ORIGINAL ARTICLE

Cardiac Sympathetic Nerve Function in Patients with Severe Aortic Stenosis Prior and After Transcatheter Aortic Valve Implantation: Evaluation by 5-Year Risk Model

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Abstract

***Background*: While the non-invasive assessment of cardiac sympathetic nerve dysfunction is readily accessible, its applicability in invasive intervention for structural heart disease has received limited investigation. Our study aimed to clarify the cardiac sympathetic nerve function in patients with severe Aortic stenosis (AS) and its postoperative changes after transcatheter aortic valve implantation (TAVI) using ^{123}I-metaiodobenzylguanidine scintigraphy (MIBG) in combination with 5-year mortality prediction model.**

***Methods*: Consecutive 26 patients (83 ± 5ys, male 4) with severe AS who underwent MIBG prior TAVI procedures were retrospectively enrolled. Of those, 15 patients underwent postoperative-follow up MIBG. The early and delayed heart-to-mediastinum ratio (e- and d-H/M), and washout rate (WR) were obtained from MIBG planner imaging. The MIBG 5-year mortality prediction model was employed to compare pre and after TAVI. Cardiac function and wall thickness were evaluated with transthoracic echocardiography.**

***Results*: Preoperative e-H/M, d-H/M, and WR were 2.4 ± 0.5, 2.3 ± 0.4, and 29 ± 14% respectively, and WR showed significant correlation to left ventricular ejection fraction (LVEF) and brain natriuretic peptide (BNP) (r=-0.4 and 0.6; p=0.03, and 0.001 for LVEF and BNP, respectively). 102 ± 28 days after TAVI, either H/M or WR did not show significant improvement among enrolled patients (2.5 ± 0.3, 2.3 ± 0.4, and 30 ± 11% for e-, d-H/M, and WR for after TAVI), while the BNP level was significantly reduced (128 ± 691 and 94 ± 194 pg/dl, for pre vs. after, p=0.008). Five patients showed a significant recovery in WR (37.0 ± 13.8 and 28.8 ± 8.5% for pre and post, p=0.04), and left ventricular wall thickness was significantly thinner compared to those who did not recover (15.2 ± 3.2 vs 11.2 ± 2.4, p=0.02; 14.2 ± 2.9 vs 10.8 ± 1.8, p=0.02 for intraventricular septum and posterior wall, respectively). In 5-year prediction risk model, 7 patients showed a significant reduction in mortality risk, and the patients who did not show risk reduction had significantly reduced renal function (eGFR 57.5 ± 18.8 vs. 38.2 ± 11.3 ml/min/1.73m^2, p=0.03 for recovered vs. not recovered).**

***Conclusion*: After a 3-month follow-up after TAVI, diverse response in cardiac MIBG parameters were observed among patients with severe AS, despite successful valve replacement. Cardiac MIBG serves as a non-invasive tool that can comprehensively evaluate and surrogate the severity of heart failure resulting from a multi-factorial condition.**

Keywords: Aortic stenosis, Cardiac sympathetic nerve dysfunction, MIBG, Transcatheter aortic valve implantation

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Aortic stenosis (AS) is one of the most common valvular diseases, causing left ventricular outflow obstruction, and is associated with dismal outcome including heart failure and sudden death (1). Surgical aortic valve replacement has been known historically well-established treatment for AS, while unacceptably elevated risk of complication or death is concerned (2). Particularly, due to degenerative and slow progressive nature, AS is frequently observed in elderly patients when symptoms become apparent (3). Transcatheter aortic valve implantation (TAVI) has emerged initially as a minimally invasive procedure, being an alternative option for inoperable candidate including super-elderly (2). Several clinical trials have shown that TAVI has halved mortality rate compared to conventional medical treatment, while the surgical procedure has been recognized as predominant choice of treatment (4). Furthermore, recent clinical trials have shown that patients after TAVI demonstrated equivalent mortality to those after surgical valve replacement (5). To date, TAVI has become a mainstay for invasive treatment for AS, and increasingly introduced for lower surgical risk candidate.

Heart failure (HF) is closely associated with severe AS, as a consequence of long standing, continuous myocardial remodeling due to increased afterload burden, resulting symptomatic congestion (6). However, given the fact that HF is multifactorial, and multi-etiological entity such as the concomitant with coronary artery disease, previous myocardial infarction, hypertensive damage, atrial fibrillation (7). Cardiac sympathetic nerve dysfunction, which is known as hallmark of neurohormonal, and autonomic imbalance in HF may have profound effects on cardiac performance. Particularly, cardiac sympathetic nerve dysfunction is known to be overt in HF, and is clinically evaluated by cardiac neuroimaging using ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy (8). MIBG is widely available in clinical routine, and has demonstrated numerous evidence particularly for the assessment of HF severity, prognostic implications, and treatment efficacy including optimal medical therapy and implantable devices (9–12). Moreover, standardization among different gamma-detectors has been established utilizing multi-center calibration, and dedicated software is commercially available (13–15). Thus, noninvasive monitoring of the recovery or worsening in cardiac autonomic dysfunction using MIBG is widely available and interchangeable among facilities. Accumulated evidence has demonstrated that the prognostic implication of MIBG, and prediction of treatment efficacy. More recently, 1 or 5-year cardiovascular related death risk model has been applied to routine MIBG scan based on multicenter cross-calibration database (13).

However, the evaluation of therapeutic efficacy by structural heart disease interventions remains to be established and requires further studies because the open chest surgery is known to effect on cardiac sympathetic nerve distribution, while TAVI procedure is mainly performed trans femoral approarch (16). Recently, the recovery of cardiac sympathetic nerve dysfunction by less invasive procedure such as TAVI has been discussed, while the reported studies have shown the controversy (17, 18). In this study, we examined ^{123}I-MIBG myocardial scintigraphy before and after treatment in patients who underwent TAVI using conventional parameters and 5-year mortality prediction model.

Methods

Patients

Consecutive 26 patients with symptomatic, severe AS (median 81.8 ± 7.5 years, 6 males) who underwent MIBG scan prior to TAVI at our institution between 2016 and 2017 were retrospectively enrolled. Of those, 15 patients (mean 83.2 ± 5.1 years, 4 males) underwent follow-up MIBG scan. Patients diagnosed or suspect of neurological, other brain disorder diseases such as Parkinson's disease, or under treatment with antidepressants which might effect on MIBG parameters were excluded. Patient profile was retrospectively collected from medical records including clinical history, medication, cardiovascular risk factors, and blood test data. The New York Heart Association (NYHA) classification was assessed for all participants prior TAVI, and follow-up evaluation was done by other attending physician who were blinded to follow up MIBG scan results. This retrospective study was approved by our institutional review board (number 19-022).

Transthoracic echocardiography

Transthoracic echocardiography was performed within 3 weeks prior TAVI procedure and MIBG scan. Follow up echocardiography was conducted within a month around follow up MIBG scan. Echocardiographic examinations were assessed by experienced cardiologists using Vivid E9 system (GE Medical Systems, Milwaukee, WI, USA). Measurements were performed in accordance with the guidelines for the clinical application of echocardiography by Japanese Circulation Society in 2010. Aortic valve area (AVA), Volumetric analysis including left ventricular end-diastolic dimension (LVDd), end-systolic dimension (LVDs), and ejection fraction (LVEF) was measured using the biplane Simpson method. The wall thickness was measured in short axis view, and interventricular and posterior wall thickness (IVST and PWT) were obtained. LV mass index was calculated from LVDd, IVST, and PWT as follows. LV mass (g)=0.8{1.04*[(LVDd+IVST+PWT)^3 -LVDd^3]}+0.6 (19). Delta value for LVEF, the early and delayed heart-to-mediastinum ratio (e- and d-H/M), and washout rate (WR) were calculated by subtracting pre TAVI from post TAVI data.

Table 1 Patient characteristics prior to TAVI (n=26)

Age (ys)	81.8 ± 7.5
Male (%)	6 (23)
Height (cm)	148.8 ± 7.1
Body weight (kg)	49.2 ± 9.9
Current Smoker (%)	2 (8)
Past medical history	
HT (%)	17 (65)
HL (%)	20 (76)
DM (%)	5 (19)
Myocardial infarction	1 (4)
CABG	2 (8)
PCI	4 (15)
Pacemaker implantation	2 (8)
Atrial fibrillation	1 (4)
Medications	
β-blocker (%)	2 (8)
CCB	12 (46)
ACE-I/ARB (%)	4 (15)
Diuretics (%)	15 (58)
Statin (%)	17 (65)
MIBG parameter	
e-H/M	2.4 ± 0.5
d-H/M	2.3 ± 0.4
WR (%)	29.4 ± 14.8

Abbreviations: HT, hypertension; HL, hyperlipidemia; DM, diabetes; ACE-I, angiotensin co-enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin receptor blockade; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; e-H/M, early heart to mediastinal ratio; d-H/M, delayed heart to mediastinum ratio; WR, washout rate

TAVI procedure

Indication for TAVI was determined based on the clinical consensus reached by a heart team, which consisted of cardiologists, cardiovascular surgeons, anesthesiologists, and imaging specialists. All patients underwent TAVI using the SAPIEN X, SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) or CoreValve™, Evolut™ R (Medtronic, Minneapolis, MN, USA). TAVI was performed using the transfemoral approach in almost all patients under general anesthesia. Two patients were treated using the trans-subclavian approach, whereas one patient was treated under local anesthesia because of severe impairment in respiratory function.

MIBG imaging

The baseline MIBG scan was performed within 2 weeks prior to TAVI procedure, and follow up MIBG scan was scheduled around 3 months after TAVI. ^{123}I-MIBG (PDR Pharma Co., Tokyo, Japan) was intravenously administered at a dose of 111 MBq. Anterior planar images were acquired at 15 min (early image) and 240 min (delayed image) after ^{123}I-MIBG injection. ^{123}I-MIBG scintigraphy was performed with Symbia T6 SPECT/CT system (Simens healthineer, Enlargen, Germany). Acquired planar image by low-energy high-resolution collimator was imported to workstation, and a commercially available software package smartMIBG® (PDR Pharma Inc., Tokyo, Japan) was used to perform semi-automatic calculation by standardizing institutional variation (14, 20). e- and d-H/M as institutional value obtained from low-energy collimator, and WR with decay and background correction were calculated using smartMIBG®. One and 5-year mortality risk for heart failure were also automatically generated by adding clinical information obtained from medical chart including age, gender, and NYHA class to MIBG parameters (13). While serial MIBG scans are commonly utilized, there is currently no universally accepted standard for defining the threshold of significant change in MIBG parameters and 5 year estimated mortality rate by smartmIBG®. Therefore, we adopted a simplified approach by comparing the parameter change with that of the previous scan.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Categorial variables were expressed as number and %. Statistical analysis was performed using EZR 1. 6 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) for non-parametric t test, paired-t including Wilcoxon test, and Spearman correlation coefficient (21).

Results

Table 1 showed the patient demographics prior to TAVI procedure. More than half of the patients were female with mean age of 83. More than 70% had hypertension and hyperlipidemia, and around 20% had diabetes mellites. Around 10% were on β-blockade, or angiotensin converting enzyme inhibitor /angiotensin II receptor blockade, while more than half were on diuretics. Blood test data at baseline showed a mild to moderate decrease in renal function and a slight decrease in hemoglobin. In MIBG parameters, e- and d-H/M were 2.4 ± 0.5 and 2.3 ± 0.4. WR was 29.4 ± 14.8%, and 11 patients showed a markedly increased value (over 20%). Figure 1 showed the plots for LVEF, brain natriuretic peptide (BNP) and MIBG parameters prior TAVI. Delayed H/M showed significant inverse correlation to BNP, while did not to LVEF (r=-0.5, p=0.008; p=0.3 for BNP and LVEF). WR showed significant positive and negative correlation to BNP and LVEF (r=0.6, p=0.001; r=0.4, p=0.03 for BNP and LVEF).

Follow-up ^{123}I-MIBG was performed 102 ± 28 days after

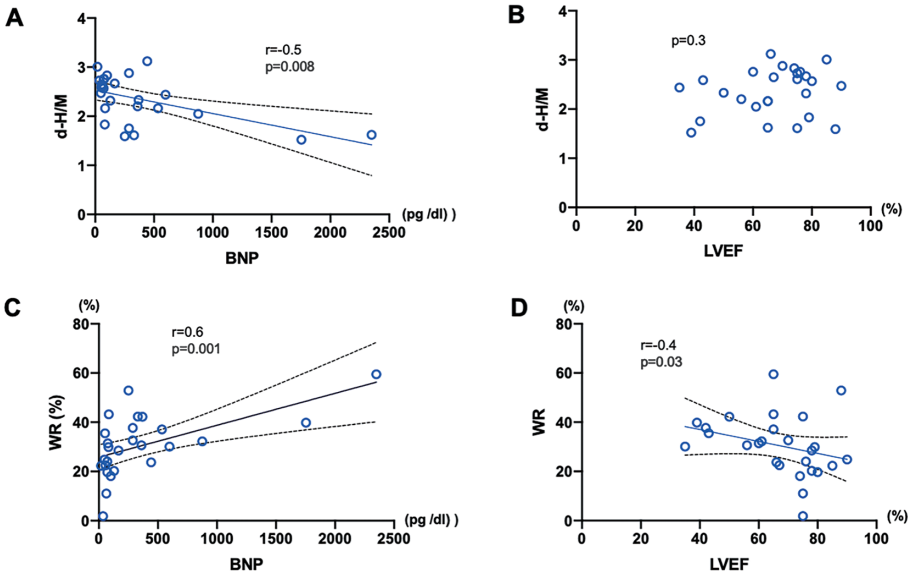

Figure 1 Correlations of MIBG parameters to BNP and left ventricular ejection fraction are shown. A significant positive correlation was observed for BNP and WR (r=0.59, p=0.005) (A). Significant negative correlations were observed for BNP and d-H/M, WR and LVEF (B and C), while not for d-H/M and LVEF (D).

Table 2 Clinical findings pre and after TAVI (n=15)

	Pre TAVI	After TAVI	P value
NYHA class			
I/II/III/IV (n)	0/4/10/1	7/8/0/0	na
Laboratory data			
Cr (mg/dl)	1.1 ± 0.4	1.0 ± 0.3	0.6
eGFR (ml/min/1.73m^2)	47.2 ± 17.8	48.9 ± 18,5	0.6
BNP (pg/dl)	128 ± 691	94 ± 194	0.007
HGB (g/dl)	11.7 ± 1.7	12.4 ± 1.0	0.1
Echocardiography data			
AVA (cm^2)	0.7 ± 0.2	1.9 ± 0.5	<0.0001
EF (%)	63.0 ± 15.5	66.0 ± 13.0	0.1
LVDd (mm)	43.0 ± 10.0	43.0 ± 8.2	0.6
LVDs (mm)	26.0 ± 10.0	25.3 ± 9.0	0.8
IVST (mm)	12.5 ± 3.3	12.0 ± 1.7	0.7
PWT (mm)	11.9 ± 2.8	12.0 ± 2.8	0.8
LV mass Index (g/m^2)	136.3 ± 41.5	136.5 ± 43.1	0.8
Moderate AR (n)	1	1	na
^{123}I-MIBG scintigraphy data			
e-H/M	2.4 ± 0.5	2.5 ± 0.3	0.6
d-H/M	2.3 ± 0.4	2.3 ± 0.3	1.0
WR (%)	29.4 ± 14.8	28.6 ± 12.0	1.0
MIBG defect score	3.8 ± 4.1	3.3 ± 3.3	0.5
1-yr mortality risk	2.4 ± 0.8	2.0 ± 1.2	0.8
5-yr mortality risk	8.5 ± 4.2	7.0 ± 5.4	0.7

Abbreviations: NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; HGB, hemoglobin; AVA, aortic valve area; EF, ejection fraction; LV, left ventricle; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; IVST, interventricular septal thickness; PWT, posterior wall thickness; e-H/M, early heart to mediastinal ratio; d-H/M, delayed heart to mediastinum ratio; WR, washout rate; HF, heart failure; na, not available or not applicable

TAVI. Table 2 showed the demographics pre and after TAVI. BNP was significantly decreased after TAVI (128 ± 691 and 94 ± 194 pg/dl, for pre vs. after, p=0.007) (Figure 2A). LVEF was not significantly different between pre and after TAVI (Figure 2B). As shown in Table 2, LV dimension did not significantly change after TAVI. Baseline echocardiographic data showed preserved left ventricular function without left ventricular enlargement, while demonstrated mildly thickened septal wall, and accordingly LV Mass index was increased. In a baseline NYHA classification, about 70% of the patients had class Ⅲ, and the rest had class II (30%) and IV (0.7%). As expected, aortic valve area showed a significant decrease after TAVI, and NYHA classification demonstrated transition from III or IV to I and II. Moderate aortic regurgitation coexisted with AS in one case prior to TAVI, and one case had postoperative moderate perivalvular regurgitation. None of the parameters did not show a significant change after TAVI including 1-yr and 5-yr risk model estimation. The defect score was mild at 3.8 ± 4.1 at baseline, and no significant change was observed after TAVI. The change in MIBG parameters after TAVI showed no statistical significance for delta LVEF, when defined as the change after TAVI from preoperative status, while there was a tendency for the change in both d-H/M and WR in line with LVEF improvement (Figure 2E, and F). Additionally, we analyzed the change of the parameters regarding eGFR, the use of diuretics, and left ventricular hypertrophy (LVH) (IVST≧12 mm). We found that the patients with LVH showed a significant improvement in LVEF after TAVI (Supplemental Table S1). In the analysis with the use of diuretics and eGFR, there was no statistically significant finding (Supplemental Table S2, and S3).

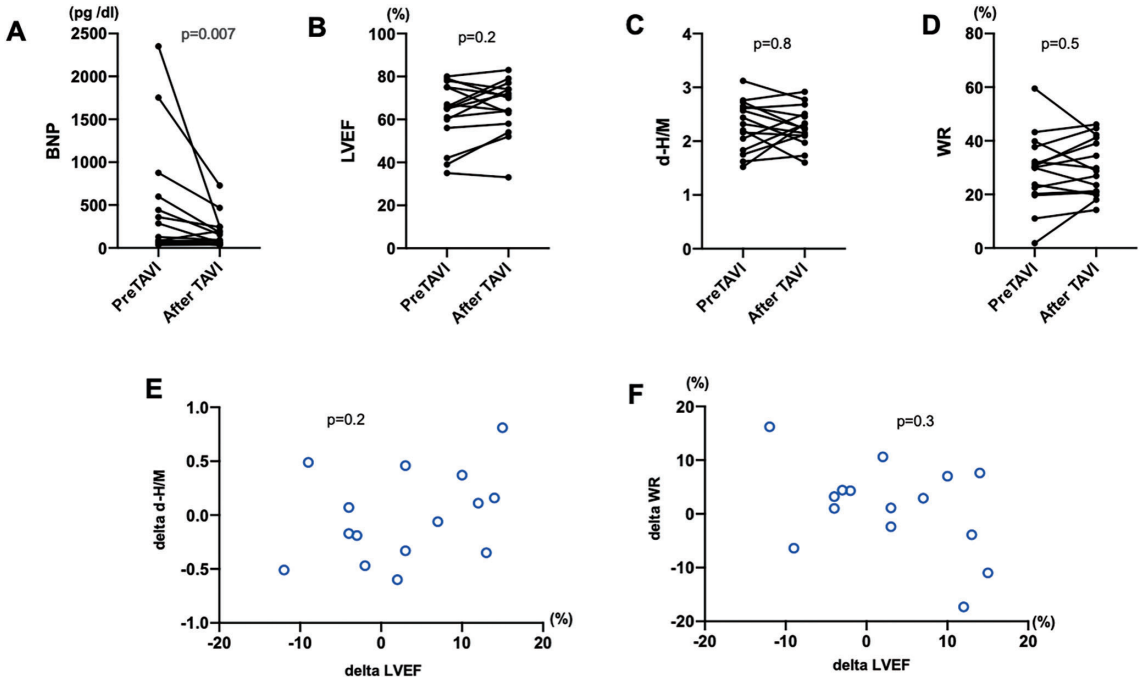

Figure 2 The change in BNP, cardiac function, and MIBG parameters pre and after TAVI are shown. A significant reduction of BNP level was observed pre and after TAVI (128 ± 691 and 94 ± 194 pg/dl, for pre vs. after, p=0.008) (A). Neither LVEF, d-H/M, or WR did not show statistically significant difference between pre and after TAVI (B, C, and D). When delta value was obtained from LVEF and MIBG parameters pre and after TAVI, there was no significant correlation between delta d-H/M, delta WR, and delta LVEF, while there was a tendency for the change in both d-H/M and WR in line with LVEF improvement (E and F).

Table 3 showed the comparison between the patients who showed WR recovery and those who did not after TAVI. Left ventricular wall thickness and the use of diuretics showed a significant difference between the patients who did not recover and who recovered (11.2 ± 2.4 vs. 15.2 ± 3.2, p=0.02; 10.8 ± 1.8 vs. 14.2 ± 2.9, p = 0.02 for intraventricular septum and posterior wall, respectively). Baseline LVEF, left ventricular dimension, and measured AVA after TAVI were not significantly different between two groups. Table 4 showed a comparison of 5- year risk model between who showed reduction and those who did not. A significant difference in eGFR observed, while other parameters such as cardiovascular risk factors and cardiac function were not between two groups (57.5 ± 18.8 vs. 38.2 ± 11.3 ml/min/1.73 m^2, p = 0.03 for recovered vs. not recovered). Figure 3 and 4 showed the representative cases who showed the improvement in WR and 5-year risk model and who did not after TAVI. Figure 3 showed a 79 years-old female with severe AS and NYHA class II, and MIBG pre-TAVI has demonstrated markedly increased washout despite preserved e-H/M. WR has significantly improved 3 months after TAVI (WR 59.5 to 42.2%, NYHA class has not been changed), and 5-year risk prediction model was re-calculated from 16% to 13%. Figure 4 showed an 80 years-old male with severe AS and NYHA class II, and MIBG parameter has demonstrated preserved e-, d-H/M, and WR. However, follow up MIBG scan revealed unchanged or relatively increased WR 3 months after TAVI.

Discussion

In the present study, cardiac sympathetic nerve dysfunction in patients with severe AS and the change after TAVI were investigated, by employing 5-year mortality prediction model. WR was significantly correlated to BNP and LVEF at baseline, and significant reduction in BNP was achieved after TAVI. According to AS related HF staging by Genereux et al., the enrolled patients should be assigned as stage 1, indicating early stage of HF due to AS (22). The mean H/M prior TAVI were relatively preserved compared to previous reports and the database from Japanese Society of Nuclear Medicine prior and after TAVI (23). However, several patients demonstrated reduced H/M when considered the variance (distributed 1.9 to 2.9, and 1.9 to 2.7, for e-, and d-H/M, respectively), but considering the optimal threshold reported by Nakata, et al (d-H/M as 1.68), the value of d-H/M for most patients was assessed as not categorized as high-risk (12). In addition to H/M, the mean value WR were around 30% prior and after TAVI, indicating the enrolled subjects have included the cases with mildly increased WR compared the Japanese database, and no patient showed rapid washout as previously reported (24, 25). After TAVI, the change in MIBG parameters as therapeutic response were diverse among enrolled patients. The change in LVEF and MIBG parameters did not show a

Table 3 Clinical demographics: recovered and not recovered MIBG-WR (baseline)

	WR recovered (n=5)	WR not recovered (n=10)	P value
Age (yrs)	80 ± 4.5	84 ± 5.0	0.3
Male Sex	0 (0)	10 (100)	0.09
Height (cm)	147 ± 6.0	151 ± 8.3	0.8
Weight (Kg)	50.5 ± 10.0	52.5 ± 12.0	0.8
BSA (cm^2)	1.4 ± 0.1	1.4 ± 0.1	0.9
Current smoker	1	1	1.0
NYHA class I-II	0	5	0.5
NYHA class III-IV	5	5	0.5
HT	4	7	1.0
HL	7	5	1.0
DM	2	1	0.5
β-blocker	1	0	0.3
CCB	1	5	0.07
ACE-I/ARB	0	2	0.5
Diuretics	5	4	0.04
Statin	4	7	1.0
Myocardial infarction	1	0	1.0
CABG	2	0	0.6
PCI	1	4	0.1
Pacemaker implantation	0	2	0.6
Cr (mg/dl)	1.2 ± 0.3	0.8 ± 0.3	0.07
eGFR (ml/min/1.73m^2)	57.4 ± 21.5	42.1 ± 15.9	0.1
BNP (pg/dl)	1095.8 ± 944.3	175.6 ± 183.4	1.0
HGB (g/dl)	11.3 ± 1.9	11.9 ± 1.8	0.6
AVA (cm^2)	0.6 ± 0.2	0.8 ± 0.2	0.08
EF (%)	62.1 ± 15.0	63.2 ± 15.3	0.9
LVDd (mm)	41.0 ± 11.1	48.2 ± 12.8	0.4
LVDs (mm)	26.6 ± 8.9	32.0 ± 14.3	0.2
IVST (mm)	11.2 ± 2.4	15.2 ± 3.2	0.02
PWT (mm)	10.8 ± 1.8	14.2 ± 2.9	0.02
LV mass index (g/m^2)	124.5 ± 38.3	161.2 ± 36.7	0.1

Abbreviations are same as Table 1 and 2.

Table 4 Characteristics of reduced or not reduced in 5-yr mortality risk by MIBG (baseline)

	5-year mortality risk reduced (n=7)	5-year mortality risk not reduced (n=8)	P value
Age (yrs)	82 ± 6	84 ± 5	0.6
Male	1	3	1.0
Height (cm)	149 ± 8.5	150 ± 7.6	0.8
Weight (kg)	49.0 ± 11.7	53.1 ± 9.4	0.5
Current smoker	1	1	1.0
NYHA class I-II	3	4	1.0
NYHA class III-IV	4	4	1.0
HT	5	6	1.0
HL	5	7	1.0
DM	2	1	0.6
β-blocker	1	0	0.9
CCB	2	4	0.8
ACE-I/ARB	0	2	0.9
Diuretics	5	4	0.6
Statin	5	6	0.6
Myocardial infarction	0	1	0.8
CABG	2	0	0.6
PCI	2	3	0.7
Pacemaker implantation	1	1	0.9
Cr (mg/dl)	0.86 ± 0.28	1.20 ± 0.29	0.05
eGFR (ml/min/1.73m^2)	57.5 ± 18.8	38.2 ± 11.3	0.03
BNP (pg/dl)	809 ± 912	199 ± 199	0.09
HGB (g/dl)	11.8 ± 0.7	11.6 ± 0.7	0.9
AVA (cm^2)	0.63 ± 0.20	0.76 ± 0.14	0.2
EF (%)	62 ± 13	64 ± 16	0.9
LVDd (mm)	40.6 ± 11.1	48.2 ± 13.0	0.4
LVDs (mm)	27.2 ± 8.6	31.0 ± 11.6	1.0
IVST (mm)	14.1 ± 3.2	11.1 ± 2.6	0.08
PWT (mm)	13.4 ± 2.8	10.6 ± 2.0	0.05
LV mass index (g/m^2)	147.7 ± 36.8	127.1 ± 42.3	0.4

Abbreviations are same as Table 1 and 2.

significant correlation, while the plots in delta WR showed a decreasing trend in line with the recovery of LVEF. In comparison between the patients who showed recovery in WR and did not, left ventricular wall thickness was significantly higher in patients who did not show WR recovery, speculating the disease caused by the infiltrative disease such as cardiac amyloidosis (26). In the WR recovered group, the rate of diuretics uses (mainly loop diuretics) was a significantly higher than the non-improvement group because all patients with WR recovered were on diuretics. It is presumed that the renin-angiotensin-aldosterone activation in response to the sodium effect of loop diuretics. Interestingly, in 5-year mortality risk estimation, the patients who were calculated as reduced risk after TAVI had significantly preserved renal function. It should be discussed the reason for significant difference in renal function between the groups, despite neither serum creatinine nor GFR was not enrolled in the calculation of prediction model (13). From the results of this study including the additional analysis, it is speculated that the patients with relatively preserved renal function, or not contraindicated to use diuretics (e.g. patients with hypertension and preserved renal function, often complicated with LVH) can be potentially reversible causes of cardiac sympathetic dysfunction among TAVI candidates for severe AS (27–29). The close relation of renal function and cardiac sympathetic nerve activity has been widely known for HF with both preserved and reduced LV function, so called cardio-renal syndrome (30). The combination of renal function and MIBG parameters to predict mortality is a significant potential to improve prognostic implication, while this has been less investigated (25, 31, 32).

Although it has been widely recognized that TAVI significantly improved the prognosis in patients with severe AS, there has been a controversy among reported studies for

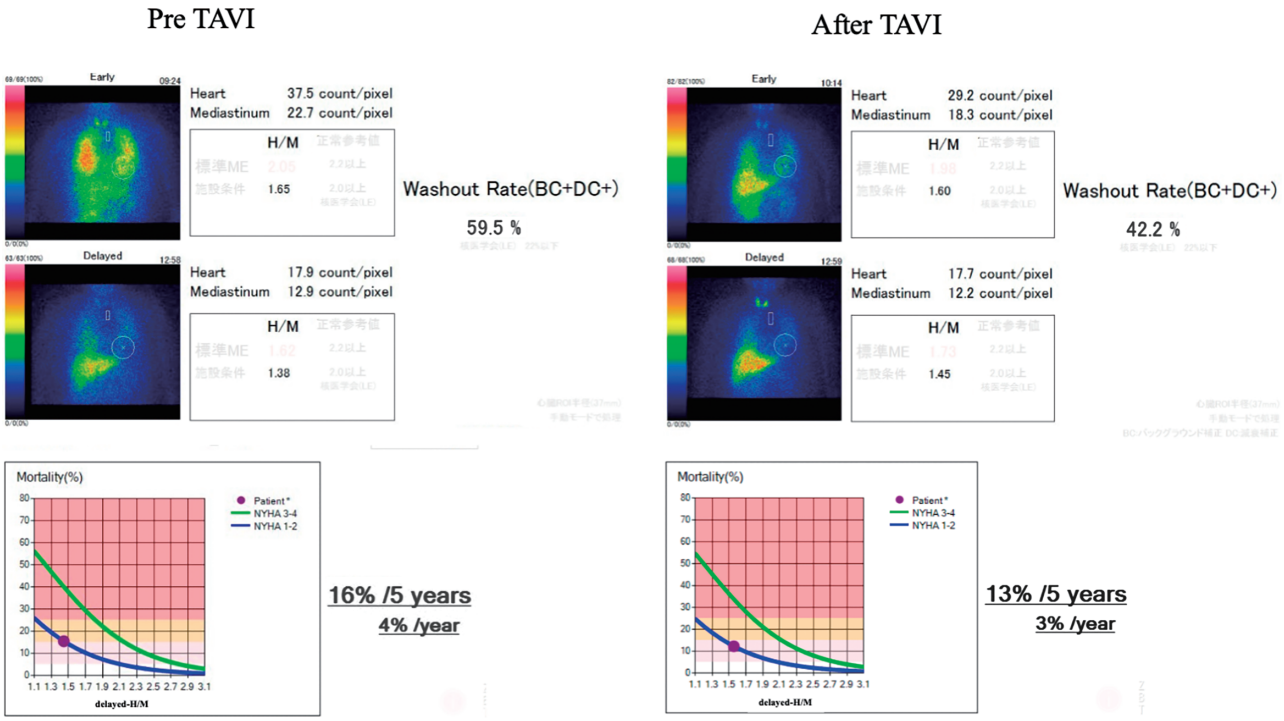

Figure 3　Representative case with significant recovery of cardiac MIBG parameters post TAVI is shown. The delayed H/M was 1.62 prior to TAVI, and recovered to 1.73 after TAVI. SmartMIBG® analysis showed increased WR, and reduced 3 months after TAVI (59.5% to 42.2%). 5-year prediction model revealed a reduction of estimated event risk (16% to 13%).

*Abbreviation: BC, background correction; DC, decay correction; HMR, heart-to-mediastinum ratio

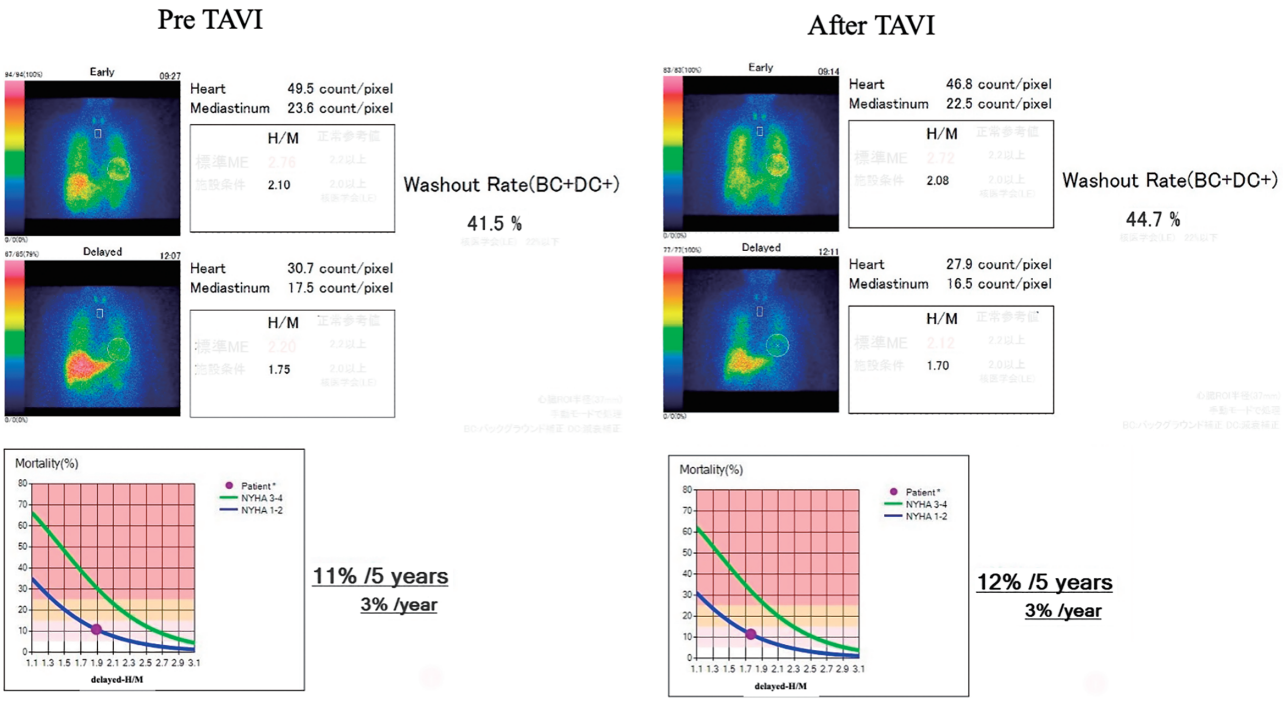

Figure 4　Representative case of unchanged or worsened in cardiac MIBG parameters after TAVI is shown. The delayed H/M and WR were 2.10, and 41.5.%, demonstrating normal MIBG uptake ratio with increased washout. However, WR remained unchanged or further increased 3 months after TAVI (41.5% to 44.7%). In 5-year mortality risk analysis, it showed unchanged or slightly worsened after TAVI from pre TAVI (11% to 12%).

*Abbreviation: BC, background correction; DC, decay correction; HMR, heart-to-mediastinum ratio

the improvement MIBG parameters. Sobajima et al. have reported the early effects in recovery of MIBG parameters. The change in MIBG parameters in 2 weeks after TAVI significantly improved among enrolled patients (18). On the other hand, Liga et al. reported showed no improvement evaluated MIBG as late as 6 months after TAVI, and also reported that left ventricular hypertrophy was a major predictor of impaired cardiac sympathetic nerve activity (12, 33–36). The one of the issues should be discussed is the optimal timing of follow up MIBG scan, indicating the follow up MIBG is not appropriate for weeks or a few months, hence serial scans with longer follow up should be conducted. Kadoya et al. in studies enrolled a largest number and longer follow-up among published, reported that a significant improve was observed early after TAVI, and serial measurement in 6 and 12 months revealed that MIBG further improved, and the baseline pressure gradient was independent predictor for improved d-H/M (1, 9, 17, 22, 37–41). In addition, the findings from our study revealed a notable inconsistency between the improvement of plasma BNP level and MIBG parameters after TAVI. Although it is widely acknowledged that both BNP and MIBG serve as independent prognostic indicators, and that the improvement with therapeutic intervention has an impact on prognosis (12). However, in this study, we observed a marked improvement in BNP levels after TAVI, whereas the changes in MIBG parameters were not uniform. The potential explanations can be listed as follows: Some of the enrolled patients may be in acute or acute on chronic status. In TAVI procedure, Aortic valve stenosis is physically and rapidly relieved, resulting in immediate improvement of the intraventricular pressure overload caused by the outflow obstruction. This improvement differs significantly from conventional therapeutic interventions such as beta-blocker therapy and biventricular pacing, which have been the mainstay of the treatment in patients with heart failure (35, 36). However, the improvement of MIBG was diverse, suggesting that the release of pressure overload does not proactively restore cardiac sympathetic function. MIBG parameters directly surrogate cardiac autonomic dysfunction due to multi-etiological status including long standing myocardial deformation and neurohumoral activation, indicating that they should be evaluated in chronic and steady state. Recent rapid introduction of minimally invasive procedure such as TAVI, mitral clip, pulmonary valve implantation may have a potential to recover cardiac sympathetic nerve dysfunction. However, latest observational study using mitral clip for mitral valvular dysfunction, MIBG was not significantly changed (39). We should be cautious that recovery of cardiac sympathetic nerve function in patients with AS was not predicted by the rapid reduction in BNP levels. Hence, MIBG is a comprehensive heart failure index tool that visualizes the severity of HF regardless of the etiology.

Although there is no standardization for optimal thresholds of a significance in the change of MIBG parameters, Kasama et al. reported that -2, and -5% change of WR in multiple MIBG scans was useful for a risk stratification of HF with reduced LVEF (25). However, regrouping with above thresholds resulted in the same patient distribution compared to simple comparison we originally used in the present study. As a strength of non-invasive imaging technique, serial monitoring with follow-up multiple MIBG scans in the combination with the commodities has a significant potential to contribute as more powerful predicative tool. Although the expanding the use of 5-year mortality risk model for the recovery after structural intervention should be carefully discussed, MIBG has a significant potential in non-invasive predicting of cardiovascular death. This is a first report to enroll MIBG derived risk model in the analysis pre and after TAVI, and further studies should be conducted to evaluate its utility.

Limitation

There are several limitations to this study. It is a retrospective study and sample size is small, thus yielding less statistically convincing. Prognostic follow-up is not available in our study.

Comorbidities (OMI, post CABG, post PCI, Af) were mixed and transthyretin type of cardiac amyloidosis was not differentiated among patients. LV mass index was calculated from echocardiographic data, which may have been overestimated in some asymmetrical septal hypertrophy cases. Wall thickness and LV mass were not measured in echocardiography after TAVI due to the retrospective nature, thus not available to evaluate the change after the procedure. Prothesis-patient mismatch after TAVI were not available in our study. We did not succeed the observation for outcome after TAVI due to lost follow up.

Conclusion

In 3-months follow up after TAVI, diverse response in MIBG parameters were observed among patients with severe AS, despite successful structural intervention. Left ventricular hypertrophy and renal dysfunction were deducible as potential factors discriminating the patients with restored cardiac sympathetic nerve dysfunction, indicating MIBG may serve as a surrogate marker for the severity of heart failure due to multifactorial manifestations.

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Conflicts of interest

None.

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