Impact of preprocedural echocardiographic parameters on increased stroke volume after transcatheter aortic valve replacement

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Abstract

Aims: Increased stroke volume (SV) is a prognosticator of severe aortic stenosis (AS) after transcatheter aortic valve replacement (TAVR). This study aimed to investigate preprocedural echocardiographic predictors of increased SV after TAVR.

Methods and results: Clinical and echocardiographic data were retrospectively analysed in 129 patients with severe AS who underwent TAVR (2013-2015). We compared the echocardiographic data and cardiac events between the decreased SV group (n=28) and the increased SV group (n=101). Univariate and multivariate analyses were used to assess the predictors of increasing SV. AS severity significantly diminished, left and right ventricular function improved, and SV index (SVi) increased after TAVR: aortic valve area index (0.46±0.13 vs. 1.18±0.33 cm², p<0.001); aortic regurgitation (AR) grade (1.85±0.55 vs. 1.60±0.54, p<0.001); left ventricular ejection fraction (59.9±12.7 vs. 64.1±12.0%, p<0.001); right ventricular fractional area change (RVFAC) (48.8±11.9 vs. 53.3±14.0%, p<0.001); SV index (SVi) (46.7±11.0 vs. 52.8±12.0 ml/m², p<0.001). Kaplan-Meier survival estimates suggested that the SVi increase was associated with the decreased cardiovascular events one year after TAVR (hazard ratio 4.08, 95% confidence interval [CI]: 1.32-12.7, p=0.02). On multivariate analysis, preprocedural AR grade (odds ratio [OR] 7.00, 95% CI: 2.76-17.8, p<0.001) and preprocedural RVFAC (OR 1.05, 95% CI: 1.01-1.10, p=0.011) correlated with the SV increase.

Conclusions: Preprocedurally, greater AR and higher RVFAC could predict an increased SVi and thus the occurrence of fewer cardiac events. Preserved preprocedural RV systolic function is crucial for an increased SV after TAVR.

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Increased SV following TA VR. We therefore investigated predictors of increased SV following TA VR, including improved left and right heart function and less severe valvular regurgitation. However, there have been few investigations of the haemodynamic parameters related to increased SV following TAVR. We therefore investigated predictors of increased SV following TAVR, evaluating the preprocedural echocardiographic parameters.

Methods

STUDY POPULATION

We retrospectively reviewed 140 consecutive patients who underwent TAVR from October 2013 to September 2015 in our institution. Among those patients, three did not have follow-up transthoracic echocardiography (TTE) records because they died during the acute phase after TAVR, and there was insufficient image quality for assessing right ventricular fractional area change (RVFAC) in eight, leaving 129 patients who were evaluated. The one-year (336.8±6.8 days) assessment after TAVR revealed that heart failure, ischaemic heart disease, arrhythmia requiring admission, and cardiac death comprised the cardiac events that had occurred during this period. Patient selection for TAVR conformed to a standard process that comprised clinical evaluation, multidetector computed tomography scanning, and echocardiography prior to when decisions about treatment were made by our multidisciplinary Heart Team. All patients received an Edwards SAPIEN XT valve (Edwards Lifesciences, Irvine, CA, USA). Data were retrieved from our computerised database, and clinical information was obtained retrospectively for all patients. The institutional review board of our institution approved the study.

COMPREHENSIVE TRANSTHORACIC ECHOCARDIOGRAPHY

Comprehensive TTE studies were performed at baseline (42.2±2.8 days before TAVR) and after TAVR (2.1±0.2 days). All TTE studies were obtained using a Philips ie33 ultrasonography system (Philips Medical Systems, Best, the Netherlands) and Vivid E9 or Vivid 7 ultrasonography system (GE Healthcare, Chicago, IL, USA). They were evaluated according to the guidelines of the American Society of Echocardiography.

Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured using the method of discs (modified Simpson’s rule), and the LVEF was calculated. The stroke volume (SV) was calculated according to the guideline using pulsed-wave Doppler recording at the left ventricular outflow tract (LVOT). The aortic valve area was calculated using the continuity equation. The area of the right ventricle was measured by outlining the endocardial borders at end-diastole and end-systole in the apical four-chamber view. The RVFAC was calculated as follows:

$$\frac{RVEDA – RVESA}{RVEDA}$$

where RVEDA is the right ventricular end-diastolic area, and RVESA is the right ventricular end-systolic area. Mitral regurgitation (MR) severity was graded as none-to-mild, moderate, moderate-to-severe, or severe, based primarily on the jet area and vena contracta width of the MR jet. Preprocedural aortic regurgitation (AR) severity was graded according to the same guideline based primarily on the jet area and vena contracta. The post-procedural AR severity was graded according to the American Society of Echocardiography guideline or other recommendations, based primarily on the circumferential extent of paravalvular regurgitation (PVL) and jet area evaluated on multiple TTE planes.

DEFINITION OF INCREASED/DECREASED SV AND CARDIOVASCULAR EVENTS ONE YEAR AFTER TAVR

The increase in SV was defined as the post-procedural SV/pre-procedural SV >1. Otherwise, the SV was considered to have worsened. Cardiovascular events were assessed at the one-year follow-up visit following TAVR. Primary cardiovascular events were heart failure, ischaemic heart disease, or arrhythmia requiring admission, and cardiac death.
STATISTICAL ANALYSIS
Data are presented as numbers with percentages for categorical variables or as means±standard deviations (SD) for continuous variables. Categorical variables were compared with a χ² test or Fisher’s exact test, as appropriate. Differences between groups were analysed by a paired or unpaired t-test in case of normal distribution or by the Wilcoxon or the Mann-Whitney U test, as appropriate, in case of non-normal distribution. Cumulative event rates were calculated using the Kaplan-Meier estimates for the increases and decreases in SV after TAVR. The log-rank test for time-to-event data at one year for cardiac events was used for statistical comparison. Multiple logistic regressions were used to identify factors associated with increased SV after TAVR. Variables with probability values <0.20 in individual analyses were included in the multivariate analysis. We analysed intra-observer and inter-observer reproducibility for preprocedural and post-procedural LVEF, RVFAC, and SV from TTE data in 15 randomly selected patients and expressed them using the Bland-Altman analysis. A two-sided value of p<0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS, Version 21.0 software (IBM Corp., Armonk, NY, USA).

Results
BASELINE CHARACTERISTICS AND PREPROCEDURAL AND POST-PROCEDURAL ECHOCARDIOGRAPHIC MEASUREMENTS
The baseline data for the 129 patients are shown in Table 1. SAPIEN XT valve diameters during the study period were 20, 23, 26, and 29 mm. The echocardiographic changes are shown in Table 2. Despite no significant difference in the LVEDV and RVEDA, the LVESV and RVESA decreased following TAVR. As a result, the LVEF and RVFAC had improved postoperatively. AS severity, assessed by mean transaortic pressure gradient and aortic valve area index, diminished following TAVR. The AR grade improved in 46 patients (35.6%), did not change in 67 patients (51.9%), and worsened in 16 patients (12.4%). There were also three patients whose AR severity was moderate or greater after TAVR (2.3%). The MR and tricuspid regurgitation (TR) grades did not change significantly following TAVR (Figure 1). Stroke volume index (SVi) increased significantly after TAVR.

BASELINE CHARACTERISTICS AND CARDIAC EVENTS OF INCREASED OR DECREASED SV PATIENTS AFTER TAVR
Overall, 12 patients had cardiac events (one cardiac death and 10 admissions for heart failure, one for sick sinus syndrome) during the observational period (336.8±6.8 days). There was no significant difference in the history of coronary artery disease (42.9% vs. 39.6%, p=0.76) or in the percentage of the transapical approach (10.7% vs. 11.9%, p=0.58) between patients with increased or decreased SV after TAVR. Kaplan-Meier survival estimates suggested that increased SV was associated with fewer cardiovascular events one year after TAVR (hazard ratio [HR] 4.08, 95% CI: 1.32-12.7, p=0.02) (Figure 2).

PREPROCEDURAL AND POST-PROCEDURAL ECHOCARDIOGRAPHIC MEASUREMENTS
Table 3 shows preprocedural and post-procedural echocardiographic measurements. Patients with increased SV had greater RVFAC and AR severity than those with decreased SV before
Predictors of increased SV after TAVR

There was no significant difference in LVEF or the severity of MR or TR. The mean transaortic gradient decreased significantly after TAVR in both groups, whereas increased LVEF and RVFAC and less severe AR and MR were observed in patients with increased SV.

PREDICTORS OF IMPROVED SV AFTER TAVR

Results of univariate and multivariate analyses of preprocedural parameters of the severity of valvular diseases and LV or RV function on increased SV are shown in Table 4. In the univariate analysis, we selected a value of p<0.2 to indicate significance for the mean aortic pressure gradient (OR 1.02, 95% CI: 1.00-1.05, p=0.099), RVFAC (OR 1.04, 95% CI: 1.00-1.08, p=0.030), and AR grade (OR 5.868, 95% CI: 2.46-14.0, p<0.001). In the multivariate analysis, RVFAC (OR 1.05, 95% CI: 1.01-1.10, p=0.011) and AR grade (OR 7.00, 95% CI: 2.76-17.8, p<0.001) were found to be independent predictors of increased SV after TAVR.

INTRA-OBSERVER AND INTER-OBSERVER VARIABILITY

The intra-observer variability for the TTE measurements, which was demonstrated by the 95% CI of the Bland-Altman method, was as follows: preprocedural LVEF −2.6 to 1.9%, RVFAC −3.4 to 4.3%, SV −4.8 to 3.8 mL, and post-procedural LVEF −2.7 to 1.4%, RVFAC −2.8 to 1.7%, SV −5.6 to 4.3 mL. The inter-observer variability differences were as follows: preprocedural LVEF −2.8 to 1.9%, RVFAC −5.0 to 5.0%, SV −2.5 to 3.9 mL, and post-procedural LVEF −3.0 to 2.2%, RVFAC −2.5 to 3.4%, SV −3.0 to 3.6 mL.

Discussion

We showed that the increased SV afforded by TAVR led to a significant decrease in cardiac events, including cardiac death and readmission due to heart failure within one year. TAVR influenced haemodynamic parameters as follows: 1) the LVEF and RVFAC increased after TAVR due to the decrease in LVESV and the systolic RV area, and 2) the severity of AR, but not of MR, was significantly diminished following TAVR. In addition, the greater severity of AR and higher RVFAC before TAVR were correlated with the increased SV following TAVR.
Table 3. Preprocedural and post-procedural echocardiographic parameters of patients with decreased SV or increased SV following TAVR.

<table>
<thead>
<tr>
<th></th>
<th>Decreased SV (n=28)</th>
<th>Increased SV (n=101)</th>
<th>Pre-parameters comparison</th>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>p-value</td>
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<tr>
<td>LV Ejection fraction, %</td>
<td>62.0±10.2</td>
<td>64.2±8.1</td>
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<td>End-diastolic volume, mL</td>
<td>77.3±24.2</td>
<td>79.4±21.1</td>
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<td>End-systolic volume, mL</td>
<td>30.2±14.8</td>
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<td>RV Fraction area change, %</td>
<td>44.4±12.0</td>
<td>44.3±13.9</td>
<td>0.924</td>
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<td>End-diastolic area, cm²</td>
<td>14.6±4.3</td>
<td>14.6±3.5</td>
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<tr>
<td>End-systolic area, cm²</td>
<td>8.2±3.4</td>
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<td>Mean transaortic gradient, mmHg</td>
<td>43.5±16.0</td>
<td>9.4±2.9</td>
<td>&lt;0.001</td>
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<td>Aortic valve area index, cm²/m²</td>
<td>0.50±0.03</td>
<td>1.1±0.3</td>
<td>&lt;0.001</td>
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<td>Aortic regurgitation grade (average)</td>
<td>none to trivial, n (%)</td>
<td>16 (57.1)</td>
<td>5 (17.9)</td>
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<tr>
<td></td>
<td>mild, n (%)</td>
<td>11 (39.2)</td>
<td>20 (71.4)</td>
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<td></td>
<td>moderate, n (%)</td>
<td>1 (3.6)</td>
<td>3 (10.7)</td>
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<td></td>
<td>severe, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>Mitral regurgitation grade (average)</td>
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<td>24 (85.7)</td>
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<td>moderate, n (%)</td>
<td>4 (14.3)</td>
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<td></td>
<td>moderate to severe, n (%)</td>
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<td>0 (0)</td>
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<td></td>
<td>severe, n (%)</td>
<td>0 (0)</td>
<td>1 (3.6)</td>
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<td>Tricuspid regurgitation grade (average)</td>
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<td>2 (7.1)</td>
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<td></td>
<td>trivial, n (%)</td>
<td>13 (46.4)</td>
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<td>11 (39.3)</td>
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<td></td>
<td>moderate, n (%)</td>
<td>2 (7.1)</td>
<td>1 (3.6)</td>
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<tr>
<td></td>
<td>severe, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>Stroke volume index, mL/m²</td>
<td>50.5±11.9</td>
<td>45.9±10.4</td>
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<td>Peak E velocity (cm/s)</td>
<td>89.5±32.2</td>
<td>89.5±32.2</td>
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<td>Deceleration time (cm/s)</td>
<td>287.6±109.6</td>
<td>249.2±88.1</td>
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<td>E/e'</td>
<td>17.2±8.7</td>
<td>14.2±5.8</td>
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<td>PA pressure (mmHg)</td>
<td>31.0±9.4</td>
<td>29.6±16.7</td>
<td>0.971</td>
</tr>
</tbody>
</table>

Values are n (%) or mean±SD. *Comparison of pre-parameters between decreased SV group and increased SV group. LV: left ventricle; PA: pulmonary artery; RV: right ventricle

CLINICAL IMPLICATION OF THE INCREASED SV

As Anjan et al previously reported, not only preprocedural but also post-procedural low flow were predictors of a poor prognosis following TAVR. Le Ven et al showed that six-month and one-year all-cause mortality of patients with normalised flow following TAVR was lower than that in those with persistent low flow regardless of their preprocedural SV. These findings suggested that increased SV was the important beneficial effect of TAVR. SV tends to be calculated higher by the Doppler method at the LVOT compared with the Simpson method in the previous validation study; our data were consistent with that report. We adopted SV calculated by the Doppler method as previously reported and demonstrated that patients with decreased SV had a higher risk of cardiac events than those with increased SV at the one-year follow-up after TAVR. These results are consistent with previous studies (Figure 2).

INFLUENCE OF THE SEVERITY OF VALVULAR DISEASE ON SV

Several studies have reported that paravalvular leak (PVL) has a negative impact on midterm and long-term prognosis following TAVR. Consequently, preventing PVL is an important requirement for TAVR. We showed herein that the severity of AR was significantly reduced following TAVR in patients with
increased SV but not in those with decreased SV (Table 3). Furthermore, the improved AR grade correlated with the increase in SV in all patients. The multivariate analysis showed that more severe AR before TAVR was an independent predictor of the subsequent increase in SV, which is consistent with the results of a previous study. Because the severity of post-TAVR AR was rated almost always “mild or less” (126/129) in our study, patients with significant AR prior to TAVR could have had a greater reduction of AR volume following TAVR, resulting in the significantly increased SV. These results suggest that the reduced AR volume, even if it was from mild to trivial, is an important therapeutic effect of TAVR in addition to expansion of a narrowed aortic valve area. Thus, sophisticated techniques designed to leave no PVL are required. We need more data to clarify the mechanism by which the reduced AR improved the SV index after TAVR.

Previous studies have reported that preprocedural significant MR predicted a poor prognosis after TAVR, and that following TAVR 38.0-77.7% of patients exhibited significantly diminished MR severity. In the present study, however, the severity of MR did not change significantly and was not correlated with the improved SV after TAVR in any patients (Figure 1, Table 4). These results indicate that the improved AR may have greater impact on the increase in SV than MR following TAVR.

### INFLUENCE OF LEFT AND RIGHT VENTRICULAR FUNCTION ON SV

Several studies, including the PARTNER trial (Placement of Aortic Transcatheter Valves), showed that a preprocedural low ejection fraction was an independent predictor of a poor prognosis, whereas others reported that it was not. Thus, the results of previous studies are controversial.

In our study, the reduction in LVESV led to increased LVEF after TAVR, and increased LVEF was observed in patients with increased SV. Preprocedural LVEF, however, was not an independent predictor of the increased SV following TAVR. The LVEF reflects the contractility of the left ventricle. It does not, however, accurately reflect the forward flow itself because of the influence of other haemodynamic factors. For instance, because aortic or mitral regurgitation (which fluctuates dynamically following TAVR) interferes with LVEF, preprocedural LVEF might not have independently predicted the increase in SV in the present study.

Several reports on RV function in patients following TAVR have described using parameters such as tricuspid annular plane systolic excursion, three-dimensional right ventricular (3D-RV) volume, RVFAC, right ventricular S’ (RV S’), TR severity, and pulmonary arterial systolic pressure. The effect of RV function on prognosis after TAVR, however, is not widely recognised. The 3D right ventricular ejection fraction (3D-RVEF), measured by 3D transthoracic echocardiography (3D-TEE) or magnetic resonance imaging, is a reliable parameter with respect to RV systolic function. Lindsay et al reported that low 3D-RVEF was a predictor of poor prognosis in patients undergoing TAVR, but LVEF was not. We adopted RVFAC – a conventional, accurate parameter of RV contraction in patients undergoing TAVR – to evaluate RV function. RVFAC was significantly increased after TAVR in patients with increased SV but not in those with decreased SV. In addition, preprocedural RVFAC was significantly higher in patients with increased SV than in those with decreased SV, and the multivariate analysis showed that preprocedural RVFAC was an independent predictor of increased SV following TAVR. There were no significant differences in the other parameters that influence RVFAC, such as preprocedural LVEF, TR severity, and morbidity associated with chronic obstructive pulmonary disease between the two groups. Actually, preprocedural RVFAC independently predicted increasing SV; however, the odds ratio was low. The reason may be that RVFAC reflected forward flow less accurately compared with 3D-RVEF. Because RV function is composed of various factors – not only RVFAC but also RV strain, 3D-RVEF, RV S’, and RV myocardial performance index (MPI) – we need more analyses of these parameters in the future. Our results suggest that preserved preprocedural RV systolic function is important in TAVR patients because it affects their SV after TAVR.

### Limitations

The study has limitations. The analyses were retrospective and observational. We were unable to measure all RV parameters, including the tricuspid annular plane systolic excursion or RV S’ in every patient. Of note, 3D-RVEF may be a more accurate parameter than RVFAC. In the present retrospective study, however, we could not accumulate an adequate number of cases with
3D-RVEF data. Therefore, we adopted RVFAC as the indicator of RV systolic function based on previous studies. Because RV function is affected by LV function in general, LV dysfunction might have resulted in low RVFAC in our study. Therefore, additional analyses focused on the LV-RV interaction in patients undergoing TAVR are now ongoing. Moreover, although the results of 28 patients with decreased SV suggested that the decreased preprocedural RVFAC was a predictor of decreased SV after TAVR, this finding should be investigated further in a larger group of patients.

Conclusions
Increased SV is an important therapeutic effect of TAVR associated with fewer cardiovascular events. Preprocedural higher AR grade and RVFAC could predict an increased SV. According to these results, the reduced AR volume by sophisticated techniques designed to leave no PVL and preserved preprocedural RV systolic function are crucial for increased SV after TAVR.

Impact on daily practice
An increased stroke volume index improves the outcomes of aortic stenosis patients following transcatheter aortic valve replacement (TAVR), as shown in previous studies. The present study revealed that preprocedural aortic regurgitation and right ventricular function are correlated with the increase in stroke volume after TAVR.

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Conflict of interest statement
K. Shimizu and K. Hayashida are clinical proctors for Edwards Lifesciences. The other authors have no conflicts of interest to declare.

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