B-type Natriuretic Peptide Regulation in Patients with Severe Aortic Stenosis Following Transaortic Valvular Implantation

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Summary

Peri-procedural elevated B-type natriuretic peptide (BNP) is also associated with worse outcomes following transcatheter aortic valve implantation (TAVI). However, the mechanism of BNP regulation in patients with severe aortic stenosis (AS) remains unknown. Consecutive patients with severe AS who were referred for TAVI were enrolled in our prospective registry. BNP levels were correlated with other clinical variables. Ninety-six patients (84.7 ± 5.0 years old, 34% males) were investigated in this study. Plasma BNP averaged 353 ± 179 pg/mL. Log₁₀ BNP had no significant correlation with severity of AS including aortic valve area and maximum flow velocity across the aortic valve ($P > 0.05$ for all), whereas a higher left ventricular end-diastolic dimension (LVDd) index was a significant factor associating with BNP >100 pg/mL with an odds ratio of 1.34 (95% confidence interval 1.06-1.52, $P = 0.004$) adjusted for several other echocardiographic parameters, with a cutoff of 30.8 mm/m² (equivalent to LVDd 44 mm). In conclusion, among the patients with severe AS who undergo TAVI, even slight eccentric hypertrophy can cause a considerable increase in BNP level.

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Key words: Heart failure, Hemodynamics, Valve disease

B-type natriuretic peptide (BNP) is secreted from left ventricular myocardium triggered by pressure or volume loading on the left ventricle.¹⁾ The BNP level increases depending on the severity of heart failure (HF) and is an essential tool to predict clinical prognosis and construct a therapeutic strategy of HF patients.²⁾

Recently, transcatheter aortic valve implantation (TAVI) has become a widely accepted therapy, especially for severe aortic stenosis (AS) patients with high operative risk due to their advanced age. Accumulating data have suggested that TAVI is as safe and efficacious as surgical aortic valve replacement in carefully chosen patients.³⁻⁵⁾

Clinical utility of BNP has also been reported in the severe AS cohort. Peri-procedural values of BNP or post-procedural improvement in BNP are useful markers to predict post-TAVI outcomes.⁶⁻⁹⁾ Nevertheless, the mechanism of elevation in BNP level remains unknown in this cohort. For example, patients with high maximum flow velocity across the aortic valve do not necessarily have a high BNP level. A different mechanism of BNP regulation might exist in such a cohort compared to the standard HF cohort. A detailed understanding of its mechanism would let us construct a better therapeutic strategy for patients with severe AS, particularly in the era of TAVI. In this study, we investigated the association between BNP and other clinical variables in patients with severe AS referred

for TAVI.

Methods

Subjects and study design: Consecutive patients with symptomatic severe AS, which was defined as aortic valve area (AVA) < 1.0 cm² and peak velocity through the aortic valve > 4.0 m/sec,^{10,11)} who received TAVI were prospectively enrolled in our registry. Patients with low-flow low-gradient AS, severe chronic kidney disease (CKD) with an estimated glomerular filtration rate less than 30 mL/minute/1.73 m², and decompensated heart failure with New York Heart Association class IV were excluded, given their considerable effects on BNP level.^{12,13)}

For the post-TAVI data collection, those with a transapical approach and major comorbidities including death, cardiac tamponade, atrio-ventricular block, severe infection, and moderate or greater residual aortic regurgitation were also excluded given their considerable impacts on BNP level.

Blood samples were obtained two days before TAVI as baseline data and two weeks post-TAVI as post-procedure data. Informed consent was obtained from all participants before enrollment and the study was approved by the institutional ethical board.

Trans-catheter aortic valve implantation: Patient selec-

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tion for TAVI was made by our heart team, which comprised cardiologists, cardiovascular surgeons, and anesthesiologists, according to the indications of the PARTNER trial.¹⁴ All patients received a balloon-expandable valve (Sapien XT or Sapien 3; Edwards Lifesciences Inc., Irvine, CA, USA) or self-expandable valve (Corevalve or Evolut R; Medtronic plc., Minneapolis, MN, USA) via a trans-femoral or trans-apical approach under general anesthesia.

Transthoracic echocardiography: Transthoracic echocardiography was performed two days before TAVI and two weeks post-TAVI by experienced sonographers who were blinded to the clinical data including BNP level. We performed conventional M-mode, two-dimensional, and Doppler studies using standard techniques. The AVA was calculated by a continuity equation.¹⁵

Statistical analysis: Continuous variables are expressed as the mean and standard deviation and categorical variables as the number and percentage. The differences between baseline and post-treatment values were analyzed by the Wilcoxon signed-rank test or paired *t*-test. The correlation coefficient was determined using Pearson's correlation coefficient. Logistic regression analyses were performed to investigate the associating variables with baseline BNP > 100 pg/mL among baseline echocardiographic data. Receiver operating characteristics analyses were performed to calculate cutoffs for baseline BNP > 100 pg/mL. A value of *P* < 0.05 was considered statistically significant. Statistical analyses were performed with JMP pro ver12 (SAS Institute Japan Ltd, Tokyo).

Results

Baseline characteristics: Ninety-six patients were enrolled. Their characteristics are summarized in Table I. The mean age was 84.7 ± 5.0 years old and they had moderate operative risk (Society of Thoracic Surgery scores $5.8 \pm 2.6\%$). The majority were female patients (76%) and the mean body surface area was 1.40 ± 0.17 m². The severity of AS and other echocardiographic parameters are shown in Table II. AVA was 0.57 ± 0.15 cm², maximum velocity across the aortic valve was 4.8 ± 0.6 m/sec, and the mean pressure gradient at the aortic valve was 55.5 ± 16.0 mmHg. The mean left ventricular end-diastolic dimension (LVDd) and left ventricular ejection fraction were within normal limits. BNP was 353 ± 179 pg/mL.

BNP level and clinical variables among baseline characteristics: Among the baseline characteristics, the severity of AS, indicated by the AVA index (Figure 1A), maximum velocity across the aortic valve, and mean pressure gradient at the aortic valve, had no significant correlation with log₁₀ BNP (*P* > 0.05 for all; Table III). On the contrary, several echocardiographic parameters had significant correlation with log₁₀ BNP; particularly the LVDd index, which had a moderate correlation (*r* = 0.49, *P* < 0.05; Figure 1B).

A multivariate logistic regression analysis showed that the LVDd index was significantly associated with baseline BNP > 100 pg/mL when adjusted for other echocardiographic parameters including interventricular septum

Table I. Patient Characteristics before and after TAVI

	Before TAVI (<i>n</i> = 96)	After TAVI (<i>n</i> = 57)
Age (years)	84.7 ± 5.0	84.7 ± 4.1
Male/Female (<i>n</i>)	23/73	14/43
Body surface area (m ²)	1.40 ± 0.17	1.38 ± 0.14
NYHA class (I/II/III/IV)	0/44/52/0	24/22/8/0
STS score (%)	5.8 ± 2.6	-
Hypertension (%)	77.6	-
Dyslipidemia (%)	51.6	-
Diabetic mellitus (%)	18.1	-
History of smoking (%)	20.2	-
β-Blocker (%)	27.4	24.6
ACEI/ARB (%)	56.8	56.0
Diuretics (%)	62.5	43.9*
Statin (%)	53.6	49.1
Hemoglobin (g/dL)	11.2 ± 1.5	10.5 ± 0.6*
Creatinine (mg/dL)	0.89 ± 0.27	0.88 ± 0.27
eGFR (mL/minute/1.73 m ²)	54.4 ± 18.4	55.2 ± 18.8
B-type natriuretic peptide (pg/mL)	353 ± 179	145 ± 156*

Continuous variables are expressed as the mean and standard deviation and were compared by the unpaired *t*-test. Categorical data are expressed as a percentage and were compared by the Wilcoxon signed-rank test. **P* < 0.01. TAVI indicates trans-catheter aortic valve implantation; NYHA, New York Heart Association; STS, Society of Thoracic Surgery; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and eGFR, estimate glomerular filtration rate.

thickness, posterior wall thickness, left atrial dimension index, left ventricular ejection fraction, mitral regurgitation grade, aortic regurgitation grade, and estimated glomerular filtration ratio (odds ratio 1.34, 95% confidence interval 1.06-1.52, *P* = 0.004), with a cutoff 30.8 mm/m² (equivalent to LVDd 44 mm) calculated by the receiver operating characteristic analysis showing an area under the curve of 0.760 (*P* < 0.01).

Post-TAVI course: For the assessment of post-TAVI data, we excluded 39 patients; those with a trans-apical approach, had died within 30 days, or had cardiac tamponade, atrio-ventricular block, severe infection, or moderate or greater aortic regurgitation. Thus, the post-TAVI analyses were conducted on 57 patients.

Following TAVI, AS improved significantly, as indicated by AVA, the maximum velocity of across aortic valve, and mean pressure gradient at the aortic valve (*P* < 0.05 for all; Table II), whereas echocardiographic parameters other than the index of AS severity remained unchanged (*P* > 0.05 for all; Table II). BNP decreased significantly to 145 ± 156 pg/mL (*P* < 0.05; Table I).

The amount of decrease in BNP following TAVI (Δ BNP) varied in each patient between -1957 and 50 pg/mL. The improvement in AVA index (Δ AVA index) had no significant correlation with Δ BNP (*P* > 0.05; Figure 2 A), whereas there was a moderate correlation between LVDd index (Δ LVDd index) and Δ BNP changes (*r* = 0.40, *P* < 0.001; Figure 2B). In other words, patients who achieved considerable reduction in LV size post-TAVI enjoyed considerable improvement in BNP level, irrespective of improvement in the severity of AS. Of note, the LVDd index increased in 25 patients.

Table II. Echocardiographic Parameters before and after TAVI

	Before TAVI (n = 96)	After TAVI (n = 57)
Aortic valve parameters		
Aortic valve area (cm ²)	0.57 ± 0.15	1.46 ± 0.28*
Maximum velocity across aortic valve (m/sec)	4.8 ± 0.6	2.3 ± 0.4*
Mean pressure gradient at aortic valve (mmHg)	55.5 ± 16.0	12.1 ± 4.9*
Other echocardiographic parameters		
Interventricular septum thickness (mm)	11.8 ± 1.2	11.3 ± 1.3
Posterior wall thickness (mm)	11.8 ± 1.2	11.4 ± 1.1
LVDd index (mm/m ²)	32.7 ± 5.3	33.7 ± 5.3
Left ventricular ejection fraction (%)	63.1 ± 11.1	64.0 ± 10.8
Left atrial dimension index (mm/m ²)	29.9 ± 8.5	30.1 ± 6.9
Mitral regurgitation (grade)	1.7 ± 0.6	1.4 ± 0.7
Aortic regurgitation (grade)	1.8 ± 0.7	1.5 ± 0.7

Variables are expressed as the mean and standard deviation and were compared by the unpaired *t*-test. **P* < 0.01. TAVI indicates trans-catheter aortic valve implantation; LVDd, left ventricular end-diastolic dimension; and LVM, left ventricular mass.

Figure 1. Correlations between BNP and AVA index (A) and between BNP and LVDd index (B). BNP indicates B-type natriuretic peptide; AVA, aortic valve area; and LVDd, left ventricular end-diastolic dimension. **P* < 0.05 by Pearson's correlation coefficient.

Table III. Correlation between Baseline BNP and Other Echocardiographic Variables

	<i>r</i> value
Aortic valve parameters	
Aortic valve area (cm ²)	-0.15
Maximum velocity across aortic valve (m/sec)	0.11
Mean pressure gradient at aortic valve (mmHg)	0.12
Other echocardiographic parameters	
Interventricular septum thickness (mm)	0.26*
Posterior wall thickness (mm)	0.24*
LVDd index (mm/m ²)	0.49**
Left ventricular ejection fraction (%)	-0.34**
Left atrial dimension index (mm/m ²)	0.21*

Pearson's correlation coefficients were analyzed. **P* < 0.05, ***P* < 0.01. LVDd indicates left ventricular end-diastolic dimension.

Discussion

In this study, we investigated the association between BNP and other baseline echocardiographic parameters to assess the mechanism of elevation of BNP in patients with severe AS. The major findings are: (1) In patients with severe AS referred for TAVI, baseline BNP was relatively elevated despite left ventricular size and contractility remaining within normal limits in most cases; (2) Higher baseline BNP had no association with the severity of AS but had a significant correlation with a larger left ventricular cavity. The cutoff of the LVDd index for BNP > 100 pg/mL was 30.8 mm/m² (equivalent to LVDd 44 mm); (3) Improvement in BNP following TAVI was not correlated with an increase in the AVA index but was associated with a reduction in the LVDd index.

BNP regulation and severity of AS: The associations between BNP level and severity of HF are well known, whereas those between BNP level and severity of AS remain unknown. Iwahashi and colleagues reported that the

Figure 2. Correlation between change in BNP and change in AVA index (A) and change in BNP and change in LVDD index (B). BNP indicates B-type natriuretic peptide; AVA, aortic valve area; and LVDD, left ventricular end-diastolic dimension. * $P < 0.05$ by Pearson's correlation coefficient.

size of the left ventricle might have an association with BNP level,¹⁶⁾ but they did not analyze the regulation of BNP before and after TAVI.

In patients with AS, the left ventricular cavity decreases via concentric hypertrophy to compensate for pressure loading on the left ventricle.¹⁷⁾ However, concentric hypertrophy increases intra-cardiac pressure due to increased diastolic dysfunction and endocardial ischemia. The left ventricular cavity would start to dilate and BNP would increase due to the increased shear stress when the compensation has collapsed.

Of note, when we define BNP > 100 pg/mL as the cutoff, for which we should intervene to unload the left ventricle,^{18,19)} the associated cutoff of the LVDD index was 30.8 mm/m^2 (equivalent to LVDD 44 mm). Even though these numbers are within normal limits for a healthy population or even those with HF, we should remember these key numbers as a specific turning point toward decompensation in AS patients.

BNP had no significant association with the severity of AS including the mean pressure gradient between the left ventricle and aorta. It would be plausible if we adapt here Laplace's law.²⁰⁾ In patients with AS, intra-cardiac pressure would increase together with the progression of AS, which in general increases the shear stress that triggers BNP secretion. However, in AS patients, both hypertrophy of the ventricular wall and narrowing of the ventricular cavity compensate for the increase of shear stress. Therefore, increased intra-cardiac pressure does not necessarily trigger BNP secretion in AS patients. At the initiation of decompensation despite this remodeling, enlargement of the cardiac cavity increases shear stress that triggers the secretion of BNP given Laplace's law.

Therapeutic strategy of severe AS: AVA or maximum velocity through the aortic valve are the most important indices to assess the severity of AS and consider the indication of any interventions to AS including TAVI.^{10,11,21)} However, these indices may not be good tools with which to assess injury to the left ventricle itself. An LVDD index

of 30.8 mm/m^2 (or LVDD 44 mm) might be an accessory good tool to consider the optimal timing of TAVI to rescue declining heart function, even though these are normal values. These novel and objective indices might be particularly useful in elderly patients when deciding upon the indication of TAVI, given it is sometimes difficult to obtain subjective symptoms in these patients.

Needless to say, an increase in the AVA index is a direct goal of TAVI. However, an increase in the AVA index was not associated with improvement in BNP following TAVI. Instead, the decrease in the LVDD index had a significant correlation with improvement in BNP. Post-TAVI lower BNP is associated with better clinical outcomes.^{22,23)} Our team also reported previously that a significant reduction in BNP ($\geq 40\%$) following TAVI was associated with lower mortality or lower HF rehospitalization rate.⁹⁾ Therefore, the Δ LVDD index may be another surrogate of successful TAVI. We do not have any answer for how we can decrease LVDD itself following TAVI, but any periprocedural parameters as well as optimal TAVI techniques might have considerable impact on reducing LVDD and BNP. Concomitant therapies consisting of anti-HF medications and cardiac rehabilitation might also have positive impacts on reducing LVDD and BNP.²⁴⁻²⁶⁾

Limitations: We should consider several limitations. The sample size was moderate and might be statistically insufficient, particularly to demonstrate similarity in some comparison analyses. This study is a proof of concept, and our findings should be confirmed in a multi-center, larger-scale cohort. Also, our study cohort consists of Japanese patients with relatively small physiques, and our results may not simply be adapted to those with larger physiques. Left ventricular contractility was relatively preserved in most cases in our cohort. We excluded those with low-flow low-gradient severe AS. We do not have any data on whether our results can be adapted to such a population. The BNP level well reflects the severity of HF among those with reduced left ventricular ejection fraction, whereas the implication of elevated BNP among AS

cohort might still remain unclear. We excluded those with comorbidities following TAVI that might have the potential to affect BNP. We did not directly measure invasive left ventricular end-diastolic pressure because it is prohibited in the guideline due to the risk of injury to the stenotic aortic valve by the catheter.¹⁰⁾ The association between BNP and actual intra-cardiac pressure remains unknown.

Conclusions

Among these patients with severe AS, even slight eccentric hypertrophy (a cutoff of LVDd index of 30.8 mm/m² or LVDd 44 mm) can cause an increase in BNP level and might be a good marker of myocardial injury.

Disclosure

Conflicts of interest: None.

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