Serial Changes in Cardiac Sympathetic Nervous Function After Transcatheter Aortic Valve Replacement: A Prospective Observational Study Using 123I-meta-iodobenzylguanidine Imaging

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Research Article

Abstract

Purpose:

Transcatheter aortic valve replacement (TAVR) can rapidly improve cardiac sympathetic nervous function (CSNF) within 2 weeks in patients with aortic stenosis (AS). However, it remains unclear whether such short-term improvements will be sustained thereafter. The present study aimed to investigate the mid-term (i.e., 6–12 months) effects of TAVR on CSNF in patients with severe AS using ^{123}I-meta-iodobenzylguanidine (MIBG) imaging.

Methods:

Patients with severe AS who were scheduled to undergo TAVR between October 2017 and June 2019 were enrolled in this single-centre, prospective, observational study. MIBG imaging was performed at baseline, within 2 weeks after TAVR, and at 6–12 months post-TAVR to evaluate the heart–mediastinum ratio (H/M) and washout rate (WR). Differences between each MIBG parameter at three time points were analysed, and factors involved in the long-term improvement in the late H/M were investigated.

Results:

Of 183 consecutive patients, 75 (19 men; median age: 86 years) were evaluated. The late H/M significantly improved within 2 weeks after TAVR (P=0.041) and further improved over 6–12 months after TAVR (P=0.041). The WR rapidly improved immediately after TAVR (P=0.003) but remained unchanged at 6–12 months (P=0.827). Multivariate analysis revealed that the baseline mean aortic valve pressure gradient (mPG) was an independent predictor of mid-term improvement in the late H/M (>0.1) (adjusted odds ratio: 0.035; 95% confidence interval: 0.004–0.070; P=0.037). Patients with a high baseline mPG (≥58 mmHg) exhibited a significantly greater increase in the late H/M than those with a low baseline mPG (<42 mmHg) (0.24 vs. 0.01; P=0.029).

Conclusions:

CSNF, as denoted by the late H/M, demonstrated sustained improvement from within 2 weeks after TAVR until 6–12 months later. Such improvement was related to baseline hemodynamic AS severity.

Introduction

Aortic stenosis (AS) is one of the leading causes of cardiac morbidity and mortality among elderly patients [1]. While surgical aortic valve replacement is considered as the established treatment for severe symptomatic AS, transcatheter aortic valve replacement (TAVR) is another important treatment option, particularly for elderly adults or patients with prohibitive surgical risk [2].

Patients with AS exhibit impairments in cardiac sympathetic nervous function (CSNF), and several studies have indicated improvements in CSNF consequent to TAVR [3, 4]. Our previous research

demonstrates that CSNF, as assessed by ^{123}I-meta-iodobenzylguanidine (MIBG) imaging, significantly improved within a short duration, approximately 1 week, after TAVR [4]. However, whether such short-term improvement in CSNF will be sustained thereafter remains unclear.

Functional improvement in cardiac sympathetic nerve endings is generally thought to require substantial time (i.e., more than a few months). Previous studies on the effects of beta-blockers or angiotensin-converting enzyme inhibitors (ACEIs) evaluated changes in MIBG parameters, including the heart–mediastinum ratio (H/M) and washout rate (WR), over a period of 6–12 months [5, 6]. To evaluate the effects of TAVR on CSNF adequately, it is necessary to observe not only the short-term changes in the indices of CSNF, but also long-term changes; whether or not TAVR-dependent early improvement is transitory or sustainable should be examined. Therefore, the present study aimed to investigate the mid-term effects of TAVR on CSNF using serial cardiac MIBG imaging.

Material And Methods

Study Population

This single-centre, prospective, observational study enrolled consecutive patients who were scheduled to undergo TAVR for severe AS between October 2017 and June 2019. Severe AS was defined according to the current American College of Cardiology/American Heart Association guidelines [2]. Cardiac MIBG imaging was planned to be performed at baseline, within 2 weeks after TAVR, and at 6–12 months after TAVR to evaluate the H/M and WR. All baseline and procedural data, including laboratory and echocardiographic findings, were prospectively collected at the same time as MIBG scintigraphy. Echocardiographic measurements during the study period were conducted in accordance with the recommendations of the American Society of Echocardiography.

The exclusion criteria for the initial MIBG evaluation of patients were as follows: (a) active cancer and/or Parkinson's disease; (b) incapability to perform MIBG imaging due to severe dementia and/or mental disorder; (c) ongoing therapy with medications known to interact with MIBG (e.g. labetalol, reserpine, tricyclic antidepressants, sympathomimetic amines, serotonin–norepinephrine reuptake inhibitors) [7]; (d) utilization of trans-apical and trans-aortic TAVR or of valve-in-valve TAVR for structural valve deterioration in bioprosthetic aortic valves; (e) unstable preprocedural conditions (e.g. cardiogenic shock) treated with intravenous catecholamine administration; (f) insufficient MIBG imaging quality; and (g) refusal to provide consent for study participation. Patients with serious procedure-related complications (e.g., left ventricular perforation, annular rupture, coronary obstruction, cardiac tamponade) were excluded from the subsequent postoperative MIBG evaluation. Furthermore, patients treated with newly added beta-blockers, ACEIs, and/or angiotensin II receptor blockers after TAVR were excluded from the final MIBG evaluation.

All procedures were performed in accordance with the ethical standards of the institutional research committee of Kyoto Prefectural University of Medicine (ERB-C-1081-3) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from

all participants. The corresponding author (K.Z.) had full access to all data in the study and takes responsibility for data integrity as well as data analyses.

Cardiac MIBG Imaging

The first MIBG imaging was performed at the time of admission for TAVR, which was a few days prior to TAVR in most cases. The second MIBG imaging was carried out at >2 days post-TAVR and when patients' conditions were stable in order to avoid the influence of perioperative transfusion or infection. In our institution, all patients were routinely followed up at 1, 6, and 12 months after TAVR. The third MIBG imaging was performed at the 6-month follow-up; depending on patients' availability, the third MIBG imaging was also permitted to be conducted at the 12-month follow-up.

MyoMIBG (FUJIFILM RI Pharma Co. Ltd., Tokyo, Japan) was intravenously administered at a dose of 111 MBq. Anterior planar images were acquired at 15 min (early image) and 240 min (late image) after MIBG injection using a large-field-of-view gamma camera (Discovery NM/CT 670; GE Healthcare, Waukesha, WI, USA) equipped with a medium-energy collimator. To obtain semi-quantitative parameters for tracer distribution, MIBG imaging analysis was performed based on the region of interest using smart MIBG software (FUJIFILM RI Pharma Co. Ltd., Tokyo, Japan), which was developed to semi-automatically determine the H/M and correct the H/M to standard medium-energy collimator conditions [8]. The H/M was determined by measuring the average counts in each region, whereas the WR from the heart was calculated as the time decay-corrected difference between early and late images. Experienced radiology technicians who were unaware of patients' information conducted all analyses.

TAVR procedure

The TAVR procedure was performed using the transfemoral or trans-subclavian approach under general anaesthesia or conscious sedation with local anaesthesia. Either the Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) or Medtronic CoreValve Evolut R/Pro (Medtronic, Minneapolis, MN, USA) was used as a prosthesis. The multidisciplinary heart team determined the indication, valve type, and/or vascular access for TAVR.

Statistical Analysis

Normality of distributions was assessed using the Shapiro–Wilk test. Categorical variables are presented as counts and percentages, whereas continuous variables are expressed as median (25th–75th percentile) given that few variables followed a normal distribution. With respect to normally distributed variables, the median and mean values were nearly identical. Depending on variable distribution, Friedman's test or repeated-measures analysis of variance (ANOVA) was performed for the comparison of laboratory, echocardiographic, and MIBG findings at the three time points. In case of significance, pairwise post hoc tests with Holm correction were performed. Multiple regression analysis was conducted to determine the predictors of improvement in the late H/M at 6–12 months after TAVR versus baseline. Following our previously established methodology, the cut-off values for the improvement in the H/M and WR were set at 0.1 and 3%, respectively, considering measurement reliability and clinical significance [9–

11]. The following variables were included as possible confounders: age, sex, body mass index, New York Heart Association class ≥ 3, Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) ≥ 5, Society of Thoracic Surgeons surgical mortality risk score, estimated glomerular filtration rate, post-TAVR new-onset complete left bundle branch block (CLBBB), post-TAVR pacemaker implantation, baseline brain natriuretic peptide (BNP), baseline left ventricular end-diastolic volume, baseline left ventricular ejection fraction (LVEF), baseline aortic valve area (AVA), baseline E/E', baseline peak velocity (Vmax), baseline mean aortic valve pressure gradient (mPG), and baseline late H/M. Among all variables with $P < 0.2$ according to the univariate analysis, clinically important variables with a lower P-value were selected as confounders, considering the number of endpoints and multicollinearity.

To further investigate the association between the baseline mPG and mid-term improvement in the late H/M, the study participants were retrospectively divided into three groups according to the baseline mPG: the low-gradient (LG) group, which consisted of patients with baseline mPG < 42 mmHg ($n = 24$); the high-gradient (HG) group, which comprised patients with mPG ≥ 42 mmHg and < 58 mmHg ($n = 26$); and the very-high-gradient (VHG) group, which included patients with mPG ≥ 58 mmHg ($n = 25$). The baseline mPG thresholds were set to ensure an even distribution of the number of patients. Subgroup analyses of changes in the late H/M were subsequently performed. To compare the late H/M and its changes among these three groups at three time points (at baseline, within 2 weeks after TAVR, and at 6–12 months after TAVR), one-way ANOVA or Kruskal-Wallis test was conducted for normally distributed or non-normally distributed variables, respectively. In case of significance, pairwise post hoc tests with Holm correction were performed.

Statistical analyses were performed using R software packages version 3.1.1 (R Development Core Team, Auckland, New Zealand), with the significance level for statistical hypothesis testing set at 0.05 and with the alternative hypothesis being two-sided.

Results

Patient Characteristics

Of 183 consecutive patients who underwent TAVR, 65 were excluded from initial evaluation, whereas 7 were excluded from post-TAVR evaluation due to periprocedural complications. During the follow-up period, 21 patients who required additional medical treatment, 8 patients who were followed up at other hospitals, and 7 patients who died before the final MIBG imaging were excluded from the final MIBG evaluation. The final study population comprised 75 patients (Fig. 1).

The baseline patient characteristics are summarized in Table 1. The median age of the study population was 86 years; 19 patients (25.3%) were males. A total of 57 patients were classified as having high-gradient severe AS (baseline mPG ≥ 40 mmHg), whereas 18 patients were deemed to have low-gradient severe AS (baseline mPG < 40 mmHg), including 15 patients who were diagnosed with "paradoxical low-

flow low-gradient severe AS" (LVEF ≥ 50%). The median period between TAVR and second MIBG scintigraphy and between TAVR and third MIBG scintigraphy was 6 and 205 days, respectively.

Table 1
Baseline Characteristics and Procedural Data

Parameters	Total ($n = 75$)
Baseline characteristics	
Age, years	86 (84 to 89)
Male sex, n (%)	19 (25.3)
Body mass index, kg/m^2	21.6 (19.7 to 24.0)
Society of Thoracic Surgeons score	5.7 (4.5 to 8.2)
CSHA-CFS score $\geq$ 5, n (%)	40 (54.1)
New York Heart Association class III/IV, n (%)	24 (32.0)
Current smoker, n (%)	2 (2.7)
Past medical history, n (%)	
Hypertension	59 (78.7)
Dyslipidaemia	38 (50.7)
Diabetes mellitus	11 (14.7)
Atrial fibrillation (chronic/paroxysmal)	8 (10.7)/9 (12.0)
Previous percutaneous coronary intervention	23 (30.7)
Previous coronary artery bypass grafting	4 (5.3)
Previous myocardial infarction	8 (10.7)
Previous cerebrovascular disease	15 (20.0)
Pacemaker implantation	9 (12.0)
Medications, n (%)	
ACEIs/ARBs	40 (53.3)
Beta-blockers	36 (48.0)
Diuretics	39 (52.0)

Categorical and continuous variables are presented as number (percentage) and median (25th–75th percentile), respectively.

ACEIs indicate angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; AS, aortic stenosis; CLBBB, complete left bundle branch block; CSHA-CFS, Canadian Study of Health and Aging Clinical Frailty Scale; LVEF, left ventricular ejection fraction; MIBG, ^{123}I-meta-iodobenzylguanidine; mPG, mean aortic valve pressure gradient; and TAVR, transcatheter aortic valve replacement.

Parameters	Total ($n = 75$)
AS categories, n (%)	
High-gradient severe AS (mPG ≥ 40 mmHg)	57 (76.0)
Low-gradient severe AS (mPG < 40 mmHg)	18 (24.0)
- Classical low-flow low-gradient severe AS (LVEF < 50%)	3 (4.0)
- Paradoxical low-flow low-gradient severe AS (LVEF ≥ 50%)	15 (20.0)
Period between TAVR and second MIBG imaging (days)	6 (4 to 8)
Period between TAVR and third MIBG imaging (days)	205 (191 to 222)
Procedural data	
Approach, n (%)	
Transfemoral	72 (96.0)
Trans-subclavian	3 (4.0)
Anaesthesia, n (%)	
General anaesthesia	74 (98.7)
Conscious sedation with local anaesthesia	1 (1.3)
Valve type, n (%)	
Edwards SAPIEN 3	36 (48.0)
Medtronic CoreValve Evolut R/Pro	39 (52.0)
Post-TAVR pacemaker implantation, n (%)	5 (6.7)
Post-TAVR new-onset CLBBB, n (%)	12 (16.0)

Categorical and continuous variables are presented as number (percentage) and median (25th–75th percentile), respectively.

ACEIs indicate angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; AS, aortic stenosis; CLBBB, complete left bundle branch block; CSHA-CFS, Canadian Study of Health and Aging Clinical Frailty Scale; LVEF, left ventricular ejection fraction; MIBG, ^{123}I-meta-iodobenzylguanidine; mPG, mean aortic valve pressure gradient; and TAVR, transcatheter aortic valve replacement.

Changes in Laboratory, Echocardiographic, and MIBG Findings After TAVR

Serial changes in laboratory, echocardiographic, and MIBG findings are summarized in Table 2. Hemodynamic AS parameters such as Vmax, mPG, and AVA improved immediately after TAVR and were

well maintained until 6–12 months post-procedurally. The LVEF increased after TAVR and was sustained after 6–12 months.

Table 2
Laboratory, Echocardiographic, and MIBG Findings at Baseline, < 2 Weeks After TAVR, and 6−12 Months After TAVR

Parameters	A: at baseline (n = 75)	B: at < 2 weeks after TAVR (n = 75)	C: at 6−12 months after TAVR (n = 75)	Overall P-value	A vs. B P-value	B vs. C P-value	A vs. C P-value
Laboratory data							
Haemoglobin, g/dL	10.7 (10.1 to 12.3)	10.2 (9.5 to 11.2)	11.3 (10.7 to 12.3)	< 0.001	0.001	< 0.001	0.010
Albumin, g/dL	3.8 (3.5 to 4.1)	3.1 (2.9 to 3.3)	3.9 (3.7 to 4.1)	< 0.001	< 0.001	< 0.001	0.003
Creatinine, mg/dL	0.83 (0.64 to 1.17)	0.77 (0.57 to 0.98)	0.91 (0.70 to 1.21)	< 0.001	< 0.001	< 0.001	0.003
eGFR, mL/min/1.73 m^2	51.5 (38.0 to 66.4)	60.4 (49.1 to 75.8)	50.3 (35.8 to 61.1)	< 0.001	< 0.001	< 0.001	0.020
BNP, pg/mL	290 (133 to 538)	136 (74 to 210)	89 (58 to 209)	< 0.001	< 0.001	0.030	< 0.001
Echocardiographic data							
Vmax, m/s	4.6 (4.1 to 5.0)	2.1 (1.8 to 2.4)	2.0 (1.7 to 2.2)	< 0.001	< 0.001	0.002	< 0.001
mPG, mmHg	49 (40 to 61)	9 (7 to 12)	8 (6 to 10)	< 0.001	< 0.001	< 0.001	< 0.001
AVA, cm^2	0.6 (0.4 to 0.7)	1.4 (1.2 to 1.7)	1.6 (1.2 to 1.9)	< 0.001	< 0.001	0.060	< 0.001
LVESV, mL	25 (20 to 40)	22 (18 to 35)	22 (18 to 27)	0.002	0.002	0.069	< 0.001
LVEDV, mL	74 (58 to 90)	74 (58 to 83)	70 (54 to 79)	0.011	0.205	0.080	0.006

Categorical and continuous variables are presented as number (percentage) and median (25th−75th percentile), respectively.

AVA indicates aortic valve area; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; E/E', ratio of early diastolic left transmitral flow velocity to septal mitral annular velocity; H/M, heart−mediastinum ratio; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; mPG, mean aortic valve pressure gradient; TAVR, transcatheter aortic valve replacement; Vmax, peak velocity; and WR, washout rate.

Parameters	A: at baseline (n = 75)	B: at < 2 weeks after TAVR (n = 75)	C: at 6–12 months after TAVR (n = 75)	Overall P-value	A vs. B P-value	B vs. C P-value	A vs. C P-value
LVEF, %	61 (52 to 69)	66 (58 to 71)	66 (59 to 69)	0.001	< 0.001	0.969	0.005
E/E'	27 (20 to 34)	26 (21 to 35)	24 (17 to 30)	0.044	0.969	0.058	0.058
MIBG data							
Early H/M	3.03 (2.66 to 3.25)	2.97 (2.56 to 3.16)	3.02 (2.70 to 3.35)	0.233	–	–	–
Late H/M	2.57 (2.12 to 2.85)	2.62 (2.26 to 2.95)	2.71 (2.39 to 3.04)	0.005	0.041	0.041	< 0.001
WR, %	32.7 (27.3 to 45.5)	27.2 (22.3 to 37.1)	29.8 (22.9 to 35.3)	< 0.001	0.003	0.827	0.003
Change from baseline level							
ΔLate H/M	–	0.09 (-0.11 to 0.26)	0.18 (-0.05 to 0.56)	0.021	–	–	–
ΔWR, %	–	-3.3 (-7.3 to 1.7)	-3.8 (-8.3 to 1.6)	0.827	–	–	–
Improvement in late H/M (> 0.1), %	–	34 (45.3)	43 (57.3)	0.072	–	–	–
Improvement in WR (> 3%), %	–	39 (52.0)	40 (53.3)	0.835	–	–	–

Categorical and continuous variables are presented as number (percentage) and median (25th–75th percentile), respectively.

AVA indicates aortic valve area; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; E/E', ratio of early diastolic left transmitral flow velocity to septal mitral annular velocity; H/M, heart–mediastinum ratio; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; mPG, mean aortic valve pressure gradient; TAVR, transcatheter aortic valve replacement; Vmax, peak velocity; and WR, washout rate.

Changes in MIBG parameters are presented in a boxplot in Fig. 2. Late H/M significantly improved within 2 weeks after TAVR (P = 0.041) and further improved over 6–12 months after TAVR (P = 0.041). WR rapidly improved after TAVR (P = 0.003) but showed no further improvement over 6–12 months (P = 0.827). Nevertheless, compared to the baseline level, the WR values were still significantly improved at 6–12 months after TAVR (P = 0.003).

The increase in the late H/M at 6–12 months post-TAVR (i.e., Δlate H/M [6–12 months - baseline]) was significantly greater than that just after TAVR (i.e., Δlate H/M [< 2 weeks - baseline]) (P = 0.021). In contrast, the decrease in the WR at 6–12 months after TAVR (i.e., ΔWR [6–12 months - baseline]) was not significantly different from that immediately after TAVR (i.e., ΔWR [< 2 weeks - baseline]) (P = 0.827). No changes in the early H/M were observed at the three time points.

Baseline mPG and Improvement in Late H/M at 6–12 Months After TAVR

Overall, 43 out of 75 patients showed improvement in the late H/M (> 0.1) at 6–12 months after TAVR. Multivariate analysis revealed that baseline mPG was associated with such mid-term improvement in the late H/M (adjusted odds ratio: 0.035; 95% confidence interval: 0.004–0.070; P = 0.037) (Table 3).

Table 3
Predictors of Improvement in Late H/M (> 0.1) at 6−12 Months After TAVR Compared to the Baseline Level

Parameters	Univariate		Multivariate	
	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (per 1 year)	0.082 (-0.040 to 0.215)	0.200		
Sex	-0.256 (-1.309 to 0.804)	0.632		
Body mass index	-0.067 (-0.208 to 0.067)	0.329		
New York Heart Association class ≥ III	0.848 (-0.161 to 1.936)	0.109		
CSHA-CFS score ≥ 5	0.967 (0.033 to 1.936)	0.045	0.810 (-0.191 to 1.839)	0.115
Society of Thoracic Surgeons score	0.062 (-0.113 to 0.246)	0.492		
eGFR	-0.007 (-0.030 to 0.015)	0.526		
Post-TAVR new-onset CLBBB	0.049 (-1.197 to 1.357)	0.939		
Post-TAVR pacemaker implantation	-1.792 (-4.793 to 0.181)	0.117		
Baseline BNP	0.001 (0.0002 to 0.003)	0.082	0.001 (0.0001 to 0.003)	0.067
ΔBNP (6−12 months - baseline)	-0.002 (-0.004 to -0.0002)	0.089		
Baseline LVEDV	0.016 (-0.003 to 0.036)	0.113		
Baseline LVEF	-0.012 (-0.053 to 0.028)	0.569		

In the multivariate model, the adjusted OR for the improvement in late H/M > 0.1 at 6−12 months after TAVR, as compared to that for the improvement in late H/M ≤ 0.1, was calculated by adjusting the following variables: CSHA-CFS score ≥ 5, baseline BNP level, and baseline mPG.

AVA indicates aortic valve area; BNP, brain natriuretic peptide; CI, confidence interval; CLBBB, complete left bundle branch block; CSHA-CFS, Canadian Study of Health and Aging Clinical Frailty Scale; eGFR, estimated glomerular filtration rate; E/E', ratio of early diastolic left transmitral flow velocity to septal mitral annular velocity; H/M, heart−mediastinum ratio; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; OR, odds ratio; mPG, mean aortic valve pressure gradient; TAVR, transcatheter aortic valve replacement; and Vmax, peak velocity.

Parameters	Univariate		Multivariate	
	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
ΔLVEF (6–12 months - baseline)	0.010 (-0.026 to 0.047)	0.582		
Baseline AVA	0.272 (-2.845 to 3.427)	0.864		
Baseline E/E'	0.025 (-0.019 to 0.074)	0.276		
Baseline Vmax	0.493 (-0.170 to 1.217)	0.157		
Baseline mPG	0.031 (0.002 to 0.062)	0.043	0.035 (0.004 to 0.070)	0.037
ΔmPG (6–12 months - baseline)	-0.030 (-0.061 to -0.001)	0.049		
Baseline late H/M	-0.228 (-1.060 to 0.574)	0.575		

In the multivariate model, the adjusted OR for the improvement in late H/M > 0.1 at 6–12 months after TAVR, as compared to that for the improvement in late H/M ≤ 0.1, was calculated by adjusting the following variables: CSHA-CFS score ≥ 5, baseline BNP level, and baseline mPG.

AVA indicates aortic valve area; BNP, brain natriuretic peptide; CI, confidence interval; CLBBB, complete left bundle branch block; CSHA-CFS, Canadian Study of Health and Aging Clinical Frailty Scale; eGFR, estimated glomerular filtration rate; E/E', ratio of early diastolic left transmitral flow velocity to septal mitral annular velocity; H/M, heart–mediastinum ratio; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; OR, odds ratio; mPG, mean aortic valve pressure gradient; TAVR, transcatheter aortic valve replacement; and Vmax, peak velocity.

The late H/M and associated clinical parameters in the three groups who were categorized according to the baseline mPG (LG group, < 42 mmHg; HG group, ≥ 42 mmHg and < 58 mmHg; and VHG group, ≥ 58 mmHg) are presented in Table 4. No significant difference in baseline LVEF was observed among the three groups. In the LG group, 21 (87.5%) out of 24 patients had baseline LVEF ≥ 50%. The increase in late H/M within 2 weeks after TAVR (i.e., Δlate H/M [< 2 weeks - baseline]) was comparable among the three groups, whereas the increase in late H/M at 6–12 months after TAVR (i.e., Δlate H/M [6–12 months - baseline]) tended to be greater in the HG group than in the LG group and in the VHG group than in the HG group. The VHG group had significantly higher Δlate H/M (6–12 months - baseline) than the LG group (*P* = 0.029) (Fig. 3).

Table 4
Late H/M and Associated Clinical Parameters in the Three Groups Categorized According to Baseline mPG: Low mPG, High mPG, and Very High mPG

Parameters	A: low mPG (n = 24)	B: high mPG (n = 26)	C: very high mPG (n = 25)	Overall P-value	A vs. B P-value	B vs. C P-value	A vs. C P-value
Laboratory data							
Baseline BNP, pg/mL	194 (45 to 437)	269 (125 to 555)	365 (211 to 574)	0.115	–	–	–
Echocardiographic data							
Baseline Vmax, m/s	4.1 (3.8 to 4.1)	4.6 (4.3 to 4.7)	5.2 (5.0 to 5.7)	< 0.001	< 0.001	< 0.001	< 0.001
Baseline mPG, mmHg	38 (33 to 39)	49 (44 to 53)	69 (61 to 80)	< 0.001	< 0.001	< 0.001	< 0.001
Baseline AVA, cm^2	0.6 (0.5 to 0.7)	0.6 (0.5 to 0.7)	0.5 (0.4 to 0.5)	0.003	0.828	0.007	0.006
Baseline LVEF, %	61 (53 to 69)	64 (57 to 69)	58 (50 to 64)	0.204	–	–	–
Baseline LVEF > 50%, n (%)	21 (87.5)	23 (88.5)	19 (76.0)	0.492	–	–	–
MIBG data							
Late H/M at baseline	2.69 (2.19 to 3.00)	2.54 (2.02 to 2.90)	2.53 (2.12 to 2.69)	0.441	–	–	–
Late H/M at < 2 weeks after TAVR	2.67 (2.36 to 3.01)	2.77 (1.93 to 2.97)	2.57 (2.19 to 2.65)	0.404	–	–	–
Late H/M at 6−12 months after TAVR ⬚	2.61 (2.34 to 3.00)	2.70 (2.06 to 3.03)	2.82 (2.56 to 3.04)	0.356	–	–	–
ΔLate H/M (< 2 weeks - baseline)	0.09 (-0.08 to 0.25)	0.11 (-0.05 to 0.26)	-0.01 (-0.20 to 0.22)	0.424	–	–	–
ΔLate H/M (6−12 months - baseline)	0.01 (-0.25 to 0.34)	0.17 (-0.04 to 0.52)	0.24 (0.07 to 0.68)	0.031	0.151	0.376	0.029

Continuous variables are presented as number (percentage) and median (25th−75th percentile), respectively.

H/M indicates heart−mediastinum ratio; MIBG, ^{123}I-meta-iodobenzylguanidine; mPG, mean aortic valve pressure gradient; and TAVR, transcatheter aortic valve replacement

Parameters	A: low mPG (n = 24)	B: high mPG (n = 26)	C: very high mPG (n = 25)	Overall P-value	A vs. B P-value	B vs. C P-value	A vs. C P-value
TAVR and second MIBG (days)	6 (5 to 7)	6 (3 to 7)	7 (4 to 8)	0.154	–	–	–
TAVR and third MIBG (days)	213 (191 to 231)	203 (197 to 218)	205 (190 to 217)	0.781	–	–	–
Continuous variables are presented as number (percentage) and median (25th−75th percentile), respectively.							
H/M indicates heart−mediastinum ratio; MIBG, ^{123}I-meta-iodobenzylguanidine; mPG, mean aortic valve pressure gradient; and TAVR, transcatheter aortic valve replacement							

Discussion

The present study yielded the following two main findings: (1) CSNF, as denoted by late H/M, demonstrated a sustained improvement from within 2 weeks after TAVR until 6−12 months later, and (2) higher baseline mPG was an independent predictor of mid-term improvement in late H/M after TAVR. As no studies have evaluated the long-term (> 6 months) effects of TAVR on CSNF, our study could provide physicians with new insights into this field.

Mid-Term Effects of TAVR on CSNF

In our results, late H/M exhibited a sustained improvement from within 2 weeks after TAVR until 6−12 months later, whereas WR displayed a rapid improvement just after TAVR but remained unchanged over the succeeding 6−12 months. Early H/M represents the amount of cardiac sympathetic nervous terminal endings and uptake-1 function, whereas WR represents sympathetic nervous tone [12]; in comparison, late H/M represents both factors. In general, the recovery of the amount of sympathetic nervous terminal endings and uptake-1 function is expected to require more than a few months, whereas sympathetic nervous tone can rapidly respond to hemodynamic changes and is susceptible to other clinical factors. The present results indicate a gradual trend towards improvement, as demonstrated by the late H/M, and a rapid but non-continuous improvement in the WR, which were thought to be consistent with the theories that have been stated [12].

Predictors of Improvement in Late H/M at 6−12 Months After TAVR

A higher baseline mPG was an independent predictor of mid-term improvement in the late H/M after TAVR; in particular, patients with a very high baseline mPG (≥58 mmHg) experienced significantly greater increase in the late H/M than those with a low baseline mPG (<42 mmHg).

The mPG assessed by Doppler echocardiography is one of the most powerful markers of AS severity in patients with normal cardiac output and preserved LVEF. High mPG is an independent predictor of mortality in patients with severe AS [13]. Moreover, patients with "very severe AS," defined as mPG ≥60 mmHg and/or Vmax ≥5 m/s, are considered at high risk, and current Japanese guidelines recommend early surgery, even when these patients are asymptomatic [14]. In our present study, patients with a very high mPG (≥58 mmHg) exhibited a higher degree of improvement in CSNF after TAVR, suggesting that patients with a very high baseline mPG would gain the greatest prognostic benefit from TAVR, considering the association of TAVR-related improvement in the late H/M with post-TAVR prognosis [15].

The effects of TAVR on patients with a low mPG should be carefully discussed. In this study, the increase in the late H/M at 6−12 months after TAVR (i.e., Δlate H/M [6−12 months - baseline]) was minimal among patients with a low baseline mPG (<42 mmHg). According to current guidelines [14,16], AS with low mPG, so-called "low-flow low-gradient" (LF-LG) severe AS can be divided into two groups—namely, classical LF-LG AS with LVEF <50% and paradoxical LF-LG AS with LVEF ≥50%. The prognosis of patients with paradoxical LF-LG AS remains controversial, with some studies reporting poor prognosis [17,18] and others indicating good prognosis [19,20]. In the present study, most patients with a low mPG (<42 mmHg) were classified as having paradoxical LF-LG AS. Therefore, the present results may represent poor CSNF response after TAVR among patients with paradoxical LF-LG AS, suggesting that patients with paradoxical LF-LG AS may gain benefit from TAVR with respect to symptomatic relief but not in terms of prognostic improvement.

Clinical Implications

The clinical outcomes of TAVR have improved due to device development and technical advancement, and its application has expanded to include younger patients as well as those with lower surgical risk [2]. Consequently, simpler, easier, and more accurate prognostic indicators are desired. Furthermore, there is an increased need for the appropriate selection of patients who would most benefit from TAVR. In our previous study, we demonstrated that CSNF assessment with MIBG imaging could provide essential information about patients' prognosis after TAVR and that patients exhibiting early improvement in late H/M after TAVR had a significantly lower incidence of cardiac events than those without such improvement [15]. The present results indicate that late H/M displayed a clearer trend towards improvement at 6−12 months than immediately after TAVR. Because it is assumed that MIBG parameters immediately after TAVR will inevitably be influenced by perioperative procedural factors such as infusion, a comparison of baseline and 6−12-month data may provide a better prognostic indicator for patients who have undergone TAVR. Furthermore, our results suggest that more careful consideration may be given to the indications for TAVR among patients with a low baseline mPG, particularly those with paradoxical LF-LG AS. Serial CSNF assessment using MIBG imaging may be useful in validating TAVR treatment for this AS category.

Study Limitations

The present study has certain limitations. First, the relatively small sample size of this study may be insufficient to fully reveal the long-term effects on CSNF by TAVR procedure. Second, the prognostic benefit from the improvement in CSNF at 6–12 months after TAVR remains unclear because the patients' prognostic information was not included in the present study. However, because the association of early TAVR-related improvement in the late H/M with better prognosis has previously been confirmed [15], the increase in the late H/M revealed in this study should also represent good clinical outcomes after TAVR. Third, there may be some selection bias in sampling, as baseline MIBG imaging could not be performed for critically ill patients with unstable general conditions. Fourth, as this study included Japanese patients only, our results cannot be generalized to other ethnicities.

Conclusion

CSNF, as denoted by late H/M, demonstrated a sustained improvement from within 2 weeks after TAVR until 6–12 months later. Such improvement was related to baseline hemodynamic AS severity. Patients with very high baseline mPG would gain the greatest prognostic benefit from TAVR.

Declarations

Disclosure of Potential Conflicts of Interest

Funding: This study was not supported by any funding.

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

Ethical approval: All procedures were performed in accordance with the ethical standards of the institutional research committee of Kyoto Prefectural University of Medicine (no. ERB-C-1081-3) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Data availability

The data will be shared on reasonable request to the corresponding author.

Author contributions

Yoshito Kadoya collected the data, performed statistical analysis, and wrote the manuscript. Kan Zen, Nagara Tamaki, Michiyo Yamano, Tetsuhiro Yamano, Takeshi Nakamura, and Satoaki Matoba revised the manuscript and figures. Shunsuke Nakamura, Tomoki Fujimoto, Masaki Yashige, Kazuaki Takamatsu,

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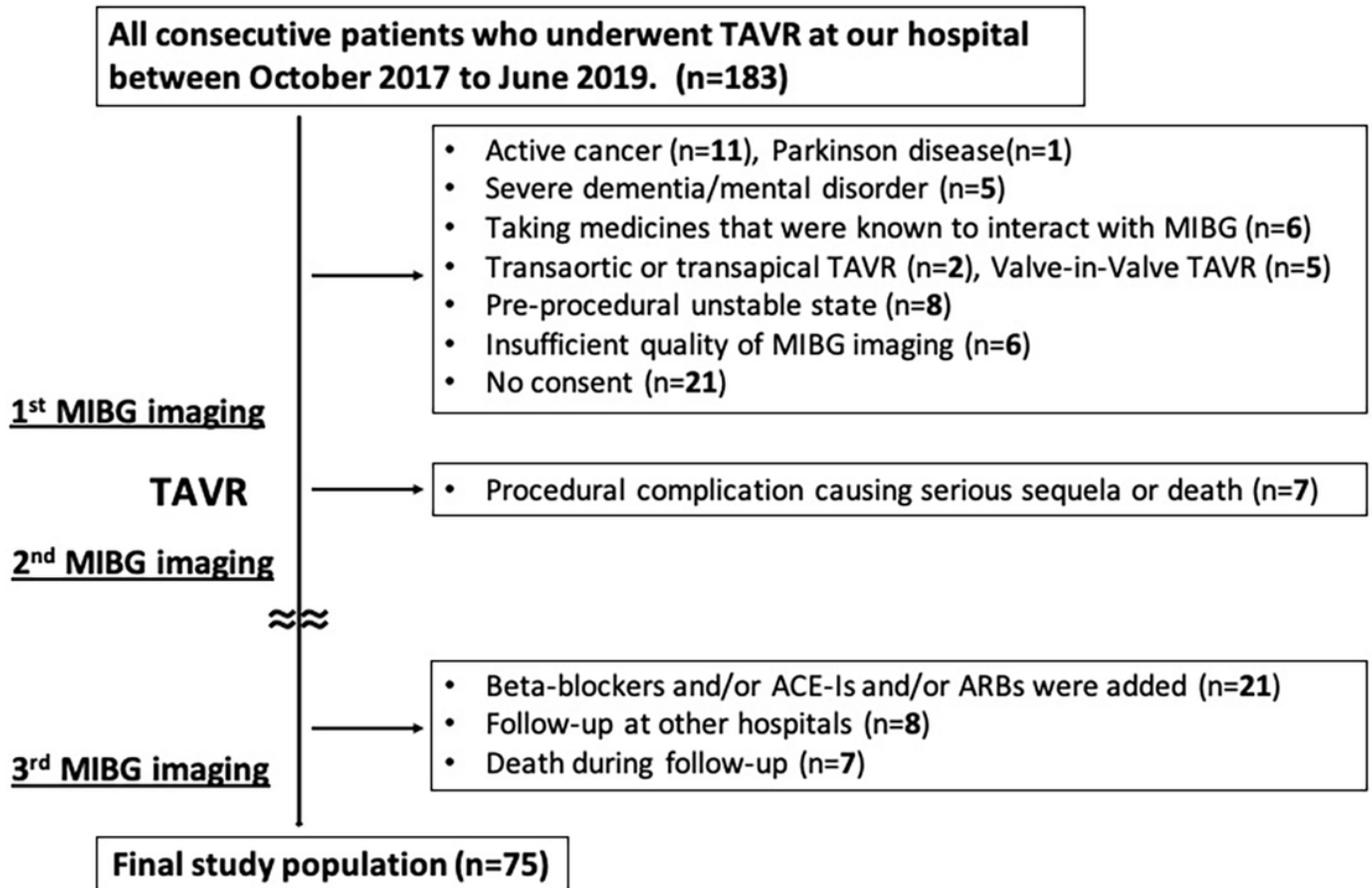
Figures

Figure 1

Flow chart illustrating patient selection ACEIs indicate angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; MIBG, 123I-meta-iodobenzylguanidine; and TAVR, transcatheter aortic valve replacement.
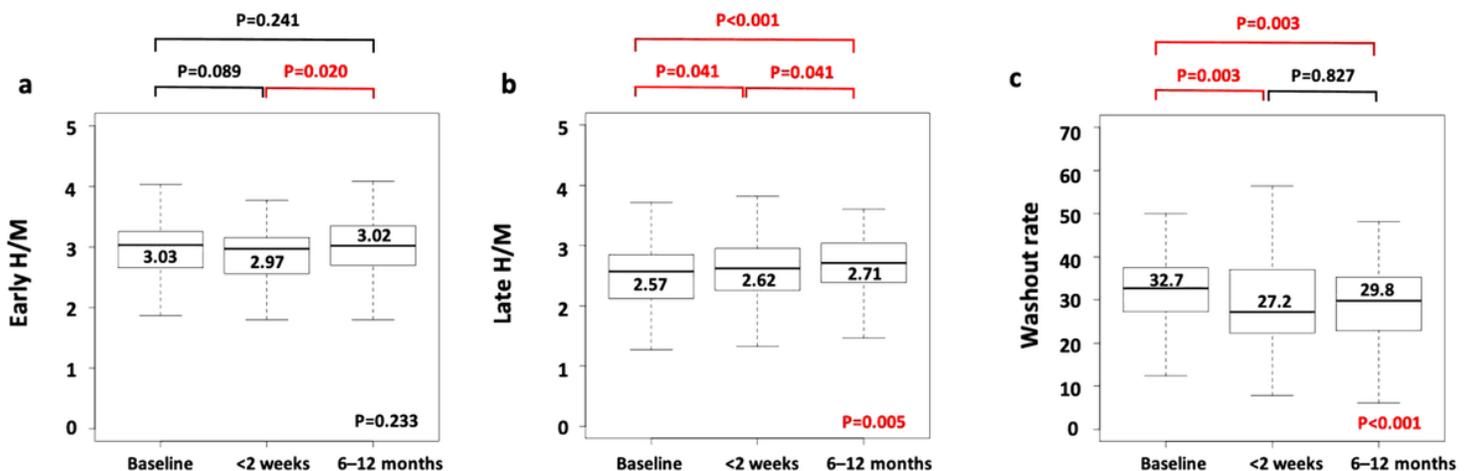
Figure 2

Changes in 123I-meta-iodobenzylguanidine parameters at baseline, <2 weeks after transcatheter aortic valve replacement (TAVR), and 6–12 months after TAVR (A) Early H/M, (B) late H/M, and (C) WR. H/M indicates heart–mediastinum ratio; and WR, washout ratio.
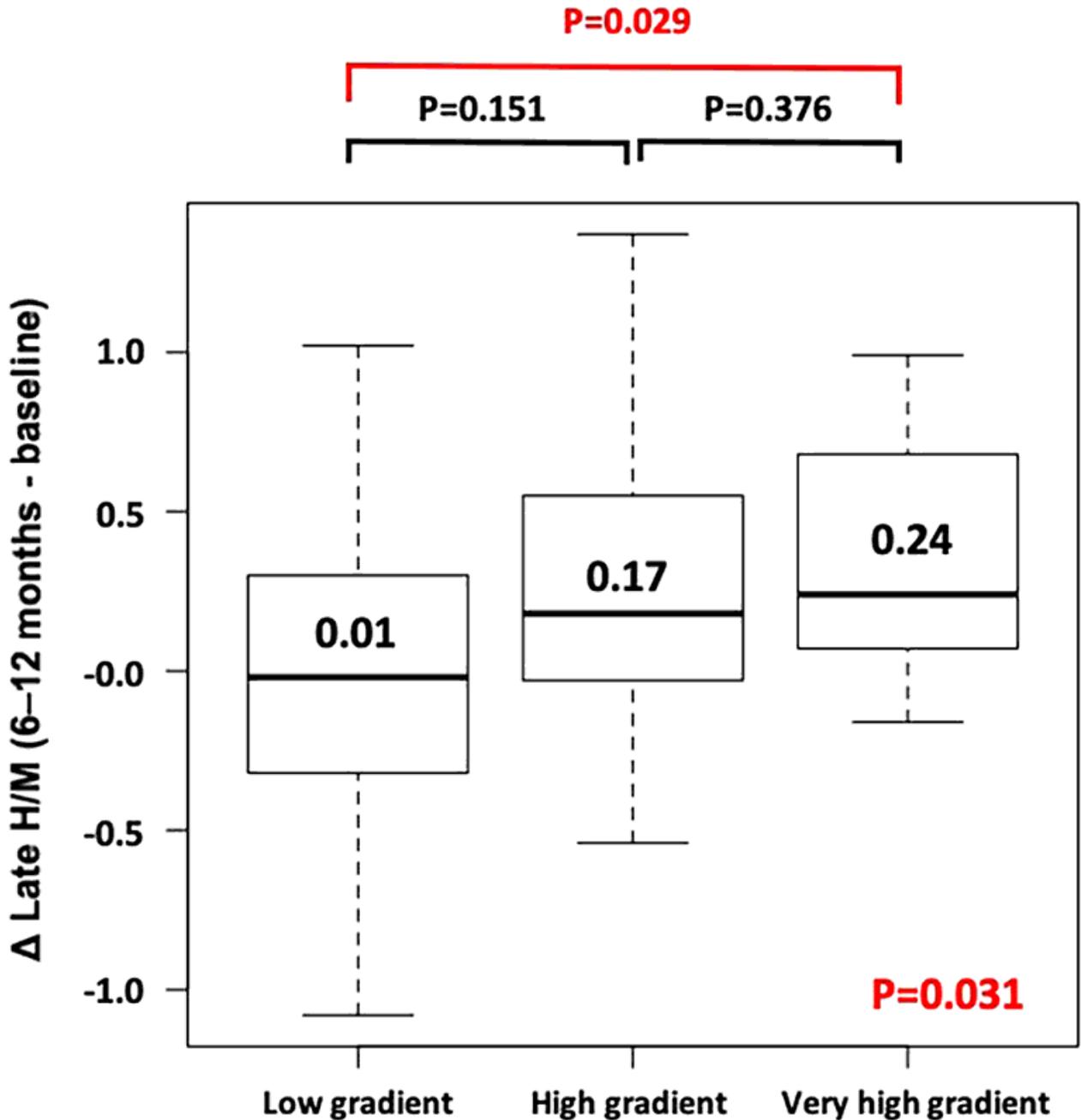

Figure 3

Increase in the late H/M at 6–12 months after transcatheter aortic valve replacement (i.e., Δlate H/M [6–12 months - baseline]) in three groups classified according to the baseline mPG H/M indicates heart–

mediastinum ratio; mPG, mean aortic valve pressure gradient; and TAVR, transcatheter aortic valve replacement.