Hemodynamic assessment of paravalvular aortic regurgitation after TAVI: estimated myocardial supply-demand ratio and cardiovascular mortality

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Patsalis PC, Konorza TF, Al-Rashid F, Plicht B, Hildebrandt HA, Wendt D, Thielmann M, Jakob HG, Eggebrecht H, Heusch G, Erbel R, Kahler P. Hemodynamic assessment of paravalvular aortic regurgitation after TAVI: estimated myocardial supply-demand ratio and cardiovascular mortality. Am J Physiol Heart Circ Physiol 304: H1023–H1028, 2013. First published January 11, 2013; doi:10.1152/ajpheart.00807.2012.—A relevant (at least moderate) paravalvular regurgitation (PAR) after transcatheter aortic valve implantation (TAVI) is in found in up to 20% of cases and associated with increased mortality. The ratio of the diastolic over the systolic pressure time integral (DPTI:SPTI) has been proposed to reflect an estimate of myocardial oxygen supply versus demand and the propensity for myocardial ischemia. We have now evaluated the potential of this ratio to predict PAR-associated cardiovascular mortality after TAVI, retrospectively analyzing data from 167 consecutive TAVI patients. PAR was graded angiographically, and the myocardial supply-demand ratio was estimated from the planimetric integration of the diastolic and systolic pressure-time area (DPTI and SPTI), respectively. PAR was observed in 113 patients (67%) and angiographically graded as mild in 89 (78.8%), moderate in 21 (18.6%) or severe in 3 (2.7%) cases. The DPTI:SPTI ratio decreased with increasing Sellers grade of PAR ($P < 0.001$). A DPTI:SPTI of $\leq 0.7$ predicted cardiovascular mortality (area under the curve = 0.96). Cardiovascular mortality at 30 days and 1 yr was increased in patients with DPTI:SPTI $\leq 0.7$ over those with DPTI:SPTI $> 0.7$ (42 vs. 2% and 63 vs. 3%, respectively; $P < 0.001$). In conclusion, DPTI:SPTI provides an excellent cutoff value of $\leq 0.7$ for the prediction of PAR-associated mortality.

aortic regurgitation; aortic stenosis; transcatheter aortic valve implantation.

THE INCIDENCE of moderate and severe paravalvular aortic regurgitation (PAR) after transcatheter aortic valve implantation (TAVI) varies from 10 to 20% (4, 5, 17, 21–23, 27), and moderate-to-severe PAR after TAVI is associated with increased in-hospital mortality and unfavorable long-term outcome (1, 11, 14, 20). PAR severity during TAVI is usually graded qualitatively using angiography. Quantitative evaluation of PAR has been recently proposed by use of the aortic regurgitation (AR) index, which is calculated as the ratio of the gradient between diastolic aortic pressure (DAP) and left ventricular (LV) end-diastolic pressure (LVEDP) to systolic blood pressure (SBP) $\times 100$ or $[(\text{DAP-LVEDP})/\text{SBP}] \times 100$ (20) or more simply by use of the pressure difference between DAP and LVEDP ($\Delta\text{DAP-LVEDP}$) (14). A pathophysiological understanding of PAR and its consequences is a prerequisite for an effective treatment and the improvement of survival.

Myocardial ischemia is traditionally viewed as an imbalance of myocardial oxygen supply over demand. Such supply-demand ratio can be estimated from the ratio of the diastolic over systolic pressure time integral (DPTI:SPTI), which sensitively reflects the propensity to myocardial ischemia, notably subendocardial ischemia (7, 8). Aortic regurgitation is typically associated with a reduced DPTI:SPTI ratio (7, 8, 9, 13, 24, 26). We have therefore now calculated the DPTI:SPTI ratio following the TAVI procedure and related it to cardiovascular mortality. Hemodynamics and outcome of these patients have been reported before (14).

MATERIALS AND METHODS

Patient population. Data from 167 consecutive high-risk patients with symptomatic aortic valve stenosis who underwent transfemoral or transsubclavian TAVI using the Medtronic CoreValve [MCV; Medtronic, Minneapolis, MN; $n = 88$ (52.7%)] or the Edwards SAPIEN [ES; Edwards Lifesciences, Irvine, CA; $n = 79$ (47.3%)] bioprosthesis were analyzed. Both valves were available in two sizes at the time of implantation and were selected according to the manufacturer’s sizing recommendations: A 23-mm ES valve was chosen for patients with an annular diameter between 18 and 22 mm and a 26-mm ES for larger annuli up to 25 mm. Similarly, a 26-mm MCV prosthesis was selected for an annular diameter between 20 and 23 mm and a 29-mm MCV prosthesis for larger annuli up to 27 mm.

The decision for TAVI was made by an interdisciplinary heart team based on current recommendations (1, 6, 23, 25). TAVI procedures were performed according to previously reported standard techniques (6, 10, 25). The present retrospective analysis was approved by the local ethics committee.

Hemodynamic and angiographic assessment of PAR. Residual PAR was graded qualitatively after final device deployment and catheter removal by the amount of regurgitant contrast media during supravalvular angiography, using the Sellers criteria (1, 18, 19): absence of PAR = 0/4, mild = 1/4, moderate = 2/4, moderate to severe = 3/4, and severe PAR = 4/4.

LV and aortic pressures were simultaneously measured after the procedure. $\Delta\text{DAP-LVEDP}$ (14), the AR index as the ratio of the gradient between DAP and LVEDP to SBP (20), and the DPTI:SPTI ratio were calculated. The DPTI was calculated from the planimetric integration of the area between the aortic and LV pressure tracings during diastole. The SPTI was defined as the area under the LV pressure curve beginning at the onset of the ventricular systole and ending at the incisura of the aortic pressure tracing (Fig. 1) (8, 24). End diastole was defined as the point just before the beginning of the next upstroke of the aortic pressure and therefore included the period of isovolumetric contraction of the subsequent systole; end systole...
was defined as the time of aortic valve closure. Simultaneous pressures were recorded at 50 mm/s and averaged over three representative cardiac cycles. Since transfemoral TAVI was performed under anesthesiologist-controlled conscious sedation, transesophageal echocardiography was not used. Nevertheless, transesophageal echocardiography was readily available on standby in case of complications. Blood gas analysis was performed, and changes were corrected by oxygen enrichment of inspired air and intravenous sodium bicarbonate infusion.

End points. The primary end point was cardiovascular mortality according to Valve Academic Research Consortium (VARC-2) definitions. Cardiac troponin I (TnI) levels were measured 24 h before TAVI and repeated after the procedure until serum levels reached their peak within 48 h and started to decrease. The peak TnI levels within 48 h after TAVI are reported. The upper reference limit was 0.01 ng/ml.

Postinterventional protocol. After TAVI, patients were transferred for 24 h to an intensive care unit for postinterventional monitoring. Besides clinical examination, electrocardiogram, body temperature, and chest X-ray, all blood parameters that had already been determined at the initial examination, were determined again. Follow-up examinations were performed 3 and 12 mo after discharge from the hospital.

Statistical analysis. Categorical data are presented as frequencies and percentages; continuous variables are expressed as means and SDs. Comparisons were made with two-sided χ²-tests or two-sided Fisher exact tests for categorical variables and one-way ANOVA for continuous variables, using Bonferroni correction for multiple testing. ANOVA was used for comparing more than two groups and t-test or Mann-Whitney test for two group comparisons. A P value <0.05 was considered significant.

Survival analyses for PAR grading according to Sellers and DPTI:SPTI were performed by the Kaplan-Meier method, with patients censored as of the last date known alive. The already established DPTI:SPTI cutoff values 0.5, 0.6, and 0.7 for AR and subendocardial ischemia were evaluated by receiver operating characteristic curve analysis for DPTI:SPTI as a potential predictor of cardiovascular mortality. All statistical analyses were performed using SPSS (version 17.0, SPSS, Chicago, IL). The authors had full access to the data and take full responsibility for their integrity.

RESULTS

Baseline and procedural characteristics. Our study cohort represents a typical TAVI patient population at high risk for open heart surgery (logistic EuroSCORE of 21.7 ± 11.9%; and STS score, 7.5 ± 5.6%) with symptomatic aortic stenosis (aortic valve area, 0.61 ± 0.3 cm²; and transvalvular gradient, 56.1 ± 11.7 mmHg). Further baseline and procedural characteristics of this patient population have been previously described (Table 1). In line with other recent studies (11, 12, 16), the logistic EuroSCORE of our patient cohort was about three times higher than the STS score.

At the end of the TAVI procedure, PAR was present in 113 (67.7%) and absent in 54 (32.3%) patients. PAR was graded as mild in 89 (53.3%), moderate PAR in 21 (12.6%), and moderate-to-severe PAR in 3 (1.8%) patients; severe residual PAR did not occur (13). No and mild PAR were equally distributed between both valves (84.1 vs. 87.4%, P = 0.6). Moderate-to-severe PAR occurred only with the MCV (3.4 vs. 0%). There were no significant differences between the two valve types regarding incidence, severity and quantitative evaluation of PAR by use of hemodynamic assessment (14). Corrective maneuvers had been performed in 24 cases during the procedure. Twenty-three patients underwent postdilatation with an improvement in PAR grade to < 2/4 in 13 (54%) of them and one patient with severe PAR due to low implantation of a MCV underwent postdeployment repositioning that resulted in PAR improvement to 1/4.

Hemodynamic assessment after TAVI. DAP was significantly lower in patients with PAR ≥ 2/4 (P < 0.001) and LVEDP was higher (P = 0.02), resulting in lower DPTI and therefore DPTI:SPTI for patients with PAR ≥ 2/4 (P < 0.001). Patients with < 2/4 and ≥ 2/4 PAR did not differ in postprocedural systolic aortic pressure and systolic LV pressure (Table 2).

There was a significant inverse correlation between DPTI:SPTI and PAR grading according to Sellers (P < 0.001) (Fig. 2). Also, DPTI:SPTI decreased with both decreasing ΔP_DAP-LVEDP and AR index (P < 0.001).

DPTI:SPTI and cardiovascular mortality in relation to PAR. As previously reported (14), the occurrence of moderate and moderate-to-severe PAR was associated with increased cardiovascular mortality at 30 days and 1 yr after TAVI (46 vs. 4% and 73 vs. 7%, respectively, P < 0.001) (Fig. 3A). Also, ΔP_DAP-LVEDP ≤ 18 mmHg (14) was associated with increased...
cardiovascular mortality at 30 days and 1 yr (21 vs. 6% and 32 vs. 13%, respectively, \( P = 0.001 \)). Patients with an AR index (20) < 25 also had increased cardiovascular mortality at 30 days and 1 yr (20 vs. 7% and 30 vs. 14%, respectively, \( P = 0.001 \)). The cause of death was cardiogenic shock/worsening heart failure (60%), cardiac arrest (20%), arrhythmia (15%), and myocardial infarction (5%).

The previously proposed DPTI:SPTI cutoff values for AR and subendocardial ischemia (8, 9, 13, 24, 26) were evaluated using receiver operator characteristic curve analysis. A cutoff point of 0.7 proved to be an excellent predictor of mortality with a sensitivity of 75%, a specificity of 100%, and an overall area under the curve of 0.96 (Fig. 4). Cardiovascular mortality at 30 days and 1 yr was increased in patients with DPTI \( \leq 0.7 \) over that in those with DPTI \( > 0.7 \) (42 vs. 2% and 63 vs. 3%, respectively, \( P < 0.001 \)). Patients with DPTI \( \leq 0.7 \) (\( n = 20 \)) had less 30-day and 1-yr cardiovascular survival than patients with DPTI \( > 0.7 \) (log rank < 0.001) (Fig. 3B).

Obviously, there was a relation between the Sellers criteria, \( \Delta P_{DAP-LVEDP} \), AR, and DPTI:SPTI for cardiovascular mortality: 83% of the patients with at least moderate PAR who died of cardiovascular causes had a DPTI:SPTI \( \leq 0.7 \), 83% of the patients with \( \Delta P_{DAP-LVEDP} \leq 18 \) mmHg who died of cardiovascular causes had a DPTI:SPTI \( \leq 0.7 \), and 85% of the patients with AR index < 25 who died of cardiovascular causes had a DPTI:SPTI \( \leq 0.7 \).

**Cardiac TnI elevation in relation to DPTI:SPTI.** Cardiac TnI peak elevation within 48 h after TAVI was significantly higher in patients with DPTI:SPTI \( \leq 0.7 \) than in those with DPTI:SPTI > 0.7 (6.9 \( \pm \) 3.4 vs. 1.4 \( \pm \) 1.8 ng/ml, respectively, \( P < 0.005 \)), whereas there was no significant difference between the two patient groups at baseline (0.06 \( \pm \) 0.2 vs. 0.08 \( \pm \) 0.16 ng/ml, respectively, \( P = 0.9 \)).

**PAR severity during follow-up.** Echocardiographic assessment of PAR severity during follow-up revealed no clinically relevant changes over time. For the ES bioprosthesis, no changes in PAR severity were observed during 3-mo and 1-yr clinical follow-up compared with the discharge examination. For MCV, a reduction of PAR severity was seen in 3.4% of patients with regression from initially mild PAR to absence of PAR. There was no increase in PAR severity over time.

**DISCUSSION**

In the present study, more than mild PAR occurred in 14.4% of patients and was associated with increased cardiovascular mortality. A decrease of DPTI:SPTI was related to the rise of PAR severity and increased cardiovascular mortality, suggest-

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PAR &lt; 2/4</th>
<th>PAR ( \geq 2/4 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>167</td>
<td>143</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>80.7 ( \pm ) 6.6</td>
<td>80.2 ( \pm ) 6.6</td>
<td>79.8 ( \pm ) 6.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>70 (41.9)</td>
<td>55 (38.5)</td>
<td>15 (62.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75.2 ( \pm ) 14.2</td>
<td>75 ( \pm ) 15.8</td>
<td>76.8 ( \pm ) 17.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166.2 ( \pm ) 8.3</td>
<td>165.4 ( \pm ) 8.5</td>
<td>170.4 ( \pm ) 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Logistic Euroscore, %</td>
<td>21.7 ( \pm ) 11.9</td>
<td>21.3 ( \pm ) 10.4</td>
<td>24.5 ( \pm ) 19.1</td>
<td>0.95</td>
</tr>
<tr>
<td>STS score, %</td>
<td>7.5 ( \pm ) 5.6</td>
<td>7.3 ( \pm ) 5.2</td>
<td>7.8 ( \pm ) 5.8</td>
<td>0.94</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.61 ( \pm ) 0.2</td>
<td>0.62 ( \pm ) 0.2</td>
<td>0.58 ( \pm ) 0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean transvalvular PG, mmHg</td>
<td>56.1 ( \pm ) 11.7</td>
<td>55.4 ( \pm ) 12</td>
<td>58.3 ( \pm ) 10.1</td>
<td>0.21</td>
</tr>
<tr>
<td>LVEF, n (%)</td>
<td>48 ( \pm ) 13</td>
<td>48 ( \pm ) 13</td>
<td>47 ( \pm ) 13</td>
<td>0.71</td>
</tr>
<tr>
<td>Aortic annulus diameter, mm</td>
<td>22.8 ( \pm ) 1.4</td>
<td>22.6 ( \pm ) 1.4</td>
<td>24.1 ( \pm ) 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>105 (62.9)</td>
<td>88 (61.5)</td>
<td>17 (70.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>4 (2.4)</td>
<td>2 (1.4)</td>
<td>2 (8.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>62 (37.1)</td>
<td>51 (35.7)</td>
<td>11 (45.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Prior heart surgery, n (%)</td>
<td>28 (16.8)</td>
<td>25 (17.5)</td>
<td>3 (12.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>25 (15.0)</td>
<td>22 (15.4)</td>
<td>3 (12.5)</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are \( n \) (%) or means \( \pm \) SD. PAR, paravalvular aortic regurgitation; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PG, pressure gradient; PVD, peripheral vascular disease (13).

### Table 2. Postprocedural hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>DPTI:SPTI &gt; 0.7</th>
<th>DPTI:SPTI ( \leq 0.7 )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>167</td>
<td>147</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Postprocedural SAP, mmHg</td>
<td>109.2 ( \pm ) 15.0</td>
<td>110 ( \pm ) 14</td>
<td>107 ( \pm ) 15</td>
<td>0.3</td>
</tr>
<tr>
<td>Postprocedural DAP, mmHg</td>
<td>51.3 ( \pm ) 7.6</td>
<td>53 ( \pm ) 9.0</td>
<td>37.2 ( \pm ) 56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postprocedural LVSP, mmHg</td>
<td>111.3 ( \pm ) 15.6</td>
<td>110.2 ( \pm ) 15</td>
<td>115 ( \pm ) 17</td>
<td>0.09</td>
</tr>
<tr>
<td>Postprocedural LVEDP, mmHg</td>
<td>4.2 ( \pm ) 9.8</td>
<td>5.3 ( \pm ) 9.0</td>
<td>37.2 ( \pm ) 56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPTI, mmHg</td>
<td>17.9 ( \pm ) 5.4</td>
<td>17.2 ( \pm ) 4.4</td>
<td>18.8 ( \pm ) 4.1</td>
<td>0.09</td>
</tr>
<tr>
<td>DPTI, mmHg</td>
<td>17.6 ( \pm ) 5.2</td>
<td>18.1 ( \pm ) 6.2</td>
<td>12.2 ( \pm ) 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DPTI:SPTI</td>
<td>1.04 ( \pm ) 0.4</td>
<td>1.1 ( \pm ) 0.2</td>
<td>0.58 ( \pm ) 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \Delta P_{DAP-LVEDP} ), mmHg</td>
<td>28.8 ( \pm ) 14.7</td>
<td>29.7 ( \pm ) 9.1</td>
<td>13.3 ( \pm ) 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic regurgitation index</td>
<td>29.1 ( \pm ) 10.1</td>
<td>28.4 ( \pm ) 6.5</td>
<td>14.1 ( \pm ) 7.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means \( \pm \) SD. DAP, diastolic aortic pressure; DPTI:SPTI, ratio of diastolic over systolic pressure time index; LVEDP, left ventricular end-diastolic pressure; LVDP, left ventricular diastolic pressure; LVSP, left ventricular systolic pressure; \( \Delta P_{DAP-LVEDP} \), pressure difference between DAP and LVEDP; SAP, systolic aortic pressure.
ing the presence of a myocardial supply and demand imbalance. Myocardial ischemia was also reflected by increased TnI in patients with significantly decreased DPTI:SPTI ratio.

Recent studies reported increased in-hospital and long-term mortality with moderate or severe PAR after TAVI (1, 11, 14, 20). AR results in an imbalance of myocardial demand to supply to the extent that there is ischemia, particularly in the subendocardium (13, 24). In the present study the propensity to ischemia secondary to TAVI-associated PAR was estimated from the ratio of DPTI:SPTI. Reduction of the DPTI:SPTI ratio in patients with PAR after TAVI appeared to be related to the hemodynamic consequences of the regurgitation, as reflected by the Sellers grade or more recent indexes such as the AR index or \( \frac{\Delta P_{DAP-LVEDP}}{H11349} \).

The characteristics of the self-expandable nitinol frame are a potential explanation for the reduction of PAR severity in 3.4% of patients during follow-up echocardiography (from initially mild PAR to absence of PAR), however, without clinical relevance for the study patients.

A critical DPTI:SPTI value has been established through the response to sudden exercise in apparently healthy men. No ischemic ST changes were seen with treadmill testing when the DPTI:SPTI was 0.6, whereas ischemia on the ECG only appeared with ratios of 0.45 (2). For AR, a critical DPTI:SPTI of 0.6 was proposed in consideration for the greater extravascular component of coronary resistance in the dilated and possibly hypertrophied heart (8, 9, 26). We found a DPTI:SPTI of 0.7 to predict cardiovascular mortality from PAR after TAVI, and a causal relation to ischemia was suggested by the higher values of peak TnI after TAVI in patients with DPTI:SPTI \( \leq 0.7 \). DPTI:SPTI may therefore more accurately predict cardiovascular mortality from PAR after TAVI and be helpful in decision making on countermeasures such as repositioning using the “snare technique,” postdilatation, or valve-in-valve implantation, especially in borderline cases (15, 20).

Limitations. Conditions other than PAR that are frequently encountered in TAVI patients (e.g., reduced LV ejection fraction, concomitant mitral regurgitation, diastolic dysfunction, and ventricular hypertrophy with decreased compliance) can also contribute to increased LVEDP and consequently reduced \( \Delta P_{DAP-LVEDP} \), AR index, and lower DPTI:SPTI. In addition, increased LVEDP resulting in increased left atrial pressure and
thus pulmonary edema could also contribute to a worse outcome, although this remains speculative. Due to the retrospective character of this study, only standard laboratory data were available. Therefore, the use of high-sensitive TnI or TnT as more precise laboratory parameter regarding possible subendocardial ischemia in patients with significantly decreased DPTI:SPTI ratio was not possible. Since changes in serial blood gas testing during the procedure were corrected by the attending anesthesiologist, no significant changes with TAVI were observed. Further prospective studies are needed to explore the hypothesis of the present study more mechanistically.

Conclusion. Angiographically moderate and moderate-to-severe PAR after TAVI was observed in 14.4% of patients and associated with increased cardiovascular mortality. A DPTI: SPTI ratio ≤ 0.7 predicts cardiovascular mortality in patients with PAR after TAVI, possibly reflecting myocardial ischemia as the underlying mechanism.

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DISCLOSURES

M. Thielmann and P. Kahler are clinical proctors for Edwards Lifesciences, Inc. Holger Eggbeech is a clinical proctor for Medtronic, Inc. The other authors report no conflict of interest.

AUTHOR CONTRIBUTIONS


REFERENCES


