ORIGINAL RESEARCH

Time-Integrated Aortic Regurgitation Index Helps Guide Balloon Postdilation During Transcatheter Aortic Valve Replacement and Predicts Survival

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***Background*—**Balloon postdilation (BPD) has emerged as an effective strategy to reduce paravalvular regurgitation (PVR) during transcatheter aortic valve replacement (TAVR). We investigated the utility of a time-integrated aortic regurgitation index (TIARI) to guide balloon postdilation (BPD) after valve deployment.

***Methods and Results*—**All consecutive patients who had echocardiography, aortography, and hemodynamic tracings recorded immediately after valve deployment during TAVR were included in the study. Catheter-derived invasive hemodynamic parameters were calculated offline. Among 157 patients who underwent TAVR, 49 (32%) patients required BPD to reduce significant PVR after valve deployment. Two experienced operators decided whether the patients required BPD for significant PVR. Median TIARI measured immediately after valve deployment was significantly lower in patients who required BPD when compared with patients who did not require BPD ($P<0.001$). In a multivariable analysis, lower TIARI (odds ratio: 0.81; $P=0.003$) and higher PVR grade on aortography and echocardiography ($P<0.001$ for both) were associated with BPD. Adding TIARI to echocardiography and aortographic PVR assessment resulted in a significant increase in global χ^2 ($P<0.001$), an integrated discrimination index of 9% ($P=0.002$), and combined C-statistics of 0.99 for predicting BPD. Higher TIARI after valve deployment was associated with better survival (hazard ratio: 0.94, $P=0.014$), while other hemodynamic and imaging parameters did not predict mortality after TAVR.

***Conclusions*—**Among patients undergoing TAVR, a TIARI measured immediately after valve deployment adds incremental value to guide BPD over aortography and echocardiography. Higher residual TIARI is associated with better survival after TAVR. **(*J Am Heart Assoc*. 2019;8:e012430. DOI: 10.1161/JAHA.119.012430.)**

Key Words: hemodynamics • paravalvular regurgitation • survival • time-integrated aortic regurgitation index • transcatheter aortic valve implantation • transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is now a widely accepted alternative to surgical replacement among patients with symptomatic severe aortic stenosis in patients with intermediate-to-high surgical risk.[1,2] However, significant residual paravalvular regurgitation (PVR) after TAVR continues to be linked to higher short-and medium-term mortality.[3–5] Hence, current practices include placing a second valve or balloon postdilation (BPD) to reduce PVR.[6] Indeed, a recent meta-analysis demonstrated that BPD was associated with a 15-fold reduction in the incidence of moderate-to-severe PVR among patients undergoing TAVR.[7] However, currently there is a lack of consensus on the intraoperative parameters guiding BPD after valve deployment during TAVR. Part of the challenge lies in the fact that despite improvements in imaging modalities, accurate intraoperative quantification of PVR remains a clinical dilema. The evaluation of PVR is challenging with the use of intraprocedural transesophageal echocardiography (TEE) because of the following considerations: (1) it is difficult to align the aortic annulus using TEE; and (2) acoustic shadows from the prosthetic valve or residual calcium can preclude PVR assessment.[8] Moreover, recent studies have demonstrated that use of minimal to no sedation during TAVR is associated with better hemodynamic stability, fewer respiratory and cardiovascular risks, shorter TAVR duration, quicker

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An accompanying Video S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012430

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Received February 22, 2019; accepted May 24, 2019.

Clinical Perspective

What Is New?

- The results of our study demonstrate that a catheter-based hemodynamic parameter—time-integrated aortic regurgitation index—could help guide management of significant paravalvular regurgitation using balloon postdilatation.
- While time-integrated aortic regurgitation index predicted mortality after transcatheter aortic valve replacement, other imaging modalities did not.

What Are the Clinical Implications?

- Real-time assessment of paravalvular regurgitation after valve deployment is necessary to guide management of paravalvular regurgitation.
- The results of our study indicate the need for operators to utilize a more quantitative index (eg, time-integrated aortic regurgitation index) to quantify paravalvular regurgitation intraoperatively.

identification of any neurological sequelae, and lower complication rates along with shorter hospital stay.[8–10] These observations have led to increased adoption of minimal sedation during TAVR and precluded the use of TEE for evaluation of PVR. Other studies seem to suggest that angiography correlates better with PVR than echocardiography.[11] Although angiographic evaluation of PVR has its advantages, it has higher intra- and interobserver variability and moderately correlated with PVR assessed using cardiac magnetic resonance imaging.[12,13] Indeed, the consensus document from the Valve Academic Research Consortium also failed to mention a criterion standard test to measure PVR.[14] Hence, recent reports have suggested the use of a multimodality approach: combining imaging and hemodynamic indices for accurate assessment of PVR.[6,15]

Sinning et al demonstrated that hemodynamic assessment, specifically aortic regurgitation index (ARI), provided improved estimation of PVR severity and demonstrated prognostic significance.[6] This index was further modified by integrating systolic time and diastolic time. The resulting time-integrated aortic regurgitation index (TIARI) was less susceptible to changes in heart rate.[16] Höllriegel et al[17] then demonstrated that another hemodynamic index (DPTI) generated by dividing the duration of diastole from the area between aortic (Ao) and left ventricular (Lv) pressure-time curves showed a stepwise decrease in value with increasing PVR when adjusted for scaling of pressure-time curve and systolic blood pressure. However, to date there are no data on the utility of catheter-derived hemodynamic indices and intraoperative imaging modalities to guide BPD among patients undergoing TAVR. Consequentially, we hypothesized that combining a catheter-based hemodynamic index (TIARI) with intraoperative echocardiography and angiography would be better to guide BPD when compared with any modality alone. We also investigated the prognostic value of residual TIARI after TAVR.

Methods

The data that support the findings of the study are available from the corresponding author upon reasonable request.

Patient Selection

We selected all consecutive patients from our prospective institutional TAVR registry who underwent TAVR for severe aortic stenosis between October 2015 and August 2016 and had analyzable hemodynamic tracings recorded immediately after valve deployment. The study protocol was approved by the Cleveland Clinic Institutional Review Board with a waiver of informed consent and data were de-identified.

Echocardiographic Evaluation of Paravalvular Regurgitations

Transthoracic echocardiography or TEE was performed immediately after valve deployment. Three consecutive cardiac

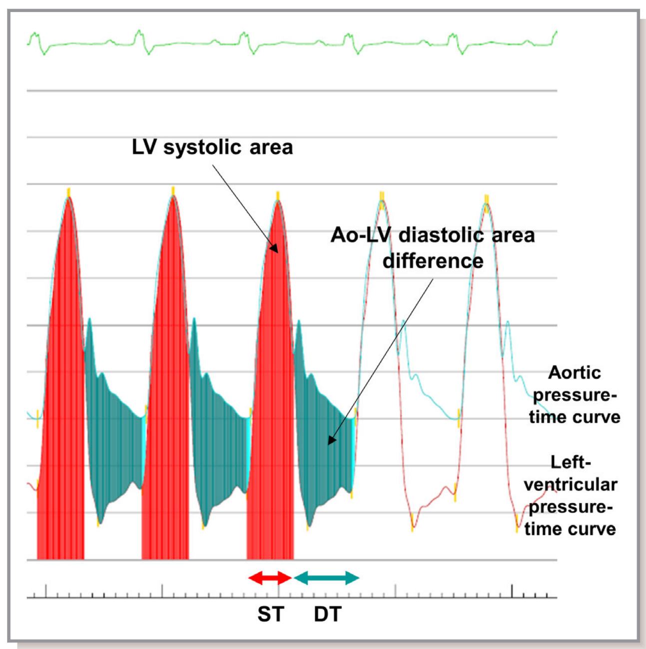

Figure 1. Hemodynamic assessment of paravalvular regurgitation after valve deployment. Simultaneous measurement of LV and aortic pressure–time curves. The area between aortic and LV pressure–time curves (dark blue) was measured during diastole to calculate TIARI. Ao indicates aortic pressure–time curves; DT, diastolic time; LV left ventricular; ST, systolic time; TIARI, time-integrated aortic regurgitation index.

Table 1. Baseline Characteristics of 157 Patients With Analyzable Postvalve Deployment Hemodynamic Tracings

	n=157	BPD (+) N=49	BPD (−) N=108	*P* Value*
Age (y)	81±9	80±9	82±9	0.38
Male	86 (55%)	21 (43%)	65 (60%)	0.04
Height (cm)	167±11	165±12	168±10	0.20
Weight (Kg)	81±18	78±15	82±19	0.50
Creatinine	1.4±0.8	1.34±0.71	1.35±0.78	0.99
NYHA ≥3	71 (45%)	24 (49%)	47 (44%)	0.52
Heart failure	42 (28%)	12 (24%)	30 (28%)	0.72
CAD	71 (45%)	27 (55%)	44 (41%)	0.09
Prior MI	32 (20%)	11 (22%)	21 (19%)	0.66
Valve size				0.43
23 mm	50 (32%)	15 (31%)	35 (32%)	
26 mm	55 (35%)	16 (33%)	39 (36%)	
29 mm	44 (28%)	13 (27%)	31 (29%)	
Valve type				<0.001
Sapien 3	128 (82%)	35 (71%)	93 (86%)	
Sapien XT	5 (3%)	0	5 (5%)	
Core valve	17 (11%)	12 (24%)	5 (5%)	
Others	7 (4%)	2 (4%)	5 (5%)	
Hemodynamic, aortographic, and echocardiographic variables				
Pre TAVR				
SAP	113 (98–133)	126 (103–138)	112 (97–129)	0.07
DAP	51 (43–60)	51 (45–61)	50 (42–60)	0.56
LVSP	156 (140–175)	161 (143–177)	152 (138–173)	0.10
LVDP	8 (4–12)	9 (4–13)	8 (4–12)	0.61
LVEDP	17 (14–23)	18 (14–23)	17 (14–21)	0.40
ARI	28 (22–36)	27 (22–35)	30 (22–37)	0.47
TIARI	38 (33–47)	39 (34–44)	38 (32–48)	0.75
DPTI	40 (35–45)	37 (34–44)	41 (35–46)	0.26
Echo AR grade > mild	38 (24%)	11 (22%)	27 (25%)	0.77
Postvalve deployment				
SAP	137 (122–157)	141 (123–159)	136 (121–155)	0.55
DAP	55 (48–63)	52 (47–61)	56 (49–65)	0.09
LVSP	138 (121–158)	144 (127–160)	137 (120–156)	0.25
LVDP	11 (7–15)	12 (8–16)	10 (7–14)	0.06
LVEDP	20 (15–24)	21 (17–26)	19 (14–23)	0.037
ARI	26 (21–31)	22 (18–28)	27 (22–32)	<0.001
TIARI	46 (41–52)	44 (38–48)	48 (44–54)	<0.001
DPTI	35 (30–39)	31 (28–37)	36 (32–40)	<0.001
Aortographic PVR grade > mild	35 (22%)	27 (55%)	8 (7%)	<0.001

Continued

Table 1. Continued

	n=157	BPD (+) N=49	BPD (−) N=108	*P* Value*
Echocardiographic PVR grade > mild	44 (28%)	42 (86%)	2 (2%)	<0.001

Data are number (%), mean±SD, or median (interquartile range). ARI indicates aortic regurgitation index; BPD, balloon postdilation; CAD, coronary artery disease; DAP, Diastolic Aortic Pressure; DPTI, diastolic pressure time index; LVDP, left ventricular diastolic pressure; LVEDP, left ventricular end-diastolic pressure; LVSP, Left Ventricular Systolic Pressure; MI, myocardial infarction; NYHA, New York Heart Association; PVR, paravalvular regurgitation; SAP, Systolic Aortic Pressure; TAVR, transcatheter aortic valve replacement; TIARI, time-integrated aortic regurgitation index.
**P* value indicates comparison between BPD (+) and BPD (−) Groups.

cycles were acquired and stored. PVR was graded offline by a level-III-trained echocardiographer (J.B.) blinded to all other clinical, hemodynamic, and imaging data, according to the updated Valve Academic Research Consortium consensus document criteria.[14] Assessment of PVR was done using simple color Doppler flow mapping, acquired in the parasternal long-axis and apical 3- and 5-chamber views (in each view color gain was carefully set to demonstrate maximal jet by avoiding color Doppler speckles). The degree of PVR was divided into "no PVR" (grade 0)=no regurgitating jet; "mild PVR" (grade I) =total regurgitating jet area <2.2 cm^2; "moderate PVR" (grade II)=total regurgitating jet area 2.2–4.2 cm^2; and "severe PVR" (grades III–IV)=total regurgitating jet area >4.2 cm^2.

Angiographic Evaluation of Paravalvular Regurgitations

Aortography was performed in biplane views including right anterior oblique 30° and left anterior oblique 60° view after valve deployment, by injecting 20 mL of 50:50 diluted dye in 1 s. Aortographic grading of PVR (grades 0–IV) was done by an experienced angiographer (K.S.) who was blinded to all clinical, echocardiographic, and hemodynamic data according to the criteria described by Sandler et al; grade 0 (no PVR)=no regurgitating contrast into the left ventricle (LV); grade I (mild PVR)=a small amount of contrast enters the LV in diastole and is cleared with each beat; grade II AR (moderate PVR)=faint opacification of the entire LV; grade III (moderately severe PVR): opacification of the entire LV to the same degree as the ascending aorta; grade IV (severe PVR): complete, dense opacification of the LV on the first beat and more densely opacified than the ascending aorta.[18]

Hemodynamic Measurements

Detailed derivation of ARI, TIARI, and DPTI have been described before.[16,17,19] Briefly: on achieving stable hemodynamics after deploying a transcatheter valve, LV and Ao invasive pressures were measured simultaneously. Pre-BPD and post-BPD Ao and LV systolic and diastolic pressures were quantified using AXIOM Sensis XP hemodynamic software (Siemens AG, Forcheim, Germany). Area between Ao and LV pressure-time curves during diastole were measured. Area under LV pressure-time curve during systole was also measured. Following pre-BPD and post-BPD, hemodynamic indices were computed offline by a blinded reviewer (R.G.) as follows (Figure 1):

1. ARI=[(Ao diastolic pressure−LV end diastolic pressure)/Ao systolic pressure]×100.
2. TIARI=[(diastolic area difference/diastolic duration)/(LV systolic area/systolic duration)]×100.
3. DPTI=[(DPTI diastolic area difference/DPTI diastolic duration)/(Ao systolic pressure)]×100.

Balloon Postdilation After Valve Deployment

The intraoperative requirement for BPD after transcatheter valve deployment was decided by 2 experienced TAVR operators (S.K., A.K.) based on their expert clinical judgment.

Table 2. Changes in Hemodynamic, Aortographic, and Echocardiographic PVR Assessment Pre- and Post-BPD Among 49 Patients Who Required BPD After Valve Deployment

	Postvalve Deployment	Post BPD	*P* Value
ARI	22 (19–29)	25 (22–30)	<0.001
TIARI	44 (38–48)	46 (43–52)	<0.001
DPTI	31 (28–37)	34 (32–38)	<0.001
Aortographic PVR grade: (mild)*	5	4	0.74
Aortographic PVR grade (>mild)*	23	0	<0.001
Echocardiographic PVR grade: (mild)*	9	5	0.21
Echocardiographic PVR grade: (>mild)*	20	2	<0.001

Data are number or median (interquartile range). ARI indicates aortic regurgitation index; BPD, balloon postdilation; DPTI, diastolic pressure time index; PVR, paravalvular regurgitation; TIARI, time-integrated aortic regurgitation index.
*Number of patients.

These operators did not have calculated TIARI index for decision making and all hemodynamic indices were calculated offline later as described above.

Statistical Analysis

Continuous data were expressed as mean±SD when normally distributed, or median (interquartile range) otherwise. An unpaired *t* test or Mann–Whitney test was used to compare hemodynamic, angiographic, and echocardiographic variables as appropriate. We performed logistic regression model analysis to assess the association between BPD and hemodynamic, angiographic, and echocardiographic assessment of PVR. In the multivariable model, all relevant variables (ARI, TIARI, DPTI, and PVR grade by aortic root angiography or echocardiography) were entered in a forward stepwise manner. Optimal cutoff value of TIARI to predict BPD was obtained from the receiver operating characteristic curve. We also calculated C-statistics, continuous net reclassification improvement, and integrated discrimination improvement from a logistic regression model.[18,19] Incremental prognostic value was also assessed with a statistically significant

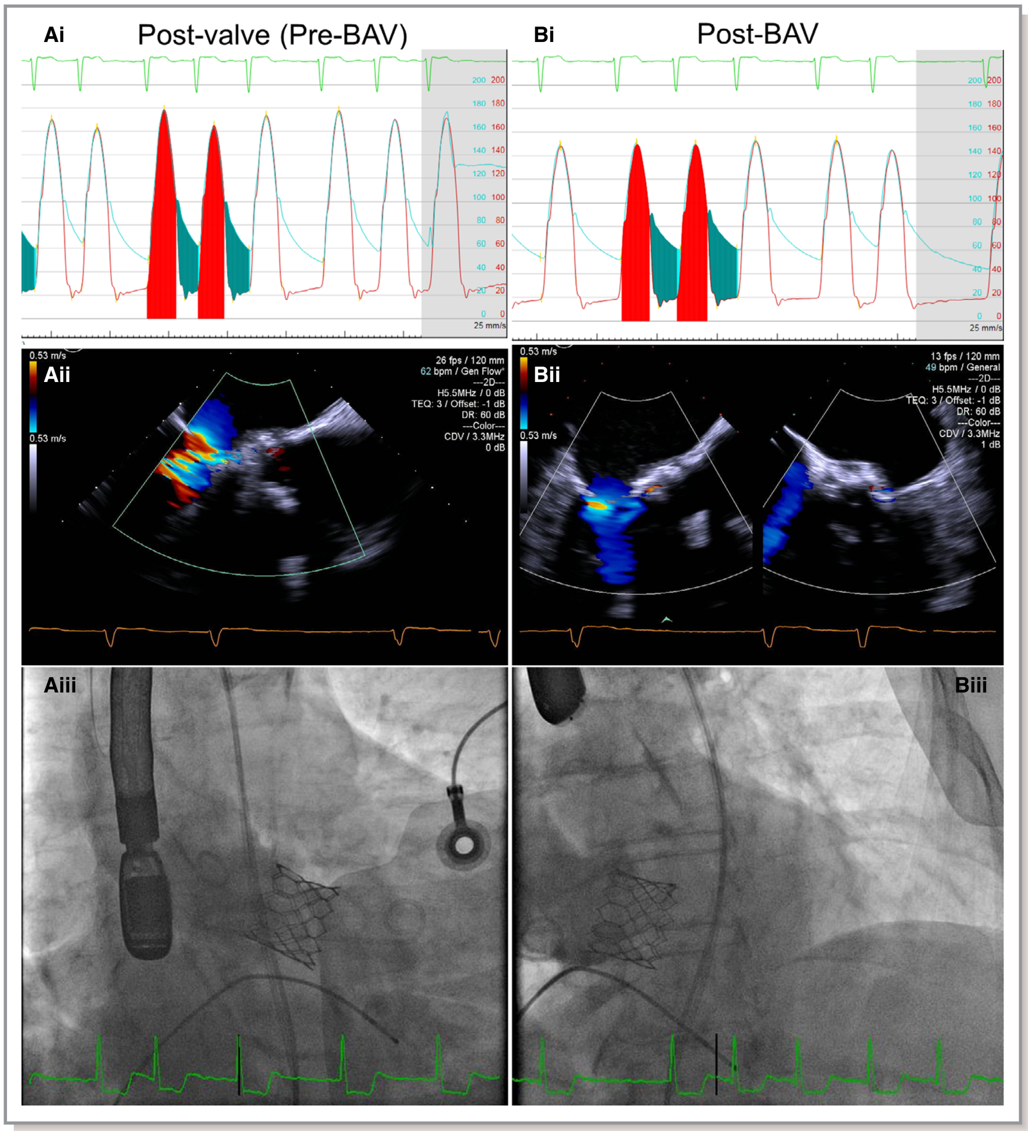

Figure 2. Hemodynamic evaluation in a patient with significant paravalvular regurgitation after valve deployment (**A**). Transesophageal echocardiography (**Aii**) and angiography (**Aiii**) demonstrated moderate PVR after valve deployment. Simultaneous measurement of LV and aortic pressure–time curve demonstrated a TIARI of 37.9 (**Ai**). After BPD, TIARI increased to 43.6 (**Bi**); echocardiography (**Bii**) and angiography showed trivial PVR (**Biii**). ARI indicates aortic regurgitation index; BPD, balloon postdilation; DPTI, diastolic pressure time index; LV, left ventricular; PVR, paravalvular regurgitation; TIARI, time-integrated aortic regurgitation index.

increase in global χ^2. Agreements between continuous variables were determined using Spearman's rank correlation coefficient. A Cox proportional hazards model was constructed and an estimated hazard ratio was reported to investigate the prognostic value of residual PVR as measured by all hemodynamic and imaging modalities. The assumption of proportional hazards was assessed based on plots of Schoenfeld residuals against time. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using JMP 10.0 (SAS Institute Inc., Cary, NC) and R software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

We identified 247 consecutive patients with severe aortic stenosis who underwent TAVR from October 2015 to August 2016. Baseline features of 157 patients who had catheter-derived hemodynamic tracings recorded immediately after valve deployment are shown in Table 1. A total of 88 (56%) patients had TEE after valve placement while the rest had transthoracic echocardiography. Almost all (n=152, 98%) patients in this cohort had an aortogram recorded after valve placement.

In total, 49 (31%) patients required BPD to reduce significant PVR after valve deployment. No patient required a second valve deployment after TAVR to reduce severe PVR.

Most procedures were performed using the Edwards SAPIEN 3 valve (n=128, 82%) while the XT valve was used in 5 patients (3%) and the Medtronic Core Valve in 17 patients (11%), St Jude Medical Portico in 2 patients, Lotus Valve System in 1 patient, and Direct Flow Medical valve system in 4 patients. When compared with patients requiring BPD, patients who did not require BPD demonstrated similar pre-TAVR hemodynamic and echocardiographic estimations. Among patients who required BPD, we observed significantly lower ARI, TIARI, and DPTI after valve deployment (*P*<0.001 for all) when compared with patients who did not require BPD. Furthermore, ARI, TIARI, and DPTI significantly increased along with decrease in the number of patients with severe aortographic and echocardiographic PVR after BPD (*P*<0.001 for all) (Table 2). Figure 2 (Video S1) demonstrates a patient with low TIARI after valve deployment along with moderate PVR on TEE and aortography. TIARI increased after BPD along with reduction of PVR by both aortography and TEE.

Incremental Ability of Hemodynamic Assessment to Predict BPD

Among 157 patients, lower ARI, TIARI, and DPTI along with higher PVR grade on aortography or echocardiography after valve deployment predicted BPD (Table 3). In multivariable logistic regression analysis, lower TIARI (odds ratio [OR]: 0.81, *P*=0.003) after valve deployment along with higher PVR grade by aortography (OR: 133, *P*<0.001) and echocardiography (OR: 56, *P*<0.001) were selected to predict BPD by forward stepwise model. Interestingly, ARI and DPTI were not selected to predict BPD in the multivariable analysis.

The optimal cut-off value of TIARI (computed after valve deployment) to predict BPD was found to be 45.5 (C-statistics=0.74, sensitivity=75%, specificity=65%) (Table 4). Adding TIARI to aortography and echocardiography improved the prediction model with integrated discrimination improvement of 9% (*P*=0.002) and combined C-statistics of 0.99 to predict BPD (Table 5, Figure 3). Similarly, adding TIARI to echocardiography and aortography also resulted in a significant increase in the global χ^2 for the model predicting BPD (*P*<0.001 for TIARI) (Figure 4).

Association of Hemodynamic Variables With PVR Severity Using Imaging Modalities

All calculated hemodynamic indices (ARI, TIARI, and DPTI) showed weak but significant correlation with PVR severity on aortographic evaluation, while only TIARI and DPTI showed

Table 3. Univariable and Multivariable Analysis for Predicting BPD Postvalve Deployment

	Univariable			Multivariable	
	OR (95% CI)	*P* Value	C Statistics	OR (95% CI)	*P* Value
ARI	0.90 (0.83–0.95)	<0.001	0.71	...	...
TIARI	0.89 (0.84–0.94)	<0.001	0.74	0.81 (0.69–0.92)	0.003
DPTI	0.87 (0.81–0.94)	<0.001	0.72	...	...
Aortographic PVR grade	63.0 (16.0–435.8)	<0.001	0.96	132.8 (14.8–5145.6)	<0.001
Echocardiographic PVR grade	33.7 (11.4–126.1)	<0.001	0.91	56.3 (7.8–966.3)	<0.001

ARI indicates aortic regurgitation index; BPD, balloon postdilation; DPTI, diastolic pressure time index; PVR, paravalvular regurgitation; OR, odds ratio; TIARI, time-integrated aortic regurgitation index.

Table 4. Test Characteristics for Predicting BPD After Valve Deployment

	C-Statistics	Sen.	Spec.	PPV	NPV
TIARI <45.5	0.74	0.75	0.65	40%	89%
Aortography >1.0	0.96	0.94	0.94	83%	98%
Echo >1.0	0.91	0.88	0.86	67%	96%
Echo+aortography	0.98	0.91	0.91	78%	99%
Echo+aortography+TIARI	0.99	1.00	0.95	82%	100%
TIARI+aortography	0.98	0.91	0.94	83%	97%

BPD indicates balloon postdilation; DPTI, diastolic pressure time index; NPV, Negative Predictive Value; PPV, Positive Predictive Value; Sen, Sensitivity; Spec, Specificity; TIARI, time-integrated aortic regurgitation index.

significant correlation with echocardiographic PVR grade (Table 6).

Among 157 patients with pre- and postvalve deployment hemodynamic assessment, 77 patients had no or trivial PVR by echocardiography before TAVR. Among these 77 patients, changes in TIARI between pre- and postvalve deployment (ΔTIARI) was still significantly associated with BPD (*P*=0.021, OR 0.92, 95% CI: 0.85–0.99).

To further investigate the value of TIARI in diagnosing PVR after valve placement, we divided the patient cohort based on pre- and post-TAVR echocardiographic PVR grades. In patients with no PVR before TAVR, who also did not demonstrate any PVR by echocardiography postvalve deployment, the median TIARI increased from 41 (36–47) to 47 (43–55) postvalve deployment (Table 7). Only 2 (5%) of these patients required BPD after valve deployment. In addition, among patients with no PVR before TAVR who then developed at least mild PVR postvalve deployment, the median TIARI increased from 37 (33–42) to 44 (38–52) after valve deployment. As many as 20 (74%) patients required BPD after valve deployment in this subgroup of patients. After valve deployment, TIARI increased from 38 (31–49) to 48 (44–53) in patients with at least mild echocardiographic PVR before undergoing a TAVR; these patients then had no PVR postvalve deployment by echocardiography. Only 3 (5%) of these patients required a BPD after valve placement. Furthermore, among patients with some degree of echocardiographic grade PVR before TAVR, who then had some degree of PVR after valve deployment, TIARI increased from 37 (33–47) to 45 (40–50) postvalve deployment. Again, 22 (71%) in this group required a BPV postvalve deployment. Overall, patients with no PVR by echocardiography postvalve deployment demonstrated higher median TIARI (47 [43–5] versus 45 [38–50], *P*=0.007) after valve deployment and required BPD less often (5 [5%] versus 41 [72%], *P*<0.001) when compared with patients who demonstrated PVR after valve deployment.

After valve deployment, 70 patients (45%) had low TIARI (TIARI ≤45.5) and 87 patients (55%) had TIARI >45.5. When we performed logistic regression analysis to determine the pre-TAVR variables associated with low TIARI after valve deployment, there were no significant associations between preprocedural PVR severity and postvalve low TIARI. In multivariable logistic regression analysis, higher preprocedural Ao systolic pressure (OR 1.04, 95% CI 1.02–1.06, *P*<0.001), lower Ao diastolic pressure (OR 0.89, 95% CI 0.84–0.94, *P*<0.001), and higher preprocedural left ventricular end-diastolic pressure (OR 1.11, 95% CI 1.04–1.19, *P*<0.001) were found to predict low TIARI.

Association of Hemodynamic Variables With Prognosis

Among 157 patients with hemodynamic tracings after valve deployment, the median follow-up period was 605 days (interquartile range: 520–689) and 22 patients (16%) died. To accurately investigate the association of PVR with mortality, we measured PVR using imaging and hemodynamic modalities after valve deployment in patients who did not require BPD. In patients who required BPD, PVR assessment using imaging and hemodynamic modalities was done after BPD. In Cox proportional hazards model analysis, only higher residual TIARI after TAVR significantly predicted better survival rates (hazard ratio 0.94, *P*=0.023; Table 8), while other hemodynamic parameters (ARI, DPTI) were not associated with mortality. PVR grade by angiography or echocardiography were also not predictive of mortality after TAVR. TIARI predicted mortality even after adjusting for possible confounding factors (hazard ratio 0.94, 95% CI: 0.89–0.99, *P*=0.014).

Table 5. Comparison of the C-Statistics, NRI, and IDI of Echocardiography Versus Adding Aortography and TIARI in Predicting BPD

	C-Statistics	*P* Value	NRI (95% CI)	*P* Value	IDI (95% CI)	*P* Value
Echo	0.91	0.004	0.30 (0.09–0.50)	0.004	0.27 (0.17–0.38)	<0.001
Echo+aortography	0.98	0.12	0.08 (−0.001 to 0.17)	0.07	0.09 (0.03–0.15)	0.002
Echo+aortography+TIARI	0.99					

BPD indicates balloon postdilation; IDI, integrated discrimination improvement; NRI, net reclassification improvement; TIARI, time-integrated aortic regurgitation index.

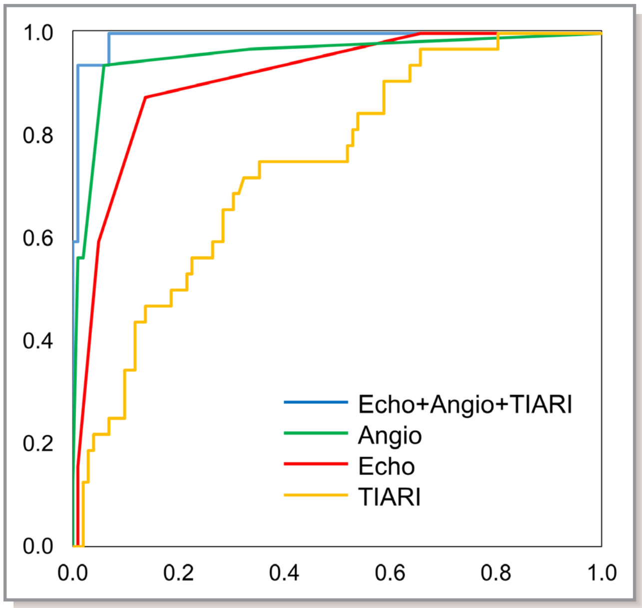

Figure 3. ROC curves showing additive value of TIARI to predict BPD postvalve deployment. Adding TIARI to the conventional evaluation by angiography and echocardiography increased the C statistics to 0.99.; BPD indicates, balloon postdilation; ROC, receiver operating characteristic; TIARI, time-integrated aortic regurgitation index.

Discussion

In patients undergoing TAVR, we analyzed intraoperative hemodynamic tracings and echocardiographic and aortographic images immediately after valve deployment and demonstrate that (1) all catheter-derived hemodynamic indices (ARI, TIARI, and DPTI) were significantly lower in patients who required BPD when compared with those who did not require BPD. (2) ARI, TIARI, and DPTI significantly increased along with decrease in aortographic and echocardiographic PVR grade after BPD. (3) Lower TIARI after valve deployment, along with higher PVR grade as measured by aortography and echocardiography, were associated with BPD after valve deployment. (4) A combination of TIARI and PVR grading by echocardiography and aortography demonstrated the best test characteristics to predict BPD with a positive predictive value of 82% and a negative predictive value of 100%. (5) Lower residual TIARI after TAVR independently predicted higher risk of mortality.

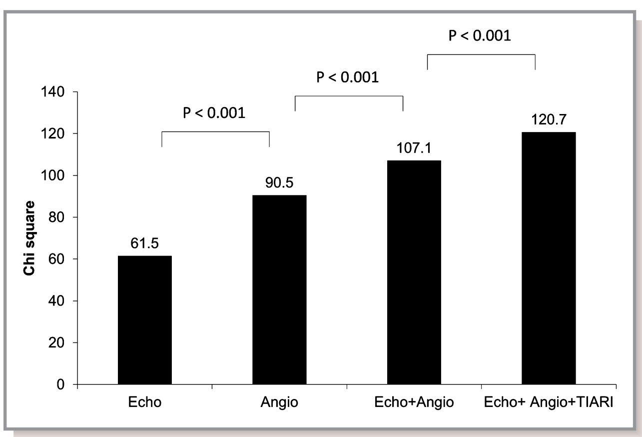

Figure 4. Incremental value of TIARI to predict BPD after valve deployment. BPD indicates balloon postdilation; TIARI, time-integrated aortic regurgitation index.

Clinical Utility of Hemodynamic Assessment in Patients Undergoing TAVR

Hemodynamic assessment is becoming an integral part of the TAVR procedure in the cardiac catheterization laboratory.[20] In a cohort of patients with high and prohibitive risk, who underwent TAVR, Bugan et al[16] observed that both ARI and TIARI decreased proportionately with increasing severity of PVR. Although the ARI is limited by factors such as heart rate, TIARI is relatively more resistant to patient-specific variables.[16,19] Indeed, we demonstrate for the first time that a catheter-derived hemodynamic index, TIARI, can provide real-time intraoperative information to identify patients who will require BPD after valve deployment. In addition, TIARI provided incremental diagnostic value over echocardiography and aortography by identifying additional patients who required BPD for clinically significant PVR even after imaging evaluation. Importantly, we show that by combining imaging modalities with hemodynamic assessment, we can rule out the need for BPD for significant PVR after valve deployment.

Prognostic Value of Hemodynamic Indices Among Patients Undergoing TAVR

In patients undergoing TAVR, moderate-to-severe PVR after prosthetic aortic valve deployment is a frequent complication associated with adverse outcomes and might be caused by (1) underexpanded prosthetic stent frame; (2) inadequate apposition against the native aortic annulus such as in heavily calcified cusps; (3) patient–prosthetic mismatch; and (4)

Table 6. Spearman Rank Correlation Coefficient Between Hemodynamic Variables and Echocardiographic and Aortographic PVR Grade

	vs Aortogram		vs Echocardiogram	
	ρ	*P* Value	P	*P* Value
ARI	−0.24	0.005	−0.16	0.06
TIARI	−0.26	0.003	−0.18	0.04
DPTI	−0.24	0.006	−0.21	0.02

ARI indicates aortic regurgitation index; DPTI, diastolic pressure time index; PVR, paravalvular regurgitation; TIARI, time-integrated aortic regurgitation index.

Table 7. Study Subgroup Stratified by Echocardiographic PVR Assessment

Study Subgroup	N	BPD	Prevalve TIARI	Postvalve TIARI	Post-TAVR TIARI
PrePVR−postPVR−	42	2 (5%)	41 (36–47)	47 (43–55)	47 (43–55)
PrePVR−postPVR+	27	20 (74%)	37 (33–42)	44 (38–52)	46 (44–53)
PrePVR+postPVR−	57	3 (5%)	38 (31–49)	48 (44–53)	48 (44–53)
PrePVR+postPVR+	31	22 (71%)	37 (33–47)	45 (40–50)	46 (40–51)
P value			0.37	0.011	0.73

BPD indicates balloon postdilation; PVR, paravalvular regurgitation; TAVR, transcatheter aortic valve replacement; TIARI, time-integrated aortic regurgitation index.

inappropriate implantation depth.[21] We demonstrate that hemodynamic assessment of residual PVR among patients undergoing TAVR might be of prognostic value. Sinning et al[22,23] demonstrated that patients with low post-TAVR ARI had a higher 1-year mortality rate. Additionally, Collas et al[19] compared hemodynamic measurements with echocardiographic and aortographic assessment of PVR after TAVR in a prospective cohort of 111 high-risk patients. These authors found no concordant relationship between ARI and echocardiographic and angiographic assessment of post-TAVR PVR. Furthermore, no prognostic information was found by assessing PVR by angiography or by ARI. In contrast, echocardiographic grading of PVR showed high observer reproducibility and provided prognostic value in selecting patients with decreased survival at 1 year.[19] Of note, these studies were done purely on self-expandable transcatheter valves and generally among higher-risk patients undergoing TAVR. More recently, DPTI was found to be the strongest predictor of 1-year mortality among 362 patients who underwent TAVR during the years 2009 to 2012 using either self-expandable or balloon-expandable valves.[17] However, the above studies did not investigate the value of catheter-derived hemodynamic indices to guide effective treatment strategies of PVR such as BPD. Our cohort of patients includes a very contemporary population of high-, low-, and intermediate-risk patients, who received valves with improved designs. Hence, it is probably not surprising that no patients had a residual PVR that was graded as "severe" by either echocardiography or aortographic after valve deployment in our study. Furthermore, only 2 patients had moderate PVR by echocardiography, while none had moderate PVR by aortography after valve deployment. Consequently, it is important to note that only residual TIARI predicted significant all-cause mortality after TAVR. Indeed, the degree of PVR with the newer generation valves might be too low to be accurately diagnosed by echocardiography or angiography, and hence we need a more quantitative assessment of PVR as provided by a catheter-based hemodynamic index that could be obtained in real time as the procedure is performed.[24]

Limitations

While we selected patients from our prospective institutional TAVR registry, all hemodynamic indices were calculated offline in retrospect. Final analysis was done only on 157/247 patients who had catheter-derived hemodynamic tracings

Table 8. Cox Proportional Hazards Model for Mortality

	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (y)	1.01 (0.96–1.07)	0.65	···	···
Male	0.95 (0.41–2.20)	0.91	···	···
Coronary artery disease	0.70 (0.29–1.67)	0.42	···	···
LVEF at baseline	0.97 (0.94–0.999)	0.045	0.97 (0.94–0.999)	0.044
Post-TAVR TIARI	0.94 (0.89–0.99)	0.023	0.94 (0.89–0.99)	0.014
ARI	0.96 (0.90–1.01)	0.13	···	···
DPTI	0.97 (0.92–1.03)	0.31	···	···
Post-TAVR PVR by angiogram ≥ mild	0.85 (0.11–6.54)	0.88	···	···
Post-TAVR PVR by echocardiogram ≥ mild	0.76 (0.30–1.95)	0.57	···	···

ARI indicates aortic regurgitation index; DPTI, diastolic pressure time index; HR, hazard ratio; LVEF, left ventricular ejection fraction; PVR, paravalvular regurgitation; TAVR, transcatheter aortic valve replacement; TIARI, time-integrated aortic regurgitation index.

recorded immediately after valve deployment. It is possible that we selected a cohort of patients who were at higher risk of PVR and hence underestimated the clinical value of catheter-derived hemodynamic indices in guiding BPD. While the results of our study are hypothesis generating, larger prospective studies investigating the value of utilizing TIARI as a deferral strategy either alone or in combination with other imaging modalities are required among patients who develop significant PVR after valve deployment during TAVR.

Conclusion

TIARI calculated immediately after valve deployment provides incremental information over aortography and echocardiography to predict BPD among patients undergoing TAVR. Patients who demonstrated lower residual TIARI after TAVR demonstrated higher mortality rates.

Disclosures

None.

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