The Heart Surgery Forum #2015-1399
19 (1), 2016 [Epub February 2016]
doi: 10.1532/hsf.1399

Online address: http://www.hsforum.com

Aortic Valve Calcium Score for Paravalvular Aortic Insufficiency (AVCS II) Study in Transapical Aortic Valve Implantation

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ABSTRACT

Background: Transapical aortic valve implantation (TAAVI) has evolved into a routine procedure for select high-risk patients. The aim was to study the impact of native aortic valve calcification on paravalvular leaks in cardiac contrast-enhanced computed tomography (CT).

Methods: The degree and distribution of valve calcification were quantified using an Aortic Valve Calcium Score (AVCS) for each cusp separately (3mensio Valves). To reduce an artificial increase of the AVCS due to the presence of contrast material, we used thresholds for density [mean aortic density + 2*SD] and volume [0, 3, 5, 25, and 50 mm3] of calcification.

Results: 111 consecutive patients prior to TAAVI with preoperative CT aged 79.8 ± 5.8 years were included using the Edwards Sapien prosthesis. Paravalvular leaks were significantly associated with eccentric calcified plaques (r [Spearman] = 0.37; χ^2-statistic = 15.4; P = .002), presence of LVOT calcium (r [Spearman] = 0.28; χ^2-statistic = 11.3; P = .009), and the commissural gap at the anatomic ventriculo-arterial junction (r [Spearman] = 0.41-0.63; χ^2-statistic = 50.8-53.0; P = .002-≤.001). There was no significant association between the total AVCS and PV leaks (r [Spearman] = 0.076; χ^2-statistic = 1.471; P = .240, 120 kV, 850 hounsfield units) with no additional use of a volume-based threshold.

Conclusion: Asymmetry of leaflet calcium distribution, LVOT calcium, and the commissural gap between leaflets were significantly associated with paravalvular leaks. Moreover, quantification of aortic valve calcification in contrast enhanced CTs shows only a weak correlation with paravalvular leakage and is therefore not reliable as a predictor, respectively.

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Received September 8, 2015; accepted December 4, 2015.

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INTRODUCTION

Transapical aortic valve implantation (TAAVI) has evolved into a routine procedure in select elderly high-risk patients with symptomatic aortic valve stenosis. However, the sutureless nature of this procedure causes the native aortic valve to be pressed against the aortic wall and can therefore result in paravalvular leaks. Despite the encouraging results since the beginning of the pioneering TAVI era, more-than-mild paravalvular leaks remain a significant drawback [Smith 2011; Leon 2010]. The issue is of specific concern as it has been repeatedly proven to be associated with worse mid-term survival [Gotzmann 2011; Abdel-Wahab 2011; Moat 2011; Tamburino 2011; Kodali 2012]. We have learned a lot about how to size TAVI devices and the procedural techniques have improved, allowing for a more predictable valve deployment in the correct intra-annular position. Sophisticated CT-based imaging and sizing has been incorporated in most centers during the last decade.

There are different methodological approaches that have been followed in the past. A large number of studies use the Aortic Valve Calcium Score (AVCS) based on contrast-enhanced imaging. The advantages of contrast-enhanced computed tomography (CT), according to current guidelines, are that it provides accurate information on annular dimensions, suitability of peripheral access vessels, and precise fluoroscopic projections [Achenbach 2012], although it is known that the density-based calcium-analysis has a 50 percent overlap with density of contrast-material and therefore cannot be differentiated statistically. It is currently unclear whether a volume-based calcium analysis, including continuous calcium bricks, allows for prediction of paravalvular leaks in contrast-enhanced CTs.

Traditional calcium scoring of the aortic valve leaflets is carried out using a non-contrast CT with a 130-HU threshold for calcium detection (Agatston scoring). Nonetheless, since it is impractical and time-consuming, only a few studies used native non-enhanced scans, detecting an influence of calcium burden on paravalvular leaks [Haensig 2012].

The interaction of aortic valve calcium and the distribution with precisely measured annular dimensions still remains poorly understood, which is especially true for

Table 1. Preoperative Patient Characteristics of all TAAVI's Included in the AVCS II Study

	n = 111
Age, mean ± SD, years	79.8 ± 5.8 (range, 72.2-86.8)
Logistic EuroSCORE, %	23.9 ± 15.6
STS-Score, %	8.3 ± 7.2
NYHA class	3.0 (2.0-4.0)
Female, n (%)	51 (45.9)
Left ventricular EF (%)	54.8 ± 14.7
Peripheral vascular disease, n (%)	23 (20.7)
Carotid artery stenosis, n (%)	22 (19.8)
Chronic lung disease, n (%)	27 (24.3)
Mean aortic gradient, mmHg	42.5 ± 16.8
Maximum aortic gradient, mmHg	67.3 ± 24.5
Effective orifice area, cm^2	0.6 (0.4-0.9)
Edwards Sapien THV, n (%)	20 (18.0)
Edwards Sapien XT, n (%)	66 (59.5)
Edwards Sapien 3, n (%)	25 (22.5)

contrast-enhanced imaging [Jilaihawi 2014]. Thus, the aim was to study the impact of native aortic valve calcification on paravalvular leaks in cardiac contrast-enhanced CTs.

MATERIALS AND METHODS

Study Design

111 patients (out of 542 TAAVIs) between February 2010 and February 2015 with preoperative 120 kV-gated contrast-enhanced CT at the Leipzig Heart Center were analyzed. Data was drawn from a prospective database and retrospectively analyzed. Mean age was 79.8 ± 5.8 years, mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) was 23.9 ± 15.6%, and Society of Thoracic Surgeons (STS) Score was 8.3 ± 7.2%. Overall 45.9% were female. Preoperative characteristics of the patients are presented in Table 1.

Primary endpoints of this single-arm study were the AVCS in contrast-enhanced CTs and the benefit of a volume-based threshold. Secondary endpoints were the postsurgical location of paravalvular leaks and annular eccentricity.

Clinical inclusion criteria were age ≥ 75 years, NYHA functional class II or higher, written informed consent, and comorbidities leading to a logistic EuroSCORE ≥15 percent. By standard protocol all patient underwent transthoracic and transesophageal echocardiography. Echocardiographic inclusion criteria were severe degenerative aortic valve stenosis indicated by an aortic valve area ≤1.0 cm^2 and/or a jet velocity >4 m/s and/or a mean gradient > 40 mmHg.

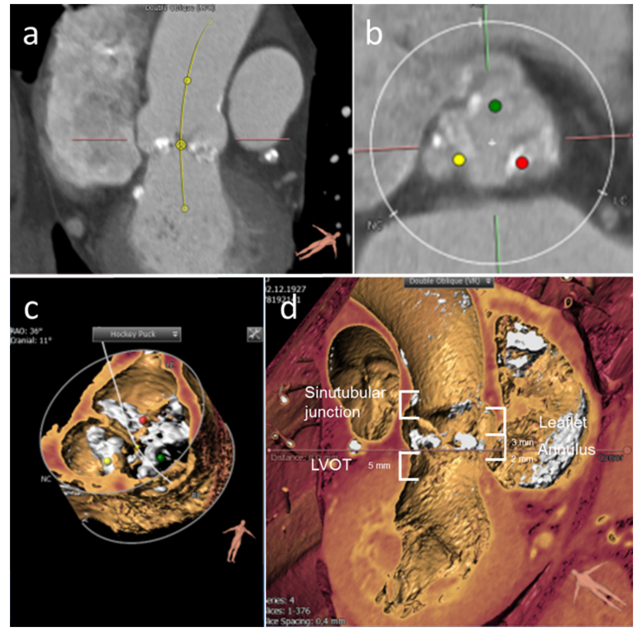

Figure 1. Assessment methodology for leaflet quantification using the valve pilot of the 3mensio Valves workstation, version 7.0, 3mensio Medical Imaging. a. Visual assessment of calcium using a volume rendered image. Segmentation is performed and an automatic centerline is created. The control points of the centerline are verified to the required position. b. To define the annulus plane markers identify the nadirs of the three leaflets. c. When checking 'Score leaflets separately', a 'star-shape' overlay will appear to quantify calcified voxels with higher density than the threshold (HU). The 3mensio workstation will calculate each segment individually and will accumulate a total calcified volume. By rotating the selected area 60 degree clockwise this step can be repeated for each separate commissure. d. Calcification was separately analysed for the supravalvular region, leaflets, aortic annulus and LVOT.

Transcatheter Aortic Valve

All treatment options including conventional surgery were discussed in an interdisciplinary Heart Team conference. For the transapical route, the balloon-expandable Edwards SAPIEN THV, XT, or SAPIEN 3 valve composed of a pericardial xenograft fixed within a cobalt chrome stent (Edwards Lifesciences, Irvine, CA, USA) was implanted. Three prosthesis sizes were used for annular diameters up to 23 mm (n = 35), 26 mm (n = 51) and 29 mm (n = 25).

Implantation Technique

All procedures were performed under general anesthesia in a fully equipped hybrid operating room. Prior to skin incision a femoral "safety-net" was established via a venous guidewire and a 6 Fr arterial sheath to ensure femoral access in case of emergency cannulation for cardiopulmonary bypass (CPB). Transapical aortic valve implantation was performed as previously described in detail [Walther 2009]. Paravalvular leaks were assessed intraoperatively by echocardiography and root angiography. In case of significant paravalvular leak the valvuloplasty balloon was introduced again and post-dilatation was performed.

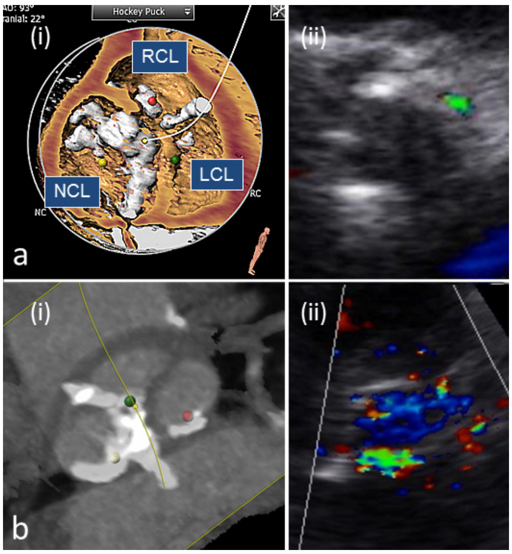

Figure 2. Impact of calcium burden on paravalvular leaks in a case of asymmetry (a) and LVOT calcium (b), (i) volume rendering (VR) shows asymmetric calcium distritbution with case A, and additional LVOT calcium below the non-coronary leaflet with case B, (ii) post-implantation transesophageal echocardiography.

CT Protocol and Aortic Valve Calcium Scoring (AVCS)

CT scans were performed on a 128-row dual source CT (Siemens Healthcare, Erlangen, Germany) using a prospectively ECG-gated technique according to the standard protocol in our facility (120 kV, 280 reference mAs with automatic tube current modulation, 0.6 mm slice thickness, rotation time 0.28 sec). The prospective triggering was set to capture the aortic root during late diastole according to the ECG. In total 70 mL (400 mg iodine/mL) of nonionic iodinated contrast medium were applied with a flow rate of 3 mL/sec.

All cardiac CTs were assessed in an anonymous interpretation by an experienced radiologist (L.L.) and cardiac surgeon (M.H.), both blinded to the clinical data. The Aortic Valve Calcium Score (AVCS) was calculated for each cusp separately using dedicated software (3mensio Valves workstation, version 7.0, 3mensio Medical Imaging, Netherlands) (Figure 1). To reduce an artificial increase of the AVCS due to the presence of contrast material, we used thresholds for density [mean aortic density + 2*SD] and volume [0, 3, 5, 25 and 50 mm^3] of calcification (Figure 2). Supravalvular calcifications and calcifications of the coronary arteries including the ostia were removed carefully by manual adaptation of the volume of interest.

Asymmetry of annular calcification was defined as the smallest leaflet score divided by the greatest leaflet score receiving a score of asymmetry between 0 and 1. In cases of high asymmetry the score value obtained was between 0 and 0.5. Asymmetry of annular calcification was assumed to be low in cases of a score between 0.51 and 1 (Table 4).

Table 2. Aortic Valve Calcium Score (AVCS) for the Aortic Valve, Cusps, and Commissures (Threshold for Density: 850 Houndsfield Units)

Aortic Valve Calcium Score	n = 111
Aortic Valve Calcium Score [Cusps]	152.4 [48.3-443.0]
Right-coronary cusp	35.5 [3.6-137.6]
Left-coronary cusp	37.5 [4.2-126.5]
Non-coronary cusp	68.9 [12.0-247.3]
Aortic Valve Calcium Score [Commissures]	152.4 [48.2-443.0]
Right-left coronary commissure	25.4 [1.1-121.2]
Left-non-coronary commissure	59.4 [18.1-196.4]
Non-right-coronary commissure	53.1 [11.6-193.3]

P values: RCC versus LCC (P = .64); RCC versus NCC (P < .001); LCC versus NCC (P = .001); RLC versus LNC (P < .001); LNC versus NRC (P = .61); RLC versus NRC (P < .001). RCC indicates right-coronary cusp; LCC; left-coronary cusp; NCC, non-coronary cusp; RLC, right-left coronary commissure; LNC, left-non-coronary commissure; NRC, non-right-coronary commissure.

Assessment of Paravalvular Leak

Paravalvular leaks were identified after release of the Edwards Sapien prosthesis by aortic root angiography according to the Sellers classification [Sellers 1964]. In addition, the degree of a paravalvular leak was assessed by transesophageal echocardiography in the midesophageal long-axis view using the vena-contracta width (mild: <0.3; moderate: 0.3-0.6; severe: >0.6 cm) and width of regurgitant jet within the LVOT (<30%; 30-50%; >50%) [Leon 2011; Kappetein 2012]. The localization was judged in the mid-esophageal short-axis view.

Statistics

All statistical analyses were performed using SPSS, version 16.0 (Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation for nearly Gaussian distributed variables and otherwise median values (interquartile range). Categorical data are given as proportions. Continuous variables were analyzed by two-tailed Student t test or by Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared with Pearson chi-square test as appropriate. A P value of less than .05 was considered statistically significant.

RESULTS

Patient Characteristics

Three prosthesis sizes were used for annular diameters up to 23 mm (n = 35), 26 mm (n = 51), and 29 mm (n = 25), respectively. Data on preoperative transesophageal echocardiography characteristics are supplied in Table 3.

Mean AVCS was comparable for the entire valve, cusps, and commissures (Table 2). In detail, the non-coronary cusp revealed a higher degree of calcification (68.9 [12.0-247.3])

Table 3. Preoperative Transesophageal Echocardiography (TOE) Results and Mean Aortic Valve Calcium Score (AVCS) for the Aortic Valve, Cusps, and Commissures Depending on the Presence of a Paravalvular Leak

	No Paravalvular Leak (n = 46)*	Paravalvular Leak (n = 65)*	*P*
TOE			
Annulus size, mm	23.8 (23.1-24.5)	22.7 (22.0-23.2)	.03
Mean aortic gradient, mmHg	43.6 ± 13.3	42.5 ± 17.8	.72
Maximum aortic gradient, mmHg	69.1 ± 19.1	67.2 ± 26.3	.72
Mean oversizing, %	11.5 (3.6-16.0)	9.5 (4.0- 8.2)	.35
AVCS			
Aortic valve	134.2 (49.6-444.5)	168.0 (44.0-469.1)	.43
Right coronary cusp	39.0 (5.7-147.9)	30.9 (3.1-108.8)	.27
Left coronary cusp	36.4 (4.9-153.0)	38.0 (2.0-108.2)	.84
Non-coronary cusp	55.9 (13.1-179.9)	104.8 (10.8-319.5)	.04
Right-left-coronary commissure	37.3 (2.4-142.6)	17.3 (0.1-96.8)	.08
Left-non-coronary commissure	57.3 (17.9-174.6)	61.6 (16.3-240.0)	.25
Non-right-coronary commissure	48.1 (6.9-159.4)	78.9 (12.4-222.6)	.12

*Confirmed by intraoperative transesophageal echocardiography (TOE) and root angiography.

than the left- and right-coronary cusps (37.5 [4.2-126.5] and 35.5 [3.6-137.6]). There was evidence for a significant difference between the right- and non-coronary cusp (*P* < .001) and left- and non-coronary cusp (*P* = .001), but not between the right- and left-coronary cusp (*P* = .64).

Any eccentric cusp calcification or LVOT calcium was present in 62 (55.9%) and 25 (22.5%) patients, respectively.

Impact of Aortic Valve Calcification on Paravalvular Leaks

The mean AVCS in patients without paravalvular leaks (n = 46) was 133.3 [53.9-395.5]; with mild paravalvular leaks (n = 47) was 152.4 [36.5-547.5]; and with moderate paravalvular leaks (n = 18) was 174.2 [58.0-462.0]. There was no significant association between the total aortic valve calcium score and paravalvular leaks (r [Spearman] = 0.076; χ^2-statistic = 1.471; *P* = .240). The additional use of the volume-based threshold did not lead to an increase of the association between the AVCS and paravalvular leakages.

In detail, the AVCS of the right-coronary cusp in patients without a local paravalvular leak was 39.0 [5.7-147.9] compared to patients with a paravalvular leak having a AVCS of 30.9 [3.1-108.8] (*P* = .27). For the left-coronary cusp the mean AVCS in patients without and with a paravalvular leak was 36.4 [4.9-153.0] and 38.0 [2.0-108.2], respectively (*P* = .84). This relation between the presence of a paravalvular leak and the AVCS only reached statistical significance for the non-coronary cusp (without and with a paravalvular leak; 55.9 [13.1-179.9] and 104.8 [10.8-319.5], *P* = .04).

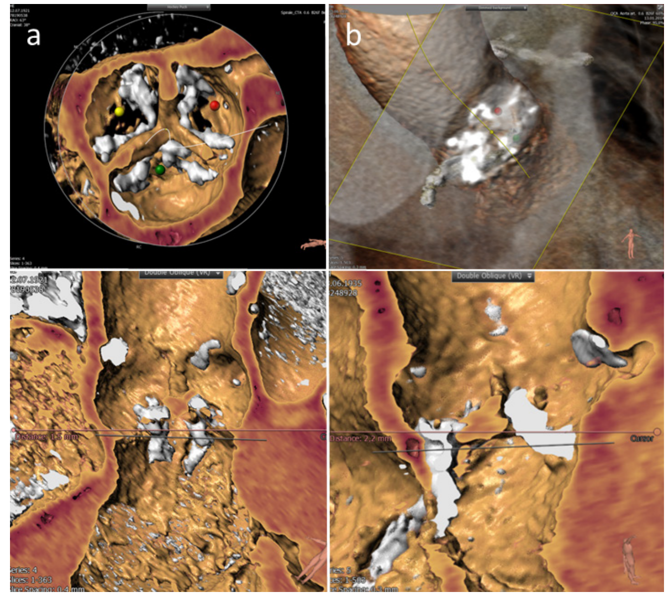

Figure 3. VOT calcium surrounding the commissure (a) and cone-like shaped (b).

When analyzing the three commissures, the AVCS of the left-non-coronary and non-right-coronary commissure in patients without a paravalvular leak was 57.3 [17.9-174.6] and 48.1 [6.9-159.4] and in patients with a paravalvular leak 61.6 [16.3-240.0] and 78.9 [12.4-222.6] (*P* = .25 and *P* = .12) (Table 3). Results for the right-left-coronary commissure were comparable (37.3 [2.4-142.6] and 17.3 [0.1-96.8], *P* = .08).

Location of Paravalvular Leaks

Among the 65 patients with greater than or equal to mild paravalvular leak, 43 had the major jet in a commissure. Among the remaining 22 patients, 7 had the major jet in the left-coronary, 7 in the right-coronary, and 8 in the noncoronary cusp. The proportion of jets corresponding with the area demonstrating the highest level of calcification was 8 of 22 (36.4%) for a single leaflet and 18 of 65 (27.7%) for LVOT calcium.

When analyzing the location of paravalvular leaks by postsurgical echocardiography, there was a significant association with asymmetry of leaflet calcium distribution. As presented in Table 4, eccentric calcification was significantly associated with the degree of paravalvular leaks (r [Spearman] = 0.37; χ^2-statistic = 15.4; *P* = .002). In addition, the location of paravalvular leaks was associated with LVOT calcium (r [Spearman] = 0.28; χ^2-statistic = 11.3; *P* = .009) and the commissural gap at the anatomic ventriculo-arterial junction (r [Spearman] = 0.41-0.63; χ^2-statistic = 50.8-53.0; *P* = .002-≤.001) (Table 5).

Table 4. Association of Annular Eccentricity and Degree of Paravalvular Leaks (χ^2 statistic = 15.4; P = .002)

Asymmetry	Degree of PVL*				
	0	0.5	1.0	2.0	
No	29	10	7	3	49
Yes	17	11	19	15	62
	46	21	26	18	111

PVL indicates paravalvular leak.
*Confirmed by intraoperative transesophageal echocardiography; asymmetry of annular calcification was defined as smallest leaflet score divided by greatest leaflet score.

DISCUSSION

Transcatheter aortic valve implantation (TAVI) has become the treatment of choice for inoperable patients with severe aortic stenosis and is a valuable therapeutic option for patients at high risk [Smith 2011; Leon 2010]. Despite impressive results, relevant aortic valve calcification will be of ongoing critical importance as it will demand future devices with distinct capabilities such as retrievability and additional PVL seal.

The principle findings of this study are the following: (i) eccentricity of annular calcification (asymmetry of leaflet calcium distribution); (ii) LVOT calcium and (iii) distance between the semilunar attachment of leaflets at the anatomic ventriculo-arterial junction correlates with the location of PV leaks in the postsurgical echo (TOE); (iv) in contrast-enhanced CTs there was only a weak association between calcium score & PV leaks; and (v) the volume-based threshold was not of any further benefit.

The non-coronary cusp demonstrated the highest degree of calcification (Table 2). Recent studies found comparable results [Wendt 2014; Khalique 2014; John 2010]. Shear stress across the endothelium of the noncoronary cusp is lower than the left and right coronary cusps because of the absence of diastolic coronary flow, which likely explains why the noncoronary cusp is often the first cusp affected [Freeman 2005].

When analyzing the localization of paravalvular leaks, confirmed by transesophageal echocardiography, asymmetry of leaflet calcium distribution revealed a significant impact (Figure 2, a). Every TAVI procedure aims to create a perfect round situation after deployment, irrespective of symmetry or asymmetry prior to implantation. In as much as this might be the reason why various studies found no influence on PVL, in line with our study Unbehaun et al found comparable results [Feuchtner 2013; Unbehaun 2012; Willson 2012]. This is an important message, particularly when eccentric cusp calcification can lead to incomplete expansion of the prosthesis, increased stress on 1 or more leaflets, and premature failure is more likely to occur [Zegdi 2008]. Furthermore, we found a significant association with LVOT calcium (Figures 2, b, and Figure 3). Comparable results were found by several studies [Jilaihawi 2014; Khalique 2014; Buellesfeld 2014]. Moreover, the localization of PV leaks was significantly associated with the distance between semilunar attachment of leaflets at the anatomic ventriculo-arterial junction (Figure 4). One possible reason for this might be the intrinsic weakness of the interleaflet triangles in this area, leading to an anatomic predisposition to paravalvular leaks.

The results suggest that there was no significant association between the total AVCS and paravalvular leaks. Besides, there was no benefit of the volume-based threshold. Thus, quantification of aortic valve calcification in contrast enhanced CTs shows only a weak correlation with paravalvular leakage and is therefore not reliable as a predictor. Elevating the scoring threshold leads to total loss of smaller or less dense calcific lesions, but it might also decrease the size of a lesion or lead to a splitting of one larger inhomogeneous lesion into several smaller lesions. As reported by Mühlenbruch et al in a small study, more lesions were detected in contrast-enhanced than in non-enhanced images with the same threshold [Muhlenbruch 2005]. One possible reason for this might be

Table 5. Association of Distance between the Semilunar Attachments of the Leaflets at the Anatomic Ventriculo-arterial Junction and Location of Paravalvular Leaks

			Localization of Paravalvular Leak (TTE) Commissure		
			Right-left-coronary**	Left-non-coronary**	Non-right-coronary**
Distance between semilunar attachments (CT)	Commissure	Right-left-coronary*	0.410 P = .002	-0.084 P = .552	-0.193 P = .165
		Left-non-coronary*	-0.135 P = .335	0.550 P < .001	-0.016 P = .909
		Non-right-coronary*	-0.286 P = .038	0.104 P = .458	0.626 P < .001

Data are presented as Spearman correlation coefficient and corresponding P values.
*Confirmed by preoperative computed tomography. **Confirmed by postoperative transesophageal echocardiography.

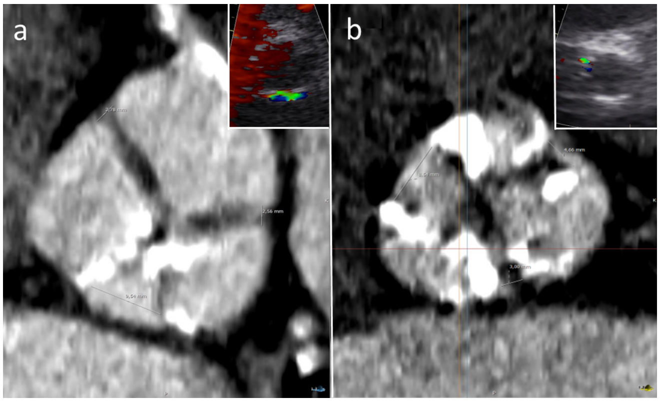

Figure 4. Distance [mm] of the commissural gap at the anatomic ventriculo-arterial junction associated with the location of paravalvular leaks in two separate patients (a-b).

simply the fact that contrast material is being falsely depicted as calcified lesions, as contrast material simulates calcification. This clearly shows the dilemma of choosing the right detection threshold for contrast-enhanced computed tomography: with a higher threshold, one underestimates the actual calcium load but reduces the inaccuracy of contrast material being depicted as calcification, and vice versa [Muhlenbruch 2005].

Thus, we choose different cut-off's (350, 433, 450, 550, 551, 850 HU) to find the optimal one with most calcium load included and the less contrast material as possible. However, none of them proved to be reliable with regard to a significant association between the total AVCS and paravalvular leaks.

This finding may be explained by a number of factors such as higher implantation height than in the early TAVI era, more aggressive re-ballooning, less undersizing due to improved preoperative sizing, and the fact that current devices may lead to better sealing. In addition, patients with severe LVOT calcium or a hypertrophied septum were excluded in advance.

Limitations

Despite a relatively broad experience with TAAVI and the fact that data were collected prospectively using a computerized database, the study was single-center and retrospective by nature. Furthermore only a ballon-expandable device was evaluated and the clinically significant thresholds of calcium burden may well be different for self-expanding devices. In addition, the presence of LVOT calcium and degree of device oversizing was not studied [Jilaihawi 2014]. Finally, the ability of calcium quantification to predict paravalvular leaks is fundamentally determined by the thresholds set to detect calcium load.

Conclusion

In summary, asymmetry of leaflet calcium distribution, LVOT calcium, and the commissural gap at the anatomic ventriculo-arterial junction was significantly associated with the location of paravalvular leaks. Moreover, quantification of aortic valve calcification in contrast enhanced CTs shows only a weak correlation with paravalvular leakage and is therefore not reliable as a predictor. In addition, there was no benefit of a volume-based threshold.

In the next years foresight-generation devices with active anti-paravalvular leak technology may lead to better sealing. New limiting factors like bicuspid valves, pure AI, larger anuli, and LVOT calcification will come to the forefront. Good solutions for these complex subsets have to be found to select the best available anatomical option for each individual patient.

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