Evaluation of calcium loss after transcatheter aortic valve implantation

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Abstract

OBJECTIVES: Aortic valve calcification and changes after transcatheter aortic valve implantation (TAVI) were specifically assessed by computed tomography (CT). The main difference between TAVI and the conventional technique is the compression of the cusps of the calcified native valve against the aortic wall before implantation. The objective of this study was to quantify the segmented calcification in the area of the basal annular plane before and after TAVI.

METHODS: The CT scans of 20 patients (13 male and 7 female; mean age: 82.9 ± 8.1 years) were assessed. The aortic valve calcification was segmented; derived from this segmentation volume, mass and Hounsfield units (HU)/density of the calcifications on the annulus and cusps before and after TAVI were evaluated. Pre- and postoperative data were compared regarding potential calcification loss and calcification distances to the left and right coronary ostia.

RESULTS: Significantly lower postprocedural mean volumes and masses for all cusps (P < 0.001) were found. The mean differences in the volume for the non-coronary, right-coronary and left-coronary cusp were −156.8 ± 53.73, −155.5 ± 62.54 and −115 ± 57.53 mm³, respectively, and differences in mass were −88.78 ± 29.48, −95.2 ± 39.27 and −71.56 ± 35.62 mg, respectively. Over all cusps, mean HU increased after intervention [784.41 ± 92.5 HU (pre) and 818.63 ± 78.71 HU (post); P < 0.004]. In 80.03% of all cusps, calcification loss was found; all patients were affected. Significantly lower (P < 0.047) postprocedural mean distances were found from the left and right coronary ostia to the next calcification point.

CONCLUSIONS: Our results show a significant loss of calcification in all patients after TAVI, with a reduction in the calcification distances to the coronary ostia and the compression of calcification in the area of the device landing zone. The clinical implications of this finding need to be investigated further.

Keywords: Aortic root • Aortic valve repair • Aortic valve replacement • Valve calcification

INTRODUCTION

With the increase in average life expectancy in the western community, the occurrence of degenerative aortic stenosis is continuously increasing and has reached a prevalence of 4.8% in patients >75 years old [1, 2]. Conventional surgical aortic valve replacement (AVR) has been performed for decades and still represents the standard of care. Improvements in surgical techniques have led to a reduction of morbidity and mortality rates to 2.3% after AVR [3].

Transcatheter aortic valve implantation (TAVI) has evolved as an alternative treatment technique for patients with severe aortic stenosis, who do not qualify for AVR owing to either multiple comorbidities or high surgical risk [4]. The PARTNER B trial, a randomized trial analysing the outcome of TAVI in comparison to optimal medical therapy in inoperable patients, demonstrated an improvement of survival of 20% at 1 year, as well as a significant decrease of symptoms in the TAVI group [5]. Since the first percutaneous transcatheter aortic valve implantation performed in 2002, despite the lack of evidence, the use of TAVI is increasingly shifting toward younger and operable patients [6].

While TAVI is clearly less invasive than AVR and does not require sternotomy and the use of cardiopulmonary bypass, major complications after TAVI include cerebrovascular events, acute kidney injury, an incidence of paravalvular leakage and postoperative atrioventricular (AV) blockages requiring pacemaker implantation [7–10]. The incidence of stroke or transient ischaemic attacks after TAVI ranging from 0.6 to 6% [1]. Rodés-Cabau demonstrated a high rate of silent cerebral ischaemic lesions in diffusion-weighted magnetic resonance imaging ranging from 66 to 71% independent of a transfemoral or transapical approach. The incidence of coronary artery obstruction during or after TAVI is reported between 0.4 and 4.1% [11]. The incidence of AV block,
with the consecutive need for a pacemaker, is up to five times higher after TAVI than after AVR [12, 13]. The main difference distinguishing TAVI from AVR is the lack of removal of the native aortic valve and its calcifications. This can lead to additional forces on the surrounding tissue after valve expansion, including the area of the AV node and the bundle of His, because these anatomical regions are near to the area of the right coronary aortic leaflet [14, 15].

The objective of this study was the quantification of the segmented calcification in the area of the basal annular plane before and after TAVI, with a particular focus on changes in mass, volume and density [Hounsfield units (HU)], and to determine the loss of calcification. In addition, the displacement of calcified debris towards the coronary ostia, as well as the compression of calcified lesions into the sensitive anatomical area of the cardiac conduction system, was evaluated.

MATERIALS AND METHODS

Study population

We retrospectively included 20 patients (13 men and 7 women; mean age: 82.9 ± 8.1 years), who underwent TAVI from June 2008 until July 2011. The preoperative risk as expressed by the mean logistic EuroSCORE was 21.4%. The indication for TAVI was approved by the local heart team and in concordance with the recent consensus statement [16]. All patients had a clinical pre- and postoperative contrast-enhanced computed tomography (CT) scan with ECG gating. The postoperative CT examination was a median of 16 days (range 6–46 days) after the procedure. Ethical approval for this retrospective study was obtained from the institutional review board.

Devices

Transcatheter aortic valve implantation was performed using the Medtronic CoreValve ReValving System (CoreValve Inc., Irvine, CA, USA; 26 and 29 mm; n = 13) and the second-generation, balloon-expandable Edwards SAPIEN XT (Edwards Lifesciences Inc., Irvine, CA, USA; 23–26 mm; n = 7). The Edwards prosthesis was implanted via a transapical approach (n = 4) or a transfemoral approach (n = 3). For the CoreValve System, a transfemoral approach was performed in all cases.

Computed tomographic data acquisition

All examinations were performed using a second-generation, 128-slice dual-source computed tomography (DSCT) system (Somatom Definition Flash; Siemens Healthcare, Forchheim, Germany). For the preoperative examination, first 45 ml iopromide (Ultravist 300, 300 mg/ml; Bayer Schering Pharma, Berlin, Germany) was injected at a flow rate of 5 ml/s, directly followed by a second bolus of 35 ml at a flow rate of 2.5 ml/s, followed by 60 ml bolus of saline solution at the same flow rate. Bolus tracking in the ascending aorta was performed with a signal-attenuation threshold of 100 HU. A crano-caudal scan direction was chosen in all protocols. The scan ranged from the apex of the lung to the symphysis. The CT scan was started automatically based on the previous 10 heartbeats in order to reach the 60% R-R interval at

the level of the sinotubular junction. Postoperative ECG-gated scans where performed with the same scan parameters in 15 patients. In five patients, postoperative native ECG-gated CT scans from the ascending aorta to the heart base were performed due to reduced renal function. In addition, ex vivo native DSCT examinations of the two different types of valve systems imbedded in water were performed and their density values evaluated.

Image analysis

Segmentation. For quantitative analysis, the centre line of the aortic root and the ascending aorta was drawn semi-automatically using dedicated software (3mensio benzlicer 4.3; Bilthoven, Netherlands). The aortic annulus was defined at the level of the insertion of the leaflets (Fig. 1). Before and after the procedure, the calcification of the aortic valve leaflets was segmented semi-automatically separately for each cusp [left coronary (LC), right coronary (RC) and non-coronary cusps (NC)]; derived from these data, the volume and mass of the calcifications were analysed (Fig. 2). The attenuation value (HU), for each single voxel within the segmented calcification was measured as a correlate to the calcification density.

Within the ex vivo devices, on three different levels three measurements of the HU were performed. As all measurements of the radiopaque stainless-steel material of the device were >2000 HU, consecutively in the postprocedural CT data during segmentation in the annulus plane, voxels of >2000 HU could be defined as device material and excluded (Fig. 2).

Distance measurements. The distances between the coronary ostia, the left coronary ostium (LCO) and respectively the right coronary ostium (RCO) to the neighbouring highest and deepest point of calcification of the valve leaflet were measured on all CT scans (Fig. 3).

Figure 1: (A) Centre line of the aortic root and the ascending aorta, (B) and (C) Anchor points at the level of the insertion of the aortic leaflets form the aortic annulus.
Statistical analysis

The mean value of HU of calcification for each cusp was calculated. The distribution was tested with the Kolmogorov–Smirnow test. Given that a normal distribution was found for HU and the distances, Student’s paired t-test was performed to compare pre- and postprocedural values. Given that there was a non-normal distribution for volume and mass, these values were correlated using a Wilcoxon signed rank test. Relationships in changes between mass, volume and HU were demonstrated by linear regression analysis. Logistic regression analysis was used to show potential correlations between the changes of mass, volume and HU in correlation to the need for postoperative pacemaker implantation. A change in mass, volume or HU of <5% was defined as stable, whereas an increase or decrease of >5% was defined as real dynamic change.

Postprocedural real calcification loss was defined first as a reduction of mass, volume and HU (scenario 1), second as a reduction of mass and volume but with stable HU (scenario 2) and third as a reduction of mass and volume with increasing HU (scenario 3). Compression of calcification without its loss was defined by as stable mass, decrease of volume and increase of HU (scenario 4; Table 1).

Continuous variables were expressed as means ± SD and categorical variables as frequencies or percentages. A P-value < 0.05 was considered as significant. Linear regression analysis was performed to assess correlations [17]. Statistical analysis was performed using commercially available software (SPSS, release 19.0 for Windows; SPSS Inc., Chicago, IL, USA).

RESULTS

In all patients, the segmented calcification of the aortic valve showed a significant loss of calcification mass. The mean calcification mass of the aortic valves measured before implantation was 258.5 ± 135.09 mg and after TAVI 173.33 ± 132.19 mg, translating into a significant decrease of calcification mass (P = 0.0007).

For all cusps—LC, RC and NC—significantly lower postprocedural mean volumes and mean masses were found (P < 0.002 and P < 0.001; Table 2). The mean differences in volume for NC, RC and LC were −156.8 ± 53.7, −155.5 ± 62.5 and −115.0 ± 57.5 mm³, respectively, and the differences in mass for NC, RC and LC were −88.8 ± 29.5, −95.2 ± 39.3 and −71.6 ± 35.6 mg, respectively.

As a result of AV block (grade III) in five cases and combined total left bundle branch block and AV block grade I one case, six

Figure 2: (A) and (B) Measurements of volume and mass of valve calcifications. (C) After native ex vivo and (D) native in vivo pixelprobes of the valve system, voxels with a threshold attenuation over 2000 Hounsfield units were excluded.
patients underwent pacemaker implantation after TAVI. Logistic regression analysis comparing volume, mass and HU in the area of the right coronary leaflet with the incidence of postoperative pacemaker implantation showed no significant correlation ($P = 0.24$, $P = 0.32$ and $P = 0.4$, respectively).

In 80.0% of all cusps, a real loss of calcification was found. These cusps are summarized in group 1. In 15% of all cusps, a compression of calcification without major calcium loss was seen, fulfilling the criteria of scenario 4, and summarized in group 2. Within the cusps in group 1, in 31.3% the criteria of scenario 1 (massive loss of calcification) were seen, in 14.6% the criteria of scenario 2 and in 56.5% of scenario 3. Unchanged parameters were seen in only one cusp (1.7%). In another cusp (1.7%), mass and HU stayed stable with a decrease of volume; while in a further cusp (1.7%), an increase of mass and HU but a stable volume was found.

**Figure 3:** Distances between the left or right coronary ostium to the nearest neighbouring highest and deepest point of calcification of valve leaflet before and after the procedure.

**Table 1:** Postprocedural changes in mass, volume and Hounsfield units

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Mass</th>
<th>Volume</th>
<th>HU</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Group 1</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>Group 1</td>
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<tr>
<td>Scenario 3</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>Group 1</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>---</td>
<td>↑</td>
<td>↑</td>
<td>Group 2</td>
</tr>
</tbody>
</table>

Group 1: loss of calcification; Group 2: compression of calcification; HU: Hounsfield units; ↓ = decrease; ↑ = increase; --- = stable.

**Table 2:** Mean volumes, masses and Hounsfield units before and after the procedure for each valve separately

<table>
<thead>
<tr>
<th></th>
<th>Preprocedure</th>
<th>Postprocedure</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Mean ± SD volume (mm$^3$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>467.85 ± 83.96</td>
<td>311.05 ± 47.67</td>
<td>0.000019</td>
</tr>
<tr>
<td>RC</td>
<td>373.1 ± 78.63</td>
<td>217.56 ± 32.03</td>
<td>0.002</td>
</tr>
<tr>
<td>LC</td>
<td>336.56 ± 76.75</td>
<td>221.59 ± 32.83</td>
<td>0.00029</td>
</tr>
<tr>
<td>Mean ± SD mass (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>313.23 ± 57.40</td>
<td>224.45 ± 37.81</td>
<td>0.00000017</td>
</tr>
<tr>
<td>RC</td>
<td>247.13 ± 51.72</td>
<td>151.93 ± 24.13</td>
<td>0.001</td>
</tr>
<tr>
<td>LC</td>
<td>215.16 ± 48.46</td>
<td>143.16 ± 22.20</td>
<td>0.00025</td>
</tr>
<tr>
<td>Mean ± SD Hounsfield units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>798.6 ± 105.7</td>
<td>849.17 ± 95.05</td>
<td>0.01</td>
</tr>
<tr>
<td>RC</td>
<td>786.2 ± 86.32</td>
<td>820.93 ± 69.57</td>
<td>0.126</td>
</tr>
<tr>
<td>LC</td>
<td>768.45 ± 86.39</td>
<td>785.79 ± 56.92</td>
<td>0.412</td>
</tr>
</tbody>
</table>

LC: left coronary cusp; RC: right coronary cusp; NC: non-coronary cusp.
Table 3: Distances to left coronary ostium (LCO) and right coronary ostium (RCO) to its next most cranial or caudal calcification of leaflet

<table>
<thead>
<tr>
<th></th>
<th>Preprocedure</th>
<th>Postprocedure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean distance ± SD to most cranial calcification of leaflet (mm)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LCO</td>
<td>9.66 ± 3.96</td>
<td>4.8 ± 3.90</td>
<td>0.00008</td>
</tr>
<tr>
<td>RCO</td>
<td>10.11 ± 2.82</td>
<td>6.93 ± 4.17</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean ± SD distance to most caudal calcification of leaflet (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCO</td>
<td>13.86 ± 5.56</td>
<td>10.03 ± 5.55</td>
<td>0.0003</td>
</tr>
<tr>
<td>RCO</td>
<td>15.62 ± 3.06</td>
<td>13.21 ± 4.18</td>
<td>0.047</td>
</tr>
</tbody>
</table>

LC: left coronary ostium; RC: right coronary ostium.

For all cusps together, the mean HU was significantly higher after the procedure (mean HU before the procedure: 784.41 ± 11.9 HU; after the procedure: 818.63 ± 103.9 HU; P = 0.004), which corroborates the theory of calcification compression after TAVI. With a focus on each valve separately, a significant change in mean HU was found in the area of the non-coronary cusp (P = 0.01). For the left coronary and right coronary cusps, no significance was detected, with P-values of P = 0.126 and P = 0.412, respectively (Table 2).

Regression analyses showed no significant differences of volume, mass and HU (P = 0.51, P = 0.38 and P = 0.26, respectively) comparing the segmentations after implantation of the CoreValve System and after implantation of the Edwards prosthesis. Regression analysis showed strong correlations between the pre- and postprocedural changes of volume and of mass, respectively, compared with HU as a dependent variable (P < 0.0001, r = 0.88).

There were significantly lower postprocedural mean distances between LCO and RCO and their nearest neighbouring cranial and caudal calcification points (P < 0.047; Table 3). Before the procedure, the mean distance between LCO and its next cranial calcification was 9.7 ± 4 mm and after TAVI 4.8 ± 4 mm; for RCO, the mean distance to its next cranial calcification was 10.1 ± 2.8 mm before and 6.9 ± 3.2 mm after TAVI, resulting in 50.3% decrease in calcification distance to LCO and 31.5% to RCO. In all patients, there were no postprocedural cardiovascular complications related to coronary impairment.

DISCUSSION

This study illustrates a loss of calcification in the area of the device landing zone in all patients after TAVI. Correlating the three parameters mass, volume and HU (density), 80.0% of all cusps were affected, as summarized in group 1 and analysed in the following three scenarios (Table 1).

Scenario 1, a decrease of all three parameters—mass, volume and calcification density—can be interpreted as surrogate for clear calcification loss during the procedure with potential high embolic load;

Scenario 2, a decrease of mass and volume, but stable calcification density, which may represent a smaller loss of calcification (this can be considered as substantial calcification loss without any sign of compression of the residual calcification); and

Scenario 3, a decrease of mass and volume, but an increase of calcification density, which translates into a loss of calcification with additional compression of the residual calcifications.

In group 2, including 15% of all cusps, scenario 4 (Table 1) with a postprocedural stable mass, a decrease of volume and an increase of calcification density was observed, which can be understood as a compression of calcification without loss.

Although we could see a compression of calcification and potential pressure in the area of the aortic annulus, no significant correlation was found with the incidence of the postprocedural need for pacemaker implantation. This can be explained by the small number of patients included in this trial, which was not powered for this end-point. In addition, in this specific cohort a significant change in calcification density was found only in the area of the non-coronary cusp and not in the more sensitive region of the right coronary cusp.

In only one cusp, before and after the procedure all parameters were unchanged, either because the calcification was very strong so that no compression or loss of calcification was possible or because the surrounding tissue had enough elasticity to compensate for the local mechanic changes induced during/after TAVI.

In one cusp, postprocedural mass and calcification density remained stable with a decrease of volume, whereas in another cusp the mass and calcification density increased with stable postprocedural volume. This could be explained by periprocedural partial dislocation of calcification to a neighbouring area within or outside the cusp, so that it could not be measured or was additionally captured in another cusp, which could equate to a ‘calcification transfer’ during the procedure. Also, scattered error in measurement could provide an explanation.

The significant decrease of postprocedural mean distances between LCO and RCO to their nearest neighbouring calcification is an important finding that highlights the importance of preoperative imaging for risk stratification of potential coronary occlusion. These changes verify the altered position of the leaflet and its calcification after TAVI, which may lead to partial or complete obstruction of the coronary ostium. In the study cohort, there was always a minimal distance of 10 mm between the aortic annulus and the coronary ostia in the CT scans, which again ensured an uncompromised postoperative coronary flow despite a significant reduction in the distances between calcifications and coronary entries. Therefore, no cardiovascular complications related to coronary obstruction were encountered. Simulation of the calcification behaviour during TAVI would be the next level of preoperative planning.

Although Webb et al. [18] showed a difference in the incidence of stroke of 5.3% for the transfemoral approach and 1.8% for the transapical approach, this could not be confirmed in later studies. Recent studies have reported a stroke rate after TAVI of 2.8-4.1% [18, 19]. Rodés-Cabau showed a high rate of silent cerebral ischaemic lesions in diffusion-weighted magnetic resonance imaging, ranging from 66 to 71%, with no differences between the transfemoral and transapical approaches. Recent studies showed an incidence of acute kidney injury of 11.7–28.8% after TAVI [9, 10, 20]. The results of our study emphasize the risk of calcification loss after TAVI and a potential relationship to the high rate of silent cerebral ischaemic lesions in diffusion-weighted magnetic resonance imaging, as well as to the known high incidence of cerebrovascular complications, with no difference for either approach [7].

Given that the manipulation and the displacement of the stenosed and rigid native leaflets by implantation of the stent frame is similar for both transfemoral and transapical approaches, the resulting dislodgement of calcification debris from the valve itself can be also considered similar.

Owing to the proven likelihood of calcification loss after TAVI and the known embolic ischaemic cerebral lesions, the development of protective shields to reduce the risk of cerebrovascular complications is currently underway. Although about 72.7-
84% of cerebral embolisms after TAVI are clinically silent, this does not rule out long-term cognitive impairment. Different concepts of protective devices are already available but not in routine clinical use; The Claret device (Claret Medical, Inc., Santa Rosa, CA, USA) or the Embrella Embolic Deflector System (Embrella Cardiovascular, Inc., Wayne, PA, USA) can be placed in the aortic arch to avoid embolic lesions [21, 22]. In a study of first-in-man use of the Claret device, although not systematically evaluated, Naber et al. could demonstrate using photographic techniques the macroscopic incidence of debris in individuals [23].

There are some limitations to the study, such as the small number of patients in our cohort. Although a significant loss of calcification was demonstrated in all patients after TAVI, as well as a decrease of calcification distances to the coronary ostia, no correlation with any postprocedural symptomatic complications could be found. However, silent cerebral lesions have been found after TAVI [7]; therefore, further studies are needed to define any risk stratification. Owing to preoperative planning, no native CT scans were performed, but contrast-enhanced CT-scans were carried out for additional evaluation of the peripheral vascular status. Cademartiri et al. [24] have shown that intraluminal enhancement significantly influences the non-calcified plaque density, but does not significantly alter the calcified plaques. Partial volume and interpolation can particularly affect neighbouring voxels, because higher attenuation of the device is associated with a higher range of densities in the neighbouring calcification [24]. To reduce the error within the segmented calcifications, a change in HU of <5% was defined as stable, and an increase or decrease of >5% was defined as real dynamic change.

As TAVI is a rapidly evolving technique that may become a true alternative to conventional AVR, especially in younger patients with lower risk profiles, further studies are needed with larger numbers of patients, powered for meaningful clinical outcomes. This may lead to a better understanding of the dynamic changes of mass, volume and calcification density during the procedure.

**Conclusion**

In conclusion, we could demonstrate a significant loss of calcification in all patients after TAVI, as well as a reduction of calcification distances to the coronary ostia. Further studies are needed to assess the potential clinical evidence of additional protective techniques and devices during TAVI procedures.

**Conflict of interest:** none declared.

**REFERENCES**


