



Original article

Impact of transcatheter aortic valve replacement on hemodynamic status in patients with aortic stenosis and mitral stenosis: Doppler echocardiographic study



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ABSTRACT

Background: Mitral stenosis (MS) is often concomitant with aortic stenosis (AS). However, little is known about the functional status following transcatheter aortic valve replacement (TAVR) alone in patients with severe AS and MS and the impact of TAVR for AS on MS hemodynamics.

Methods: We enrolled 11 patients (age 83.6 ± 4.7 years, eight women) with severe AS and MS who underwent TAVR. We compared New York Heart Association (NYHA) functional class and mean transmitral pressure gradient (MPG), mitral valve area (MVA), and stroke volume (SV) measured by transthoracic Doppler echocardiography between baseline and after TAVR. We also examined the calcification of the mitral annulus and mitral leaflet opening.

Results: NYHA functional class improved after TAVR in all 11 patients. As SV increased after TAVR (52 ± 12 mL to 63 ± 18 mL, $p = 0.041$), MPG decreased and MVA increased (6.9 ± 3.8 mmHg to 5.1 ± 2.5 mmHg, $p = 0.011$ for MPG and 1.12 ± 0.25 cm² to 1.49 ± 0.43 cm², $p = 0.035$ for MVA). However, MPG increased in one patient in whom calcification extended into the entire anterior mitral leaflet (AML) and AML mobility was severely reduced.

Conclusions: NYHA functional class and hemodynamic status of MS improved after TAVR in patients with severe AS and MS. TAVR might provide therapeutic efficacy for selected symptomatic severe AS patients with MS.

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Introduction

Although the vast majority of mitral stenosis (MS) in the world results from rheumatic heart disease, senile degenerative MS is common in the elderly population [1,2]. Especially, in elderly patients with symptomatic severe calcific aortic stenosis (AS), there is a high prevalence of MS [2–4]. Mitral annular calcification (MAC), which is reported to exist in about 50% of severe AS patients

[5–7], can be a cause of MS in senile calcific aortic stenosis [1,8]. However, indications for intervention in patients with combined AS and degenerative MS are not defined in the current guideline [1]. There could be two main reasons for this. First, double valve replacement tends to be avoided due to the operative risk. The overall operative risk of simultaneous double valve replacement (DVR) lies between 4% and 13% and is much higher than the risk of either aortic valve replacement (AVR) or mitral valve replacement (MVR) alone [1,9,10]. Second, little is known about the hemodynamic effect of AVR alone on patients with coexistent AS and MS.

As the alternative therapy to surgical AVR for severe AS, the safety and efficacy of transcatheter aortic valve replacement

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(TAVR) has been established [11,12]. Recently, there has been rising use of TAVR in patients with combined severe AS and MS [4]. Concomitant MS is typically left untreated in this setting. The observation of mitral valve hemodynamics following TAVR can provide a potential explanation for isolated AVR as a treatment option in patients with severe AS and MS. The main aim of the present study was to evaluate the influence of TAVR alone on the patients with AS and MS.

Methods

Population

We retrospectively investigated patients with severe AS and severe MS in 109 patients who underwent TAVR from January in 2016 to July in 2017 at Tokyo Bay Urayasu/Ichikawa Medical Center. All patients underwent transthoracic echocardiography (TTE) to assess the feasibility of TAVR. Exclusion criteria were patients who underwent prior MVR or mitral valve repair. All perioperative data, including clinical and echocardiographic findings, operative reports, and postoperative records were collected in medical records.

The present study was approved by the human ethics committee at the Tokyo Bay Urayasu/Ichikawa Medical Center. Informed consent regarding participation in the present study was obtained from all subjects.

Transthoracic echocardiography at baseline and follow up

TTE was performed by commercially available ultrasound transducer and equipment. Our echocardiography laboratory is maintained under the guidelines of the Japanese Society of Echocardiography [13]. Conventional TTE parameters including cardiac dimensions and left ventricular ejection fraction (EF) by a biplane Simpson's method were calculated according to guidelines

[14]. Peak transaortic velocity and mean transaortic pressure gradient were derived from transaortic flow velocity waveform recorded with continuous wave Doppler (CWD) using a multi-window approach. Aortic valve area (AVA) was calculated using the continuity equation. Severe AS was defined as $AVA \leq 1.0 \text{ cm}^2$, peak velocity $\geq 4.0 \text{ m/s}$, or mean pressure gradient $\geq 40 \text{ mmHg}$ [15]. Diastolic mitral jets with aliasing were identified with color Doppler and diastolic mitral flow velocity was recorded by CWD at baseline as shown in Fig. 1. Mean transmitral pressure gradient (MPG) and pressure half time (PHT) were derived from transmitral flow velocity waveform recorded by CWD using a multi-window approach. Mitral valve area (MVA) was calculated according to the continuity equation. Severe MS was defined as $MVA \leq 1.5 \text{ cm}^2$ [1] and significant MS was defined as Doppler velocity index (DVI) > 2.5 [16] (DVI was calculated as the ratio of the VTIs (velocity time integral) of the mitral valve inflow to those of the left ventricular outflow). The severity of mitral regurgitation (MR) and aortic regurgitation (AR) was assessed using an integrated approach according to current guidelines [1,17,18]. They were graded as none (0), trivial to mild (grade 1), moderate (grade 2), and severe (grade 3).

Mitral leaflet mobility was evaluated to measure the mitral leaflet opening angle in the parasternal long-axis view with TTE at early diastole. The angles between the anterior mitral leaflet (AML) or posterior mitral leaflet (PML) and inner mitral annulus line ($\alpha 1$ and $\alpha 2$) were measured manually as shown in Fig. 1 [3,19].

Multi detector computed tomography

We used 320-slice multi detector computed tomography (MDCT) (Toshiba AquilionOne Dynamic Volume CT, Otawara, Japan) for all patients to assess distribution of calcification on the mitral annulus the feasibility of TAVR [20]. The tube voltage was 100 kV and the tube modulation was 300–550 mA. Data were analyzed on a post-processing workstation (Ziostation2 and

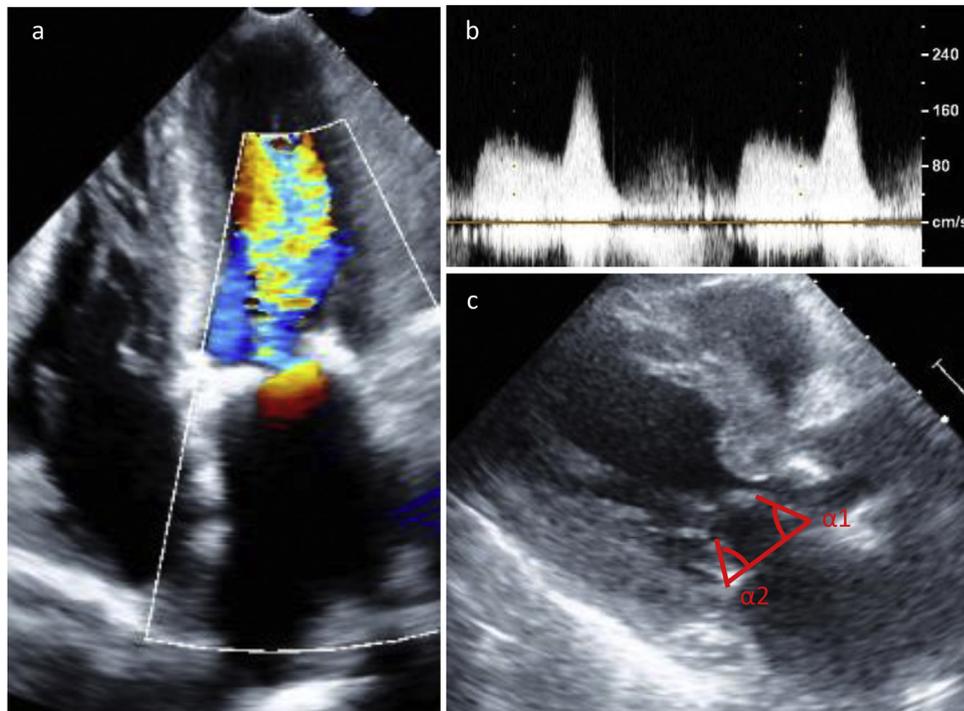


Fig. 1. An example of mitral stenosis. Diastolic mitral jets with aliasing were identified with color Doppler in apical view (a) and Doppler diastolic mitral flow by continuous wave Doppler was recorded with transthoracic echocardiography (b). The angles between the anterior or posterior mitral leaflet and inner mitral annulus line ($\alpha 1$ and $\alpha 2$) were measured (c).

PhyZiodynamics Technology, Ziosoft Inc., Tokyo, Japan). Axial views at the mitral annular level as well as maximal intensity projection (MIP) reconstruction were used to evaluate the severity of MAC.

MAC was defined as the presence of dense calcium deposits at the base of mitral leaflets between the left atrium and ventricle [5,6,21,22]. MAC severity was qualitatively determined by the circumferential involvement of the mitral ring: mild = less than 1/3 of the annulus involved; moderate = between 1/3 and 1/2; and severe = calcification in more than half of the mitral annulus circumference [5].

TAVR procedure

Valve type and sizing for TAVR was made at the operator's discretion, using data from a prospective knowledge of cross-sectional CT measurements. The diameters of the sinuses of Valsalva and the ascending aorta, the extent of sinotubular and aortic root calcification, and the height of the coronary ostia were considered when choosing the size of valves. The Sapien XT (Edwards Lifesciences, Irvine, California, USA) were available in 23-, 26-, and 29-mm nominal diameters and the Sapien 3 (Edwards Lifesciences, Irvine, California, USA) in 20-, 23-, 26-, and 29-mm nominal diameters. CoreValve and Evolute R (Medtronic, Minneapolis, Minnesota, USA) were available in 26- and 29-mm nominal diameter.

Follow up

Follow-up TTE was performed within 4 days after TAVR. NYHA functional class was assessed at the 30-day follow-up office visit. We investigated all-cause 30-day mortality, stroke, and the combined safety endpoint in severe AS patients with MS compared with those without MS. The combined 30-day safety end points included all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury stage 3 (including renal replacement therapy), periprocedural myocardial infarction, major vascular complications, and further intervention attributable to valve dysfunction.

Statistical analysis

Continuous data are expressed as mean \pm standard deviation and categorical data as frequency or percentage. Comparisons of echocardiography parameters between baseline and post TAVR were performed using paired *t* test. Comparisons of outcome between severe AS patients with and without MS were performed using χ^2 test. Statistical analysis was performed using the SPSS 24.0 software (SPSS Inc., Chicago, IL, USA). The differences were considered significant at $p < 0.05$.

Results

Patient population

We enrolled 11 patients with severe AS and MS. Clinical findings in the 11 patients are presented in Table 1. Three were male and eight were female, with a mean age of 83.6 ± 4.7 years. Atrial fibrillation was present in two patients and one patient had a permanent pacemaker for complete atrioventricular block. Beta blockers were taken in six patients (54%) and diuretics in seven patients (63%). The mean EF was $58 \pm 8.5\%$. All patients had tricuspid severe AS (AVA: $0.50 \pm 0.15 \text{ cm}^2$, peak velocity $5.1 \pm 1.0 \text{ mmHg}$, mean transaortic pressure gradient $60.2 \pm 25.1 \text{ mmHg}$). Moderate or greater AR and MR were observed in one patient for each.

The Sapien XT and Sapien 3 were used in eight patients, the CoreValve and Evolute R were used in three patients. The procedure was performed via the transfemoral approach in six patients, the transapical route in four, and the direct aorta route in one.

Hemodynamic study with Doppler echocardiography

Echocardiographic parameters at baseline and after TAVR are shown in Table 2 and flow chart according to the change of stroke volume (SV), MPG, and MVA are shown in Fig. 2. Blood pressure and heart rate were stable in all patients. Although SV increased after TAVR in nine patients, MPG decreased and MVA increased in eight of them. In only one patient (patient 5), MPG increased and MVA did not change.

SV increased significantly after TAVR ($52 \pm 12 \text{ mL}$ to $63 \pm 18 \text{ mL}$, $p = 0.041$), and MPG decreased ($6.9 \pm 3.8 \text{ mmHg}$ to $5.1 \pm 2.5 \text{ mmHg}$, $p = 0.011$) and MVA increased ($1.12 \pm 0.25 \text{ cm}^2$ to $1.49 \pm 0.43 \text{ cm}^2$, $p = 0.035$) as shown in Fig. 3. Heart rate slightly decreased ($75 \pm 11 \text{ bpm}$ to $71 \pm 13 \text{ bpm}$, $p = 0.30$). In two patients, SV decreased (patients 1 and 3) and MPG decreased. DVI was >2.5 in six patients before AVR and decreased to <2.5 after TAVR in five patients as shown in Table 2. In one patient (patient 5), DVI was high both before and after TAVR.

Mitral annular calcification and mitral leaflet mobility

Severe MAC was observed in four patients (patients 5, 6, 7, 11) and AML mobility was reduced severely before TAVR in these patients as shown in Table 3. Opening angle of AML ($\alpha 1$) was 30–40 degrees in them. AML mobility improved after TAVR in two patients (patients 6 and 7) as shown in Fig. 4. In one of the other two patients (patient 5), calcification extended into the entire AML and AML mobility did not improve. AML opening angle increased more than 10 degrees after TAVR in five patients (patients 2, 4, 6, 7, 8). In four of them (patients 2, 4, 7, 8), MVA increased more than

Table 1
Patient characteristics.

Age (years)	83.6 \pm 4.7
Male	3 (27)
Height (cm)	146 \pm 9.9
Weight (kg)	46.3 \pm 8.1
Atrial fibrillation	2 (18)
Pacemaker	1 (9)
Coronary artery disease	1 (9)
Cerebral vascular disease	1 (9)
Medicine	
ACE-I/ARB	3 (27)
B-Blockers	6 (54)
Calcium channel blocker	2 (18)
Diuretics	7 (63)
Echocardiographic data	
Ejection fraction (%)	58.2 \pm 8.5
Aortic valve	
Max velocity (m/s)	5.1 \pm 1.0
Mean pressure gradient (mmHg)	60.2 \pm 25.1
Aortic valve area (cm ²)	0.50 \pm 0.15
Aortic regurgitation greater than mild	2 (18)
Mitral regurgitation greater than mild	1 (9)
TAVR procedure	
Valve type	
Sapien valves	8 (73)
CoreValve or Evolut R	3 (27)
Approach	
Trans femoral	6 (55)
Trans apical	4 (36)
Direct aorta	1 (9)
CE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker; TAVR, transcatheter aortic valve replacement.	

Table 2
Hemodynamic changes of mitral valve with Doppler echocardiography.

	Baseline										Post TAVR									
	HR (bpm)	NYHA	LVSV (mL)	MPG (mmHg)	MVA (cm ²)	PHT (ms)	DVI	RVSP (mmHg)	AR	MR	HR (bpm)	NYHA	LVSV (mL)	MPG (mmHg)	MVA (cm ²)	PHT (ms)	DVI	RVSP (mmHg)	AR	MR
1	79	III	59.8	5.9	1.41	18.8	2.3	29	1	1	86	II	49.2	4.1	1.51	73.5	2.2	28	1	1
2	89	IV	22.0	10.9	0.53	45.6	5.0	66	1	1	92	II	54.0	5.4	1.60	68.4	1.5	22	1	1
3	86	IV	49.4	8.4	1.39	48.5	1.8	24	0	1	56	II	43.3	6.8	1.30	45.6	2.3	23	0	1
4	64	II	68.0	3.9	1.17	119	4.5	33	2	1	66	II	103	3.2	2.28	133	2.2	36	1	1
5	75	III	52.4	6.5	0.91	196	2.9	50	1	1	76	III	54.3	7.9	0.92	151	2.6	47	1	1
6	77	IV	50.7	15.6	1.16	81.0	2.2	63	1	1	59	II	60.6	10.7	0.80	142	3.1	25	0	0
7	90	II	42.0	9.8	0.92	39.2	2.5	22	0	1	88	II	49.3	6.4	1.41	45.2	2.1	31	1	0
8	82	II	56.4	2.8	1.17	114	2.5	17	1	1	58	II	63.8	2.3	1.52	80.6	2.2	19	1	0
9	60	III	63.8	3.8	1.37	140	1.9	23	1	1	67	II	92.3	3.4	2.22	89.2	1.4	27	1	1
10	59	II	61.7	3.5	1.17	107	1.9	24	1	1	65	II	61.9	3.5	1.35	96.8	1.9	34	2	1
11	65	IV	50.1	4.6	1.13	116	2.8	55	1	2	65	II	62.8	2.8	1.52	112	2.3	53	2	2

AR, aortic regurgitation; DVI, Doppler velocity index; HR, heart rate; LVSV, left ventricular stroke volume; MPG, mean transmittal pressure gradient; MR, mitral regurgitation; MVA, mitral valve area; NYHA, New York Heart Association; PHT, pressure half time derived from transmitral flow; RVSP, right ventricular systolic pressure; TAVR, transcatheter aortic valve replacement.

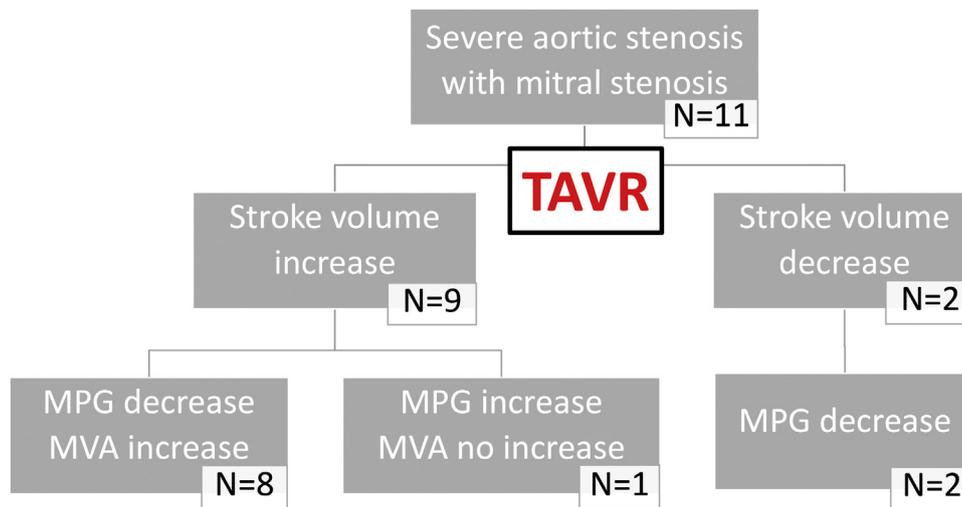


Fig. 2. Patients flow chart according to hemodynamic change after TAVR. MPG, mitral pressure gradient; MVA, mitral valve area; TAVR, transcatheter aortic valve replacement.

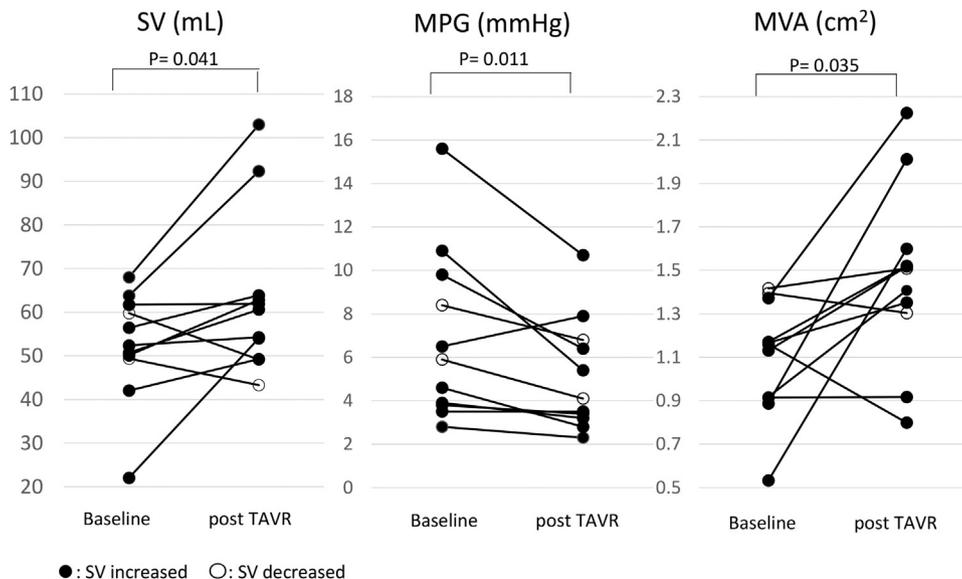


Fig. 3. Hemodynamic analysis with echocardiography. MPG, mitral pressure gradient; MVA, mitral valve area; SV, stroke volume; TAVR, transcatheter aortic valve replacement.

Table 3

Mitral annular calcification severity and mitral valve opening angles.

	MAC severity	Calcification deposit	MV opening angle			
			Baseline		Post TAVR	
			$\alpha 1$	$\alpha 2$	$\alpha 1$	$\alpha 2$
1	Absent	none	44	71	46	66
2	Mild	A3	32	44	46	56
3	Absent	none	47	67	50	72
4	Mild	A3	40	58	57	52
5	Severe	A1, A2, A3, P1, P2, P3	32	64	31	59
6	Severe	A1, P1, P2, P3.	41	58	56	66
7	Severe	A1, A3, P1, P2, P3	32	72	43	78
8	Mild	P3	43	48	55	70
9	Mild	P2, P3	58	62	58	55
10	Moderate	A2, P2, P3	40	71	41	72
11	Severe	A3, P1, P2, P3	42	68	40	61

MAC, mitral annular calcification; MV, mitral valve; TAVR, transcatheter aortic valve replacement.

0.3 cm² after TAVR. The sensitivity, specificity, and accuracy of the increase of more than 10 degrees in AML opening angle for MVA increasing more than 0.3 cm² was 80%, 67%, and, 73%. Most cases with mild or moderate MAC had calcium deposits in PML. We could not observe the relation between PML mobility and calcium deposits of PML.

In-hospital course and early outcome

All 11 patients were alive at 6 months, while 1 patient died in 98 patients without MS (all-cause mortality: 0% vs. 1.0%, $p = 0.73$). TAVR procedures were performed completely without conversion to surgery in all patients with MS. A periprocedural cerebrovascular accident was observed in one (patient 2) of patients with MS, while in 4 of 98 patients without MS (9.1 vs. 4.1%, $p = 0.45$). The safety endpoint was observed in one (patient 2) of patients with MS, while 27 of 98 patients without MS (9.1% vs. 27.6%, $p = 0.18$). Postprocedural AR grade ≥ 2 was observed in two patients (cases 10 and 11) owing to para valvular leak.

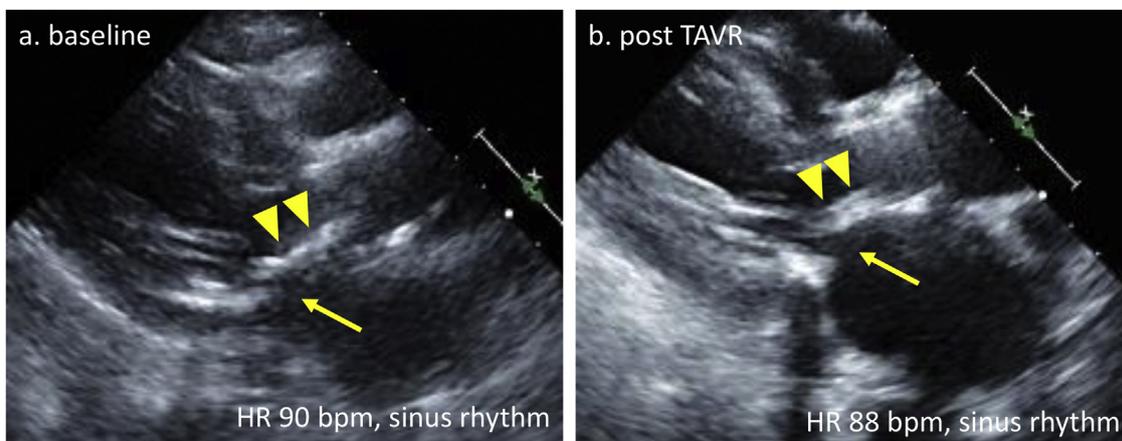


Fig. 4. An example of patient 7 in which mitral leaflet mobility improved after TAVR. Parasternal long-axis view in the early diastole. Anterior mitral leaflet (arrow head) mobility severely reduced at baseline (a). It improved after TAVR (b). An increase in mitral orifice after TAVR was observed (arrow). HR, heart rate; TAVR, transcatheter aortic valve replacement.

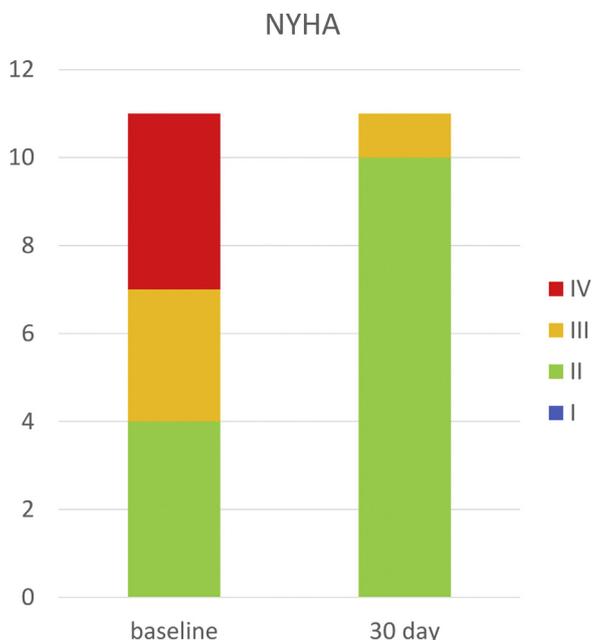


Fig. 5. Functional status by New York Heart Association (NYHA) class. Functional class improved to class II in six patients at 30-day follow-up.

NYHA functional class improved to class II in six patients at 30-day follow-up as shown in Fig. 5. It did not change in the other five patients.

Discussion

To the best of our knowledge, this is the first report to evaluate the change of hemodynamic and functional status among severe AS patients with MS undergoing TAVR. Our study showed that the improvement in hemodynamic and functional status after TAVR was observed in most patients.

TAVR was performed safely among severe AS patients with MS in our study. The procedure outcome in severe AS patients with MS was not inferior to the previous data of AS patients who were at high risk for increased operative complications and death [23]. A recent study reported that severe MS was not an independent predictor of poor in-hospital outcomes following TAVR [4]. Although MAC frequently coexists with senile sclerotic AS, 30-day mortality and major complications following TAVR were similar between patients with and without MAC [5]. These results may lead to consideration of TAVR for symptomatic severe AS patients with concomitant MS.

However, concomitant severe MS was reported to be an independent predictor of 1-year adverse clinical outcomes following TAVR [4]. Concomitant severe MAC was also reported to be an independent strong predictor of 1-year overall all-cause mortality following TAVR [5]. Poor short-term outcome of TAVR for patients with severe AS and MS might be because MAC frequently coexists with senile sclerotic AS. MAC was a marker for multiple comorbidities and drives mortality rather than being the direct cause of increased mortality [24,25]. The etiology of concomitant MS should be considered in future studies.

Our study showed that decrease in MPG and increase in MVA were observed after TAVR. These hemodynamic changes have not been reported before. The mechanisms were not completely examined in this study. However, we consider that increase in SV due to relief from severe AS could increase MVA itself. Consequently, increase in MVA might lead to decrease in MPG. Our study included many cases with MAC and these hemodynamic changes tend to be observed especially in degenerative MS patients. Mechanisms of degenerative MS include a rigid annulus which fails to dilate during diastole and extension of disease to involve mitral leaflet calcification [26]. Reduced anterior mitral leaflet (AML) mobility appeared to be a necessary precondition to have gradient greater than 5 mmHg [3,27,28]. Extension of calcification to the middle segment of AML (A2) demonstrated a decisive role in the degree of stenosis [29]. We experienced as well that one patient with increased MPG after TAVR had circumferential heavy calcification of AML including A2 and reduced AML mobility. Hemodynamics in degenerative MS patients might be according to distribution of calcium deposits and AML mobility.

Clinical implications

The hemodynamic status of MS might improve with the intervention of aortic valve alone in most patients with severe AS and MS. Our results indicated that some patients with severe AS and MS might have pseudo MS, in which MVA increased with increase of SV. However, we need to pay attention to calcification deposit of the AML and opening angle of AML less than 40 degrees because significant MS may persist after TAVR. In our study, functional status improved following TAVR in patients with severe AS and MS. In-hospital mortality and procedural outcome were not inferior in severe AS patients with MS to those without MS as previous studies described [4,5]. Our results indicated that TAVR may cause therapeutic efficacy for selected symptomatic severe AS

patients with MS. In patients with severely reduced mobility of AML, further investigation about clinical outcomes would be needed with a large population. It is not known whether DVR improves the prognosis in those patients. A staged procedure for MS, such as transcatheter MVR, would be expected in symptomatic patients with untreated MS after TAVR.

Limitations

Our study had some limitations. First, our study was performed in a single institution and the sample size was small. A study with a larger population would be necessary to confirm the impact of TAVR in patients with AS and MS. Second, we included patients with atrial fibrillation, significant AR, and MR. The current guideline recommends that the continuity equation should not be used in cases of atrial fibrillation or associated significant MR or AR [30]. Third, most patients took some medicines that lower blood pressure and heart rate such as beta blockers and diuretics which may have impacted hemodynamics. Finally, we considered only patients who underwent TAVR. These results should be discussed in patients who underwent surgical AVR in the future studies.

Conclusion

The hemodynamic and functional status of MS improved following TAVR in most patients with severe AS and MS. Extension of calcification to the middle segment of AML may identify patients with less favorable hemodynamic status after TAVR. TAVR might cause therapeutic efficacy for selected symptomatic severe AS patients with MS.

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Conflict of interest

The authors declare that there is no conflict of interest.

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