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Prognostic Impact of B-Type Natriuretic Peptide in Elderly Patients With Severe Aortic Stenosis

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Objective: There are limited data on the correlation between B-type natriuretic peptide (BNP) and outcomes in elderly patients with aortic stenosis (AS). This study aimed to evaluate the relationship between BNP and outcomes in elderly patients with severe AS. Methods: In this retrospective study, we measured valve-related events (VRE) defined as a composite of cardiac death, aortic valve replacement (AVR), and hospitalization due to heart failure, as the endpoint. Patients or Materials: Data of 88 patients with severe AS who were ≥75 years old were analyzed. Results: At the 2-year follow-up, 27 patients had VRE. Multivariable analyses revealed that a plasma BNP level of ≥234 pg/mL, that was the cut-off value for the detection of VRE by ROC curve analyses, was an independent predictor of VRE. Conclusion: Elderly patients with severe AS and high plasma BNP levels had a significantly worse prognosis than those with low BNP levels. Our results suggest that the plasma BNP level may provide significant incremental prognostic information in elderly patients with severe AS.

Key words: B-Type natriuretic peptide, aortic stenosis, elderly, cardiac death

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INTRODUCTION

Aortic stenosis (AS) is one of the most prevalent forms of valvular disease, representing the third most common cardiovascular disease in developed countries [1]. As the growth rate of the elderly population continues to increase, AS prevalence is dramatically increasing [2].

The therapeutic management of patients with AS relies heavily on the onset of symptoms, which is related to poor prognosis [3]. Although surgical aortic valve replacement (SAVR) is an effective treatment for patients with symptomatic severe AS, it is associated with an increased risk of morbidity and mortality in elderly patients [4] who may be difficult to assess symptoms due to their low level of physical activity. Moreover, it is often challenging for physicians to differentiate between the causes of symptoms due to the high frequency of comorbidities [5].

Several studies have reported that plasma B-type natriuretic peptide (BNP) levels are correlated with symptom severity [6] and that they are predictive of the development of symptoms and cardiac events in asymptomatic patients with severe AS [7, 8]. However, in the majority of the aforementioned studies, patients were younger than those included in our study, which included an aging population with mild, moderate, or severe AS [6-8]. Although AS is a common cardiovascular disease and plasma BNP level is frequently measured in the outpatient clinic, study focused on the relation between plasma BNP levels and clinical outcomes in elderly patients with severe AS remains scarce. Therefore, this study aimed to investigate the relationship between plasma

BNP and outcomes in elderly patients with severe AS.

MATERIALS AND METHODS

Patients

In this study, we retrospectively reviewed data of 166 patients between January 2008 and December 2013. Patients who were 75 years or older, had severe AS (aortic valve area < 1.0 cm^2 on echocardiography), and were not initially planned to undergo surgery were included. Patients with a significant valve disease (severe aortic regurgitation, severe mitral regurgitation, moderate or severe mitral stenosis, or prior valve replacement surgery), decompensated heart failure (HF), prior cardiac operation, missing laboratory tests, or were undergoing hemodialysis were excluded. In total, data of 88 patients were analyzed (age; 84 ± 4 years; 33% male, aortic valve area [AVA]; 0.73 ± 0.2 cm^2). The study protocol was approved by the ethics committee of Shimane University Faculty of Medicine in Izumo, Japan.

Laboratory and echocardiographic data

Plasma was immediately separated from blood samples by centrifugation and plasma BNP concentrations were measured with an immunoenzymometric assay specific for human BNP using commercial kits (Shionogi Co Ltd, Osaka, Japan).

Echocardiography and laboratory tests were performed within a short duration from each other for comparable analysis. A standard echocardiographic examination that included comprehensive 2-dimensional and Doppler echocardiography using a multi-window approach was performed in all patients by experienced sonographers.

The severity of AS was assessed by the peak aortic valve (AV) velocity, mean AV pressure gradient, and AV area, which was calculated with the continuity equation using the left ventricular (LV) outflow tract diameter and flow velocity [9].

The end-diastolic volume (EDV) and end-systolic volume (ESV) were measured using Simpson's method on 2D images from the apical 4- and 2-chamber views. LV ejection fraction (LVEF) was calculated using the equation 100 × (EDV − ESV)/EDV [10].

LV mass was estimated using diastolic measurements of the LV internal diameter and the wall thickness from the parasternal long axis view: LV mass/mL = 0.8 × (1.04 [(intraventricular septum thickness + left ventricular internal dimension + posterior wall thickness)^3 − (left ventricular internal dimension)^3]) + 6 mL. Afterward, LV mass index was calculated as LV mass/body surface area. LV hypertrophy was defined as more than 115 mL/body surface area (BSA) for men and more than 95 mL/BSA for women [10].

Two-dimensional measurements were used to calculate the left atrial volume (LAV) at the end-systole (just prior to the opening of the mitral valve) using Simpson's method in the apical 4- and 2-chamber views. LAV index was calculated per BSA [10].

The transmitral flow velocity was recorded from an apical 4-chamber view by placing the sample volume at the level of the mitral valve leaflet tips. To assess the diastolic function, mitral inflow velocities during early (E) and late (A) diastolic filling, calculated as the E/A ratio, were obtained. Early diastolic velocity (E') was obtained from the septal annulus motion of the LV on tissue Doppler imaging. The ratio between the peak E and E' was calculated (E/E'). Transtricuspid pressure gradient (TRPG) was estimated by continuous-wave Doppler using the simplified Bernoulli equation of tricuspid regurgitation peak velocity [10].

Follow-up

All study patients were followed up after the initial laboratory examination at the hospital for severe AS. Follow-up data were obtained from a detailed review of all medical records. Adverse valve-related events (VRE) were defined by a composite of cardiac death, SAVR, and hospitalization for congestive HF due to AS. For assessment of outcomes, we evaluated the association between plasma BNP levels and adverse events during the follow-up period (until 730 days). Cardiac death was defined as sudden death, death from HF, or myocardial infarction.

Statistical analysis

We divided the study population into two groups based on the presence of VRE and compared the clinical and echocardiographic characteristics of patients between the two groups. Categorical variables were reported as numbers and percentages, while quantitative variables were described as a mean ± standard deviation or a median (interquartile range). The distribution of quantitative variables was evaluated using the Shapiro-Wilk test. Normally distributed groups of quantitative variables were compared using t-tests and non-normally distributed groups of continuous variables were compared using the Mann-Whitney U test. The chi-square test was used to compare samples of qualitative variables. A P value of <0.05 was considered statistically significant.

A receiver operating characteristics (ROC) curve was generated and the area under the curve calculated to determine the optical cut-off value of BNP predicting the VRE. And survival analysis was performed using a Kaplan-Meier analysis and differences between groups were calculated with the log-rank test.

To identify predictors of VRE at 2 years, we used Cox proportional hazard analysis. In univariable analysis, significant different variables based on the presence of VRE (P values of <0.05) were includes. Variables with P values of <0.05 in the univariable analysis were included in the multivariable analysis. All statistical analyses were performed using SPSS Statistics Desktop Version 22.0 (IBM, Armonk, NY)

RESULTS

Baseline characteristics

Baseline characteristics of patients are depicted in Tables 1 and 2. The mean age of the cohort was 84 ± 4 years with 29 (33%) men included. The mean peak velocity was 4.1 ± 0.8 m/s, mean pressure gradient was 40 ± 17 mmHg, and mean AV area was 0.73 ± 0.19 cm^2. The median plasma BNP level was 211 (69–353) pg/mL. The mean duration of follow-up was 596–730 days with a 94% follow-up rate at 2 years.

Differences in the clinical and echocardiographic characteristics between patients in the VRE group (n = 27) and those in the non-VRE group (n = 61) are shown in Tables 1 and 2. There were no significant differences between the two groups with regards to sex; BSA; presence of hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, prior cerebral infarction; use of β-blockers and ACE inhibitors/ARBs; LV dimension; LVEF; and moderate aortic regurgitation. However, patients in the VRE group were older, presented with worse symptoms, and received diuretics more frequently ($P<0.05$ for all) than those in the non-VRE group (Table 1). Biological and echocardiographic data indicated that patients in the VRE group had more severe aortic valve stenosis, concomitant mitral regurgitation and pulmonary hypertension (Table 2).

A BNP cut-off value of 234 pg/mL was used to detect the presence of VRE with a sensitivity, specificity, and accuracy of 74%, 67%, and 69%, respectively. The area under the curve (AUC) was 0.74 ($p < 0.001$; Fig. 1).

Event-free survival

During the 2-year follow-up, 27 patients had VRE. In particular, AVR was observed in 8 patients, hospitalization for congestive HF in 23 patients, and cardiac death in 11 patients (8 patients died due to heart failure, while 3 patients had sudden death). VRE was significantly higher in patients in the high BNP group at the 2-year follow-up ($p<0.001$) (Table 3). BNP levels seemed to affect the event-free survival rate. The outcomes of patients in the high BNP group were significantly different from those of patients in the low BNP group. The 1-year and 2-year event-free survival rates of patients in the low BNP group were 96 ± 3% and 84 ± 6%, respectively, whereas those of patients in the high BNP group were 58 ± 8% and 46 ± 8%, respectively ($p<0.001$; Fig. 2).

Univariate and multivariate predictors of composite events

Table 4 shows the results of the univariable and multivariable analyses for predictors of VRE. The univariable analysis showed that age, use of diuretics, LVEF, E/E', TRPG, concomitant moderate mitral regurgitation, AVA, prior HF hospitalization, New York Heart Association (NYHA) function class, concomitant anemia, and plasma BNP levels ≧234 pg/mL were significant predictors. The multivariable

Table 1. Clinical characteristics of the population overall and according to the presence of valve-related-event

Characteristics	Overall population (n=88)	VRE group (n=27)	Non VRE group (n=61)	p Value
Age, years	84 ± 4	86 ± 5	83 ± 4	0.003
Men, n (%)	29 (33)	8 (30)	21 (34)	0.67
Body surface area, m^2	1.41 ± 0.15	1.41 ± 0.14	1.38 ± 0.18	0.51
Comorbidities, n (%)				
Hypertension	66 (75)	18 (67)	48 (79)	0.23
Diabetes mellitus	19 (22)	4 (15)	15 (25)	0.3
Dyslipidemia	26 (30)	8 (30)	18 (30)	0.99
Atrial fibrillation	18 (21)	7 (26)	11 (18)	0.4
Ischemic heart disease	13 (15)	4 (15)	9 (15)	0.99
Prior cerebral infarction	6 (7)	1 (4)	5 (8)	0.44
Prior heart failure hospitalization	46 (52)	22 (82)	24 (39)	<0.001
Medication, n (%)				
β-Blockers	14 (16)	4 (15)	10 (16)	0.85
ACE inhibitors/ARBs	45 (51)	12 (44)	33 (54)	0.4
Diuretics	31 (35)	14 (52)	17 (28)	0.03
NYHA functional class, n (%)				0.004
Ⅰ	45 (51)	7 (26)	38 (62)	
Ⅱ	35 (40)	15 (56)	20 (33)	
Ⅲ	8 (9)	5 (19)	3 (5)	

Angiotensin converting enzyme: ACE, angiotensin receptor blocker: ARB, New York Heart Association: NYHA.

Table 2. Biological and echocardiographic characteristics of the population overall and the presence of valve-related-event

Characteristics	Overall population (n=88)	VRE group (n=27)	Non VRE group (n=61)	p Value
Hemoglobin, g/dL	11.3 ± 1.8	10.9 ± 1.9	11.5 ± 1.7	0.09
Estimated GFR, mL/min/1.73 m^2	53 ± 20	49 ± 19	55 ± 19	0.18
Plasma BNP, pg/mL				0.003
mean	285 ± 311	475 ± 420	202 ± 202	
median (25, 75%)	211 (69-353)	329 (211-694)	157 (50-259)	
Echocardiographic characteristics				
Aortic valve area, cm^2	0.73 ± 0.19	0.62 ± 0.18	0.78 ± 0.17	<0.001
Aortic jet velocity, m/s	4.1 ± 0.8	4.4 ± 0.8	4.0 ± 0.8	0.049
Mean aortic gradient, mm Hg	40 ± 17	45 ± 18	38 ± 16	0.08
LV end-diastolic dimension, mm	42 ± 6	41 ± 7	42 ± 6	0.42
LV end-systolic dimension, mm	27 ± 6	27 ± 6	27 ± 6	0.99
LV septal wall thickness, mm	12 ± 2	13 ± 2	12 ± 2	0.13
LV posterior wall thickness, mm	12 ± 2	12 ± 2	12 ± 2	0.11
LV mass index, mm^3	135 ± 43	137 ± 43	131 ± 43	0.56
LV ejection fraction, %	64 ± 10	61 ± 10	65 ± 10	0.08
LA volume index, mm^3	61 ± 24	60 ± 17	62 ± 26	0.74
Moderate MR, n (%)	11 (13)	7 (26)	4 (7)	0.01
Moderate AR, n (%)	11 (13)	4 (15)	7 (12)	0.66
e’, cm/s	4.2 ± 1.9	3.8 ± 1.7	4.4 ± 2.0	0.23
E/e’	21 ± 12	25 ± 14	20 ± 11	0.06
TR pressure gradient, mm Hg	29 ± 8	31 ± 8	27 ± 8	0.046

Glomerular filtration rate: GFR, B-type natriuretic peptide: BNP, left ventricle: LV, left atrium: LA, mitral valve regurgitation: MR, aortic valve regurgitation: AR, tricuspid valve regurgitation: TR.

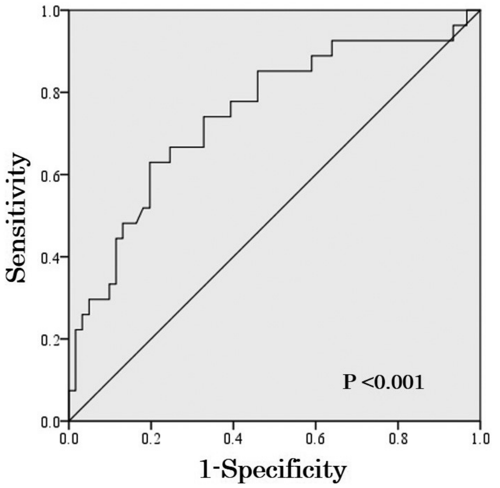
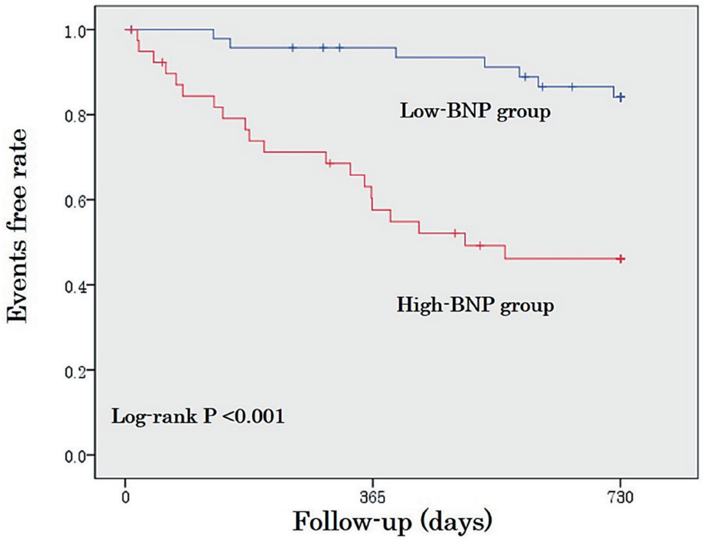


Fig. 1. Receiver operating characteristic curve analysis of B-type natriuretic peptide in patients with valve-related events (cardiac death, aortic valve replacement, or hospitalization due to heart failure)



Days	0 days	365 days	730 days
High BNP (No at risk)	40	21	15
Low BNP (No at risk)	48	42	34

Fig. 2. Kaplan-Meier curve comparing valve-related events (cardiac death, aortic valve replacement, and hospitalization due to heart failure) between patients in the low B-type natriuretic peptide (BNP) group (BNP <234 pg/mL, n=48) and those in the high BNP group (BNP ≧234 pg/mL, n=40).

Table 3. Valve-related events at the 2-year follow-up

Characteristics	Overall population (n=88)	Low BNP (n=48)	High BNP (n=40)	*p* Value
All cause death, n (%)	20 (23)	6 (13)	14 (35)	0.01
Cardiac death, n (%)	11 (13)	1 (2)	10 (25)	0.001
Aortic valve replacement, n (%)	8 (9)	4 (8)	4 (10)	0.79
Heart failure hospitalization, n (%)	23 (26)	7 (15)	16 (40)	0.007
Composite event (cardiac death, AVR, HF), n (%)	27 (31)	7 (15)	20 (50)	<0.001

Aortic valve replacement: AVR, heart failure: HF.

Table 4. Univariable and multivariable analysis of valve-related events (cardiac death, aortic valve replacement, and hospitalization due to heart failure) at the 2-year follow-up

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	*p* Value
Age, years	1.1 (1.04 - 1.22)	0.005	-	-
Diuretics	2.3 (1.1 - 4.8)	0.03	-	-
LV ejection fraction	0.95 (0.91 - 0.99)	0.02	-	-
E/E'	1.03 (1.01 - 1.06)	0.02	-	-
TRPG	1.06 (1.01 - 1.1)	0.02	-	-
Moderate mitral regurgitation	3.7 (1.6 - 8.9)	0.003	-	-
Aortic valve area, cm^2	0.05 (0.01 - 0.37)	0.001	0.03 (0.01 - 0.24)	0.001
Prior heart failure hospitalization	5.4 (2.1 - 14.4)	0.001	-	-
NYHA class	2.6 (1.6 - 4.5)	0.001	-	-
Hemoglobin, g/dL	0.79 (0.64 - 0.98)	0.03	-	-
Plasma BNP ≧ 234 pg/mL	5.0 (2.1 - 11.9)	0.001	5.1 (2.0 - 13.1)	0.001

Left ventricle: LV, left atrium: LA, New York Heart Association: NYHA, glomerular filtration rate: GFR, B-type natriuretic peptide: BNP.

Cox proportional hazard model revealed that the AVA (hazard ratio [HR], 0.06; 95% confidence interval [CI], 0.01–0.45; $p = 0.006$) and plasma BNP levels $\geqq 234$ pg/mL (HR, 5.0; 95% CI, 2.0–12.7; $p = 0.001$) were independent predictors of the study endpoint.

DISCUSSION

This study showed that plasma BNP level was a significant predictor of poor outcomes such as cardiac death, AVR, and hospitalization for congestive HF in elderly patient with severe AS.

BNP is a cardiac hormone that is released in response to intracardiac pressure increase. Hence, plasma BNP levels are elevated in symptomatic HF patients [6]. In patients with moderate to severe AS, chronic pressure overload on the LV leads to progressive LV hypertrophy, diastolic dysfunction, and left atrial dilatation [11], which can subsequently lead to a rise in BNP levels due to the increased wall stress and filling pressure [12-14].

Several studies reported the prognostic significance of BNP in patients with severe AS. A recent study showed that the combination of longitudinal data of BNP values and time to events (death and freedom from aortic valve intervention) may provide valuable prognostic information in patients with severe AS [15]. In particular, an increasing BNP trend over time was found to be a significant predictor of death. In a prospective study on 70 consecutive patients with preserved LVEF, Lim et al. [16, 17] found that BNP serum levels assisted in the differentiation between symptomatic and asymptomatic patients with severe AS and that BNP was an independent predictor of patient outcomes (cardiovascular death), suggesting that it may be used in the risk stratification of these patients. And a prospective observational study investigated the correlation of N-terminal (NT) pro-BNP with different degrees of AS severity in patients with functional classes as assessed by the NYHA classification and with the indication of AVR [18]. The authors concluded that NT pro-BNP was correlated with the severity of AS and the NYHA class and that it can serve as an indicator of AVR.

Several asymptomatic patients with severe AS are difficult to be assessed due to their lack of physical activity or under-reporting [6]. Although a watchful waiting approach is generally justified in asymptomatic patients with severe AS, the consideration of an early elective surgery in those patients might be due to the high rates of events and the possibility of rapid deterioration [19]. Different natriuretic peptides cutoff values were associated with cardiac death, the need for AVR, and onset of symptoms [11, 16]. However, they were not adjusted according to age. Age-adjusted BNP was highly predictive of outcomes in asymptomatic patients with moderate to severe AS [8]. The present study showed that an increased BNP level is an important independent predictor of outcomes in elderly patients with severe AS.

Although the aforementioned studies suggested that natriuretic peptides were robust prognostic markers in patients with AS, several other studies reported conflicting results including those reporting that a high BNP level in high-risk patients with severe AS was not an independent marker of mortality, BNP levels were not significantly correlated with the degree of AS severity, and NT-proBNP was not of prognostic significance in severe AS [20, 21]. This may be due to the dependency of plasma BNP levels on age, age-related diastolic dysfunction, and renal dysfunction rather than on the complications of AS [22-24]. Notably, Sasaki et al. [25] concluded that factors influencing plasma BNP levels may be various in elderly patients with severe AS, and plasma BNP levels may be more influenced by those factors rather than by severity of AS in elderly patients.

Study Limitations

Our study had several limitations. First, it was a retrospective study with a relatively small sample size. Second, although follow-up mortality data were collected, frailty and quality of life was not assessed. Finally, the study was not designed to assess and compare the mortality rates between patients who had surgical interventions and those who received medical treatments. Since transcatheter aortic valve replacement (TAVR) was approved for clinical use, it is believed that it will be offered to more patients as an alternative to AVR before BNP levels increase, as the experience with TAVR increases. Thus, in order to verify the present results, further prospective large-scale studies in elderly patients are needed.

CONCLUSION

Elderly patients with severe AS and high plasma BNP levels had a significantly worse prognosis than those with low BNP levels. Our results suggest that the plasma BNP level may provide significant incremental prognostic information in elderly patients with severe AS.

Conflict of interest: The authors have nothing to declare.

REFERENCES

1) Saikrishnan N, Kumar G, Sawaya FJ, Lerakis S, Yoganathan AP. Accurate assessment of aortic stenosis: a review of diagnostic modalities and hemodynamics. *Circulation* 2004;129:244-53.
2) Iung B, Baron G, Butchart EG, *et al*. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003;24:1231-43.
3) Nishimura RA, Otto CM, Bonow RO, *et al*. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57-185.
4) Rosenhek R. Almanac 2011: valvular heart disease. The national society journals present selected research that has driven recent advances in clinical cardiology. *Heart* 2011;97:2007-17.
5) Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. *J Clin Epidemiol* 2001;54:661-74.
6) Gerber IL, Stewart RA, Legget ME, *et al*. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. *Circulation* 2003;107:1884-90.
7) Pellikka PA, Sarano ME, Nishimura RA, *et al*. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005;111:3290-5.
8) Clavel MA, Malouf J, Michelena HI, *et al*. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. *J Am Coll Cardiol* 2014;63:2016-25.
9) Otto CM, Pearlman AS, Comess KA, Reamer RP, Janko CL, Huntsman LL. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. *J Am Coll Cardiol* 1986;7:509-17.
10) Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39 e14.
11) Bergler-Klein J, Klaar U, Heger M, *et al*. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;109:2302-8.
12) Iwanaga Y, Nishi I, Furuichi S, *et al*. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. *J Am Coll Cardiol* 2006;47:742-8.
13) Vanderheyden M, Goethals M, Verstreken S, *et al*. Wall stress modulates brain natriuretic peptide production in pressure overload cardiomyopathy. *J Am Coll Cardiol* 2004;44:2349-54.
14) Bergler-Klein J, Gyongyosi M, Maurer G. The role of biomarkers in valvular heart disease: focus on natriuretic peptides. *Can J Cardiol* 2014;30:1027-34.
15) Andrinopoulou ER, Rizopoulos D, Geleijnse ML, Lesaffre E, Bogers AJ, Takkenberg JJ. Dynamic prediction of outcome for patients with severe aortic stenosis: application of joint models for longitudinal and time-to-event data. *BMC Cardiovasc Disord* 2015;15:28.
16) Lim P, Monin JL, Monchi M, *et al*. Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide. *Eur Heart J* 2004;25:2048-53.
17) Patel DN, Bailey SR. Role of BNP in patients with severe asymptomatic aortic stenosis. *Eur*

Heart J 2004;25:1972-3.

18）Weber M, Arnold R, Rau M, *et al*. Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis. *Am J Cardiol* 2004; 94:740-5.

19）Rosenhek R, Zilberszac R, Schemper M, *et al*. Natural history of very severe aortic stenosis. *Circulation* 2010;121:151-6.

20）Ben-Dor I, Minha S, Barbash IM, *et al*. Correlation of brain natriuretic peptide levels in patients with severe aortic stenosis undergoing operative valve replacement or percutaneous transcatheter intervention with clinical, echocardiographic, and hemodynamic factors and prognosis. *Am J Cardiol* 2013;112:574-9.

21）Cimadevilla C, Cueff C, Hekimian G, *et al*. Prognostic value of B-type natriuretic peptide in elderly patients with aortic valve stenosis: the COFRASA-GENERAC study. *Heart* 2013;99:461-7.

22）Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005;352:666-75.

23）Tsutamoto T, Wada A, Sakai H, *et al*. Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2006;47:582-6.

24）Xu B, Daimon M. Cardiac aging phenomenon and its clinical features by echocardiography. *J Echocardiogr* 2016;14:139-45.

25）Sasaki S, Daimon M, Kawata T, *et al*. Factors responsible for elevated plasma B-type natriuretic peptide levels in severe aortic stenosis: comparison between elderly and younger patients. *J Cardiol* 2014;64:476-81.