Quantitative image analysis for planning of aortic valve replacement

Elattar, M.A.I.M.

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Chapter 4

Dynamics of the Aortic Annulus in 4D CT Angiography for Transcatheter Aortic Valve Implantation Patients

Mustafa Elattar
Leon Vink
Jan Baan
Ed VanBavel
Nils Planken
Henk Marquering

Under Review
Chapter 4

4.1 Abstract.

**Background:** Transcatheter aortic valve implantation (TAVI) is a well-established treatment for patients with severe aortic valve stenosis. This procedure requires pre-operative planning by assessment of aortic dimensions on CT Angiography (CTA). It is well-known that the aortic root dimensions vary over the heart cycle. However, sizing is commonly performed at either mid-systole or end-diastole only, which has resulted in an inadequate understanding of its full dynamic behavior.

**Study Goal:** We studied the variation in annulus measurements during the cardiac cycle and determined if this variation is dependent on the amount of calcification at the annulus.

**Methods:** We measured and compared aortic root annular dimensions and calcium volume in CTA acquisitions at 10 cardiac cycle phases in 51 aortic stenosis patients. Sub-group analysis was performed based on the volume of calcium by splitting the population into mildly and severely calcified valves subgroups.

**Results:** For most annulus measurements, the largest differences were found between 10% and 70 to 80% cardiac cycle phases. Mean difference (±standard error) in annular minimum diameter, maximum diameter, area, and aspect ratio between mid-systole and end-diastole phases were 1.0 ± 0.29 mm, 0.30 ± 0.24 mm, 24.1 ± 7.6 mm², and 0.041 ± 0.012 (p-values of 0.065, 0.74, <0.001, and 0.039) respectively. Calcium volumes varied strongly during the cardiac cycle. The dynamic annulus area was behaving differently between mildly and severely calcified subgroups. Furthermore, patients with severe aortic calcification were associated with larger annulus diameters.

**Conclusion:** There is a significant variation of annulus area and calcium volume during the cardiac cycle. The dynamic variation of the annulus area was dependent on the severity of the aortic calcification. The annulus area is significantly larger in mid-systole compared to end-diastole.

**Keywords**

Dynamic, Comparison, Aortic annulus, Calcium score, Transcatheter aortic valve implantation, CT Angiography, Cardiac cycle phases
Aortic Annulus Dynamics in 4D CTA for TAVI Patients

4.2 Introduction

Aortic valve stenosis (AS) is the most common valve disease in elderly. AS has a strong age-associated prevalence of 0.2% in adults between 50-59 years, increasing to 9.8% for the age of 80-89 years [1, 2]. Approximately one-third of all patients with severe aortic stenosis are not eligible for surgery, mainly because of high age, left ventricular dysfunction, or other significant co-morbidities [3, 4].

Transcatheter aortic valve implantation (TAVI) has been introduced as an alternative treatment for these high-risk patients. TAVI provides sustained clinical and hemodynamic benefits in selected high-risk patients rejected for conventional aortic valve replacement [4–6]. Preprocedural evaluation of the aortic root sizing parameters, especially aortic annular dimensions, is pivotal for selecting the optimal prosthesis size [7–10]. CT Angiography (CTA) imaging plays an important role in preoperative interventional planning and patient selection [11–13].

In clinical practice, aortic root dimensions are typically determined by CTA at either of two points in the cardiac cycle [14, 15]. Some use mid-systole, where the valve is open to facilitate the annular insertion point identification [16]. Others prefer end-diastole, at 75% of the R-R interval, when the aortic valve movement is minimal and the motion artifacts are reduced, which makes the analysis easier and more robust [17].

Studies in animal models and healthy humans have shown annulus diameter variations between mid-systole and end-diastole of as much as 7.5% [18–21]. Such variations seem relevant for prosthesis selection. Yet, it is not clear whether similar dynamic variations in annular dimensions exist in elderly patients with calcified aortic stenosis (AS) in whom aortic compliance is likely to be substantially reduced. Earlier studies on dynamic changes in annular dimensions in the context of TAVI have produced conflicting results [9, 22, 23]. In addition, these studies were limited to two time points, mid-systole and end-diastole. Yet, aortic dimensions change continuously during the cardiac cycle, and measuring differences between only these time points may underestimate the complexity of the dynamics [9]. A recent study assessed aortic root dimensions along the cardiac cycle to find the largest diameter measurements in TAVI populations [24].

Calcification of the annulus is highly relevant for TAVI planning, since it is strongly associated with aortic regurgitation after prosthetic implantation [25, 26]. Furthermore, the elasticity of the aortic annulus is dependent on the extent of calcium deposit [27]. Because of the large density differences between calcifications and its surroundings and the limited spatial and temporal resolution, it is expected that calcium volume measurements on CT imaging are susceptible to motion related artifacts. However, no previous studies have evaluated the dynamic variation of calcium scoring during the cardiac cycle. Severity of calcium at the annulus level may increase the partial volume averaging effect (blooming) altering the quality of the annulus sizing [10].

The purpose of the current study is to evaluate dynamic variations in annulus dimensions and calcium score in patients with aortic stenosis. We exploit the capacity of current CT scanners to construct 4D ECG-gated CTA at 10 cardiac phases. In
addition, we assess the effect of calcification severity on the annulus sizing measurements.

4.3 Methods

4.3.1 Study Population

The study included 51 patients with severe symptomatic aortic stenosis who were referred to our institute (Academic Medical Center, The Netherlands) for TAVI who underwent preprocedural ECG-gated cardiac 4D CTA. Patients with permanent pacemaker, coronary artery bypass grafting and aortic root dilation were excluded from the study.

4.3.2 Scan Protocol

All CT-scans were performed on a Philips Brilliance 64 slice CT scanner; imaging parameters were 120 kV, matrix 512, and convolution kernel B. The chest, abdomen, and pelvis were scanned using one bolus of 120 ml contrast Iomeron 400, intravenously infused at a rate of 5 ml/s. Image volumes contained 500 to 600 slices. The dimensions of each slice were 512 × 512 pixels with a 16 bit depth. The in-plane image resolution was isotropic and varied between 0.44 mm and 0.68 mm. The slice thickness for all data sets was 0.9 mm with an overlap of 0.45 mm. The 4D CTA scanning protocol produced successive 10 cardiac cycle phase volumes covering the full cardiac cycle (each 10% of RR-interval).

4.3.3 Aortic root analysis

Aortic root measurements were performed by two independent observers using the 3mensio structural heart application [28, 29]. Rater 1 analyzed 22 subjects and rater 2 analyzed 34 subjects with an intersection of five subjects for the interobserver variability assessment. Each cardiac cycle phase volume was loaded after which the centerline of the aortic root was automatically detected. Subsequently, the observer could adjust the aortic root centerline by refining centerline control points, resulting in an adjusted multi-planar reconstruction images (MPRs). In the next step, the software automatically defined the annulus plane that lies between the aortic root and the left ventricle outflow tract. It was manually adjusted to assure that the annulus plane included the three hinge points. The hinge points correspond to the three anchors at the nadir of each of the attachments of the aortic cusps [30]. The annulus plane adjustment was performed on two oblique MPRs and the perpendicular plane to the initial centerline (Figure 4.1).
After confirmation of the annulus plane, two oblique stretched vessel views were generated showing the left ventricle outflow tract (LVOT), aortic valve, and ascending aorta along the centerline. This oblique stretched vessel view facilitated the manual hinge point selection. In this manner, the selected annulus plane was assured to include the three hinge points of the annulus.

Minimum and maximum diameters were measured using a straight line annotation tool on the annulus plane. On the same plane, annulus area and perimeter were determined after drawing a polygon along the aortic annulus edge as shown in Figure 4.2. The polygon was drawn following the annulus wall even if there was calcification; the polygon line was drawn through the calcium deposits sticking to the vessel wall. The annulus aspect ratio was calculated by dividing minimum diameter by the maximum diameter.
A calcium scoring tool was used to assess the calcification volume after choosing the threshold in Hounsfield Units (HU) that separates the calcification from the contrast-enhanced blood and aortic wall intensities (Figure 4.3). Calcification volume was calculated after setting a volume of interest (VOI) including aortic annulus and leaflet calcifications. This VOI was set to exclude calcifications in the LVOT, coronary arteries, and ascending aorta. Subsequently, raters determined the proximal and distal cutting planes such that these areas were excluded. If there were still other undesirable calcium deposits within the VOI, a contour editing tool was used to exclude extra deposits.

Within a single patient, the same calcium threshold and VOI were used for all cardiac cycle phases. For the interobserver analysis, calcium threshold values and cutting planes were identical for every patient for both raters.
4.3.4 Calcium Subgroup Analysis

Two subgroups were generated based on the amount of annulus and leaflet calcification. Patients with calcification volumes exceeding 250 mm$^3$ were assigned to the severely calcified patient group. The mildly calcified group included patients with calcification volumes less than 250 mm$^3$. This threshold of 250 mm$^3$ was determined by fitting the probability distribution of a Bi-Modal Gaussian distribution with the histogram of all calcium volume measures.

We compared both subgroups annulus measurements by calculating the dynamic variation during the cardiac cycle by means of standard deviation, range, and their significance. Average measurements per subgroup and per cardiac cycle phase are calculated and reported.

4.3.5 Statistical Analysis

Continuous data that follow normal distribution are presented as mean ± standard deviation (SD). Statistical analyses were performed with MATLAB (Version R2013b, The Mathworks Inc., and Natick, MA) and SPSS (version 19.0, SPSS Inc., and Chicago, IL). We also reported the average of all measurements per each subgroup created based on the amount of calcification (lower and higher than 250mm$^3$).

Significance of differences of annulus measurements (diameters, aspect ratios, areas, and perimeters) between the cardiac cycle phases was determined by paired t-tests for normally distributed data and Kolmogorov-Smirnov tests for data that did not follow normal distribution. Aortic annulus measures were compared between all cardiac phases. P-value matrix plots were used to visualize all comparisons between the measurements of the various cardiac cycle phases. Differences with p-values of 0.05 or less were considered statistically significant.

Since annulus area, perimeter, and calcification volume varied widely between patients, we normalized them. These measures were scaled to fall between 0 and 1 for each patient independently.

4.3.6 Interobserver Variability

Five arbitrarily selected patients were evaluated by two raters resulting in 100 measured minimum and maximum diameters. For these, scatter plots were generated and the intraclass correlation coefficient was calculated. Inter-observer variability was furthermore assessed by Bland and Altman analysis.

4.4 Results

The population consisted of 31 [62%] female and 20 males with an average age of 82.2 ± 6.5 years. The aortic annulus measurements in the ten cardiac phases are presented in Table 4.1. Mean difference (± standard error of the mean) between mid-systole and end-diastole phases were 1.0 ± 0.29 mm (p = 0.065), 0.30 ± 0.24 mm (p = 0.738), 0.041 ± 0.012 mm (p = 0.039), 24.1 ± 7.6 mm$^2$ (p < 0.001), 2.1 ± 0.8 mm (p < 0.001) for
annulus minimum diameter, maximum diameter, aspect ratio, area, and perimeter respectively.

Average minimum and maximum annulus diameters were 24.2 ± 3.0 mm and 29.4 ± 2.9 mm at mid-systole and 23.2 ± 2.6 and 29.2 ± 2.8 mm at end-diastole, respectively. These differences were not statistically significant with p-values of 0.065 and 0.738, respectively. However, statistically significant differences in aortic root measurements for various phase combinations were observed as shown in Figure 4.4.

Table 4.1: Mean and standard deviation of annulus measurements (minimum, maximum diameter, minimum to maximum diameter ratio, area, and perimeter) and aortic annulus calcification volume. Mid-systole and end-diastole phases are gray highlighted in the table.

<table>
<thead>
<tr>
<th>Cardiac Cycle Phase</th>
<th>Minimum Diameter (mm) Mean ± STD (n = 51)</th>
<th>Maximum Diameter (mm) Mean ± STD (n = 51)</th>
<th>Minimum to Maximum Diameter Ratio Mean ± STD (n = 51)</th>
<th>Area (mm²) Mean ± STD (n = 32)</th>
<th>Perimeter (mm) Mean ± STD (n = 51)</th>
<th>Calcium Volume (mm³) Mean (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>23.6 ± 2.7</td>
<td>29.3 ± 3.1</td>
<td>0.81 ± 0.07</td>
<td>548 ± 107</td>
<td>83.8 ± 8.9</td>
<td>325</td>
</tr>
<tr>
<td>10%</td>
<td>24.3 ± 2.7</td>
<td>29.3 ± 2.9</td>
<td>0.83 ± 0.07</td>
<td>558 ± 103</td>
<td>84.2 ± 8.0</td>
<td>286</td>
</tr>
<tr>
<td>20%</td>
<td>24.3 ± 2.9</td>
<td>29.3 ± 2.7</td>
<td>0.83 ± 0.08</td>
<td>559 ± 108</td>
<td>84.6 ± 8.9</td>
<td>291</td>
</tr>
<tr>
<td>30%</td>
<td>24.2 ± 3.0</td>
<td>29.4 ± 2.9</td>
<td>0.83 ± 0.06</td>
<td>559 ± 108</td>
<td>84.6 ± 8.5</td>
<td>315</td>
</tr>
<tr>
<td>40%</td>
<td>23.6 ± 2.9</td>
<td>29.2 ± 3.1</td>
<td>0.81 ± 0.07</td>
<td>544 ± 111</td>
<td>83.6 ± 9.1</td>
<td>337</td>
</tr>
<tr>
<td>50%</td>
<td>23.4 ± 2.8</td>
<td>29.2 ± 3.2</td>
<td>0.80 ± 0.07</td>
<td>533 ± 111</td>
<td>83.4 ± 8.7</td>
<td>306</td>
</tr>
<tr>
<td>60%</td>
<td>23.4 ± 2.7</td>
<td>29.2 ± 3.0</td>
<td>0.80 ± 0.07</td>
<td>538 ± 114</td>
<td>83.5 ± 9.0</td>
<td>305</td>
</tr>
<tr>
<td>70%</td>
<td>23.2 ± 2.6</td>
<td>29.2 ± 2.8</td>
<td>0.79 ± 0.07</td>
<td>535 ± 106</td>
<td>82.5 ± 8.2</td>
<td>319</td>
</tr>
<tr>
<td>80%</td>
<td>23.1 ± 2.4</td>
<td>29.1 ± 3.2</td>
<td>0.79 ± 0.07</td>
<td>534 ± 105</td>
<td>83.1 ± 8.8</td>
<td>320</td>
</tr>
<tr>
<td>90%</td>
<td>23.1 ± 2.9</td>
<td>28.9 ± 2.9</td>
<td>0.80 ± 0.08</td>
<td>537 ± 113</td>
<td>82.8 ± 9.1</td>
<td>307</td>
</tr>
</tbody>
</table>

The annulus aspect ratio was 0.83 ± 0.06 and 0.79 ± 0.07 for mid-systole and end-diastole, respectively, which was statistically significant different (p = 0.039).

Aortic annulus area was significantly different between mid-systole and end-diastole (p = 0.001) with areas of 559 ± 108 mm² and 535 ± 106 mm² respectively. Cardiac cycle phases of 10% to 30% showed significant differences with all cardiac cycle phases between 40% and 90% as shown in Figure 4.4. The annulus perimeter dynamic behavior was similar to the annulus area during the cardiac cycle where average perimeter at mid-systole was 84.6 ± 8.5 mm and at end-diastole it was 82.5 ± 8.2 mm. Minimum diameter, aspect ratio, and annulus area showed similar dynamic characteristics through the cardiac cycle, with increasing values at mid-systole and reaching minimum values at late diastole.

The average and standard deviation of threshold to separate calcified tissue was 650 ± 70 HU. There was no significant difference in annular calcium volume between end-diastole and end mid-systole measurements (p = 0.69). However, there was a
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statistical significant difference in calcium volume between 10% and 40% with an average calcium volume of 286 mm$^3$ and 337 mm$^3$, respectively ($p < 0.001$) (Figure 4.4).

Average measurement variation per patient was found to be significantly different between subgroups for only normalized annulus area ($p < 0.001$) and there were no difference for other measurements between subgroups (Table 4.2). However, the average measurements were different between subgroups for minimum and maximum diameters (both $p < 0.001$) which can be observed in Figure 4.5.

Average minimum, maximum diameter, diameters ratio, and area for the heavily and mildly calcified populations are shown in Figure 4.5. In Figure 4.6, average normalized

Figure 4.4: $P$-value matrices showing statistically significant difference between all combinations of cardiac cycle phases for annulus minimum diameter, minimum to maximum diameter ratio, normalized annulus area, and normalized calcifications volume.
calcification volume is presented for the calcification subgroups and the whole population combined.

Table 4.2: Average dynamic variation of annulus measurements per cardiac cycle for both subgroup (mildly annulus calcified subgroup (≤ 250 mm³) and severely annulus calcified subgroup (> 250 mm³)). Annulus measurements included are minimum diameter, maximum diameter, annulus aspect ratio, normalized annulus area, and normalized calcium volume. P-values for significant subgroup difference for dynamic variation and absolute measurements are shown in the last two rows. Severely annulus calcified subgroup is gray highlighted in the table.

<table>
<thead>
<tr>
<th></th>
<th>Average Temporal Measures</th>
<th>Minimum (mm)</th>
<th>Maximum (mm)</th>
<th>Annulus Aspect Ratio</th>
<th>Normalized Annulus Area</th>
<th>Normalized Calcium Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mildly Annulus Calcified Group (&lt; 250 mm³)</strong></td>
<td>STD</td>
<td>1.40</td>
<td>1.08</td>
<td>0.06</td>
<td>0.32</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>4.36</td>
<td>3.42</td>
<td>0.18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>20.8</td>
<td>26.9</td>
<td>0.72</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>25.1</td>
<td>30.3</td>
<td>0.90</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Severely Annulus Calcified Group (&gt; 250 mm³)</strong></td>
<td>STD</td>
<td>1.22</td>
<td>1.32</td>
<td>0.05</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>3.75</td>
<td>4.34</td>
<td>0.17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>22.7</td>
<td>27.7</td>
<td>0.74</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>26.5</td>
<td>32.0</td>
<td>0.91</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Groups Dynamic Difference P-value</strong></td>
<td>(0.22)</td>
<td>(0.09)</td>
<td>(0.28)</td>
<td>(&lt; 0.001)</td>
<td>(0.74)</td>
<td></td>
</tr>
<tr>
<td><strong>Groups Difference P-value</strong></td>
<td>(&lt; 0.001)</td>
<td>(&lt; 0.001)</td>
<td>(0.87)</td>
<td>(0.02)</td>
<td>(&lt; 0.001)</td>
<td></td>
</tr>
</tbody>
</table>
**Figure 4.5:** Average annulus minimum diameter, maximum diameter, aspect ratio, and area for all patients (dotted blue line), subgroup 1 with patients with calcium volume less than 250 mm$^3$ (dashed red line), and subgroup 2 for calcium volume exceeding 250 mm$^3$ (solid green line).

**Figure 4.6:** Average normalized calcium volume for all patients (dotted blue line), patients with calcium volume lower than 250 mm$^3$ (dashed red line), and calcium volume exceeding 250 mm$^3$ (solid green line).
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The agreement between rater measurements is illustrated in a scatter plot in Figure 4.7. Intraclass correlation coefficient (ICC) showed strong agreement (\(p = 0.89\)) between raters for both minimum and maximum diameters. Bland–Altman analyses showed a mean paired difference of 1.67 mm and standard deviation of 1.9 mm for the diameter measurements (Figure 4.7).

![Figure 4.7: (Left) Scatter plot of annulus diameter measurements of rater 1 versus rater 2. (Right) Bland–Altman plot of the agreement between rater 1 and rater 2 for the annulus minimum and maximum diameters.](image)

4.5 Discussion

This study shows significant dynamic variations in aortic annular minimum diameter, area, perimeter, and aspect ratio during the cardiac cycle in TAVI-eligible patients. Only the aspect ratio, area, and perimeter were significantly different between systolic and diastolic phases. Annular minimum and maximum diameters did not show a difference between systolic and diastolic phases. However, a significant difference in annular minimum diameter was found between the 30% and 80% phases. We found large differences exceeding 33% in the dynamic calcium volume measurements. The smallest volumes were around the 10% cardiac phase and the largest volumes around the 90% of the cardiac phase. Surprisingly, the volumes did not differ between the systolic and diastolic phases.

The dynamic behavior of the annulus area was significantly different along the cardiac cycle between the severely and mildly calcified subgroups. Severely calcified patients were found to have significantly larger minimum and maximum diameters in comparison with the patients with mildly calcified aorta annulus and leaflets for all cardiac cycle phases. Annulus aspect ratio and normalized calcium volume did not show different dynamic behavior between both subgroups. The calcification measurements have shown low values especially at the 10% of R-R interval and higher at the 40% of R-R interval. The largest difference was found to be between these two cardiac cycle phases with about 38% change in volume on the normalized scale.
Anatomical changes in the aortic annulus and aortic root between mid-systole and end-diastole have been suggested by earlier experimental and imaging studies [5, 6]. A previous study using transthoracic echocardiography of 292 patients data suggested significant aortic annular diameter changes with a mean change of 7.5% [20]. This is in line with the distensible annular behavior in other studies who studied the dynamic behavior of the aorta in patients with and without aortic stenosis [9, 18, 19, 31]. However, in our study this effect was not observed (between end-diastole and mid-systole). It should be noted that in the study of Yankah et al, the majority of patients were free from aortic stenosis (60%) [20]. This could explain the smaller differences found in our study with changes of minimum and maximum diameters between mid-systole and end-diastole of 4% and 0.8% respectively.

Another two studies on CTA, showed no significant differences in annulus dimensions between mid-systole and end-diastole. In [32], only 25 patients data free from aortic stenosis was used, where in [23] 52 patients with aortic calcification were analyzed. However, in these studies only measurement differences between mid-systole and end-diastole was assessed. None of the mentioned studies have assessed the dynamic behavior in cardiac cycle phases other than mid-systole and end-diastole.

In a recent study, Jurencak et al. also concluded that within a heart cycle there were significant differences in most aortic root measures. They also observed that the maximum diameter was not significantly changing. However, in this work [24] calcium measures and the effect of calcium severity, which is common in TAVI populations, on the annulus measurements were not studied.

Our observation of that the ellipticity of the annulus lumen increases during the diastolic phases and decreases during the systolic phases (10% to 30%) where the highest difference was between 10% and 70% confirms previous findings [33, 24] that the annulus remains elliptical during the whole cardiac cycle.

The similarity of maximum annulus diameter measures between mid-systole and end-diastole can be explained by relatively old patients in our TAVI population. Older patients usually suffer from higher levels of aortic wall stiffness due to alteration in collagen fibers that tend to be thicker and denser [34, 35], which results in a reduction of the distensibility of the annulus.

The annulus diameters were found to be larger in patients with a severely calcified annulus. We believe that annular calcifications may have biased the measurement because of calcium blooming effect leading to an over estimation of the diameters.

The aortic valve closes between 10% and 40% phases. In this time window, leaflet motion is maximal. This contributes to motion artifacts, which in CT are expected to cause blurring of the calcium. This blurring may exaggerate the true calcium volume. This agrees with our findings of having the maximum difference in calcium volume between the 10% and 40% phases.

To the best of our knowledge, this is the first study that studied the dynamic behavior of the annulus anatomical measurements over the full cardiac cycle and in relation to annulus calcifications in TAVI candidates. Full cardiac cycle measurements allowed us
to generate p-value matrices that show the significance of differences in measurements for different cardiac cycle phases.

This is a single center retrospective patient study including a relatively small number of patients, which may not be a representative sample of the wider TAVI population. The number of patients and the number of raters that was used for the interobserver variability analysis was small. Also, there was a small bias between the two observers. Further analysis is needed to confirm the dynamic behavior observed in this study. Some measures were normalized because of large inter-patient differences e.g. area, perimeter, and calcium volume. This normalization may have reduced the statistical significance.

This study excluded patients without calcification and patients with a bicuspid valve, which may have biased our results. However, out of 52 patients we only excluded 2 patients (4%).

It is well known that the aortic root is distensible. Still, only mid-systole and end-diastole cardiac phases are used for aortic root sizing in clinical practice. We actually found that the largest and smallest measures were at other time phases than mid-systole and end-diastole. Therefore, it would be interesting to study the dynamic behavior in TAVI patients with ruptured aortas, migrating valve stents, and left bundle branch block (LBBB) since the measurement at one phase might not represent the variation of the aortic annulus.

We found that in mid-systole, the aortic annulus area was larger than measured at end-diastole. This difference may influence the size selection. Therefore, the cardiac phase of measurement should be taken into consideration during planning. Surprisingly, this difference was not observed for the annulus diameter measurements.

Valve size selection guidelines suggest specific range of the annulus area for each valve size [36, 37]. There is an overlap of 6 mm² between these ranges for different valve sizes. Since the variation in dynamic annulus area measures is approximately four times as large as this value, is expected that these differences may affect the selection of the valve size.

With the small differences found in annulus diameters, this study suggests that for TAVI sizing there is little added value in having multiple cardiac phase image reconstructions. Calcium volume analysis suggests measurements at 10% of the cardiac cycle because the calcium volume is minimal, it is expected that the blooming effect is minimal at that cardiac cycle phase.

## 4.6 Conclusion

There is variation of annular anatomical and calcium measurements along the cardiac cycle. This dynamic variation was not depending on the severity of the aorta calcification. Variations of calcium volumes may be as large as 48%. Small or no differences in minimum and maximum annulus diameters were found between mid-systole and end-diastole.

**Informed consent**
The Institutional Review Board granted approval of the study design and waived informed consent since solely data obtained in the context of clinical care is utilized.

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