

Aortic valve calcium scoring is a predictor of paravalvular aortic regurgitation after transcatheter aortic valve implantation

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Introduction

Degenerative aortic stenosis is the most common native valve disorder in the ageing population of industrialized nations. Surgical aortic valve replacement has excellent clinical outcomes but there is an increasing number of patients with severe aortic stenosis who are not considered surgical candidates because of significant co-morbidity. Transcatheter aortic valve implantation (TAVI) has been established as a clinically accepted minimally invasive therapeutic option for selected high-risk patients with symptomatic aortic valve stenosis (1-4).

The Edwards SAPIEN™ prosthesis (Edwards Lifescience, Irvine, USA) which can be deployed via both transfemoral and transapical routes, and the CoreValve Revalving System® (CoreValve Inc., Irvine, California) which is inserted only via a transfemoral approach, represent the currently used transcatheter aortic valves. The technical feasibility has been shown for both approaches (5,6) and when successful, transcatheter aortic valve replacement results in marked hemodynamic and clinical improvements (7,8). However, despite a clear benefit of survival and improvement in symptoms (1,2), TAVI is also associated with post-implantation paravalvular aortic regurgitation (PAR) in up to 60% of patients (3).

In contrast with surgery, TAVI does not involve excision of the diseased native valve. The metal stent of the implanted device leads to compression of native valve cusps and associated calcification against the aortic annulus and aortic wall. The precise mechanism behind this phenomenon remains unclear. PAR may be related to the specific anatomy of the annulus and aortic root, as well

as to the amount and distribution of leaflet and annular calcification (9).

Although efforts have been made to reduce this incidence significantly (10,11), PAR still necessitates additional interventions in a considerable number of patients and its presence is known to confer a higher mortality rate amongst patients undergoing TAVI procedures (12). This has led to guarded acceptance of TAVI in patients others than those in high-risk or inoperable patient populations. Therefore, careful patient selection is of fundamental importance to avoid intraoperative complications. Excessive calcification of the aortic valve cusps may result in haemodynamically relevant PAR (10), further sustaining pressure overload, which is poorly tolerated by these patients. As a result, several imaging methods have been routinely used for procedure planning and proper device selection (9,13-20).

The size of the aortic annulus is commonly assessed by transoesophageal echocardiography (TEE) (9), and multidetector row computed tomography (MDCT) (14,15). MDCT has increased its role because it not only enables the evaluation of the distances from the annulus to the coronary ostia, but also allows accurate detection, localization and quantification of aortic valve calcification and calcification of the entire aorta (14-22). It has been demonstrated that the amount of aortic valve calcium is associated with unfavorable prognosis (23). Recent studies using MDCT have focused on the role of aortic valve calcium (AVC) and its relation to post TAVI AR (17-22).

We are providing a video presentation entitled "Aortic valve calcium scoring is a predictor of paravalvular aortic regurgitation after transcatheter aortic valve implantation" (*Video 1*).

Aortic valve calcium assessment using MDCT

Wood *et al.* analyzed preoperative MDCT of 26 patients who underwent TAVI procedures and did not find any significant association between either the shape of the aortic annulus or amount of aortic valve calcium and subsequent development of perivalvular aortic regurgitation (16). Koos *et al.* (17), examined the preoperative MDCT of 57 patients who received TAVI using both CoreValve (33% patients) and Sapien prosthesis (67% patients). For quantitative assessment of aortic valve calcification a total valvular Agatston (AGS) score was calculated. The AGS score is generally calculated using a weighted value assigned to the highest density of calcification on the aortic valve (18). The density is measured in Hounsfield units and score of 1 for 130-199 HU, 2 for 200-299 HU, 3 for 300-399 HU, and 4 for 400 HU and greater. This weighted score is then multiplied by the area (in pixels) of aortic valve calcification. In most patients, postprocedural PAR was mild (AR 1+, 77%) moderate (AR 2 and 3+, 14%). All patients with PAR grade 3+ showed extremely calcified aortic valves on MDCT scans. There was no association between the distribution of AVC and the degree of AR after TAVI as assessed by angiography ($r=-0.02$, $P=0.88$) and echocardiography ($r=0.06$, $P=0.69$). However, AGS aortic valve calcification scores were significantly higher in patients with PAR grade ≥ 3 ($5,055 \pm 1,753$) than in patients with PAR grade < 3 ($1,723 \pm 967$, $P=0.03$). There was a significant association between the severity of AVC and the degree of PAR after AVR ($r=0.50$, $P<0.001$). All patients with relevant paravalvular aortic regurgitation showed severely calcified valves with AGS AVC scores above 3,000. In addition, patients requiring redilatation of the trans-catheter valve showed a trend towards higher AGS AVC scores ($3,884 \pm 2,188$) than patients without need for redilatation (AGS AVC score $1,731 \pm 1,005$, $P=0.06$). Aortic valve calcification score above 3,000 showed a sensitivity of 86%, a specificity of 80%, a positive predictive value of 70% and a negative predictive value of 98% for PAR grade ≥ 3 or the need for redilatation.

Leber *et al.* (19) performed preoperative MDCT in 68 patients who underwent TAVI using the CoreValve device to evaluate the AVC. They determined the degree of valve calcification by calculating the calcium mass score located within the aortic valve structures. They calculated the mass score because they considered it more reproducible than the volume and AGS score in particular if performed in contrast enhanced scans (22,23). They observed a significant correlation between the valve calcium score and

the occurrence of MACCE (Death, AMI, Stroke, Spearman correlation coefficient $r=0.27$, $P=0.027$, 95% CI: 0.04-0.48). The authors also observed a significant correlation between the amount of calcification and the occurrence of PAR ($r=0.33$, $P=0.02$). The valve calcium score was significantly higher in patients with PAR $>$ Grade 2 compared to patients with PAR grades 1-2 and with patients with PAR Grade 1 or smaller (858 ± 238 vs. 568 ± 165 vs. 289 ± 199 , $P<0.01$). Patients with post procedural PAR > 2 had a non-significant trend towards higher 1-year mortality rate compared to patients with less severe AR (37.5% vs. 9%, $P=0.07$). By selecting a score-threshold of 750, the authors were able to identify more than 70% of patients who suffered subsequently from MACCE or died within the first year. On the other hand low valve calcium scores identified patients with excellent functional outcome and a complication rate and mortality rate below 5%.

John *et al.* (20) also studied the influence of the calcification at the "device landing zone" (DLZ) on the procedural success of the CoreValve prosthesis. They performed MDCT before intervention in 100 patients scheduled for TAVI. Calcification load of the valve and the adjacent outflow tract was estimated by the AGS Score, and the amount and distribution of calcification was semi-quantitatively assessed and graded as DLZ-calcification score (DLZ-CS). The AGS and DLZ-CS showed a significant correlation with the grade of PAR (AGS: $r=0.341$, $P=0.001$; DLZ-CS: $r=0.300$, $P=0.002$) at any time after the procedures. In particular, they have observed that DLZ-CS ≥ 3 and/or an AGS $\geq 3,000$ AU predicts relevant PAR after initial release of the CoreValve prosthesis as well as the need for "second maneuvers" (i.e., post-dilatation after initial release of the CoreValve prosthesis).

Using MDCT, Ewe *et al.* (21) studied 79 patients who received balloon expandable TAVI using the Edwards Sapien device. Aortic valve calcification was quantified in cubic millimeters instead of using the AGS score. Authors have shown that the main determinant of any detectable PAR, originating from the aortic wall site, was the amount of calcium at the corresponding aortic wall. Calcium at other locations such as the valvular edge or body was less important in determining the presence of PAR. The main determinant of commissural PAR was the amount of calcium at the corresponding commissure of the native valve. Therefore, the results of the study have highlighted the important role of both the AVC load and its location, in predicting the development of PAR after TAVI. The authors conclude that these results suggest that extra caution should

be given to those patients, with significant calcium load along the circumference of the native aortic annulus, and perhaps, additional maneuvers such as prolonged ballooning or reballoning might be necessary when PAR is present after valve deployment.

Haensig *et al.* (22) reviewed 120 MDCT of patients that received trasapical TAVI using the Edwards Sapien prosthesis. The mean AVC, calculated as AGS, in patients without PAR (n=66) was $2,704 \pm 1,510$, with mild PARs (n=31) was $3,804 \pm 2,739$ (P=0.048) and with moderate PAR (n=4) was $7,387 \pm 1,044$ (P=0.002). There was a significant association between the AVC and PAR [odds ratio (OR; per AVCS of 1000), 11.38, P=0.001]. When analysing the localization of any PAR by intraoperative echocardiography, there was a significant association with the AVC and the presence of PAR in this region. These results suggest that the preoperative AVC can identify patients at risk of developing significant post-implant PAR.

Aortic valve calcium assessment using transesophageal echocardiography

Transthoracic echocardiography (TTE) is routinely used for the diagnosis of AS and for postoperative functional assessment after valve surgery. Transesophageal echocardiography (TEE) is frequently used for the preoperative screening of patients undergoing TAVI and during the procedures to assess valve and ventricular function. We recently presented the results of a study that investigated the performance of a new echocardiographic calcium score in predicting the occurrence of postoperative PAR after TAVI (9).

We reviewed 103 TEE in patients who received transapical TAVI using the Sapien prosthesis to assess the load and localization of aortic valve calcification. The calcification score index (24) is a semiquantitative echocardiographic cardiovascular score that uses simple transthoracic echocardiographic parameters (anterior mitral annular calcification, aortic valve sclerosis, and aortic root sclerosis) allowing characterization of the risk of developing cardiovascular disease.

We modified this score adding information on specific structures of the aortic root (i.e., aortic annulus, sinotubular junction, and aortic valve commissures) that we considered potentially important to assess the risk of postoperative PAR after TAVI. We independently analyzed all the components of the resultant calcification scoring system for possible associations with the postoperative PAR and transvalvular AR.

The aortic commissures and the 3 aortic valve cusps were the identified anatomical structures to be statistically associated with postimplantation PAR.

The sum of calcification scores obtained from the 3 aortic cusps and commissures was called the TAVI echocardiographic calcification score (TAVI-ECS). The TAVI-ECS ranged from 0 (normal native aortic valve) to 8 (diffuse calcification of all 3 aortic cusps and commissures). In our study population, the TAVI-ECS ranged from 1 to 8. A TAVI-ECS of 6, 7, or 8 were the most frequent. The TAVI-ECS correlated significantly with the presence of moderate PAR (OR 8.5, CI 1.2-58.9, P=0.0001). The TEE is a fast, inexpensive and radiation free method of performing a systematic preoperative analysis of the anatomy of the aortic valve and root, and in particular may allow better characterization of aortic valve calcification. The results of TAVI-ECS study correlate with the results of the other studies performed using MDCT. More calcified are the valve and the commissures, greater is the risk of post-implantation PAR.

Although the mechanism is not entirely clear, the most likely explanation is that the calcified, native aortic valve is pushed outward toward the walls of the aorta; when a bulky calcification is present at the level of commissures or at the circumference of the native valve, it can potentially prevent perfect apposition between the prosthesis and aortic walls and, thus, result in PAR at these sites.

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