Transcatheter Aortic Valve Implantation Improves Cardiac Sympathetic Nerve Activity on ^{123}I -Metaiodobenzylguanidine Myocardial Scintigraphy in Severe Aortic Valve Stenosis

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Background: There is a consensus that overactivation of the cardiac sympathetic nervous system (CSN) proportionately increases the severity of heart failure and is accompanied by worse prognosis. Because it is unknown whether patients with aortic valve stenosis (AS) have similar CSN activation, we investigated the effect of transcatheter aortic valve implantation (TAVI).

Methods and Results: We enrolled 31 consecutive patients with AS treated by TAVI. ^{123}I -metaiodobenzylguanidine (MIBG) myocardial scintigraphy was performed at baseline and at 2 weeks after TAVI. At baseline, the early heart-mediastinum ratio (H/M) was within normal limits (3.0 ± 0.5), but the delayed H/M was low (2.6 ± 0.6) and the washout rate (WR) was high ($34 \pm 13\%$). WR negatively correlated with aortic valve area ($r = -0.389$, $P < 0.01$) and cardiac output ($r = -0.595$, $P < 0.01$) and positively correlated with norepinephrine ($r = 0.519$, $P < 0.01$) and log NT-proBNP level ($r = 0.613$, $P < 0.01$). After TAVI, there were significant decreases in the norepinephrine level (366 ± 179 ng/mL vs. 276 ± 125 ng/mL, $P < 0.01$) and WR (34 ± 13 vs. $26 \pm 11\%$, $P < 0.01$).

Conclusions: The WR of MIBG was a useful marker of CSN activity and severity of AS. Immediate improvement of CSN activity after TAVI implied that AS hemodynamics per se enhanced CSN.

Key Words: ^{123}I -metaiodobenzylguanidine (MIBG); Aortic valve stenosis; Cardiac sympathetic nerve activity; Transcatheter aortic valve implantation (TAVI)

Chronic heart failure (CHF) patients have overactivation of the renin-angiotensin-aldosterone and sympathetic nervous systems, which creates a vicious cycle of remodeling and an accompanying worse prognosis.^{1,2} The established standard therapy for such cases had been to counteract these neurohormonal factors with the use of β -blockers, angiotensin-converting enzyme inhibitors (ACEI), or aldosterone blockers to improve cardiac sympathetic nerve (CSN) activity, cardiac function, or prognosis.^{3–8} However, these benefits only apply to cases of HF with reduced ejection fraction (HFrEF), such as dilated or ischemic cardiomyopathy. It remains unknown whether similar neurohumoral activation occurs in patients with aortic valve stenosis (AS). To date, aortic valve replacement (AVR) is the only option to improve the prognosis of AS, but its effect on CSN activity is also unclear.

Recently, transcatheter aortic valve implantation (TAVI) has become a widely accepted novel therapy, especially for severe AS patients with high operative risk because of

advanced age. Accumulating data suggest that TAVI is as safe and efficacious as surgical AVR in carefully chosen patients.^{9–11} By nature, TAVI is less invasive than open heart surgery, so the procedural impact on CSN may be minimal. Moreover, CSN activity in the early postoperative phase can be evaluated because the patient's recovery from bed rest is immediate.

In clinical practice, ^{123}I -metaiodobenzylguanidine (MIBG) myocardial scintigraphy has been used to assess CSN activity. Regarding the application of MIBG in CHF, many studies have shown that a low heart-to-mediastinum ratio (H/M) and a high washout rate (WR) are related to poor outcomes and progression of CHF; these may reflect high central sympathetic tone, as well as downregulation of β receptors.^{12–15} Moreover, medical treatment for CHF such as ACEI,¹⁶ angiotensin-receptor blockers,¹⁷ β -blockers,¹⁸ or spironolactone can improve CSN activity on MIBG.^{19,20} However, there are no data on CSN activity in patients with AS, especially those who have undergone TAVI.

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Table 1. AS Patients Characteristics and the Effect of TAVI

	Before TAVI	After TAVI
Age (years)	85.5±3.9	–
Male/Female (n)	8/23	8/23
Height (cm)	149.7±8.4	–
Body weight (kg)	51.5±10.3	50.7±10.4**
BSA (m ²)	1.44±0.16	1.43±0.16**
NYHA (I/II/III/IV)	0/14/15/2	8/19/4/0**
STS score	5.6±2.6	–
Hypertension (%)	71	–
Dyslipidemia (%)	48	–
Diabetic mellitus (%)	13	–
Smoker (%)	16	–
β-blocker (%)	29	35
ACEI/ARB (%)	61	55
Diuretics (%)	71	48*
Statin (%)	48	55
Hemoglobin (g/dL)	10.9±1.9	10.5±1.3
Creatinine (mg/dL)	1.1±0.4	1.0±0.3
eGFR (mL/min/1.73 m ²)	45.8±15.7	46.5±15.7
CRP (mg/dL)	0.37±0.99	0.43±0.57
NT-proBNP (pg/dL)	4,246±5,101	1,216±1,252**
Norepinephrine (pg/mL)	366±179	273±127*
AVA (cm ²)	0.57±0.15	1.53±0.36**
EF (%)	63±11	64±10
CTR (%)	60±7	57±7**
CO (L/min)	3.87±0.83	–
CI (L/min/m ²)	2.68±0.52	–
PAWP (mmHg)	12.1±5.0	–
Early H/M	3.0±0.5	2.9±0.5
Delayed H/M	2.6±0.6	2.6±0.6
WR (%)	34±13	26±11**

Logarithm was adapted for comparison of norepinephrine and NT-proBNP. Values are mean±SD. *P<0.05 vs. before TAVI, **P<0.01 vs. before TAVI. ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; CI, cardiac index; CO, cardiac output; CRP, C-reactive protein; CTR, cardiothoracic ratio; EF, ejection fraction; eGFR, estimated glomerular filtration rate; H/M, heart-to-mediastinum ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional classification; PAWP, pulmonary artery wedge pressure; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; WR, washout rate.

Accordingly, the purpose of the present study was to use MIBG scintigraphy to evaluate overactivation of CSN in AS patients, and whether CSN improves after TAVI.

Methods

Subjects and Study Design

The study group comprised 31 consecutive patients who had symptomatic severe AS, defined as aortic valve area (AVA) <1.0 cm², and had undergone TAVI were included. MIBG scintigraphy was performed on all patients 2 days before and 2 weeks after TAVI. Transthoracic echocardiography and chest X-ray, as well as serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and plasma norepinephrine (NE) levels were examined at the same time.

Cardiac output (CO) and pulmonary artery wedge pressure (PAWP) within 3 months before TAVI were determined by Swan-Ganz catheter. Patients with untreated severe coronary artery disease, Parkinson's disease, and those taking medicines that were known to interact with MIBG were excluded.²¹

TAVI

Patient selection for TAVI was made by the heart team, which comprised cardiologists, cardiovascular surgeons, and anesthesiologists, according to the indications of the PARTNER trial.²² All patients received an Edwards Sapien valve (Sapien XT or Sapien 3; Edwards Lifesciences Inc., Irvine, CA, USA) and underwent a transfemoral approach with general anesthesia. Patients treated by the transapical approach were excluded.

¹²³I-MIBG

¹²³I-MIBG (Fujifilm RI Pharma Co., Tokyo, Japan) at a dose of 111 MBq was diluted in 20 mL saline and administered intravenously. The 5-min planar images were acquired using a 3-headed gamma camera (GCA-9300A/DI; Toshiba, Tokyo, Japan) with a low- to medium-energy parallel-hole collimator at 30 min (early image) and 240 min (delayed image) following MIBG injection.

Using smart MIBG software (Fujifilm RI Pharma Co.), which was developed to semi-automatically determine the H/M ratios and correct them to standard medium-energy collimator conditions,^{23,24} an experienced radiology technician who was unaware of patient information analyzed the images based on the region of interest to obtain semiquantitative parameters for tracer distribution. Early and delayed H/M ratios were calculated, as previously reported.²⁵ WR (%) was calculated as [(H–M) early–(H–M) delayed/k]×100/(H–M) early using background subtraction and time-decay correction (k=time-decay coefficient), where H and M are the count/pixels in the heart and upper mediastinum, respectively.²⁶

Transthoracic Echocardiography

We performed conventional M-mode, 2D, and Doppler transthoracic echocardiographic studies using standard techniques. The AVA was calculated by a continuity equation.²⁷ Briefly, because the volume flow proximal to the valve is equal to that through the narrowed orifice, it is calculated as the cross-sectional area (CSA) of flow multiplied by the velocity-time integral (VTI) of flow at that site. In the left ventricular outflow tract (LVOT), flow just proximal to the stenotic valve is relatively laminar with a flat velocity profile. Thus, AVA×VTI_{AS}=CSA_{LVOT}×VTI_{LVOT}.

Statistical Analysis

Results are expressed as mean±SD. Unpaired t-test was used to analyze differences in the early and delayed H/M values between this study and the normal database of the Japanese Society of Nuclear Medicine (JSNM) working group (average, SD, and number were adapted for analysis).²⁸ According to the JSNM database, the average early and delayed H/M values with a low- to medium-energy collimator converted to the condition of the most common medium-energy general-purpose collimator with a conversion coefficient of 0.88 (i.e., equal to our method) are 3.1±0.5 and 3.3±0.6, respectively, and the WR is 13% (range 0–34%) in normal subjects (n=62).²⁸ The differences between baseline and post-treatment values were

Figure 1. Correlations of washout rate (WR) with cardiac parameters before TAVI. Correlations between (A) the WR and AVA, and (B) between WR and log NT-proBNP, (C) between WR and norepinephrine, and (D) between WR and CO at baseline. The correlation coefficient was determined using the Pearson product moment correlation coefficient. AVA, aortic valve area; CO, cardiac output; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TAVI, transcatheter aortic valve implantation.

analyzed by Wilcoxon signed-rank test or paired t-test. The correlation coefficient was determined using the Pearson product moment correlation. A multiple regression analysis was performed to identify the independent determinants of TAVI-induced changes in the WR. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed with JMP pro ver12 (SAS Institute Japan Ltd., Tokyo, Japan).

Results

Patients' Characteristics and Baseline Indices

The characteristics of the patients before and after TAVI are summarized in **Table 1**. In general, the 31 enrolled consecutive patients were old (mean age, 85.5 ± 3.9 years) and had moderate operative risk; the majority were women with a small body surface area (mean, $1.44 \pm 0.16 \text{ m}^2$). At baseline, there was no significant difference in the early H/M (3.0 ± 0.5 vs. 3.1 ± 0.5 ; NS) values, but the delayed H/M was significantly lower (2.6 ± 0.6 vs. 3.3 ± 0.6 ; $P < 0.01$) and the WR was higher ($34 \pm 13\%$) as compared with JSNM database.²⁸ At baseline, the WR positively correlated with log NT-proBNP ($r = 0.613$, $P < 0.01$), NE ($r = 0.519$, $P < 0.01$) and the cardiothoracic ratio (CTR) on chest X-ray ($r = 0.466$, $P < 0.01$); it negatively correlated with AVA ($r = -0.389$, $P < 0.01$) and CO ($r = -0.595$, $P < 0.01$) (**Figure 1**). Plasma NE levels had no correlations with NT-proBNP, CTR, AVA, PAWP or CO.

When the patients were divided into 2 groups according

to the lower limit of normal delayed H/M (delayed H/M < 2.2),²⁸ there were 10 patients with reduced delayed H/M. These patients were characterized by lower ejection fraction (EF) ($55.0 \pm 10.7\%$ vs. $66.7 \pm 9.9\%$; $P < 0.01$) as well as higher NE levels ($438 \pm 155 \text{ pg/mL}$ vs. $332 \pm 183 \text{ pg/mL}$; $P < 0.05$) and WR ($43 \pm 7\%$ vs. $30 \pm 13\%$; $P < 0.01$) compared with the preserved delayed H/M group ($n = 21$) (**Table 2**). There were no differences in AVA between these groups.

Effects of TAVI

In all patients, TAVI was successfully done without major complications and the patients' clinical symptoms improved (**Table 1**). After 2 weeks, there were no changes in hemoglobin and C-reactive protein levels, renal function or EF (**Table 1**), but there were significant improvements in serum NT-proBNP ($4,246 \pm 5,101 \text{ pg/mL}$ vs. $1,216 \pm 1,252 \text{ pg/mL}$; $P < 0.01$) and NE levels ($366 \pm 179 \text{ pg/mL}$ vs. $273 \pm 127 \text{ pg/mL}$; $P < 0.05$), CTR ($60 \pm 7\%$ vs. $57 \pm 7\%$; $P < 0.01$), and AVA ($0.57 \pm 0.15 \text{ cm}^2$ vs. $1.53 \pm 0.36 \text{ cm}^2$; $P < 0.01$) (**Table 1**, **Figure 2**). Early and delayed H/M values were unchanged (3.0 ± 0.5 vs. 2.9 ± 0.5 ; NS, 2.6 ± 0.6 vs. 2.6 ± 0.6 ; NS, respectively), but the WR significantly decreased ($34 \pm 13\%$ vs. $26 \pm 11\%$; $P < 0.01$) (**Table 1**, **Figure 2**). The WR had a positive correlation with NE level ($r = 0.379$, $P < 0.05$); likewise, the changes in WR had a positive correlation with those in NE level ($r = 0.371$, $P < 0.05$) (**Figure 3**). The multivariate analysis revealed that plasma levels of NE before TAVI was the only independent determinant of changes in WR (**Table 3**).

In both of the groups with reduced delayed H/M (< 2.2)

Table 2. Comparison Between Patients With Preserved Delayed H/M and Those With Reduced Delayed H/M

	Preserved delayed H/M	Reduced delayed H/M
Age (years)	84.8±3.7	87.0±4.2
Male/Female (n)	5/16	3/7
Height (cm)	149.5±8.2	150.1±9.2
Body weight (kg)	51.5±10.9	51.6±9.3
BSA (m ²)	1.44±0.16	1.45±0.17
NYHA (I/II/III/IV)	0/9/11/1	0/4/5/1
mBP (mmHg)	79.3±11.9	71.1±8.8 [†]
PR (beats/min)	72.4±7.8	74.3±16.6
Hypertension (%)	71	70
Dyslipidemia (%)	52	40
Diabetic mellitus (%)	14	10
Smoker (%)	19	10
β-blocker (%)	29	30
ACEI/ARB (%)	62	60
Diuretics (%)	67	90
Statins (%)	52	40
Hemoglobin (g/dL)	10.9±2.0	11.1±1.4
Creatinine (mg/dL)	1.0±0.5	1.2±0.3
eGFR (mL/min/1.73m ²)	49.3±16.1	38.6±12.8
NT-proBNP (pg/dL)	2,794±3,454	7,296±6,707 ^{††}
Norepinephrine (pg/mL)	332±183	438±155 [†]
AVA (cm ²)	0.56±0.17	0.59±0.11
EF (%)	66.7±9.9	55.0±10.7 ^{††}
LVEDD (mm)	42.8±4.9	51.6±4.5 ^{††}
LVESD (mm)	27.1±5.5	36.8±6.2 ^{††}
CTR (%)	58.5±6.7	62.4±8.1
CO (L/min)	4.0±0.8	3.6±0.8
CI (L/min/m ²)	2.8±0.5	2.5±0.5
PAWP (mmHg)	12.2±5.1	12.0±5.0
Early H/M	3.3±0.4	2.5±0.3 ^{††}
Delayed H/M	2.9±0.5	2.0±0.2 ^{††}
WR (%)	30±13	43±7 ^{††}

Logarithm was adapted for comparison of norepinephrine and NT-proBNP. Values are mean±SD. [†]P<0.05 vs. preserved delayed H/M group, ^{††}P<0.01 vs. preserved delayed H/M group. LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; mBP, mean blood pressure; PR, pulse rate. Other abbreviations as in Table 1.

and preserved delayed H/M (≥ 2.2), the WR significantly improved 2 weeks after TAVI ($43\pm 7\%$ vs. $33\pm 8\%$; $P<0.01$, $30\pm 13\%$ vs. $23\pm 11\%$; $P<0.01$, respectively), but the delayed H/M did not change (**Figure 4**).

A total of 4 patients with reduced EF ($<50\%$) had lower H/M and higher WR (early H/M= 2.5 ± 0.4 , delayed H/M= 2.1 ± 0.5 , WR= $39.3\pm 15.1\%$) compared with the other patients; these values did not significantly improve after TAVI (early H/M= 2.4 ± 0.2 , delayed H/M= 2.0 ± 0.3 , WR= $35.9\pm 13.6\%$).

Discussion

In this study patients with severe AS had preserved early H/M but reduced delayed H/M and accelerated WR. The positive correlation of WR with severity of CHF and NE level suggested overactivation of the CSN in AS patients. Soon after TAVI, WR decreased and hemodynamics improved. To the best of our knowledge, this is the first report showing improved CSN activity after TAVI, as evaluated by MIBG scintigraphy, in severe AS patients.

Merlet et al reported that delayed H/M was a strong predictor of prognosis in patients with dilated or ischemic cardiomyopathy.²⁹ Moreover, it has been reported that the WR and its serial changes are also useful for determining the prognosis of patients with HFrEF.^{30,31} Similarly, in patients with HF with preserved EF, such as a hypertensive heart, accelerated WR reflects a worsening prognosis.³² However, reports regarding MIBG or CSN activity in AS patients are few.

The amount of CSN terminal endings and the function of uptake-1, which is the transporter reuptaking noradrenaline from the synaptic cleft, are represented by the early H/M, whereas the cardiac response to central nervous system impulses are represented by the WR; both of these are represented by the delayed H/M.³³ In this study of severe AS patients, the average of the early H/M values was comparable to the normal values in the reference database, indicating a preserved amount of CSN terminal; on the other hand, the increased WR and decreased delayed H/M indicated accelerated sympathetic nervous tone and impaired CSN terminal function.

Several mechanisms have been proposed to explain overactivation of the sympathetic nervous system in patients

Figure 2. Changes in (A) plasma norepinephrine and (B) washout rate (WR) with transcatheter aortic valve implantation (TAVI).

Table 3. Determinants of TAVI-Induced Improvement in the WR				
Variable	Univariate analysis		Multivariate analysis	
	r	P value	β	P value
NT-proBNP	0.377	0.04	-0.280	0.09
Norepinephrine	0.508	0.004	-0.447	0.009
AVA	0.167	0.378	—	—
CO	0.139	0.465	—	—

Abbreviations as in Table 1.

with HF. First is suppression of the sympathoinhibitory cardiovascular reflexes, such as the arterial baroreceptor reflex. Second is augmented sympathoexcitatory reflex, such as the arterial chemoreceptor and cardiac sympathetic afferent reflexes.³⁴ Central facilitation of the augmented cardiovascular sympathetic afferent reflex is mediated by increases in angiotensin-II and cytokines and a decrease in nitric oxide, which contribute to tonic enhancement of sympathetic output.^{35,36}

In HFrEF patients, long-standing CSN overactivation eventually depletes NE at the cardiac sympathetic nerve terminals and downregulates β receptors, resulting in a vicious cycle that deteriorates cardiac function.^{37,38} Imamura et al reported that in Japanese patients with HFrEF (i.e., EF $27\pm 10\%$), early H/M decreased to 1.78 ± 0.27 , delayed H/M decreased to 1.64 ± 0.28 , and WR increased to $46\pm 12\%$.³⁰ It seems that HFrEF patients, who were likely to have accompanying low output syndrome, have higher

CSN activity and more deteriorated sympathetic nerve terminal function than severe AS patients with comparable symptoms and serum NT-proBNP levels. On the other hand, there were 10 patients with reduced delayed H/M (<2.2) in the present study and they had a more reduced EF than the preserved delayed H/M (≥ 2.2) patients. Moreover 4 patients with reduced EF ($<50\%$) had lower H/M and higher WR compared with the other patients. Accordingly, these cases suggested that in AS patients, reduced EF would lead to higher CSN activity (i.e., WR) and more depressed CSN terminal function (i.e., H/M). Indeed, a relatively low EF has been consistently reported to predict poor prognosis after TAVI.³⁹

The precise mechanisms of CSN overactivation in AS patients are unknown, but a decrease in baroreflex function on muscle sympathetic nerve activity (MSNA) has been reported; moreover, baroreflex function and MSNA activity improved after TAVI.⁴⁰ In our study, improvements in AVA, CTR, and NT-proBNP after TAVI were accompanied by immediate improvement in CSN activity. We considered that the AS hemodynamics are a contributor to CSN enhancement. The WR inversely correlated with CO at baseline, but there was no correlation between WR and PAWP. It seems that a reduction in CO and the resulting decreased baroreflex function may be strongly involved in increasing CSN activity in AS patients. Changes in the MIBG scintigraphy findings were mostly evaluated at 6 to 12 months in previous reports,^{16–19} and 2 weeks post-TAVI might be too short to evaluate improvements in the H/M value. In our study, the WR had improved at 2 weeks, but the H/M did not improve, suggesting that overactivation of CSN tone was inhibited quickly but that CSN terminal function had not recovered in that short time period. Plasma NE level was also improved at 2 weeks and its level before TAVI was an independent predictor of changes in WR, indicating improvement of WR reflected mainly inhibition of CSN tone.

An advantage of MIBG over MSNA is the former's ability to evaluate "cardiac" sympathetic nervous system activity and CSN terminal status. In fact, non-uniform sympathetic nerve responses have been reported.^{41,42} The plasma NE level, albeit a prognostic factor for HFrEF,¹ did not specifically reflect cardiac NE spillover. In fact, the plasma NE level did not correlate with AS severity. Another merit of MIBG scintigraphy is that it can be performed clinically in many hospitals without the need for special techniques. Furthermore, H/M and WR can be measures of cardiac load secondary to AS in elderly patients who are difficult to evaluate in terms of exercise-induced symptoms and surgical indications. The WR of MIBG helps evaluate both the severity of AS and the therapeutic effect of TAVI. Moreover, a reduced delayed H/M on MIBG scintigraphy indicates especially severe patients even among severe AS patients.

Study Limitations

There were several limitations that should be accounted for when interpreting the present results. First, the number of participants was small and insufficient to understand the precise mechanisms of the effect of TAVI on CSN activity in patients with AS. Further studies are needed to investigate the influence of atherosclerotic risk factors and medications on the improvement of CSN activity after TAVI. Second, the duration of the beneficial effects of TAVI for the CSN system and the contribution of WR

improvement to prognosis have to be clarified. Third, we did not have a control group; however, a Japanese database of normal values for the same collimator was substituted for this comparison.

In conclusion, in AS patients assessed by MIBG scintigraphy after TAVI, the early H/M ratio was preserved, but the delayed H/M ratio was reduced and the WR was accelerated according to the hemodynamic severity of AS, which was improved early by TAVI.

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None.

Disclosures

The authors declare no conflicts of interest.

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