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Impact of Aortic Elasticity on Plasma B-Type Natriuretic Peptide Levels in Patients with Preserved Left Ventricular Ejection Fraction

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1. Abstract

1.1. Background: Measurement of plasma B-type natriuretic peptide (BNP) levels is used for ruling out heart failure (HF) in clinical practice. However, elevated plasma BNP levels are often observed in patients with preserved left ventricular ejection fraction (LVEF) and with no symptoms of HF. Elevations of plasma BNP levels are multifactorial. Therefore, we investigated the relationship between the aortic elasticity indices; i.e., aortic distensibility (AoDis) and aortic stiffness (AoStif), and plasma BNP levels in such patients.

1.2. Methods: This was a single-center retrospective study. Fifty-four patients with preserved LVEF (LVEF ≥50%) who underwent transthoracic and transesophageal echocardiography (TEE) were investigated (age 68.4 ± 11.46 years; male 63.6%). All patients had no symptoms of HF. Aortic elasticity indices were evaluated using TEE.

1.3. Results: According to the cardiac rhythm at the time of TEE, patients were divided into two groups; sinus rhythm (SR) group (n = 54) and atrial fibrillation (AF) group (n = 34). The median plasma BNP level was 94.6 (IQR, 45.9−201.1) pg/mL. AoDis and AoStif were 1.4 ± 1.0 (10-3mmHg-1) and 19.0 ± 11.6, respectively. The mean E/e' was 10.3 ± 4.8. Plasma BNP levels were significantly correlated with mean E/e' ($r = 0.36$, $p = 0.001$), AoDis ($r = -0.51$, $p < 0.001$), and AoStif ($r = 0.56$, $p < 0.001$). In multivariable analyses, both AoDis (Beta = −0.22, $p = 0.02$) and AoStiff (Beta = 0.20, $p = 0.04$) were selected as independent determinants of plasma BNP levels.

1.4. Conclusions: Both AoDis and AoStif assessed using TEE were the independent determinants of plasma BNP levels in patients with preserved LVEF. Impaired aortic elasticity, as evidenced by TEE, may account in part for elevated BNP plasma levels in such patients.

2. Introduction

The usefulness of plasma B-type natriuretic peptide (BNP) has been established in the diagnosis of the presence of heart failure (HF) [1, 2] and the prediction of HF prognosis [3, 4]. In daily clinical practice, the measurement of plasma BNP levels is mainly used for ruling out HF. The European Society of Cardiology (ESC) guideline states that the absence of an increase in plasma BNP levels is one of the exclusion criteria for a diagnosis of HF with preserved left ventricular ejection fraction (LVEF) (HFpEF) and mid-range LVEF (HFmEF) (i.e., except HF with reduced LVEF; HFrEF) [5]. However, elevations of plasma BNP levels are multifactorial. Some cardiovascular or non-cardiovascular factors, such as atrial fibrillation, age, and renal failure, complicate the interpretation of plasma BNP levels [6]. Some patients with preserved LVEF (LVEF ≥50%) who have no symptoms of HF show increased plasma BNP levels without definite reasons in daily practice. An increase in plasma BNP levels has an association with left ventricular (LV) diastolic dysfunction, regardless of whether the patients have preserved or reduced LVEF [7, 8]. LV diastolic function is closely related to exercise tolerance [9, 10]. On the other hand, exercise tolerance is determined by aortic distensibility (AoDis) evaluated by magnetic

resonance imaging (MRI) in not only patients with HFpEF but also elder people without HF [11]. Previously, a relationship between the stiffness of the carotid artery, which is a muscular vessel, and plasma BNP levels has been reported [12]. However, there were few data on the relationship between aortic elasticity indices [Ao-Dis/aortic stiffness (AoStif)], which was directly obtained from the elastic aorta, and plasma BNP levels in patients with preserved LVEF. Aortic elasticity indices could be measured directly using transesophageal echocardiography (TEE) [13]. Thus, we investigated the impact of aortic elasticity evaluated by TEE on elevated plasma BNP levels in patients with preserved LVEF.

3. Methods

3.1. Study Population and Protocol

The study patients included 251 consecutive patients who underwent transthoracic echocardiography (TTE) and TEE for clinical evaluation at the Nagoya City University Hospital from September 2017 to April 2019. Among patients with preserved LVEF, eighty-eight patients were eligible for the current study (age 68.4 ± 11.46 years; male 63.6%). Patients with hypertrophic cardiomyopathy (n = 5) and maintenance hemodialysis patients (n = 1), which are expected to be associated with elevated BNP, were excluded. Patients with severe valvular disease and worsening conditions such as acute decompensated HF and acute coronary syndrome were not found in this study (Figure 1). According to the cardiac rhythm at the time of examination, patients were divided into patients with sinus rhythm (SR group; n = 54) and patients with atrial fibrillation (AF group; n = 34). Patients' baseline characteristics were gathered from their medical reports, including age, sex, body mass index, underlying disease, laboratory data, including plasma BNP levels, medication, and echocardiographic data. To calculate aortic elasticity indices, blood pressure (BP) was also collected during the TEE study in addition to resting BP and HR. Hypertension was defined as systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg or on treatment with antihypertensive drugs in daily practice, not during the TEE. Hyperlipidemia was defined as the low-density lipoprotein-cholesterol level of > 140 mg/dL or treatment with cholesterol-lowering medicine. Diabetes mellitus was defined as a HgA1c level of ≥ 6.5 % or treatment with blood glucose-lowering medicine. This study was carried out by the opt-out method of our hospital website. The study protocol was approved by Nagoya City University Graduate School of Medical Sciences and Nagoya City University Hospital Institutional Review Board and was carried out following accordance with the Declaration of Helsinki (approval identification number: 832).

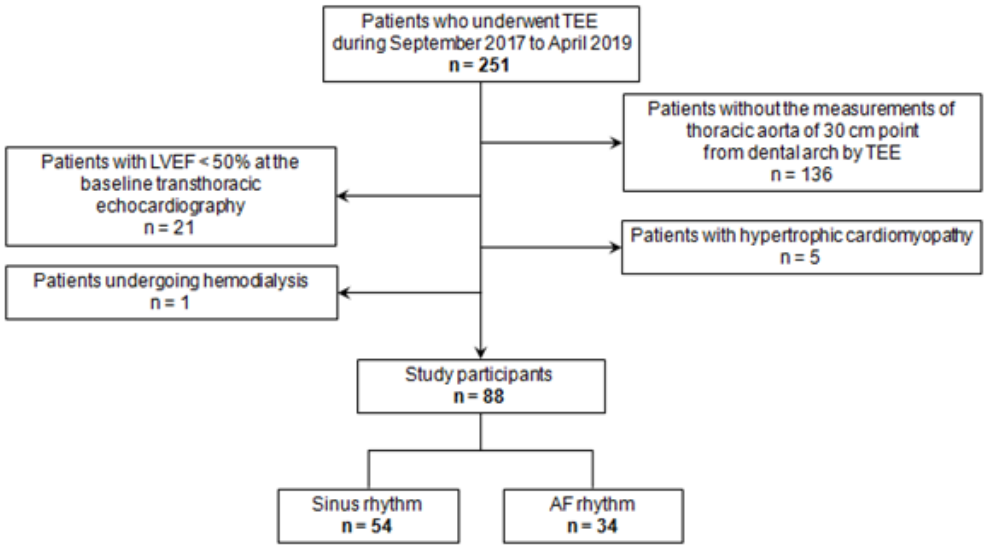

Figure 1: Diagram from patient's screening to final participants eligible for analyses in the current study. LVEF, left ventricular ejection fraction; TEE, transesophageal echocardiography.

3.2. Transthoracic Echocardiography

Transthoracic echocardiography (TTE) studies were performed using a commercially available system (Vivid Seven, GE-Vingmed Ultrasound, Horten, Norway). The TTE studies were collected in accordance with the recommendations of the American Society of Echocardiography [14]. LV end-diastolic and end-systolic diameters, and LV wall thicknesses at end-diastole were measured. The mean LV wall thickness was obtained from the interventricular septum and the posterior ventricular wall. LVEF was calculated using the Teichholz method. The left atrial diameter was obtained from a two-dimensional image of the parasternal long-axis view. The severity of valvular heart disease was diagnosed semi-quantitatively. The Doppler method was used to calculate trans-mitral early and late flow velocities (E- and A-wave components), and deceleration time. The ratio of early trans-mitral flow velocity to early mitral annular velocity (E/e') was measured by tissue Doppler imaging [15].

3.3. Measurements of AoDis and AoStif (TEE)

The aortic size was measured using TEE at the thoracic aorta of 30 cm point from the dental arch at the end of diastole and systole, to evaluate the aortic properties of ascending aorta; aortic elastic indices, i.e., AoDis and AoStif. Aortic diameters of the systolic phase (AoS) and diastolic phase (AoD) were obtained from M-mode images of the short-axis aorta (Figure 2). AoD was obtained at the peak of the R wave at the simultaneously recorded ECG, and AoS was obtained at the maximal anterior motion of the aortic wall. The following indices of aortic elasticity were calculated according to the formula below: AoDis = [2 × (AoS−AoD) / AoD ∗ pulse pressure (PP)] (mm Hg−1) [16]; (AoStif) = ln (SBP/DBP) / [(AoS−AoD) / AoD] (pure number) [17, 18], where SBP and DBP refer to brachial SBP and DBP, respectively, in mmHg and PP was calculated as SBP – DBP.

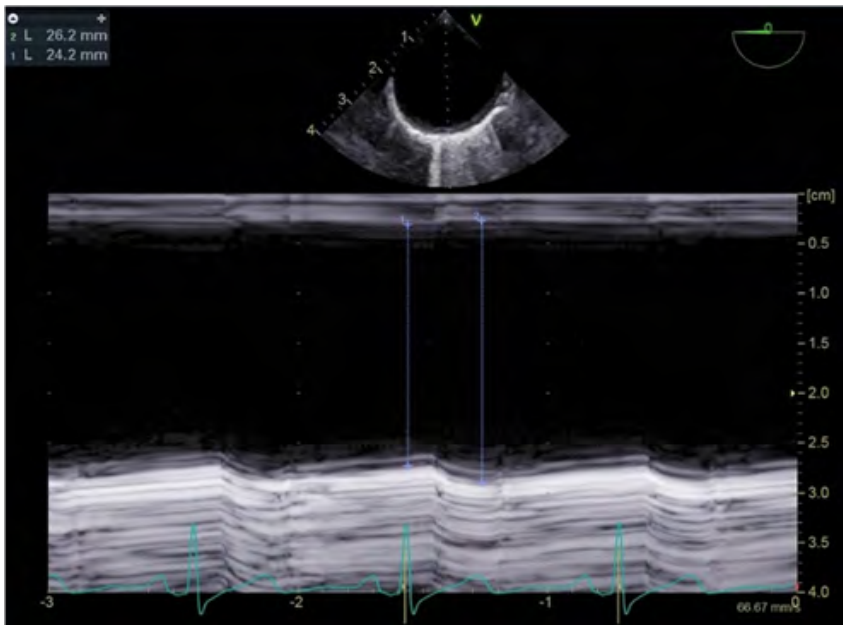

Figure 2: The representative imaging of measurement of descending aorta by transesophageal echocardiography (TEE). The diastolic diameter was measured at the same phase of the peak R wave of simultaneously recorded electrocardiography for monitoring. The largest diameter was adopted as systolic diameter.

TEE, transesophageal echocardiography.

4. Statistical Analysis

Statistical analysis was performed with SPSS ver.26 (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ± SD for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Categorical variables are summarized as the frequency (%). For comparisons between the groups, continuous variables were compared by unpaired Student's t-tests for normally distributed variables and Mann–Whitney U-tests for non-normally distributed variables. Differences in prevalence between the groups were compared using the chi-square test. Relationships between variables were evaluated by univariable linear regression analysis. Multivariable regression analysis was performed to identify the parameter that determined plasma BNP level independently. The variables entered into the model included age, AF rhythm, hypertension, estimated GFR, LV mass index, left atrium diameter, and mean E/e' ratio. AoDis was entered in one model, and AoStif was entered in another model. All p-value <0.05 were considered statistically significant.

5. Results

5.1. Clinical Characteristics

The clinical characteristics of all patients and subgroup demographics are summarized in Table 1. The prevalence of patients with hypertension was 72.7%, that with dyslipidemia was 35.2%, and that with diabetes mellitus was 14.8%. Patients without these above three diseases were 19.3%, those with one disease were 44.3%, those with two diseases were 30.7%, and those with three diseases were 5.7%. The prevalence of patients with prior HF was 10.2%. SBP, DBP, mean BP, PP, and heart rate at rest and during TEE were shown in Table 1. Each parameter showed a similar trend between at rest and during TEE. The median plasma BNP level was 94.6 (IQR, 45.9−201.1) pg/mL, indicating patients in this study had a mild ventricular overload. Echocardiographic indices were also shown in Table 1. The mean E/e' was 10.3 ± 4.8. The prevalence of patients with mean E/e' > 14 and tricuspid regurgitant velocity > 2.8 m/sec was 19.3 % and 4.5 %, respectively. The mean left atrial diameter was 39.0 ± 7.8 mm. Mean AoDis was 1.4 ± 1.0 (10^{-3}mmHg^{-1}) and mean AoStif was 19.0 ± 11.6 (Table 1). Plasma BNP levels were significantly higher in the AF group than in the SR group (200.1 [IQR, 90.9-299.1] vs. 64.7 [IQR, 32.7-105.7], p < 0.001). The E/e' did not differ between the groups. AoDis did not differ between the groups. AoStif was significantly higher in the AF group compared to the SR group (24.4 ± 14.5 vs 15.6 ± 7.7, p < 0.001).

Table 1: Baseline Characteristics of the Study Population

Characteristics	All patients	SR (n=54)	AF (n=34)	P value
Age, years	68.4 ± 11.4	67.6 ± 11.8	69.7 ± 10.6	0.4
Male, no. (%)	56 (63.6)	33 (61.1)	23 (67.6)	0.54
Body mass index, kg/m^2	24.0 ± 3.8	23.6 ± 4.0	24.6 ± 3.3	0.26
Hypertension, no. (%)	64 (72.7)	38 (70.4)	26 (76.5)	0.53
Dyslipidemia, no. (%)	31 (35.2)	17 (31.5)	14 (41.2)	0.35
Diabetes mellitus, no. (%)	13 (14.8)	7 (13.0)	6 (17.6)	0.55
Prior heart failure, no. (%)	9 (10.2)	7 (13.0)	2 (5.9)	0.29
Current smoker (%)	21 (23.9)	13 (24.1)	8 (23.5)	0.79
Systolic blood pressure (rest), mm Hg	122.0 ± 15.3	124.4 ± 16.1	118.5 ± 13.4	0.08
Diastolic blood pressure (rest), mm Hg	74.7 ± 11.7	72.3 ± 10.5	78.7 ± 12.3	0.008
Mean blood pressure (rest), mm Hg	90.4 ± 10.8	89.7 ± 10.3	92.0 ± 11.6	0.29
Pulse pressure, (rest) mm Hg	47.4 ± 15.1	52.1 ± 15.4	39.7 ± 10.7	<0.001
Heart rate, (rest) beat/min	70.0 ± 14.5	69.9 ± 11.5	78.4 ± 15.5	<0.001
Systolic blood pressure (TEE), mm Hg	153.7 ± 28.5	161.1 ± 29.7	142.1 ± 22.3	0.002
Diastolic blood pressure (TEE), mm Hg	79.4 ± 15.4	81.3 ± 16.7	76.3 ± 12.7	0.14
Mean blood pressure (TEE), mm Hg	105.4 ± 19.8	110.3 ± 20.9	99.2 ± 14.6	0.02
Pulse pressure (TEE), mm Hg	74.3 ± 19.6	79.7 ± 8.7	65.8 ± 18.0	0.001
Heart rate (TEE), beat/min	76.4 ± 16.1	69.9 ± 11.5	86.4 ± 17.1	<0.001
Laboratory measurements				
Hemoglobin, g/dL	13.9 ± 1.8	13.6 ± 1.7	14.5 ± 1.7	0.01
eGFR, mL/min/1.73 m^2	59.9 ± 14.7	62.6 ± 16.5	54.8 ± 13.2	0.009
BNP, pg/mL	94.6 (IQR, 45.9−201.1)	64.7 (IQR, 32.7−105.7)	200.1 (IQR, 90.9−299.1)	<0.001
Echocardiographic parameters				
LV diastolic diameter, mm	44.6 ± 5.8	44.9 ± 6.0	44.1 ± 5.6	0.55
LV systolic diameter, mm	28.2 ± 5.3	28.0 ± 5.6	28.7 ± 4.9	0.54
LV ejection fraction, %	66.3 ± 7.9	67.6 ± 8.0	64.2 ± 7.4	0.05
LV mass index, g/m^2	96.3 ± 48.6	89.5 ± 23.6	107.2 ± 71.7	0.1
Left atrial diameter, mm	39.0 ± 7.8	37.2 ± 7.2	41.7 ± 8.0	0.01
E, cm/sec	69.0 ± 18.7	64.9 ± 17.3	75.4 ± 19.2	0.01
Septal e', cm/sec	6.2 ± 1.7	5.7 ± 1.8	6.9 ± 1.5	0.003
Lateral e', cm/sec	8.6 ± 3.0	8.2 ± 2.8	9.2 ± 3.2	0.13
Mean e', cm/sec	7.3 ± 2.1	6.9 ± 2.2	8.0 ± 1.9	0.02
Mean E/e'	10.3 ± 4.8	10.4 ± 5.1	10.2 ± 4.5	0.82
E/e' >14, no. (%)	17 (19.3)	11 (20.1)	6 (17.6)	0.74
Deceleration time, ms	171.1 ± 57.9	181.7 ± 64.5	154.5 ± 41.5	0.03
MR ≥ moderate, no. (%)	7 (8.0)	3 (5.6)	4 (11.8)	0.3
TR ≥ moderate, no. (%)	15 (17.0)	8 (14.8)	7 (20.6)	0.48
TR velocity > 2.8 m/sec	4 (4.5)	1 (1.9)	3 (8.8)	0.13
Aortic distensibility, 10^{-3}mm Hg^{-1}	1.4 ± 1.0	1.5 ± 1.0	1.2 ± 1.0	0.14
Aortic stiffness	19.0 ± 11.6	15.6 ± 7.7	24.4 ± 14.5	<0.001
Medication				
β-blockers, no. (%)	53 (60.2)	31 (57.4)	22 (64.7)	0.5
CCBs, no. (%)	40 (45.5)	24 (44.4)	16 (47.1)	0.81
ACEIs or ARBs, no. (%)	38 (43.2)	24 (44.4)	14 (41.2)	0.76
Loop diuretics, no. (%)	12 (13.6)	6 (11.1)	6 (17.6)	0.38

Data are presented as mean ± standard deviation, median (interquartile range) or percentages.

SR, sinus rhythm; AF, atrial fibrillation; TEE, Trans esophageal echocardiography; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LV, left ventricular; E, early diastolic transmitral flow velocity; e', mitral annular velocity during early diastole; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

5.2. Relationship between BNP level and AoDis or AoStif

Plasm BNP levels (log) were significantly related with age (r = 0.40, p <0.001), with AF rhythm (r = 0.48, p <0.001), hypertension (r = 0.23, p = 0.04), estimated GFR, mL/min/1.73 m2 (r = −0.48, p <0.001), left atrial diameter (r = 0.30, p = 0.004), LV mass index (r = 0.33, p = 0.001), mean e' (r = −0.30, p = 0.005), and mean E/e' (r = 0.36, p = 0.001) (Table 2). Plasma BNP level (log) also had significant associations with AoDis (r = −0.51, p < 0.001), and AoStif (r = 0.56, p <0.001) (Table 2, Figure 3). In multivariable analyses that entered parameters that had a significant correlation with plasma BNP levels (log), both AoDis (Beta = −0.22, p = 0.02) and AoStiff (Beta = 0.20, p = 0.04) were selected as independent determinants of plasma BNP levels (Table 3). Mean E/e' and AF rhythm were selected as a determinant of BNP in both models. Age was not selected as an independent determinant.

Table 2: Univariate liner regression analysis for plasma BNP levels (log)

Values	All patients		SR		AF	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
Age, years	0.4	< 0.001	0.52	<0.001	0.17	0.33
Body mass index, kg/m^2	−0.11	0.32	−0.07	0.6	−0.41	0.02
Systolic blood pressure (rest), mm Hg	−0.08	0.47	0.11	0.42	0.31	0.08
Diastolic blood pressure (rest), mm Hg	0.18	0.09	−0.03	0.81	0.24	0.17
Mean blood pressure (rest), mm Hg	0.17	0.12	0.04	0.8	0.29	0.1
Pulse pressure (rest), mm Hg	−0.06	0.56	0.14	0.31	0.11	0.54
Heart rate (rest), beats/min	0.17	0.12	−0.24	0.09	0.23	0.19
Systolic blood pressure (TEE), mm Hg	−0.007	0.95	0.14	0.32	0.18	0.31
Diastolic blood pressure (TEE), mm Hg	−0.10	0.36	−0.14	0.32	0.21	0.23
Mean blood pressure (TEE), mm Hg	−0.05	0.65	−0.06	0.74	0.28	0.11
Pulse pressure (TEE), mm Hg	0.07	0.54	0.35	0.01	0.72	0.69
Heart rate (TEE), beats/min	0.08	0.44	−0.11	0.44	0.45	0.008
AF rhythm	0.48	< 0.001	-	-	-	-
Hypertension	0.23	0.04	0.3	0.03	0.07	0.69
Hyperlipidemia	0.09	0.43	−0.005	0.97	0.08	0.66
Diabetes mellitus	−0.03	0.79	0.09	0.52	−0.25	0.15
Prior heart failure	0.2	0.06	0.3	0.03	0.31	0.08
Smoking	0.002	0.99	0.04	0.8	−0.11	0.55
Hemoglobin, g/dL	−0.18	0.1	−0.43	0.001	−0.15	0.39
estimated GFR, mL/min/1.73 m^2	−0.48	<0.001	−0.47	<0.001	−0.45	0.007
LV mass index	0.33	0.001	0.33	0.02	0.36	0.04
LV ejection fraction, %	0.01	0.92	0.08	0.59	0.19	0.3
LV diastolic diameter, mm	0.004	0.97	0.07	0.61	−0.04	0.83
LV systolic diameter, mm	−0.02	0.85	−0.15	0.92	−0.13	0.45
Left atrial diameter, mm	0.3	0.004	0.36	0.005	−0.06	0.74
Mean E/e'	0.36	0.001	0.49	0.001	0.43	0.01
Aortic distensibility, mm Hg^{-1}	−0.51	< 0.001	−0.54	< 0.001	−0.41	0.02
Aortic stiffness	0.56	< 0.001	0.58	< 0.001	0.45	0.007

Data are presented as mean ± standard deviation, median (interquartile range) or percentages.

SR, sinus rhythm; AF, atrial fibrillation; TEE, Trans esophageal echocardiography; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LV, left ventricular; E, early diastolic transmitral flow velocity; e', mitral annular velocity during early diastole; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

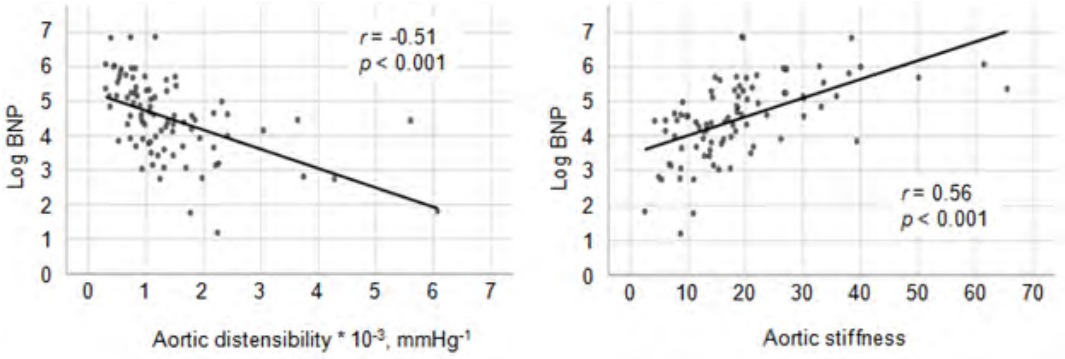

Figure 3: Linear regression analyses between plasma BNP level (Log) and aortic distensibility or aortic stiffness. BNP, B-type natriuretic peptide

Table 3: Multivariate liner regression analysis for plasma BNP level (log) in all patients

Values	Multivariate 1		Multivariate 2	
	Beta	*p*-value	Beta	*p*-value
Age, years	0.03	0.79	0.06	0.57
AF rhythm	0.27	0.002	0.22	0.02
Hypertension	0.05	0.58	0.05	0.56
estimated GFR, mL/min/1.73 m^2	−0.18	0.058	−0.20	0.03
LV mass index, g/m^2	0.15	0.11	0.15	0.11
Left atrial diameter, mm	0.1	0.25	0.12	0.16
Mean E/e'	0.31	0.001	0.28	0.004
Aortic distensibility, mm Hg^{-1}	−0.22	0.02	-	-
Aortic stiffness	-	-	0.2	0.04

Data are presented as mean ± standard deviation, median (interquartile range) or percentages.

SR, sinus rhythm; AF, atrial fibrillation; TEE, Trans esophageal echocardiography; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LV, left ventricular; E, early diastolic transmitral flow velocity; e', mitral annular velocity during early diastole; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

6. Discussion

The principal finding of this study was that aortic elastic indices, i.e., AoDis and AoStiff obtained by TEE were the independent determinants of plasma BNP levels in patients with preserved LVEF and no symptoms of HF. The elasticity of the ascending aorta, as evaluated by TEE, may account in part for elevated BNP plasma levels in such patients.

6.1. Plasma BNP Levels and Patient Cohort of this Study

The elevation of plasma BNP levels is multifactorial. Although, LV systolic dysfunction is one of the important factors for increased plasma BNP levels, patients with reduced LVEF were excluded from this study. Another important cardiac factor for increasing BNP levels is LV diastolic dysfunction. The ESC guideline has proclaimed that one of the diagnostic criteria in patients with HFpEF includes plasma BNP levels >35 pg/mL [5]. The median plasma BNP levels in this study were higher than the cut-off value that the ESC guideline proposed. However, patients with prior HF were only 13% and the patients with overt HF at the time of TEE were excluded from this study. Therefore, we focused on the patients without apparent HF in this study. The mean E/e' was lower than the American Society of Echocardiography (ASE) / the European Association of Cardiovascular Imaging (EACI) guidelines for the diagnosis of LV diastolic dysfunction in patients with preserved LVEF [19]. The prevalence of patients with E/e' >14 or tricuspid velocity >2.8m/sec, which are also proposed in that guideline, was scarce. Because the left atrial volume was not available in this study, the diagnostic algorithm for LV diastolic dysfunction recommended by ASE/EACI guidelines cannot be used. However, the mean e' value in this study was lower than those proposed by the guidelines. Therefore, this present study seemed to include patients with some degree of LV diastolic dysfunction and without apparent HF.

6.2. AoDis/AoStif and BNP

Strong associations between plasma BNP level and aortic elastic indices, i.e., AoDis and AoStif were observed in our study. Furthermore, these indices were independent determinants of increased plasma BNP levels. To date, several types of vascular function examinations have been established. Among them, carotid artery stiffness β and brachial-ankle pulse wave velocity (baPWV) have been reported to be associated with plasma BNP levels. Although there are differences in the testing modalities and targeted vessels, our study is consistent with these results. GR Shroff et al. reported

an association between stiffness parameter β of the carotid artery, which is a muscular vessel, and plasma BNP levels in patients with chest pain [12]. An association between baPWV and plasma BNP levels has also been reported in healthy Japanese men [20] and patients with coronary artery disease [21]. However, baPWV reflects the stiffness of both the aorta which is an elastic artery, and the limb artery which is a muscular vessel. The strength of this study was the evaluation of the AoStif obtained in the ascending aorta, which is an elastic vessel and closely related to Windkessel function, during TEE examinations. The relationship between AoDis and plasma BNP levels was also clarified as well as AoStif in this study. Previously, the relationship between AoDis and exercise tolerance has been reported [11]. The relationship between exercise tolerance and plasma BNP levels is also a well-known fact [22]. Therefore, it is not surprising that the correlation between AoDis and plasma BNP levels was found in this study.

The considerable mechanisms of increased plasma BNP levels are as follows [23-26]. As the aorta stiffer, the PWV along with the aorta increases. As a result, the reflected PWV arrives earlier at the ascending aorta and augments the late-systolic ascending aortic pressure waveform [27]. This augmented late-systolic ascending aortic pressure load to the left ventricle, which results in deteriorated LV diastolic function. In fact, our study included patients with some degree of LV diastolic dysfunction and without apparent HF, as previously described. Therefore, our results are supportive of the above mechanism.

Note that age was not selected as a determinant of increased plasma BNP levels in multivariate analysis. This means the increased plasma BNP levels may be related to the decrease in vascular elasticity independent of the aging process.

6.3. AF, E/e' and BNP

In the present study, AF was selected as an independent determinant of increased plasma BNP levels. The mean E/e' was also selected as an independent determinant of increased plasma BNP levels. It is commonly reported that plasma BNP levels are higher in patients with AF than in those with SR, reflecting increased LV filling pressure in patients with AF. However, E/e' did not differ between the SR groups and the AF groups in this study. On the other hand, elevated BNP in patients with AF has been reported not to be associated with the presence of congestion. [28] Therefore, this current study is consistent with this previous study. Thus, the finding that AF rhythm was a determinant of elevated BNP level in this study may be a direct contribution not mediated by E/e'.

7. Clinical Implication

The implication of these findings is that the elevated plasma BNP levels may be a marker of reduced aortic elasticity resulting from atherosclerotic diseases in patients with preserved LVEF who do not have clinically apparent HF (even though with some degree of LV diastolic dysfunction). In fact, approximately three-fourths of this study patients consisted of those with some atherosclerotic disease. Moreover, decreased AoDis has been reported as an independent risk factor for all-cause mortality in the participants without overt cardiovascular disease [32]. Therefore, when patients with elevated plasma BNP levels but no apparent HF are presented in the clinical setting, more aggressive interventions for atherosclerotic diseases should be considered. In addition, if the patient has atrial fibrillation, intervention for atrial fibrillation should be considered. It will be interesting to see how BNP levels change as a result of the active intervention.

Furthermore, arterial stiffness is associated with the hospitalization of HFpEF patients [33]. Therefore, these patients who were investigated in this study may be associated with the future development of HFpEF. In this regard, further investigation is also needed.

8. Limitations

The present study had several limitations that should be considered. First, this is a single-center, and retrospective study, with a small number of participants. Second, this study consisted of patients who underwent TEE. TEE is not a standard examination that can be performed for all patients. Therefore, it is unclear whether these results could be applied to all patients. Furthermore, the aortic elasticity indices were obtained under certain invasive conditions. Therefore, the question of whether the aortic indices under the elevated BP are equivalent to those at rest is raised. Thus, the results of this study are required to validate using other less invasive modalities. In addition, due to the small number of participants in this study, it was not possible to specify the plasma BNP levels as an indicator of impaired aortic elasticity in the SR group and the AF group, respectively. However, our results indicate that it is useful to assess aortic stiffness when plasma BNP levels predicted from cardiac function are unexpectedly high, either in patients with sinus rhythm or AF rhythm. We believe that the obtained data are important for deducing the increase in plasma BNP levels in patients without overt HF despite the above-mentioned limitations.

9. Conclusions

Both AoDis and AoStif were significantly associated with the plasma BNP level. In patients with preserved LVEF, impaired elasticity of the large arteries, as evidenced by TEE, may account in part for elevated BNP plasma levels.

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