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Valvular Heart Disease

Temporal Change in Paravalvular Leakage after Transcatheter Aortic Valve Replacement with a Self-Expanding Valve: Impact of Aortic Valve Calcification

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Background: In patients undergoing transcatheter aortic valve replacement (TAVR), the severity of paravalvular leakage (PVL) may change during follow-up, however its mechanism is poorly understood. We aimed to explore temporal changes in PVL and possible predictors following TAVR.

Methods: A retrospective analysis was performed of all patients who had received a self-expanding valve. Multidetector computed tomography was performed as pre-TAVR evaluation, including assessment of aortic valve calcification (AVC). The patients received transthoracic echocardiography at baseline and 30 days, 6 months, and 1 year after TAVR.

Results: In total, 93 patients who had received a self-expanding valve during TAVR were identified. Various degrees of PVL were seen in 63 patients, with moderate/severe PVL in 21 (22.6%). In multivariate analysis, the predictors of moderate/severe PVL were: chronic pulmonary disease, high degree of AVC, and an increased annulus perimeter. After 1 year of follow-up, PVL deteriorated from mild to moderate in 2 patients, while an improvement of ≥ 1 grade was seen in 25 patients. Of 21 patients with post-TAVR moderate/severe PVL, 9 had an improvement of ≥ 1 grade and 12 did not. The degree of AVC was significantly lower in those with PVL improvement (Agatston score 3068 ± 1816 vs. 6418 ± 3222; p = 0.01). AVC was a good predictor for an improvement in PVL, and the area under the receiver operating characteristic curve was 0.82 (95% confidence interval = 0.63-1.00, p = 0.01), with a cut-off value of 5210.

Conclusions: In this study, 43% (9/21) of the patients with moderate/severe PVL after self-expanding TAVR had an improvement of ≥ 1 grade within 1 year, and a low degree of AVC was predictive of this improvement.

Key Words: Aortic valve calcification • Paravalvular leakage • Transcatheter aortic valve replacement

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has evolved as an alternative to surgical aortic valve replacement in patients with symptomatic severe aortic stenosis who are considered to be at very high or prohibitive operative risk, and its benefit was also been demonstrated in Asian populations.[1,2] Paravalvular leakage (PVL) after TAVR remains a significant issue,[3] as it has an adverse impact on short- and long-term outcomes.[4-6] According to previous studies, the severity of PVL may

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change during extended follow-up.[7,8] To date, no study has explored the mechanisms behind changes in PVL in individual cases, nor provided metrics that may explain or predict such changes.

The incidence of moderate/severe PVL has been reported to be higher following the use of self-expanding valves compared to balloon-expandable valves,[6] probably due to either inadequate radial strength or an insufficient immediate seal. However, the continuous expansion of their nitinol frames may negotiate and adapt to the surrounding tissue structure over time and reduce the paravalvular space. The aim of this study was to explore temporal changes in PVL in patients who had undergone TAVR with a self-expanding valve (CoreValve, Medtronic Incorporation, MN, USA) and their clinical determinants.

METHODS

Patient population

From September 2010 to June 2016, 93 patients with symptomatic severe aortic stenosis underwent TAVR with a self-expanding valve (CoreValve, Medtronic Incorporation, MN, USA) at National Taiwan University Hospital. Multi-detector computed tomography (MDCT) was routinely used for pre-TAVR assessment, except for the first 10 cases. TAVR was performed through a transfemoral approach in 91 patients and a trans-aortic approach in 2. All procedures were performed under either general anesthesia or conscious sedation. Surgical cut-down or suture-mediated closure devices were used to close the vascular access.

Ethical approval statement

All patients signed informed consent at our clinic, and all clinical information was collected according to the protocol of the Asian TAVR registry (NCT02308150), which was also approved by our local institutional review board. Demographic, clinical, echocardiographic, and procedural data were prospectively collected at our center for retrospective analysis.

MDCT study

MDCT was performed pre-operatively with a Brilliance iCT system (256-MDCT, Philips, Eindhoven, The Netherlands). Prospective electrocardiogram-gated MDCT was performed to measure the aortic annulus, aortic root, and valve morphology. The RR interval was set to 60-80%, with a slice thickness of 0.75-1.0 mm. Three-dimensional reconstructions of MDCT images were performed using 3mensio Valves software (version 6.1, 3mensio Medical Imaging, Bilthoven, Netherlands). The aortic annulus was defined as the virtual basal plane containing the basal attachment of the 3 aortic cusps, and its area and perimeter were quantified in the diastolic phase. The maximal and minimal diameters and perimeter of the annulus were retrospectively measured by a radiologist according to the standard protocol.[9] For quantitative assessments of aortic valve calcification (AVC), the Agatston calcium score of the aortic valve was assessed by the same MDCT analysis software in non-contrast scans, with the zone of interest confined to the volume from the aortic annulus to the level of the coronary ostia, excluding the left ventricular outflow tract (LVOT).[10] The threshold for the detection of calcium was set at 130 HU.[11] The covering index was defined as 100 × (nominal prosthesis perimeter-annulus perimeter)/annulus perimeter, which was adjusted from a previous study analyzing balloon-expandable valves.[12] The eccentricity index was defined as 100 × (1 – aortic annulus minimum diameter/maximal diameter).[13] The annulus angle was defined as the angle between the axis of the proximal ascending aorta (the line from the mid-valve point upwards, parallel to the left posterior wall of the proximal 5 cm of the ascending aorta) and the LVOT axis (the perpendicular line on the mid-point of the LVOT plane).[14]

Echocardiographic study

Comprehensive transthoracic echocardiography was performed pre-operatively and at 30 days, 6 months, and 12 months after TAVR using an iE33 ultrasound systeme quipped with a S5-1 transducer (Philips Medical Systems, Best, The Netherlands) by an echocardiographer who did not attend the procedure. The valve morphology, severity of aortic valve stenosis, and left ventricular function were measured according to the standards of the European Association of Cardiovascular Imaging/American Society of Echocardiography.[15] The degree of PVL was assessed according to the Valve Academic Research Consortium-2 (VARC-2).[16]

Statistical analysis

Continuous variables are presented as the median if normally distributed, or the interquartile range if not normally distributed. Categorical variables are presented as number and frequency. The Student's t test was performed for comparisons of continuous variables between 2 groups, and the chi-square test or Fisher's exact test was used for comparisons of categorical variables between 2 groups. Multivariate logistic regression analysis was performed to estimate the predictors of PVL; odds ratios (ORs) and 95% confidence intervals (CIs) were also recorded. We also used the area under receiver-operator characteristic (ROC) curve to assess the ability of the Agatston calcium score in the aortic valve to predict PVL improvement. The level of statistical significance was set at a 2-tailed p value of less than 0.05. The statistical analysis was performed using Stata/SE 14.2 for Windows (Stata Corporation, TX, US).

RESULTS

Baseline characteristics

All 93 patients (median age: 82.3 ± 6.2 years, men: 57.0%) with severe symptomatic aortic stenosis received a self-expanding TAVR. The aortic valve area was 0.68 ± 0.20 cm^2 and the mean aortic valve gradient was 46.4 ± 17.1 mmHg. The left ventricular ejection fraction was 65.5 ± 13.0%. Eighty patients (86.0%) had a New York Heart Association functional class III or IV. Five patients (5.4%) received 31-mm prostheses, 41 patients (44.2%) received 29-mm prostheses, 45 patients (48.4%) received 26-mm prostheses, and 2 patients (2.2%) received 23-mm prostheses. Five patients received more than 1 valve, 2 due to high and 3 due to low implant positions.

Early PVL after TAVR and predictors

No patient died in the 30 days immediately following TAVR. The first echocardiographic assessment was performed at 30 days post-TAVR in all patients. No or trace PVL was observed in 22 (23.7%) and 10 (10.8%) patients, respectively. Mild PVL was observed in 40 (43.0%) patients, and moderate/severe PVL was observed in 21 (22.6%) patients.

The patients were divided into 2 groups according to 30-day PVL severity: ≤ mild and moderate/severe PVL groups. Table 1 shows the baseline clinical and echocardiographic characteristics of the 2 groups. The patients with moderate/severe PVL were more likely to be male (90.5% vs. 47.2%; p < 0.001), more likely to have chronic pulmonary disease (47.6% vs. 9.7%; p < 0.001), and less likely to have hypertension (42.9% vs. 72.2%; p = 0.02). Table 2 summarizes the imaging and procedural variables of the 2 groups. The patients with moderate/severe PVL had higher Agatston calcium scores in the aortic valve (4910 ± 3127 vs. 2728 ± 1528; p < 0.001), larger annulus perimeter (78.3 ± 5.9 vs. 72.0 ± 6.6 mm; p = 0.001), larger implant size, lower covering index (14.4 ± 4.9% vs. 19.3 ± 6.3%; p = 0.007), and were more likely to have post-dilatation (55.3% vs. 22.2%; p = 0.007).

Multivariate analysis was performed to identify independent predictors of moderate/severe PVL 30 days after implantation (Table 3). Valve size was not included in the multivariate model, because valve size shares a high degree of co-linearity with annulus diameter. Chronic pulmonary disease (OR 5.7, 95% CI 1.5-22.4; p = 0.01), higher Agatston calcium score in the aortic valve (OR 1.003, 95% CI 1.00007-1.0006; p = 0.01), and larger annulus perimeter (OR 1.24, 95% CI 1.0003-1.54; p = 0.05) were found to be independent predictors of moderate/severe PVL.

Temporal changes in PVL and predictors of improvement

Eleven patients died within 1 year, including 2 cardiovascular deaths (sudden cardiac death in 1 and death of unknown cause in 1). Eighty-two patients, including 1 who required surgical aortic valve replacement for severe PVL, were followed for the full 1 year after TAVR. At the 1-year follow-up visit, 2 patients had worse PVL (from mild to moderate), and 25 had improved PVL (1 from severe to moderate, 8 from moderate to mild, 11 from mild to trace, 5 from trace to none). In 9 patients with moderate/severe PVL post-TAVR, 5 had an improvement during 1 to 6 months, and 4 had an improvement during 6 to 12 months. In 11 patients with mild PVL post-TAVR, 6 had an improvement during 1 to 6 months, and 5 had an improvement during 6 to 12 months. The 21 patients with moderate/severe PVL at 30 days after TAVR were divided into 2 groups: improvement of ≥ 1 grade (9/21, 42.9%) and no improvement (12/21, 57.1%) groups. Table 4 summarizes the clinical, echocardio-

Table 1. Clinical characteristics and echocardiographic variables according to the severity of PVL 30-day after TAVR

N (%)	≤ mild PVL (n = 72)	Moderate/severe PVL (n = 21)	p value
Age (years)	82.8 ± 5.5	80.4 ± 7.9	0.10
Male sex	34 (47.2%)	19 (90.5%)	< 0.001
Body mass index (kg/m^2)	23.6 ± 3.8	22.2 ± 2.8	0.12
Atrial fibrillation	2 (14.3%)	7 (14.0%)	0.74
Diabetes mellitus	23 (31.9%)	6 (28.6%)	0.77
Hypertension	52 (72.2%)	9 (42.9%)	0.02
Hyperlipidemia	24 (33.3%)	7 (33.3%)	1.00
Old myocardial infarction	7 (9.7%)	2 (9.4%)	1.00
Coronary artery disease	34 (47.2%)	10 (47.6%)	0.97
Prior stroke	14 (19.4%)	1 (4.8%)	0.32
Previous CABG	5 (6.9%)	0 (0%)	0.58
Previous PCI	16 (22.2%)	6 (28.6%)	0.55
Peripheral vascular disease	12 (16.7%)	1 (4.7%)	0.28
Chronic kidney disease	29 (40.3%)	5 (23.8%)	0.36
Chronic pulmonary disease	7 (9.7%)	10 (47.6%)	< 0.001
NYHA functional class III/0IV	60 (84.3%)	20 (95.3%)	0.25
STS score	7.5 ± 5.3	6.9 ± 4.5	0.29
Echocardiographic variables before TAVR			
LVEF (%)	65.6 ± 13.2	64.8 ± 14.2	0.82
Ao max PG (mmHg)	80.4 ± 29.8	80.1 ± 25.3	0.96
Ao mean PG (mmHg)	46.7 ± 18.3	44.6 ± 14.2	0.63
Aortic valve area (cm^2)	0.68 ± 0.17	0.69 ± 0.25	0.72
Moderate/severe aortic regurgitation	30 (41.7%)	13 (61.9%)	0.37

Mean ± SD are shown.

Ao max PG, aortic valve maximal pressure gradient; Ao mean PG, aortic valve mean pressure gradient; CABG, coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVL, paravalvular leakage; SD, standard deviation; STS score, Society of Thoracic Surgeons score; TAVR, transcatheter aortic valve replacement.

Table 2. Imaging and procedural variables according to the severity of PVL 30-day after TAVR

N (%)	≤ mild PVL (n = 72)	Moderate/severe PVL (n = 21)	p value
Bicuspid aortic valve	6 (8.3%)	3 (14.3%)	0.42
calcium score of the aortic valve	2728 ± 1528	4910 ± 3127	< 0.001
Annulus perimeter	72.0 ± 6.6	78.3 ± 5.9	0.001
Covering index (%)	19.3 ± 6.3	14.4 ± 4.9	0.007
Eccentricity index	0.20 ± 0.07	0.24 ± 0.07	0.09
Annulus angle	48.3 ± 9.7	45.7 ± 10.6	0.37
Valve size			0.005
23 mm	2 (2.8%)	0 (0%)	
26 mm	41 (56.9%)	4 (19.0%)	
29 mm	25 (34.7%)	16 (76.2%)	
31 mm	4 (5.6%)	1 (4.8%)	
Pre-dilatation	50 (69.4%)	16 (76.2%)	0.55
Post-dilatation	16 (22.2%)	11 (55.3%)	0.007
Implantation position			0.32
Optimal	38 (55.8%)	9 (47.4%)	
High implantation	6 (8.8%)	4 (21.0%)	
Low implantation	24 (35.3%)	6 (31.6%)	
Second valve implantation	4 (5.6%)	1 (4.7%)	0.88
AR index	0.24 ± 0.08	0.23 ± 0.08	0.67

Mean ± SD are shown.

AR index, aortic regurgitation index, calculated as ratio of the diastolic pressure gradient between aorta and left ventricle to the systolic pressure at aorta. Abbreviations are in Table 1.

Table 3. Multivariate analysis according to the severity of PVL 30-day after TAVR

	Multivariate adjusted odds ratio (95% confidence interval)	p value
Male sex	4.3 (0.95-19.2)	0.06
Hypertension	0.31 (0.09-1.07)	0.07
Chronic pulmonary disease	5.7 (1.5-22.4)	0.01
Agatston calcium score of the aortic valve	1.003 (1.00007-1.0006)	0.01
Annulus perimeter	1.24 (1.0003-1.54)	0.05
Covering index (%)	-	0.96
Post-dilatation	-	0.42

Abbreviations are in Table 1.

Table 4. Comparison of variables in patients with and without ≥ 1 grade improvement at 1-year from ≥ moderate PVL at 30-day follow-up

N (%)	Improvement (n = 9)	No improvement (n = 12)	p value
Age	78.7 ± 9.4	81.5 ± 6.8	0.44
Male	8 (88.9%)	11 (91.7%)	0.83
Body mass index (kg/m^2)	23.2 ± 2.2	21.2 ± 2.8	0.09
Diabetes mellitus	3 (33.3%)	3 (25.0%)	0.68
Hypertension	4 (44.4%)	5 (41.2%)	0.89
Hyperlipidemia	3 (33.3%)	4 (33.3%)	1.00
Coronary artery disease	4 (44.4%)	6 (50.0%)	0.80
Chronic kidney disease	3 (33.3%)	2 (16.7%)	0.59
Chronic pulmonary disease	4 (44.4%)	6 (50.0%)	0.80
LVEF (%)	62.4 ± 14.5	66.7 ± 14.4	0.51
Ao max PG (mmHg)	83.3 ± 21.2	77.7 ± 28.7	0.63
Ao mean PG (mmHg)	46.4 ± 12.1	43.3 ± 15.9	0.63
Aortic valve area (cm^2)	0.69 ± 0.23	0.69 ± 0.28	0.98
Bicuspid aortic valve	1 (11.1%)	2 (16.7%)	0.72
Calcium score of the aortic valve	3068 ± 1816	6418 ± 3222	0.01
Annulus perimeter (mm)	80.6 ± 3.3	75.5 ± 7.3	0.10
Covering index (%)	13.1 ± 4.8	17.0 ± 6.2	0.15
Eccentricity index	0.23 ± 0.05	0.26 ± 0.08	0.44
Annulus angle	44.9 ± 12.2	46.3 ± 9.8	0.81
Valve size			0.77
26 mm	1 (11.1%)	3 (25.0%)	
29 mm	8 (88.9%)	8 (66.7%)	
31 mm	0 (0%)	1 (8.3%)	
Pre-dilatation	7 (77.8%)	9 (75.0%)	1.00
Post-dilatation	5 (55.6%)	6 (50.0%)	1.00
Implantation position			1.00
Optimal	5 (55.5%)	6 (50.0%)	
High implantation	1 (11.1%)	3 (25.0%)	
Low implantation	3 (33.4%)	3 (25.0%)	
Second valve implantation	1 (11.1%)	9 (0%)	1.00
AR index	0.22 ± 0.08	0.23 ± 0.08	0.85

Mean ± SD are shown.
Ao max PG, aortic valve maximal pressure gradient; Ao mean PG, aortic valve mean pressure gradient; LVEF, left ventricular ejection fraction.
AR index, aortic regurgitation index, calculated as ratio of the diastolic pressure gradient between aorta and left ventricle to the systolic pressure at aorta. Abbreviations are in Table 1.

graphic, imaging, and procedural variables of these 2 groups. In the patients with improvement, the Agatston calcium score in the aortic valve (3068 ± 1816 vs. 6418 ± 3222; p = 0.01) was significantly lower than in those without. The area under the ROC curve of Agatston calcium score for predicting PVL improvement was 0.82 (95% CI = 0.63-1.00, p = 0.01), with a cut-off value of 5210 (Figure 1).

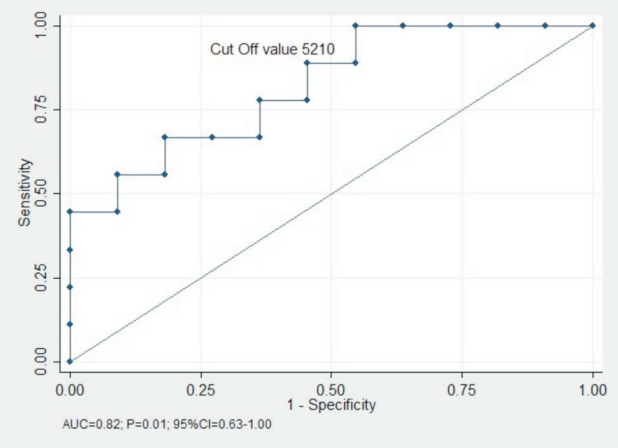

Figure 1. *Receiver operating characteristic (ROC) curve of aortic valve calcification as predictor for improvement of paravalvular leakage at the 1-year follow-up.*

DISCUSSION

There are 2 major findings in this study: 1) chronic pulmonary disease, high degree of AVC, and larger annulus perimeter were independent predictors of moderate/severe PVL 30 days after TAVR with a self-expanding valve; and 2) in patients with moderate/severe PVL at 30 days after TAVR, a lower degree of AVC predicted PVL improvement at 1 year post-surgery. To the best of our knowledge, this is the first study to explore the possible determinants of improvement from significant PVL after TAVR.

High degree AVC, as measured by the Agatston score, has been identified as a predictor of post-TAVR PVL in published self-expanding valve studies.[11,17-19] In addition, mismatch between the annulus and prosthesis diameter,[5,12,20] suboptimal device implantation,[21-23] and larger annulus[24] have also been reported to be major causes of post-TAVR PVL. Our findings are consistent with previous findings. In our study, the covering index in patients with a larger annulus perimeter was reduced, suggesting a tendency towards relative under-sizing of the prostheses in these patients, although the covering index was not found to be significant in multivariate analysis. However, the correlation between chronic pulmonary disease and PVL was not clear, and further studies are needed to elucidate this issue.

Despite the recently updated VARC 2 criteria,[14] the precise quantification of PVL after TAVR remains challenging, most semi-quantitative Doppler parameters of aortic regurgitation (AR) severity are best applied in central regurgitation jets, and hence may not be ideal to quantify the frequently diffuse and eccentric PVL with circumferential extent in TAVI patients. Despite the use of an integrative approach including several indirect parameters to determine AR, the methodology remains imprecise. The measurement of AR index is a more objective and easier way to quantify PVL during the procedure. And it has been reported to be a predictor of 1-year mortality after TAVR.[3] The mismatch between AR index and the echocardiographic measurements of PVL severity in our results illustrates the importance of using a multimodal approach to precisely quantify PVL immediately after valve implantation, and to identify the patients who will benefit from corrective measures.

The incidence of moderate/severe PVL after TAVR with a self-expanding valve varies widely from 2% to 40%,[22-24] and seems to be higher than that with a balloon expandable valve.[25-28] A possible cause of PVL after self-expanding valve TAVR is the extreme angulation between the LVOT and ascending aorta preventing the self-expanding prosthesis from forming a tight seal.[4] Another possibility is the relatively weaker radial strength of CoreValve in the presence of heavy calcification,[29] which may result in incomplete device expansion and mal-apposition of the prosthesis to the native annulus and LVOT. Adequate oversizing, balloon pre- and post-dilatation, and the addition of external sealing skirts may help to overcome these issues.

Interestingly, observational data have suggested that a reduction in PVL severity during extended follow-up may occur without any interventions. Ussia et al. found that moderate/severe PVL decreased from 15% to 10% at 3 years post-surgery.[7] In the CoreValve US pivotal trial,[30] the frequency of moderate/severe PVL was lower at 1 year post-TAVR (4.2%) than at discharge (10.7%, p = 0.004). In the present study, we demonstrated that if the Agatston calcium score was < 5200, there was an 82% chance of PVL improvement at 1 year. An adequately oversized nitinol framework will continue to expand after deployment, especially against less heavily calcified surrounding structures. Thus, our results suggest that baseline Agatston score should be used for decision-making in the presence of significant PVL after self-expanding valve implantation. If significant PVL persists after adequate post-dilation in a properly sized and

positioned self-expanding valve, it would be reasonable to stop the procedure if the Agatston score is < 5200. Improvements can be expected and complications related to further aggressive intervention can be avoided.

The main limitation of this study is that our cohort was small and the follow-up period was relatively short. The cut-off value of 5210 in AVC should be verified in further studies with more patients. In addition, the conclusions of the present study were obtained with first-generation self-expanding valves, and the results may not be extrapolated to other balloon-expandable or newer-generation prostheses.

CONCLUSIONS

In the patients who received TAVR with a self-expanding valve with moderate/severe PVL, 43% (9/21) improved by ≥ 1 grade within 1 year. A high Agatston calcium score in the aortic valve was predictive of moderate/severe PVL after TAVR, but a score of < 5200 was associated with improvements in PVL.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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