–1.45)</td>
<td>0.06</td>
<td>Dropped</td>
<td>–</td>
</tr>
<tr>
<td>Annulus calcium area per 10 mm²</td>
<td>1.15 (1.01–1.31)</td>
<td>0.014</td>
<td>Dropped</td>
<td>–</td>
</tr>
<tr>
<td>Self-expandable vs. Balloon</td>
<td>1.3 (0.8–7)</td>
<td>0.12</td>
<td>Dropped</td>
<td>–</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.3 (0.45–2.8)</td>
<td>0.78</td>
<td>Not entered</td>
<td>–</td>
</tr>
<tr>
<td>Aces site (apical/femoral)</td>
<td>1.4 (0.5–4.2)</td>
<td>0.47</td>
<td>Not entered</td>
<td>–</td>
</tr>
</tbody>
</table>

All variables shown entered into stepwise forward logistic regression multivariable model. Not entered, not entered into the model as univariate P > 0.1; Dropped, dropped by multivariable model; OR, odds ratio.

Table 5  CT aortic annular measurements compared in diastole and systole in 15 randomly selected cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diastole (n = 15)</th>
<th>Systole (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D annulus area (mm²)</td>
<td>503 ± 87</td>
<td>496 ± 86</td>
<td>0.28</td>
</tr>
<tr>
<td>2D annulus (BVR)</td>
<td>399 ± 58</td>
<td>448 ± 77</td>
<td>0.001</td>
</tr>
<tr>
<td>Dmax (mm)</td>
<td>24.3 ± 2.3</td>
<td>24.9 ± 2.6</td>
<td>0.089</td>
</tr>
<tr>
<td>Dmin</td>
<td>19.7 ± 1.7</td>
<td>21.8 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dmax/Dmin</td>
<td>1.23 ± 0.08</td>
<td>1.14 ± 0.08</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

BVR, basal virtual ring; Dmax and Dmin, maximal and minimal diameter derived from cross-sectional 2D measurement of BVR. P-value derived from paired t-test.

Supporting this, our study had shown that the 3D-annulus area do not change significantly throughout the cardiac cycle and the 3D-cover index is near zero for patients without regurgitation, meaning that, the prosthesis expands to achieve and to match exactly the 3D-anatomic inextensible annulus.

In contrast, the basal ring seems able to enlarge since post-TAVR deployed THV area is greater than the basal ring area, as shown by
Figure 5  (A) Virtual basal ring (bottom left) composed of the three nadirs of the cusps as well as the muscular septum (blue curve) and the membranous structures, such as the anterior mitral leaflet (yellow curve) and the membranous septum (red curve).  (B) 3D and 2D annulus measured during systolic phase and during diastolic phase. 3D annulus area (green curve) has no significant variation during cardiac cycle (425 vs. 415 mm²). There is a difference of 57 mm² (14%) between 2D annulus area (red curve) measured in systole vs. diastole. 2D-Annulus appears more elliptical in diastolic phase (ratio A/B).
a positive value of the 2D-cover index. Due to expandable membranous included into the component of the basal ring, such as the anterior mitral leaflet and membranous septum. As seen in Figure 6, the aortic root is tighter at the level of nadirs and larger at the level of commissures, depending on how wide the angle is between basal plane and each commissure. Therefore, the 3D anatomic annulus projected area is larger and circumscribes the basal ring area (see Figure 7).

We observed a mean 19% underestimation of the real 3-dimensional anatomic annulus area when using basal ring area. However, it is worth to note that this difference is not the same in all patients since it is significantly greater, up to 26%, in the group with PAR ≥ mild and 15% in patients without regurgitation. There was no correlation between delta index and 2D-annulus area ($R^2 = 0.006$). Thus, the delta index cannot be predicted by 2D annulus area but does depend on the 3D annulus shape. Otherwise, Delta difference was found as an independent (OR = 2.9 per 10%) factor related to PAR (+), and a cut-off +21% generated by ROC curves showed 82% sensitivity and 73% specificity for PAR +. This significant clinical cut-off of 21% (93 mm² absolute difference) means that a larger prosthesis than THV based on BVR area should have been chosen. Consequently, if 3D anatomic annulus sizing were applied overall, changing decision concerning prosthesis size would have occurred in 30 of 92 patients (32%): 12 patients would have received a prostheses of 26 mm instead of 23 mm, and 12 patients a 29 mm instead of 26 mm, while 6 patients would have received a CoreValve 31 mm instead of 29 mm.

**Paravalvular aortic regurgitation**

Prior studies showed a similar incidence of PAR$^2$ as we observed in our study and a comparable predictive value of 2D-oversizing index for PAR.$^3$ But the use of the 3D-oversizing index added a significant improvement of the predictive value.

The Partner cohort trial$^3$ showed PAR ≥ mild were associated with an increased late mortality, but only severe paravalvular regurgitation in Pivotal Extreme Risk Trial.$^7$ The meta-analysis by Athappan et al.$^2$ confirmed the unfavourable overall 1-year mortality in patients with moderate and severe PAR, but this was less apparent with mild PAR, related in part to the challenges in quantification of PAR.

For this reason, we performed an additional analysis for predictive value using post-TAVR PAR ≥ mild as the event (Table 6). The results were consistent and 3D-oversizing index was the most predictive independent factor for any PAR.

In a recent study, Wilson et al.$^{14}$ showed that oversizing might reduce the risk of moderate or severe PAR, with a mean 2D-oversizing index of 14 + 18%, based on basal ring area. However, a systematic strategy of greater oversizing in all patients may come at a cost, with potential greater risk of annular rupture as shown in a multicentric study, where it pointed out patients who experienced aortic root rupture had a greater degree of oversizing 30.5 + 15.8% than the rest of TAVR cohort 11.3 + 19.7%.$^{15}$

Our results suggest that the amount 2D-oversizing compensates in fact the percentage of underestimation ≏ 20% of the real anatomic annulus by the basal ring. However, in some patients, 3D annulus and basal ring may be similar and then the same oversizing induces a risk of rupture.

When considering the real three-dimensional anatomic annulus, 3D-oversizing index near zero or slightly positive may avoid PAR with a predictive negative value of 95%.

**Impact of calcification on PAR**

Our study focused on the assessment of the discriminant value of each confounding factors in the setting of PAR, including geometrical aortic annulus parameters, device positioning, and aortic valve calcification.

In our analysis, we quantified valve calcium volume and annulus calcium apposition all along the festooned anatomic annulus, also taking into account the nadirs of the cusps insertion as well as commissures regions.

Our results confirmed the impact of aortic root calcification$^{16,17}$ on PAR post-TAVR by showing a similar predictive value for annulus calcium area (AUC = 0.75) or valve calcium volume (0.68)
as previously reported by Khalique et al.\textsuperscript{18} In their study, valve calcium volume and annulus LVOT calcium were independent predictors of PAR with similar odds ratio when taking into account 2D-oversizing index, which is consistent with our results. Nevertheless, we clearly showed that calcifications are significantly less predictive than 3D-oversizing index for PAR ($+$).

Calcifications of the aortic valve complex may impair the seal of THV to the aortic annulus and may contribute to incomplete deployment, resulting in PAR.

However, our data suggest only a limited correlation between 3D-cover index (post-TAVR) and calcium volume (coefficient of determination, $R^2 = 0.148$) and less with calcium annulus area ($R^2 = 0.10$). Also, the calcium annulus area or valve calcium had only limited predictive positive values: 45 or 41%, respectively (Table 3).

Furthermore, in a multivariable binary logistic regression model for PAR $>$mild, only the 3D-oversizing index has shown an independent predictive value.

**Limitations**

First, this is a single-centre study. Second, PAR quantification might be controversial since PISA method cannot be applied in this setting, as a result of image artefacts caused by metal-stent shadowing.\textsuperscript{10}
Nevertheless, a recent study has shown a good accuracy of planimetry of the vena-contracta to quantify PAR.19

Systolic motion CT artefacts and BVR area systole–diastole variations may be an important limitation for 2D annulus sizing. However, 3D-annulus showed no significant changing throughout the cardiac cycle.

**Conclusion**

The aortic virtual basal ring is a weak approximation that underestimates the real anatomic annulus, resulting in a deleterious impact on the appropriate THV sizing strategy. The real aortic anatomic annulus is an inextensible, fibrous, 3-dimensional structure of which MDCT 3Dmodelling and measurement allow a more comprehensive aortic root analysis and a more accurate THV sizing than the virtual basal ring does.

The use of 3-dimensional anatomic annulus may potentially reduce PAR since the 3D-oversizing index value is the most predictive independent factor for PAR > mild post-TAVR.

**Conflict of interest:** None declared.

**References**