CLINICAL STUDY

Impact of Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Replacement on Changes in Cardiac Sympathetic Nervous Function

Assessment by 123I-Metaiodobenzylguanidine Myocardial Scintigraphy

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Summary

The impact of prosthesis-patient mismatch (PPM) after transcatheter aortic valve replacement (TAVR) on changes in cardiac sympathetic nervous (CSN) function remains unclear. Using 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy, we investigated the impact of PPM after TAVR on CSN activity.

We enrolled 44 of 117 patients with severe aortic stenosis who underwent TAVR for analysis in the present study. We conducted 123I-MIBG scintigraphy at baseline and at about 9 months after TAVR. Differences between baseline and post-TAVR 123I-MIBG parameters were compared between cases with and without PPM.

There were 17 and 27 patients with and without PPM, respectively. Those without PPM exhibited significantly decreased left ventricular mass index (122 ± 36 g/m² versus 108 ± 30 g/m², P < 0.001) following TAVR, whereas those with PPM did not (117 ± 21 g/m² versus 110 ± 17 g/m², P = 0.09). Significant improvements in delayed heart-to-mediastinum (H/M) ratio (2.8 ± 0.4 versus 3.0 ± 0.4, P = 0.004) and washout rate (WR) (33% ± 10% versus 24% ± 12%, P < 0.001) were observed after TAVR in patients without PPM but not in those with PPM. Multivariable linear regression analysis revealed PPM to be a negative predictor of improvements in delayed H/M ratio and WR.

Delayed H/M ratio and WR improve significantly after TAVR in the absence of PPM, whereas these improvements are not observed in patients with PPM. Hence, the presence of PPM is a negative predictor of improvements in delayed H/M ratio and WR in patients undergoing TAVR.

Key words: Aortic stenosis, Cardiac sympathetic nervous system

Aortic stenosis (AS) is a cardiovascular disease that is common among elderly patients.1) Transcatheter aortic valve replacement (TAVR) has recently emerged as a minimally invasive therapeutic option, with benefits for patients at intermediate or high operative risk.2,3) Moreover, the impact of the procedure on cardiac sympathetic nervous (CSN) activity is considered to be minimal because thoracotomy is not needed in most cases.4) However, prosthesis-patient mismatch (PPM)-which occurs when the effective orifice area of the implanted prosthetic valve is too small in relation to the patient’s body surface area-is an essential potential complication of TAVR.5,6) Several studies have shown PPM to be associated with increased mortality after TAVR.7,8) 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy has been widely used for the assessment of CSN activity and represents a useful prognostic marker in patients with heart failure.9,10) Nevertheless, the impact of PPM after TAVR on changes in CSN function remains unclear. The present study aimed to examine the impact of PPM after TAVR on CSN activity using 123I-MIBG scintigraphy.

Methods

Study population: This study was a single-center retrospective study. We recruited a total of 117 patients with symptomatic severe AS who underwent TAVR between February 2016 and May 2019 at the Hiroshima University Hospital. Severe AS was defined as an aortic valve area (AVA) of < 1.0 cm² and a resting or inducible peak transaortic velocity > 4 m/second or mean pressure gradient of ≥ 40 mmHg.9) Of these, 58 underwent 123I-MIBG...
scintigraphy at baseline and at about 9 months after TAVR. Exclusion criteria were as follows: (1) prior cardiac surgery \((n = 2)\), (2) presence of unstable pre-procedural conditions \((n = 2)\), (3) undergoing TAVR with the trans-apical or transaortic approach \((n = 3)\), and (4) permanent pacemaker implantation \((n = 6)\) or hemodialysis \((n = 1)\) after TAVR. Finally, 44 patients eligible for analysis were enrolled in the present study. There were no patients with Parkinson’s disease or taking medications that were known to interact with 123I-MIBG including labetalol, reserpine, tricyclic antidepressants, sympathomimetic amines, or serotonin-norepinephrine reuptake inhibitors.11 The Ethics Committee for Epidemiology of Hiroshima University approved the study protocol, and all study patients provided informed consent.

**Transcatheter aortic valve replacement:** Eligibility for TAVR was decided by a heart team comprising cardiologists, cardiovascular surgeons, anesthesiologists, and imaging specialists. The procedure was conducted using either a balloon-expandable Edwards Sapien XT/Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) or self-expandable Medtronic CoreValve Evolut R (Medtronic, Minneapolis, MN, USA) device. All patients underwent both transcatheter echocardiography and contrast-enhanced multidetector computed tomography prior to TAVR for the evaluation of the device landing zone, vascular access site, and coronary artery disease. On the basis of the results of these tests, the heart team considered the risk of complications, such as aortic root rupture, paravalvular regurgitation, permanent pacemaker, and coronary obstruction, and finally decided the type and size of the device. All patients were treated using a transfemoral approach under general anesthesia.

**123I-metaiodobenzylguanidine scintigraphy:** 123I-MIBG (Fujifilm RI Pharma Co., Tokyo, Japan) was administered intravenously at a dose of 111 MBq. Anterior planar images were obtained at 15 minutes (early image) and 210 minutes (delayed image) after injection using a dual-detector 90° γ-camera (Brightview XCT, Philips Healthcare, Milpitas, CA, USA) with a medium-energy general collimator. We used the following settings: image acquisition time, 5 minutes; matrix size, 128 × 128; magnification factor, 1.46; energy window, 159 keV with a 20% energy window; and pixel size, 3.2 mm. Images were analyzed based on the region of interest determined using dedicated software (Jetpack, Hitachi) by an experienced radiology technician who was blinded to the clinical status of the patients. The Jetpack software was able to semi-automatically determine heart-to-mediastinum (H/M) ratios and correct them to standard medium-energy collimator conditions. Early and delayed H/M ratios were calculated by measuring the average counts in each region.4,12 The washout rate (WR) was calculated using the following equation: \([H - M] \text{ early} - \frac{(H - M) \text{ delayed}}{k} \times 100/(H - M)\) early, with background subtraction and time decay correction \((k = \text{time decay coefficient})\).4,12 Changes between pre- and post-procedural 123I-MIBG parameters were calculated using the following formulas: (1) \(Δ\text{H/M} = \text{post-procedural H/M ratio} - \text{baseline H/M ratio}\) and (2) \(Δ\text{WR} = \text{post-procedural WR} - \text{baseline WR}\).

**Transcatheter echocardiography:** We obtained echocardiographic data at baseline and at 7 days and 9 months after TAVR. Using a Vivid E9 ultrasound system with a 2.5 MHz transducer (GE Vingmed Ultrasound, Horten, Norway), comprehensive echocardiographic assessments were conducted by three experienced sonographers who had no knowledge of the patients’ clinical statuses.11,14 Using Echo Pac software version 112 (GE Vingmed Ultrasound), all imaging data were digitized and saved onto an optical disk for offline analysis. Echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography.14,15 The AVA and mean pressure gradient values were calculated using a continuity equation and Bernoulli’s formula, respectively. Left ventricular (LV) ejection fraction was measured using the bileplane Simpson formula, and the values of LV internal dimension (LVID), interventricular septal thickness (IVS), and posterior wall thickness (PWT) were measured at the end-diastole. We calculated LV mass using the following formula: \(LV \text{ mass} (g) = 0.8 \times 1.04 [(LVID + IVS + PWT)^3 - (LVID)^3] + 0.6\). The LV mass index (LVMi) was defined as the LV mass divided by the body surface area. Using an indexed effective orifice area, the severity of PPM was classified into moderate defined as \(≥ 0.65\) and \(≤ 0.85 \text{ cm}^2/\text{m}^2\) and severe defined as \(< 0.65 \text{ cm}^2/\text{m}^2\)7,16 and was evaluated via echocardiogram at 7 days after TAVR.

**Statistical analysis:** Continuous variables are expressed as mean ± standard deviation, categorical variables as counts and percentages. Using the Wilcoxon signed-rank test or paired \(t\)-test for continuous variables and the McNemar test for categorical variables, differences between baseline and post-procedural data were analyzed. Procedural data and Δ123I-MIBG parameters were compared between patients with and without PPM using Student’s \(t\)-test for continuous variables and the chi-square test for categorical variables. Univariable and multivariable linear regression analyses were conducted to determine factors associated with post-procedural improvements in 123I-MIBG parameters. Univariable and multivariable logistic regression analyses were conducted to determine predictors of PPM. Variables that reached significance (\(P < 0.10\)) in univariable analysis were entered into the multivariable model. Using JMP 12 software (SAS Institute Inc., Cary, NC, USA), all statistical analyses were conducted. A two-tailed \(P\)-value of \(< 0.05\) was considered statistically significant.

**Results**

Patient characteristics prior to transcatheter aortic valve replacement in relation to patient-prosthesis mismatch: Table I summarizes patient characteristics prior to TAVR in relation to the presence or absence of PPM. There were nine male and 35 female patients with a mean age of 84 ± 4 years. Forty-three patients (98%) had hypertension, and eight patients (18%) had diabetes. There were no significant differences in terms of age, sex, body surface area, body mass index, past medical history, serum creatinine, medications, and transthoracic echocardiographic data between patients with PPM and those without PPM prior to TAVR. As for 123I-MIBG parameters:
Table I. Patient Characteristics Before Transcatheter Aortic Valve Replacement in Relation to Prosthesis-Patient Mismatch

| Variables                  | Total (n = 44) | Without PPM (n = 27) | With PPM (n = 17) | P value |
|----------------------------|----------------|----------------------|-------------------|---------|
| Age (years)                | 84 ± 4         | 85 ± 4               | 84 ± 5            | 0.88    |
| Male                       | 9 (20%)        | 8 (30%)              | 1 (6%)            | 0.06    |
| Body surface area (m²)     | 1.43 ± 0.15    | 1.45 ± 0.15          | 1.40 ± 0.15       | 0.30    |
| Body mass index (kg/m²)    | 24 ± 3         | 24 ± 3               | 24 ± 4            | 0.97    |
| STS score                  | 7.5 ± 2.1      | 7.5 ± 2.3            | 7.5 ± 1.8         | 1.00    |
| NYHA classification        |                |                      |                   | 0.68    |
| Functional class II        | 25 (57%)       | 16 (59%)             | 9 (53%)           |         |
| Functional class III       | 19 (43%)       | 11 (41%)             | 8 (47%)           |         |
| Past medical history       |                |                      |                   |         |
| Hypertension               | 43 (98%)       | 26 (96%)             | 17 (100%)         | 0.42    |
| Diabetes mellitus          | 8 (18%)        | 5 (19%)              | 3 (18%)           | 0.94    |
| Dyslipidemia               | 24 (55%)       | 14 (52%)             | 10 (59%)          | 0.65    |
| Coronary artery disease    | 10 (23%)       | 7 (26%)              | 3 (17%)           | 0.52    |
| Laboratory data            |                |                      |                   |         |
| Hemoglobin (mg/dL)         | 11.5 ± 1.1     | 11.6 ± 1.1           | 11.3 ± 1.1        | 0.39    |
| Creatinine (mg/dL)         | 0.89 ± 0.37    | 0.86 ± 0.26          | 0.93 ± 0.51       | 0.54    |
| NT-proBNP (pg/dL)          | 2010 ± 3864    | 2280 ± 4797          | 1579 ± 1551       | 0.56    |
| C-reactive protein (mg/dL) | 0.29 ± 0.72    | 0.17 ± 0.20          | 0.48 ± 1.13       | 0.18    |
| Medications                |                |                      |                   |         |
| ACEIs or ARBs              | 31 (70%)       | 18 (67%)             | 13 (76%)          | 0.49    |
| Beta blockers              | 12 (27%)       | 7 (26%)              | 5 (29%)           | 0.80    |
| Diuretics                  | 23 (52%)       | 13 (48%)             | 10 (59%)          | 0.49    |
| Statins                    | 21 (48%)       | 11 (41%)             | 10 (59%)          | 0.24    |
| Transthoracic echocardiographic data |              |                      |                   |         |
| LVEF (%)                   | 65 ± 6         | 64 ± 8               | 65 ± 3            | 0.65    |
| Aortic valve area (cm²)    | 0.64 ± 0.19    | 0.65 ± 0.17          | 0.62 ± 0.23       | 0.68    |
| Peak pressure gradient (mmHg) | 96 ± 28       | 97 ± 26              | 95 ± 32           | 0.89    |
| Mean pressure gradient (mmHg) | 56 ± 18       | 55 ± 16              | 57 ± 22           | 0.69    |
| LVESV (mL)                 | 27 ± 13        | 28 ± 16              | 25 ± 6            | 0.52    |
| LVEDV (mL)                 | 75 ± 21        | 76 ± 23              | 73 ± 17           | 0.69    |
| LVMI (g/m²)                | 120 ± 31       | 122 ± 36             | 117 ± 21          | 0.66    |
| 123I-MIBG Scintigraphy     |                |                      |                   |         |
| Early H/M ratio            | 3.0 ± 0.4      | 3.1 ± 0.3            | 2.9 ± 0.3         | 0.04    |
| Delayed H/M ratio          | 2.8 ± 0.4      | 2.8 ± 0.4            | 2.8 ± 0.3         | 0.87    |
| Washout rate (%)           | 30 ± 11        | 33 ± 10              | 26 ± 12           | 0.04    |

Data are presented as mean ± standard deviation or number (%). PPM indicates prosthesis-patient mismatch; STS, the Society of Thoracic Surgeons; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVMI, left ventricular mass index; MIBG, metaiodobenzylguanidine; and H/M, heart-to-mediastinum.

Results: In patients without PPM, the peak pressure gradients before and after TA VR were significantly smaller than those with PPM (AVA, 20.6 ± 16.7 mmHg versus 22.3 ± 18.5 mmHg, P = 0.02; mean pressure gradient, 11.3 ± 9.5 mmHg versus 12.8 ± 10.7 mmHg, P = 0.02). Patients without PPM also exhibited significant improvements in NYHA functional class (3.3 ± 0.7 versus 2.3 ± 0.7, P = 0.02) and 123I-MIBG scintigraphy parameters (early and delayed H/M ratio, P = 0.02 and 0.01, respectively) compared to those with PPM.

Discussion: Transcatheter aortic valve replacement (TAVR) in patients with prosthesis-patient mismatch (PPM) is associated with significant improvements in NYHA functional class and 123I-MIBG scintigraphy parameters compared to those with PPM. The time interval between TAVR and post-operative 123I-MIBG scintigraphy was approximately 9 months (9.2 ± 0.2 months). Patients without PPM exhibited significant improvements in delayed H/M ratio and WR after TAVR, whereas those with PPM did not (Figure 1).

Comparison of transcatheter aortic valve replacement procedure and improvements in 123I-metaiodobenzylguanidine scintigraphy parameters in relation to patient-prosthesis mismatch: Patients with PPM were more frequently treated using Edwards Sapien valves and smaller prostheses than those without PPM (Table III). The delayed H/M ratio and AWR were significantly larger among patients without than those with PPM.
predictors of patient-prosthesis mismatch: Univariable logistic regression analysis showed that male gender, the use of a balloon-expandable device, and smaller prosthesis size (20 or 23 mm) were independent predictors of PPM (Table VI). However, these factors were not statistically significant in multivariable logistic regression analysis.

Representative case: Figure 2 shows representative images of early and delayed anterior planar 123I-MIBG scintigraphy prior to (upper panels) and after (lower panels) TAVR in a patient without PPM. Delayed H/M ratio and WR prior to TAVR were 2.5% and 39%, respectively. At 9 months after TAVR, delayed H/M ratio increased to 2.8, whereas WR decreased to 12%.

Discussion

This investigation of the impact of PPM after TAVR on changes in CSN function using 123I-MIBG scintigraphy demonstrates the following: (1) delayed H/M ratio and WR improve significantly after TAVR for patients without PPM, whereas patients with PPM do not experience these improvements, and (2) PPM is a negative predictor of improvements in delayed H/M ratio and WR in patients undergoing TAVR.

Although the use of TAVR is expanding rapidly, particularly for patients at intermediate or high surgical risk, the risk of PPM remains a potential limitation of the procedure.7,8

Table II. Patient Characteristics Before and After Transcatheter Aortic Valve Replacement in Relation to Prosthesis-Patient Mismatch

| Variables | Without PPM (n=27) | With PPM (n=17) | P value |
|-----------|-------------------|-----------------|---------|
| Age (years) | 85 ± 4 | 84 ± 5 | 0.12 |
| Male | 8 (30%) | 1 (6%) | 0.10 |
| Body surface area (m²) | 1.45 ± 0.15 | 1.43 ± 0.16 | 0.03 | 1.40 ± 0.15 | 1.39 ± 0.13 | 0.70 |
| Body mass index (kg/m²) | 24 ± 3 | 23 ± 3 | 0.02 | 24 ± 4 | 24 ± 3 | 0.34 |
| NYHA classification | 7.5 ± 2.3 | 7.5 ± 1.8 | 0.005 |
| Functional class II | 16 (59%) | 24 (89%) | 0.04 |
| Functional class III | 11 (41%) | 3 (11%) | 0.04 |
| Past medical history | | | |
| Hypertension | 26 (96%) | 17 (100%) | 0.56 |
| Diabetes mellitus | 5 (19%) | 3 (18%) | 0.26 |
| Dyslipidemia | 14 (52%) | 10 (59%) | 0.04 |
| Coronary artery disease | 7 (26%) | 3 (17%) | 0.04 |
| Laboratory data | | | |
| Hemoglobin (mg/dL) | 11.6 ± 1.1 | 11.1 ± 1.5 | 0.07 | 11.3 ± 1.1 | 11.0 ± 1.5 | 0.37 |
| Creatinine (mg/dL) | 0.86 ± 0.26 | 0.93 ± 0.38 | 0.14 | 0.93 ± 0.51 | 1.04 ± 0.57 | 0.03 |
| NT-proBNP (pg/dL) | 2280 ± 4797 | 784 ± 1112 | 0.07 | 1579 ± 1551 | 1028 ± 998 | 0.07 |
| C-reactive protein (mg/dL) | 0.17 ± 0.20 | 0.20 ± 0.29 | 0.70 | 0.48 ± 1.13 | 0.32 ± 0.72 | 0.64 |
| Medications | | | |
| ACEIs or ARBs | 18 (67%) | 20 (74%) | 0.32 | 13 (76%) | 12 (71%) | 0.56 |
| Beta blockers | 7 (26%) | 8 (30%) | 0.56 | 5 (29%) | 6 (35%) | 0.56 |
| Diuretics | 13 (48%) | 9 (33%) | 0.10 | 10 (59%) | 7 (41%) | 0.08 |
| Statins | 11 (41%) | 11 (41%) | 1.00 | 10 (59%) | 6 (35%) | 0.046 |
| Transthoracic echocardiographic data | | | |
| LVESV (mL) | 28 ± 16 | 28 ± 13 | 0.86 | 25 ± 6 | 25 ± 8 | 0.71 |
| LVEDV (mL) | 76 ± 23 | 80 ± 25 | 0.31 | 73 ± 17 | 69 ± 17 | 0.40 |
| LVMi (g/m²) | 122 ± 36 | 108 ± 30 | <0.001 | 117 ± 21 | 110 ± 17 | 0.09 |

Data are presented as mean ± standard deviation or number (%). PPM indicates prosthesis-patient mismatch; TAVR, transcatheter aortic valve replacement; STS, the Society of Thoracic Surgeons; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVMi, left ventricular mass index; MIBG, metaiodobenzylguanidine; and H/M, heart-to-mediastinum.

metaiodobenzylguanidine parameters: Multivariable linear regression analysis revealed PPM (β = -0.34, P = 0.02) was a negative predictor of improvement in delayed H/M ratio (Table IV). Furthermore, PPM (β = -0.31, P = 0.04) and baseline WR (β = 0.31, P = 0.048) were independent predictors of improvement in WR (Table V).

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Cardiac sympathetic nervous function after transcatheter aortic valve replacement

November 2020 1191CARDIAC SYMPATHETIC NERVOUS FUNCTION AFTER TAVR

In the heart, aortic pro B-type natriuretic peptide

Male 8 (30%) 1 (6%)

NYHA classification

Functional class II 16 (59%) 24 (89%) 0.04

Functional class III 11 (41%) 3 (11%) 0.04

Past medical history

Hypertension 26 (96%) 17 (100%) 0.56

Diabetes mellitus 5 (19%) 3 (18%) 0.26

Dyslipidemia 14 (52%) 10 (59%) 0.04

Coronary artery disease 7 (26%) 3 (17%) 0.04

Laboratory data

Hemoglobin (mg/dL) 11.6 ± 1.1 11.1 ± 1.5 0.07 11.3 ± 1.1 11.0 ± 1.5 0.37

Creatinine (mg/dL) 0.86 ± 0.26 0.93 ± 0.38 0.14 0.93 ± 0.51 1.04 ± 0.57 0.03

NT-proBNP (pg/dL) 2280 ± 4797 784 ± 1112 0.07 1579 ± 1551 1028 ± 998 0.07

C-reactive protein (mg/dL) 0.17 ± 0.20 0.20 ± 0.29 0.70 0.48 ± 1.13 0.32 ± 0.72 0.64

Medications

ACEIs or ARBs 18 (67%) 20 (74%) 0.32 13 (76%) 12 (71%) 0.56

Beta blockers 7 (26%) 8 (30%) 0.56 5 (29%) 6 (35%) 0.56

Diuretics 13 (48%) 9 (33%) 0.10 10 (59%) 7 (41%) 0.08

Statins 11 (41%) 11 (41%) 1.00 10 (59%) 6 (35%) 0.046

Transthoracic echocardiographic data

LVESV (mL) 28 ± 16 28 ± 13 0.86 25 ± 6 25 ± 8 0.71

LVEDV (mL) 76 ± 23 80 ± 25 0.31 73 ± 17 69 ± 17 0.40

LVMi (g/m²) 122 ± 36 108 ± 30 <0.001 117 ± 21 110 ± 17 0.09

123I-MIBG Scintigraphy

Early H/M ratio 3.1 ± 0.3 3.0 ± 0.3 0.12 2.9 ± 0.3 2.8 ± 0.4 0.35

Delayed H/M ratio 2.8 ± 0.4 3.0 ± 0.4 0.04 2.8 ± 0.3 2.8 ± 0.4 0.44

Washout rate (%) 33 ± 10 24 ± 12 <0.001 26 ± 12 25 ± 10 0.76

Data are presented as mean ± standard deviation or number (%). PPM indicates prosthesis-patient mismatch; TAVR, transcatheter aortic valve replacement; STS, the Society of Thoracic Surgeons; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVMi, left ventricular mass index; MIBG, metaiodobenzylguanidine; and H/M, heart-to-mediastinum.
Several studies have shown that PPM after surgical aortic valve replacement is associated with reduced regression in LVMI, less symptomatic improvement, and increased mortality.\textsuperscript{17,18} However, the impact of PPM after TAVR on prognosis remains controversial, and published results are less consistent.\textsuperscript{5,8,19,20} Patients undergoing TAVR are characterized by older age, extensive comorbidities, frailty, and longer exposure to the hemodynamic effects of AS, which may affect a lower susceptibility to the adverse effects of PPM.\textsuperscript{21}

Several studies have demonstrated that $^{123}$I-MIBG scintigraphy, an index of CSN activity, is useful for predicting clinical outcomes of patients with heart failure.\textsuperscript{9,10} Sympathetic overactivity is known to contribute to the progression of heart failure, and is correlated with an unfavorable prognosis.\textsuperscript{22} Several studies have demonstrated...
Table III. Comparison of Transcatheter Aortic Valve Replacement Procedure and Improvements in 123I-Metaiodobenzylguanidine Scintigraphy Parameters in Relation to Prosthesis-Patient Mismatch

| Variables                  | Without PPM (n = 27) | With PPM (n = 17) | P value |
|----------------------------|----------------------|-------------------|---------|
| TAVR procedure             |                      |                   | 0.01    |
| Sapien XT/Sapien 3         | 16 (59%)             | 16 (94%)          |         |
| Evolut R                   | 11 (41%)             | 1 (6%)            |         |
| Prosthesis size            |                      |                   | 0.006   |
| 20 mm                      | 1 (4%)               | 4 (23%)           |         |
| 23 mm                      | 11 (41%)             | 12 (71%)          |         |
| 26 mm                      | 13 (48%)             | 1 (6%)            |         |
| 29 mm                      | 2 (7%)               | 0 (0%)            |         |
| 123I-MIBG scintigraphy     |                      |                   |         |
| ΔEarly H/M ratio           | −0.11 ± 0.35         | −0.08 ± 0.35      | 0.82    |
| ΔDelayed H/M ratio         | 0.15 ± 0.24          | −0.07 ± 0.35      | 0.02    |
| ΔWashout rate (%)          | 9.5 ± 7.7            | 0.9 ± 11.4        | 0.004   |

Data are presented as mean ± standard deviation or number (%). TAVR indicates transcatheter aortic valve replacement; MIBG, metaiodobenzylguanidine; PPM, prosthesis-patient mismatch; and H/M, heart-to-mediastinum.

CSN overactivation among patients with AS due to various hemodynamic and mechanical changes such as pressure overload and LV hypertrophy.1,12,20

Although Sobajima, et al. and Kadoya, et al. have reported the early effects of TAVR on CSN function using 123I-MIBG scintigraphy,1,12 the impact of PPM after TAVR on changes in CSN function is not well established. Thus, we conducted the present study to address this gap in the knowledge.

Our findings of the impact of PPM after TAVR on changes in CSN function may be explained by the association between PPM and reduced hemodynamic improvement after TAVR. The main hemodynamic consequence of PPM is the generation of high transvalvular gradients through normally functioning prosthetic valves.20 We found that patients with PPM experienced less favorable changes after TAVR compared with those without PPM including lower AVA, higher peak and mean pressure gradients, and limited LVMI regression. Similar findings have been reported in previous studies.25,26 Additionally, Poulin, et al. showed that greater reverse LV remodeling using myocardial strain in patients without PPM compared with those with moderate or severe PPM.21 Based on these findings, the small indexed effective orifice area and its residual high-pressure gradient may suppress improvements in 123I-MIBG parameters. There may be differences in the impact on CSN improvement between moderate PPM and severe PPM. To fully elucidate the impact of moderate or severe PPM on LV remodeling and changes in CNS function, larger studies are required.

Our findings suggest that the prevention of PPM is essential to achieve adequate improvement of CSN function. Strategies to prevent or minimize PPM would be beneficial, especially for patients with CSN overactivation.

The present study has several limitations that should be acknowledged. First, this was a single-center retrospective study, involving consecutive patients who underwent both TAVR and 123I-MIBG scintigraphy. Thus, there may have been some degree of selection bias. However, no significant differences were found in terms of age, sex, body surface area, body mass index, NYHA Functional Classification III or IV, past medical history, serum creatinine, medications, and transthoracic echocardiographic data between the enrolled patients and excluded patients prior to TAVR. Second, the effects of improvements in CSN function after TAVR in terms of clinical outcome or clinical implications are unclear. Further studies are required to

Table IV. Univariable and Multivariable Linear Regression Analyses to Identify Factors Associated with Improvement in the Delayed Heart-to-Mediastinum Ratio

| Variable        | Univariable β | P value | Multivariable β | P value |
|-----------------|---------------|---------|-----------------|---------|
| Age             | −0.11         | 0.48    |                 |         |
| Male gender     | 0.25          | 0.11    |                 |         |
| STS score       | 0.05          | 0.73    |                 |         |
| Hemoglobin      | 0.26          | 0.09    | 0.15            | 0.32    |
| Serum creatinine| 0.12          | 0.44    |                 |         |
| NT-proBNP       | 0.16          | 0.31    |                 |         |
| C-reactive protein | −0.18      | 0.23    |                 |         |
| LVEF before TAVR| −0.24         | 0.11    |                 |         |
| Aortic valve area before TAVR | −0.26 | 0.09 | −0.24 | 0.10 |
| LVEDV before TAVR | 0.20        | 0.20    |                 |         |
| LVEDV after TAVR |              |         |                 |         |
| Mean pressure gradient | −0.08   | 0.59    |                 |         |
| PPM             | −0.35         | 0.02    | −0.34           | 0.02    |
| Baseline delayed H/M ratio | −0.26 | 0.09 | −0.15 | 0.34 |

STS indicates the Society of Thoracic Surgeons; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; TAVR, transcatheter aortic valve replacement; LVEDV, left ventricular end-diastolic volume; PPM, prosthesis-patient mismatch; and H/M, heart-to-mediastinum.

Table V. Univariable and Multivariable Linear Regression Analyses to Identify Factors Associated with Improvement in the Washout Rate

| Variable        | Univariable β | P value | Multivariable β | P value |
|-----------------|---------------|---------|-----------------|---------|
| Age             | −0.08         | 0.59    |                 |         |
| Male gender     | −0.04         | 0.79    |                 |         |
| STS score       | −0.15         | 0.32    |                 |         |
| Serum creatinine| −0.24         | 0.11    |                 |         |
| NT-proBNP       | −0.13         | 0.39    |                 |         |
| C-reactive protein | −0.25   | 0.10    |                 |         |
| LVEF before TAVR| −0.03         | 0.85    |                 |         |
| Aortic valve area before TAVR | −0.19 | 0.21 |                 |         |
| Mean pressure gradient after TAVR | −0.29 | 0.06 | 0.01 | 0.92 |
| TAVR            |              |         |                 |         |
| LVEDV before TAVR | −0.07         | 0.63    |                 |         |
| Aortic valve area after TAVR | 0.19        | 0.21    |                 |         |
| Mean pressure gradient after TAVR | −0.29 | 0.06 | 0.01 | 0.92 |
| PPM             | −0.42         | 0.004   | −0.31           | 0.04    |
| Baseline washout rate | 0.45        | 0.002   | 0.31            | 0.048   |

STS indicates the Society of Thoracic Surgeons; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; TAVR, transcatheter aortic valve replacement; LVEDV, left ventricular end-diastolic volume; and PPM, prosthesis-patient mismatch.
Table VI. Univariable and Multivariable Logistic Regression Analyses to Determine Factors Associated with Prosthesis-Patient Mismatch

| Variable                                | Univariable        | Multivariable       | P value | P value |
|-----------------------------------------|--------------------|---------------------|---------|---------|
| Age                                     | 0.99 (0.85-1.15)   | 0.88                |         |         |
| Male gender                             | 0.15 (0.008-0.94)  | 0.04                | 0.22 (0.01-2.06) | 0.19 |
| Body surface area                       | 0.10 (0.001-6.85)  | 0.29                |         |         |
| Body mass index                         | 1.00 (0.83-1.21)   | 0.97                |         |         |
| LVEF before TAVR                        | 1.02 (0.93-1.16)   | 0.63                |         |         |
| Aortic valve area before TAVR           | 0.49 (0.02-12.55)  | 0.67                |         |         |
| A balloon-expandable device             | 11.00 (1.81-213.13) | 0.006               | 2.94 (0.10-97.27) | 0.49 |
| 20 or 23 mm prosthesis                  | 20.00 (3.34-387.28) | < 0.001             | 7.58 (0.49-301.50) | 0.15 |

LVEF indicates left ventricular ejection fraction; TAVR, transcatheter aortic valve replacement; OR, odds ratio; and CI, confidential interval.

Figure 2. Representative images of early and delayed anterior planar 123I-metaiodobenzylguanidine scintigraphy prior to (A) and after (B) transcatheter aortic valve replacement in a patient without patient-prosthesis mismatch. H/M indicates heart-to-mediastinum; TAVR, transcatheter aortic valve replacement; and WR, washout rate.

To conclude, our findings suggest that delayed H/M ratio and WR improve significantly after TAVR for patients who do not experience PPM. Because of the nega-
Conflicts of interest: The authors declare no conflicts of interest.

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