Long-term Implications of Post-Procedural Left Ventricular End-Diastolic Pressure in Patients Undergoing Transcatheter Aortic Valve Implantation

Yishay Szekely, MD*, Ariel Borohovitz, MD, Aviram Hochstadt, MD, Yan Topilsky, MD, Maayan Konigstein, MD, Amir Halkin, MD, Samuel Bazan, MD, Shmuel Banai, MD, Ariel Finkelstein, MD, and Yaron Arbel, MD

Current risk models have only limited accuracy in predicting transcatheter aortic valve Implantation (TAVI) outcomes and there is a paucity of clinical variables to guide patient management after the procedure. The prognostic impact of elevated left ventricular end-diastolic pressure (LVEDP) in TAVI patients is unknown. The aim of the present study was to evaluate the prognostic value of after-procedural LVEDP in patients who undewent TAVI. Consecutive patients with severe symptomatic aortic stenosis who undewent TAVI were divided into 2 groups according to after-procedural LVEDP above and below or equal 12 mm Hg. Collected data included baseline clinical, laboratory and echocardiographic variables. We evaluated the impact of elevated vs. normal LVEDP on in-hospital outcomes, short- and long-term mortality. Eight hundred forty-five patients were included in the study with complete in-hospital and late mortality data available for all survivors (median follow-up 29.5 months [IQR 16.5 to 48.0]). The mean age (±SD) was 82.3± 6.2 years and mean Society of Thoracic Surgery score was 4.0%±3.0%. Patients with LVEDP>12 mm Hg (n = 591, 70%) and LVEDP≤12 mm Hg (n = 254, 30%) had a 6-months mortality rate of 6.8% and 2%, respectively (P=0.004) and a 1-year mortality rate of 10.1% vs 4.9%, respectively (p = 0.017). By multivariable analysis, after-procedural LVEDP>12 mm Hg was independently associated with all-cause mortality (HR 2.45, 95% CI 1.58 to 3.76, p <0.001) during long-term follow-up. In conclusion, elevated after-procedural LVEDP in patients who undewent TAVI is an independent predictor of mortality following TAVI. Further research regarding the use of LVEDP as a tool for after-procedural medical management is warranted. **(Am J Cardiol 2021;146:62−68)**

Left ventricular end-diastolic pressure (LVEDP) has evolved as the gold standard of left ventricular diastolic function.[1] Elevated LVEDP has been shown to be associated with worse short- and long-term prognosis following ST-segment elevation myocardial infarction (STEMI).[2,3] The use of LVEDP as a guide for fluid administration after cardiac catheterization was found to be safe and effective in preventing contrast-induced nephropathy.[4] Measurement of LVEDP is readily obtainable in patients with severe aortic stenosis (AS) who undergo transcatheter aortic valve implantation (TAVI). Some patients who underwent TAVI have only limited benefit from the procedure,[5] and better patient selection, timing of the procedure and after-procedural management may increase it. Unfortunately, current risk models have only limited accuracy in predicting TAVI outcomes.[5,6] Studies addressing the prognostic impact of elevated LVEDP in TAVI patients are scarce.[7] Therefore, we aimed to define the prevalence and determinants of elevated LVEDP in TAVI patients, as well as its prognostic impact.

Methods

Consecutive patients (n=845) who underwent nonemergent TAVI between October 2011 and December 2018 constituted the patient population of the present study. Following informed consent, participants were enrolled in the Tel-Aviv Prospective Angiography Study, approved by the institutional ethical committee as previously described.[8] The diagnosis of severe symptomatic AS was made on the basis of clinical and echocardiographic criteria. Suitability and eligibility for TAVI were determined by a Heart Team consisting of an interventional cardiologist, a cardiac surgeon and a cardiac imaging specialist.[8]

Procedural stages have been described in detail previously.[9] All patients underwent pre-procedural transthoracic echocardiography, coronary and peripheral angiography and cardiac computed tomography angiography. Paravalvular leak (PVL) was assessed angiographically at the end of the procedure,[10] and with after-procedural echocardiography.[11]

LVEDP was measured after valve implantation by placing an angled 6-French pigtail catheter in the mid-cavity of

From the Department of Cardiology, Tel Aviv Medical Center, Tel Aviv; and affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Israel. Manuscript received December 7, 2020; revised manuscript received and accepted January 19, 2021.

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

See page 67 for disclosure information.

*Corresponding author: Tel: (972) 3-6973222; fax: (972) 3-6962334.

E-mail address: yishays@tlvmc.gov.il (Y. Szekely).

0002-9149/
https://doi.org/10.1016/j.amjcard.2021.01.022

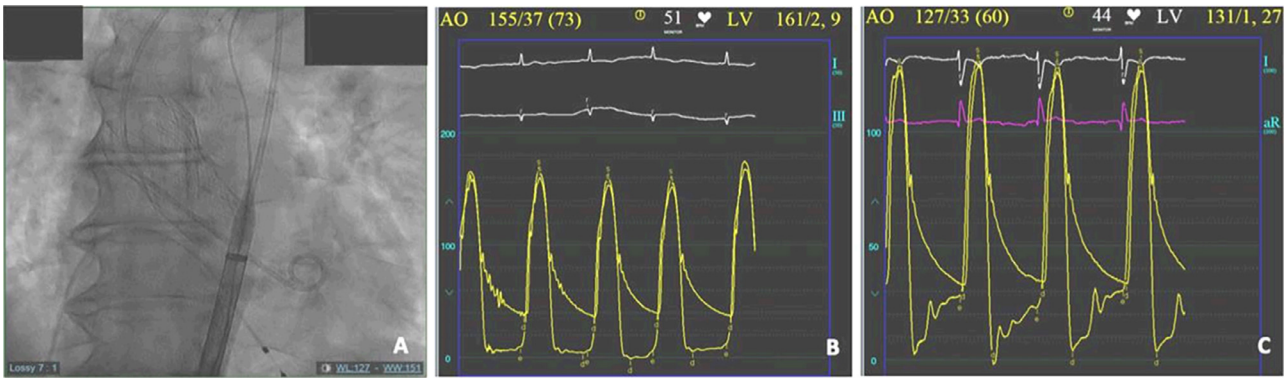

Figure 1. **Panel A:** Angiography of LVEDP measurement at the end of TAVI.
Panel B: Normal LVEDP, measuring 9 mm Hg.
Panel C: Elevated LVEDP, measuring 27 mm Hg.

the left ventricle. The catheter was repositioned if necessary to minimise ventricular ectopy. Next, the transducer was zeroed at mid chest level. Then, LVEDP was measured and recorded at end diastole by commercially available haemodynamic monitoring software (Version 1.5.9.1900, Philips Medical Systems, Bothell, Washington). All measurements were reviewed by 2 independent cardiologists and discrepancies were reviewed by a third cardiologist (Figure 1). Normal LVEDP was defined as 12 mm Hg or less, according to the common definition of normal range for LVEDP.[12–14] In 75% of patients, LVEDP was also measured before valve implantation.

Transthoracic echocardiography studies (iE33, Philips Medical Systems, Bothell, Washington) were performed within 24 hours following TAVI, in a standard manner.[8] Left ventricular (LV) ejection fraction (LVEF), LV diameters, inter-ventricular septal and posterior wall width were recorded as recommended.[15] Tricuspid regurgitation velocity and estimated right atrial pressure were used to calculate the systolic pulmonary artery pressure (SPAP).[16] Early (E) and atrial (A) trans-mitral flow velocities, and early diastolic mitral septal and lateral annular velocity (e′) were measured in the apical 4-chamber view. The average ratio of peak E to peak e′ was calculated (mitral E/e′ ratio) from the average of at least 3 cardiac cycles. Left atrial volume index (LAVI) was calculated using the biplane area length method at end systole. Diastolic function was assessed by integrating measurements of the mitral inflow, SPAP, LAVI, and Doppler tissue imaging of the mitral annulus, based on recent guidelines[17] and classified into 3 categories, as previously described.[18]

Clinical data for all participants were collected at baseline and then at hospital discharge. The primary study end point was all-cause mortality. Data concerning mortality following discharge was obtained from the computerized hospital record system that is linked to a national database by identification numbers. Additional in-hospital adverse events rates were collected and analyzed according to the VARC-II criteria[11] that included in-hospital mortality, stroke, acute kidney injury (AKI), major bleeding, major vascular complications, new onset atrial fibrillation or heart failure and requirement for permanent transvenous cardiac pacing.

All data for continuous variables is presented as mean (±SD) and for categorical variables as number (percentage). Continuous variables were compared using an independent samples Mann-Whitney-*U* test. Categorical variables were compared using a Fisher's exact test. Kaplan-Mayer curves were used to assess differences in mortality during follow up among different groups. The significance of the difference between curves was assessed using a Log-rank test. For multivariable tests, missing values of covariates were imputed using a non-parametric random forest method. Multivariable Cox regressions were used to evaluate associations with all-cause mortality. Cox models proportional hazard assumption was assessed using graphs of the scaled Schoenfeld residuals against the transformed time. Multivariable logistic regression was used to assess independent predictors of high LVEDP. To create all multivariable models, a combined backward and forward Akaike Information Criteria (AIC) dependent stepwise approach was used to select the covariates for the final models, seed model was built using Tables 1 and 2. A 2-tailed p-value less than 0.05 was considered as statistically significant. All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

This study cohort consisted of 845 patients. Elevated after-procedural LVEDP was measured in 70% of patients. Baseline demographic, clinical and echocardiographic characteristics of patients stratified by LVEDP are presented in Table 1. Elevated LVEDP, compared with normal LVEDP, was associated with prior myocardial infarction (MI), prior stroke, effort dyspnea as the presenting symptom, chronic obstructive pulmonary disease, hyperlipidemia, lower estimated glomerular filtration rate (eGFR) and lower levels of pre-procedural hemoglobin. Use of angiotensin receptor blockers or angiotensin-converting-enzyme inhibitors (ACEI) was more frequent among patients with elevated LVEDP. There was no significant difference in heart failure hospitalizations 6 months prior to TAVI, frailty assessment, Society of Thoracic Surgery (STS) score, presence of

Table 1
Baseline clinical, laboratory and echocardiographic characteristics in patients stratified by LVEDP

	LV end-diastolic pressure (mm Hg)			
	Entire group (n = 845)	≤ 12 (n = 254)	> 12 (n = 591)	p
Variable				
Age (years), mean±SD	82.3±6.2	82.3±6.0	82.3±6.2	0.79
Women	393 (46.5%)	111 (43.7%)	282 (47.7%)	0.29
Hypertension	706 (83.6%)	208 (81.9%)	498 (84.3%)	0.54
Hyperlipidemia	609 (72.1%)	165 (65.0%)	444 (75.1%)	**0.004**
Diabetes Mellitus	321 (38.0%)	89 (35.0%)	232 (39.3%)	0.31
Current smoker	42 (5.0%)	14 (5.5%)	28 (4.7%)	0.61
Coronary artery disease	421 (49.8%)	116 (45.7%)	305 (51.6%)	0.13
Prior CABG	131 (15.5%)	31 (12.2%)	100 (16.9%)	0.1
Prior PCI	320 (37.9%)	95 (37.4%)	225 (38.1%)	1.00
Prior myocardial infarction	113 (13.4%)	24 (9.4%)	89 (15.1%)	**0.04**
Prior stroke	108 (12.8%)	23 (9.1%)	85 (14.4%)	**0.04**
Peripheral artery disease	35 (4.1%)	8 (3.1%)	27 (4.6%)	0.27
History of atrial fibrillation/flutter	238 (28.2%)	65 (25.6%)	173 (29.3%)	0.32
Dialysis	21 (2.5%)	5 (2.0%)	16 (2.7%)	0.64
Chronic lung disease	76 (9.0%)	15 (5.9%)	61 (10.3%)	**0.048**
Oncological disease	73 (8.6%)	25 (9.8%)	48 (8.1%)	0.42
Frail	238 (28.2%)	79 (31.1%)	159 (26.9%)	0.13
NYHA class III-IV, pre-procedural	728 (86.2%)	210 (82.7%)	518 (87.6%)	0.07
Effort dyspnea	573 (67.8%)	151 (59.4%)	422 (71.4%)	**<0.001**
Heart failure hospitalization 6 months prior to TAVI	166 (19.6%)	47 (18.5%)	119 (20.1%)	0.57
STS score (%), mean±SD	4.0±3.0	3.95±2.83	4.08±3.06	0.2
Estimated glomerular filtration rate (ml/min/1.73m^2), mean±SD	57.8±22.0	60.8±21.6	56.7±22.1	**0.03**
Hemoglobin (g/dL), mean±SD	11.9±1.5	12.1±1.6	11.9±1.4	**0.045**
Albumin (g/dL), mean±SD	39.8±4.0	39.6±4.3	39.8±3.8	0.48
ACEI or ARB therapy prior to TAVI	422 (49.9%)	113 (44.5%)	309 (52.3%)	**0.02**
Beta blocker therapy prior to TAVI	481 (56.9%)	151 (59.4%)	330 (55.8%)	0.32
Calcium channel blocker therapy prior to TAVI	308 (36.4%)	97 (38.2%)	211 (35.7%)	0.48
Loop diuretic therapy prior to TAVI	283 (33.5%)	85 (33.5%)	198 (33.5%)	1.00
Left bundle branch block prior to TAVI	75 (8.9%)	31 (12.2%)	44 (7.4%)	**0.04**
Right bundle branch block prior to TAVI	84 (9.9%)	23 (9.1%)	61 (10.3%)	0.61
Pre-procedural echocardiographic features				
Transvalvular gradient (mmHg), mean±SD	45.6±14.6	44.9±15.0	45.9±14.4	0.29
LVEF (%), mean±SD	55.9±8.5	56.3±7.8	55.7±8.8	0.54
Left ventricle end-diastolic diameter (mm), mean±SD	46.9±6.8	46.3±6.4	47.1±6.9	0.44
Left ventricle end-systolic diameter (mm), mean±SD	30.3±7.8	29.7±7.0	30.5±8.1	0.63
Left ventricle posterior wall diameter (mm), mean±SD	11.7±2.7	11.7±1.8	11.7±3.0	0.34

ACEI= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; CABG= coronary artery bypass grafting; LVEDP= left ventricular end-diastolic pressure; LVEF= left ventricular ejection fraction; NYHA= New York Heart Association; PCI= percutaneous coronary intervention; STS= Society of Thoracic Surgery; TAVI= transcatheter aortic valve implantation.

oncological disease, estimated LVEF, ventricular dimensions and pre-procedural echocardiographic aortic valve gradients. There was also no significant difference in the use of beta blockers or loop diuretics. Procedural characteristics and after-procedural echocardiographic parameters are presented in Table 2. There was no difference in the prosthetic valve type used (self-expandable vs. balloon-expandable) between the 2 groups. Significant PVL was more frequent among patients with elevated LVEDP. Complete evaluation of after-procedural diastolic dysfunction grade per echocardiography could be determined in 436 patients. In this subset of patients, patients with elevated LVEDP had higher after-procedural tricuspid regurgitation (TR) gradients, with no significant difference in after-procedural mitral average E/e' ratio and LAVI compared with patients with normal LVEDP. We also performed a Pearson's correlation test between LVEDP as a continuous variable and mitral average E/e' ratio that also did not show a significant correlation between values (R=0.039, p = 0.39).

Determinants of elevated LVEDP (Table 3) were analyzed by multivariable modeling accounting for the clinical and echocardiographic variables listed in Tables 1 and 2. Elevated LVEDP was independently associated with Effort dyspnea, use of beta blockers, pre-procedural left bundle branch block, hemoglobin levels, after-procedural TR gradient and moderate or severe PVL. There was no association with the valve type used for TAVI or other after-procedural echocardiography diastolic parameters.

Adverse event rates in patients stratified by LVEDP are shown in Table 4. New onset atrial fibrillation was more frequent among elevated LVEDP patients, who also had longer length of hospitalization. Other in-hospital adverse

Table 2
Procedural and after-procedural echocardiographic characteristics in patients stratified by LVEDP

	LV end-diastolic pressure (mmHg)			
	Entire group (n = 845)	≤ 12 (n = 254)	> 12 (n = 591)	p
Procedural characteristics				
Prosthetic valve type				0.54
Self-expanding	492 (41.8%)	152 (59.8%)	340 (57.5%)	
Balloon-expandable	353 (58.2%)	102 (40.2%)	251 (42.5%)	
Systolic blood pressure (mmHg), mean±SD	122.8±45.4	119.4±68.5	124.5±28.8	**<0.001**
Diastolic blood pressure (mmHg), mean±SD	48.8±13.6	45.3±13.3	50.4±13.4	**<0.001**
After-procedural echocardiographic features				
Paravalvular leak, moderate or severe	18 (2.3%)	1 (0.4%)	17 (3.1%)	**0.02**
Mitral average E/e' ratio, mean±SD	19.0±7.0	18.4±6.3	19.2±7.3	0.42
Left atrial volume index (mL/m^2), mean±SD	53.0±31.8	51.3±15.8	53.6±35.8	0.94
Tricuspid regurgitation gradient (mmHg), mean±SD	33.7±11.3	31.4±9.8	34.4±11.7	**0.01**
Diastolic dysfunction grade	n=436	n=120	n=316	0.17
3	35 (8.0%)	5 (4.2%)	30 (9.5%)	
2	163 (37.4%)	45 (37.5%)	118 (37.3%)	
1	238 (54.6%)	70 (58.3%)	168 (53.2%)	

LVEDP= left ventricular end-diastolic pressure.

Table 3
Multivariable correlates of elevated LVEDP

LVEDP > 12 mmHg	Odds ratio	95% CI	p
Prior stroke	1.63	[1.00,2.75]	0.06
Prior myocardial infarction	1.60	[0.97,2.70]	0.07
Chronic lung disease	1.73	[0.97,3.27]	0.08
Hyperlipidemia	1.34	[0.95,1.90]	0.10
Effort dyspnea	1.65	[1.18,2.30]	**0.003**
NYHA III-IV	1.54	[0.99,2.38]	0.05
Frailty	0.72	[0.51,1.03]	0.07
Beta blocker therapy	0.69	[0.50,0.94]	**0.02**
ACEI or ARB therapy	1.26	[0.92,1.73]	0.14
Tricuspid regurgitation gradient*	1.02	[1.01,1.04]	**0.01**
Paravalvular leak, moderate or severe	8.76	[1.7,161]	**0.038**
Left bundle branch block	0.55	[0.33,0.92]	**0.02**
Hemoglobin (g/L)†	0.88	[0.77,1.00]	**0.047**
Albumin (g/L)†	1.04	[0.99,1.09]	0.14

ACEI= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; LVEDP= left ventricular end-diastolic pressure; NYHA= New York Heart Association.

* 1 mmHg increments.

† 1 g/L increments.

events rates, including death, stroke or AKI, did not differ significantly between the 2 groups.

During follow-up, while 1-month mortality rates did not differ significantly between groups, 6-months and 1-year mortality rates were higher among the elevated LVEDP group compared with the normal LVEDP group (6-months: 6.8% vs 2.0%, respectively, p = 0.004; HR 3.52 95% CI [1.39 to 8.91], p = 0.005; 1-year: 10.1% versus 4.9%, respectively, p = 0.017; HR 2.24 95% CI [1.17 to 4.27], p = 0.012).

Median follow-up was 29.5 months [IQR 16.5 to 48.0]. One hundred sixty-two (19.2%) patients died during the study period. Crude mortality rates at late follow-up in patients stratified by elevated or normal LVEDP are presented in Figure 2. Mortality was higher among elevated LVEDP patients compared with those with a normal LVEDP (HR 1.94 95% CI [1.27 to 2.96], p = 0.0017). As can also be seen in Figure 2, separation of the unadjusted mortality curves commenced at approximately 1 month after TAVI.

By multivariable analysis (Table 5), elevated LVEDP was independently associated with all-cause mortality (HR=2.45 [1.58 to 3.76], p <0.001). Adding after-procedural echocardiographic parameters to the model, including E/e' ratio, SPAP and estimated right atrial pressure did not improve its efficiency, and thus were not included in the final multivariate model. Adjusted all-cause mortality curves for patients stratified by LVEDP are presented in Figure 3. Pre-TAVI LVEDP, measured in the same procedure but before valve implantation, was available in 75% of patients, and was also found to be an independent predictor of late mortality, though to a lesser extent compared with after-TAVI LVEDP (Table S1).

Discussion

To our knowledge, this is the first study examining the relation between after-procedural LVEDP and outcomes following TAVI. Its principal findings are: (1) Elevated after-procedural LVEDP is identified in approximately 70% of patients who underwent TAVI. (2) Elevated LVEDP is associated with an increased risk of after-procedural new-onset atrial fibrillation and a longer length of after-procedural hospitalization. (3) Elevated LVEDP was independently associated with higher long-term mortality, despite successful TAVI.

Diastolic dysfunction and increased LV filling pressures are associated with worse outcomes in AS patients.[19,20] Diastolic dysfunction that accompanies AS results from elevated afterload that causes myocardial hypertrophy, left ventricular remodeling and eventually, fibrosis. This leads to stiffening of the left ventricle, impaired relaxation and elevated filling pressures.[19,21] Other co-morbidities, such as aging, diabetes and coronary artery disease, which often coincide with AS, further aggravate this pathological

Table 4
Adverse event rates in patients stratified by LVEDP

Event	LV end-diastolic pressure (mmHg)			p
	Entire group (n = 845)	≤ 12 (n = 254)	> 12 (n = 591)	
In-hospital				
All-cause mortality	17 (2.0%)	3 (1.2%)	14 (2.4%)	0.42
Stroke	14 (1.7%)	5 (2.0%)	9 (1.6%)	0.77
New onset atrial fibrillation	16 (2.3%)	0 (0.0%)	16 (3.1%)	**0.009**
Major vascular complication	24 (2.9%)	6 (2.4%)	18 (3.1%)	0.66
Major bleeding	35 (4.1%)	8 (3.1%)	27 (4.6%)	0.45
Acute kidney injury	82 (9.7%)	18 (7.1%)	64 (10.8%)	0.13
Permanent pacemaker implantation	135 (16.0%)	37 (14.6%)	98 (16.6%)	0.91
Heart failure	28 (3.3%)	4 (1.6%)	24 (4.9%)	0.13
Hospitalization days, median [IQR]	6.00 [5.00,8.00]	5.00 [4.00,8.00]	6.00 [5.00,8.00]	**0.002**
Follow-up				
One month mortality	12 (1.4%)	2 (0.8%)	10 (1.7%)	0.53
Six months mortality*	45 (5.3%)	5 (2.0%)	40 (6.8%)	**0.004**
One year mortality*	67 (8.6%)	11 (4.9%)	56 (10.1%)	**0.02**

LVEDP= left ventricular end-diastolic pressure.
* The percentages were calculated from all patients who completed the indicated follow-up period.

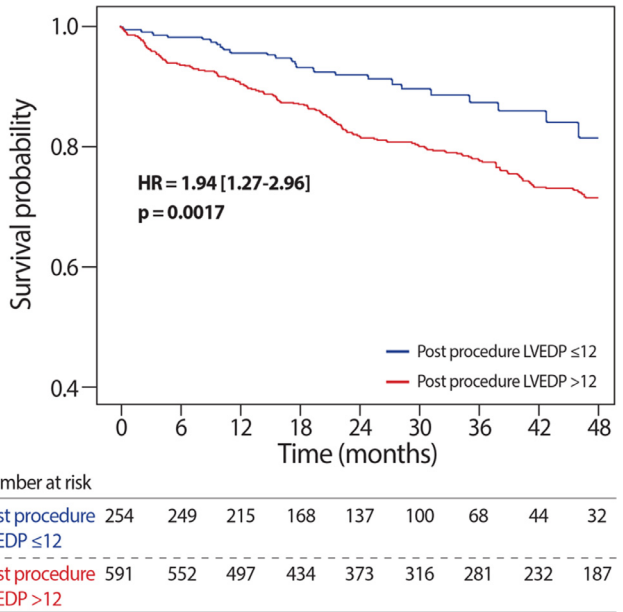

Figure 2. Unadjusted all-cause mortality curves for patients stratified by LVEDP.

process. Even though replacement of the aortic valve usually normalizes left ventricular afterload and as a result leads to reverse chamber remodeling and regression of hypertrophy, irreversible fibrosis may never regress, reducing the chance of improving diastolic function.[19,22] These irreversible mechanisms have been associated with heart failure and mortality in AS patients.[23] Our findings are consistent with this concept. Replacement of the valve may not fully resolve the diastolic dysfunction of all patients, and therefore, patients with higher LVEDP had worse long-term prognosis. It is yet unknown whether earlier intervention, before myocardial fibrosis ensues, might improve outcomes in this patient population.[24]

Previous research has focused on patients with severe AS who have undergone surgical aortic valve replacement, in which elevated LVEDP was associated with abnormal

Table 5
Multivariable correlates of late mortality

	Hazard ratio	95% CI	p
LVEDP > 12 mmHg	2.45	[1.58,3.76]	**<0.001**
Left atrial volume index*	1.01	[1.00,1.01]	**<0.001**
Coronary artery disease	2.27	[1.48,3.47]	**<0.001**
Effort dyspnea	2.62	[1.68,4.08]	**<0.001**
Heart failure hospitalization 6 months prior to TAVI	1.75	[1.23,2.49]	**0.002**
NYHA III-IV	2.02	[1.1,3.71]	**0.024**
Prior PCI	0.53	[0.36,0.79]	**0.002**
ACEI or ARB therapy	1.37	[0.97,1.95]	0.073
STS score†	1.07	[1.03,1.11]	**<0.001**
Frailty	0.68	[0.46,0.99]	**0.045**
Estimated glomerular filtration rate‡	0.99	[0.98,1.00]	**0.004**
Hemoglobin on TAVI-hospitalization admission§	0.88	[0.78,0.98]	**0.02**
Age‖	1.03	[1.00,1.06]	0.06
Paravalvular leak, moderate or severe	19.02	[8.11,44.58]	**<0.001**

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEDP, left ventricular end-diastolic pressure; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgery; TAVI, transcatheter aortic valve implantation.
* 1 mL/m^2 increments.
† 1 percent increments.
‡ 1 mL/min/1.73m^2 increments.
§ 1 g/dL increments.
‖ 1 year increments.

myocardial structure in myocardial biopsy[25], or balloon aortic valvuloplasty, in which elevated LVEDP was an independent predictor of poor in-hospital outcomes.[26] A study evaluating AS patients who underwent TAVI calculated an index of LV stiffness, using LVEDP among other echocardiographic parameters, and found that elevated stiffness was an independent 1-year mortality predictor.[27] Finally, another study reported a full pre-procedural invasive hemodynamic assessment of an heterogenous group of

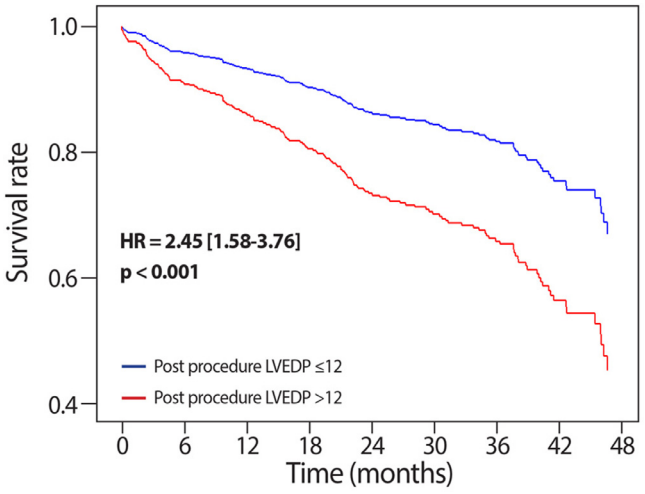

Figure 3. Adjusted all-cause mortality curves for patients stratified by LVEDP.

TAVI and surgical aortic valve replacement patients. Patients with pulmonary vascular disease or significant right ventricular, tricuspid valve or right atrial dysfunction had an increased risk of death, while elevated LVEDP or elevated left atrial pressure did not carry worse prognosis.[7]

In the current study, elevated LVEDP was associated with an increased risk of all-cause mortality at late follow-up, even after accounting for other strong predictors of mortality, such as after-procedural paravalvular leak, coronary artery disease, STS score, frailty, hemoglobin levels and renal function. This is consistent with data from most earlier studies mentioned above. Although present guidelines encourage the use of echocardiography as a safe, inexpensive and robust mean of diastolic LV function evaluation, our results suggest that in the particular population of elderly patients with severe AS who underwent TAVI, invasive evaluation of LV filling pressures may have an added value over the noninvasive approach. One possible explanation could be the relatively high rate of mitral annulus calcification in this subset of elderly patients, which limits the echocardiographic evaluation of LV filling pressures.[28] PVL can itself be associated with both elevated LVEDP and after-procedural outcomes. Elevated LVEDP was shown to be a significant predictor of mortality, even after accounting for moderate to severe PVL. The added value in risk stratification and the fact that crossing of the aortic valve is done as a routine part of the procedure, not exposing the patient to a significant excess risk, encourage its use. The results and the time point (≈1 month) at which the survival curves of patients stratified by LVEDP began to separate in this study, suggest that after-procedural LVEDP is a marker of both short- and long-term mortality. Most in-hospital adverse event rates including mortality, heart failure, AKI and stroke were not more frequent in patients with elevated versus normal LVEDP. However, elevated LVEDP was associated with higher rates of new-onset atrial fibrillation during the index hospitalization. This can be attributed to myocardial fibrosis and stretching, which is linked to elevated LVEDP as well as atrial fibrillation.[29] It was also associated with longer length of hospitalization, which might represent a subset of patients in need for a more complex after-procedural management. Our secondary analysis shows that pre-procedural LVEDP, measured in the same procedure but before valve implantation, was also a predictor of late mortality, and warrants further research regarding its use as a factor in patient selection and pre-procedural management.

The retrospective nature of this study is acknowledged. We used a multivariable regression analysis in an attempt to control for identified confounders, such as variables found to be associated with increased mortality in our univariable analysis and in previous studies, as well as variables found to be significantly different between the 2 LVEDP groups. Nevertheless, the existence of unidentified confounders linked both to LVEDP and prognosis cannot be completely ruled out. A full hemodynamic assessment of patients, including left atrial, pulmonary and right sided pressures, was not included, as right heart catheterization was not routinely done during TAVI. The cause of death was not consistently documented in this cohort, and cardiovascular mortality would have been a better end point, that may further direct possible after-procedural management. Data regarding other adverse long-term outcomes, such as heart failure hospitalizations, AKI, MI and stroke could have added significantly to the study, but these outcomes were not documented.

In conclusion, after-procedural elevated LVEDP is independently associated with higher mortality at short- and long-term follow-up after TAVI. This study substantiates and expands previous research on the prognostic implications of elevated LV filling pressures in severe AS.

Credit Author Statement

Yishay Szekely, MD: conceptualization, methodology, Writing- original draft, Writing- review and editing **Ariel Borohovitz, MD:** Investigation, Project administration **Aviram Hochstadt, MD**: Formal analysis, Writing- review and editing **Yan Topilsky, MD**: Writing- review and editing **Maayan Konigstein, MD**: Investigation, Writing- review and editing **Amir Halkin, MD**: Investigation **Samuel Bazan, MD**: Investigation **Shmuel Banai, MD**: Writing- review and editing, Supervision **Ariel Finkelstein, MD**: Investigation, Writing- review and editing, Supervision **Yaron Arbel, MD:** conceptualization, methodology, Writing- original draft, Writing- review and editing

Disclosures

Ariel Finkelstein reports receiving consultation fees from Medtronic and Edwards Lifesciences. Amir Halkin reports receiving consultation fees from Abbott Laboratories and Boston Scientific. All other authors have no conflict of interests to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.022.

1. Iskandrian AS, Segal BL, Hakki AH. Left ventricular end-diastolic pressure in evaluating left ventricular function. *Clin Cardiol* 1981;4:28–33.
2. Ndrepepa G, Cassese S, Hashorva D, Kufner S, Xhepa E, Hasimi E, Fusaro M, Laugwitz K-L, Schunkert H, Kastrati A. Relationship of left ventricular end-diastolic pressure with extent of myocardial ischemia, myocardial salvage and long-term outcome in patients with ST-segment elevation myocardial infarction. *Catheter Cardiovasc Interv* 2019;93:901–909.
3. Planer D, Mehran R, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Mockel M, Reyes SL, Stone GW. Prognostic utility of left ventricular end-diastolic pressure in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2011;108:1068–1074.
4. Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AY-J, Jorgensen M, Dua A, Short L, Kane K. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet Lond Engl* 2014;383:1814–1823.
5. Puri R, Iung B, Cohen DJ, Rodes-Cabau J. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J* 2016;37:2217–2225.
6. Martin GP, Sperrin M, Ludman PF, Belder MA de, Gale CP, Toff WD, Moat NE, Trivedi U, Buchan I, Mamas MA. Inadequacy of existing clinical prediction models for predicting mortality after transcatheter aortic valve implantation. *Am Heart J* 2017;184:97–105.
7. Maeder MT, Weber L, Weilenmann D, Haager PK, Joerg L, Taramasso M, Buser M, Ehl NF, Maisano F, Rickli H. Invasive hemodynamic staging classification of cardiac damage in patients with aortic stenosis undergoing valve replacement. *Can J Cardio* 2020;36:1667–1674.
8. Schwartz LA, Rozenbaum Z, Ghantous E, Kramarz J, Biner S, Ghermezi M, Shimiaie J, Finkelstein A, Banai S, Aviram G, Ingbir M, Keren G, Topilsky Y. Impact of right ventricular dysfunction and tricuspid regurgitation on outcomes in patients undergoing transcatheter aortic valve replacement. *J Am Soc Echocardiogr* 2017;30:36–46.
9. Szekely Y, Finkelstein A, Bazan S, Halkin A, Abbas Younis M, Erez J, Keren G, Banai S, Arbel Y. Red blood cell distribution width as a prognostic factor in patients undergoing transcatheter aortic valve implantation. *J Cardiol* 2019;74:212–216.
10. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of paravalvular regurgitation following TAVR: A proposal of unifying grading scheme. *JACC Cardiovasc Imaging* 2015;8:340–360.
11. Kappetein AP, Head SJ, Genereux P, Piazza N, Mieghem NM van, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es G-A van, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403–2418.
12. Zipes DP, Libby P, Bonow RO, Mann DL, Tomasseli GF, Braunwald E. *Cardiac catheterization*. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. p 358, 11th ed. Philadelphia, PA: Elsevier/Saunders; 2018:358–360.
13. Falicov RE, Resnekov L. Relationship of the pulmonary artery end-diastolic pressure to the left ventricular end-diastolic and mean filling pressures in patients with and without left ventricular dysfunction. *Circulation* 1970;42:65–73.
14. Kern MJ, Christopher T. Hemodynamic rounds series II: the LVEDP. *Cathet Cardiovasc Diagn* 1998;44:70–74.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W. Recommendations for chamber quantification. *Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol* 2006;7:79–108.
16. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713. quiz 786–788.
17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277–314.
18. Szekely Y, Topilsky Y, Bazan S, Revivo M, Banai S, Konigstein M. The impact of coronary sinus narrowing on diastolic function in patients with refractory angina. *Int J Cardiol* 2019;291:8–12.
19. Kampaktsis PN, Kokkinidis DG, Wong S-C, Vavuranakis M, Skubas NJ, Devereux RB. The role and clinical implications of diastolic dysfunction in aortic stenosis. *Heart Br Card Soc* 2017;103:1481–1487.
20. Biner S, Rafique AM, Goykhman P, Morrissey RP, Naghi J, Siegel RJ. Prognostic value of E/E' ratio in patients with unoperated severe aortic stenosis. *JACC Cardiovasc Imaging* 2010;3:899–907.
21. Villari B, Campbell SE, Hess OM, Mall G, Vassalli G, Weber KT, Krayenbuehl HP. Influence of collagen network on left ventricular systolic and diastolic function in aortic valve disease. *J Am Coll Cardiol* 1993;22:1477–1484.
22. Hess OM, Ritter M, Schneider J, Grimm J, Turina M, Krayenbuehl HP. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. *Circulation* 1984;69:855–865.
23. Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V, Bauer EP, Klovekorn W-P, Schaper J. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation* 2003;107:984–991.
24. Anon. Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients With AsYmptomatic Severe Aortic Stenosis (EARLY TAVR). Available at https://clinicaltrials.gov/ct2/show/study/NCT03042104 Accessed March 1, 2020.
25. Hita A, Baratta S, Vaccarino G, Navia J, Oleno D, Telayna JM, Costantini R, Chejtman D, Matoso M, Gelpi RJ, Donato M, Morales C. Severe aortic stenosis with preserved ejection fraction and evidence of impairment in structure, myocardial strain and ventricular function: a new contribution to clinical decision making. *Cardiol J* 2015;22:613–621.
26. Cubeddu RJ, Don CW, Horvath SA, Gupta PP, Cruz-Gonzalez I, Witzke C, Inglessis I, Palacios IF. Left ventricular end-diastolic pressure as an independent predictor of outcome during balloon aortic valvuloplasty. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2014;83:782–788.
27. Conte L, Fabiani I, Pugliese NR, Giannini C, La Carruba S, Angelillis M, Spontoni P, De Carlo M, Petronio AS, Di Bello V. Left ventricular stiffness predicts outcome in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *Echocardiography* 2017;34:6–13.
28. Abudiab MM, Chebrolu LH, Schutt RC, Nagueh SF, Zoghbi WA. Doppler echocardiography for the estimation of LV filling pressure in patients with mitral annular calcification. *JACC Cardiovasc Imaging* 2017;10:1411–1420.
29. Dzeshka MS, Lip GYH, Snezhitskiy V, Shantsila E. Cardiac fibrosis in patients with atrial fibrillation: mechanisms and clinical implications. *J Am Coll Cardiol* 2015;66:943–959.