# Factors responsible for elevated plasma B-type natriuretic peptide levels in severe aortic stenosis: Comparison between elderly and younger patients

Original Article (Revision2 Marked)

# Factors Responsible for Elevated Plasma B-type Natriuretic Peptide Levels in Severe Aortic Stenosis: Comparison between Elderly and Younger Patients

Short title: Comparison of BNP in severe AS between elderly and young

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**Abstract**

**Background**: Elevated plasma B-type natriuretic peptide (BNP) levels are a predictor of outcome and helpful for risk stratification in aortic stenosis (AS). However, left ventricular (LV) diastolic dysfunction progresses with aging and may also influence plasma BNP levels in elderly patients. We hypothesized that plasma BNP levels may be influenced by age in severe AS, and that factors that affect the elevation of plasma BNP levels may be different between elderly and younger patients with AS.

**Methods**: We performed echocardiography in 341 patients with severe AS (aortic valve area (AVA) <1.0 $cm^2$) and classified them into 2 groups by age (elderly ≥75 years old, n=201; younger patients <75 years old, n=140). We used multivariate linear regression analysis to assess the factors that determine plasma BNP levels in both groups.

**Results**: Age was found to be one of the independent determinants of plasma BNP levels in all patients (β=0.135, p=0.005). Although AVA was similar in the two groups, plasma BNP levels and E/e' were significantly higher in elderly than younger patients (133.0 (IQR;73.3-329.7) vs 92.8 (IQR;40.6-171.8) pg/dl, p<0.01; 20±8 vs 16±6, p<0.01; respectively). In multivariate stepwise linear regression analysis, AVA index, LV ejection fraction, mass index, E/e', estimated systolic pulmonary artery pressure (eSPAS) and the presence of atrial fibrillation were independent determinants of plasma BNP levels in younger patients. In contrast, the independent determinants of plasma BNP levels in elderly patients were LV ejection fraction, mass index, E/e', eSPAS, the presence of atrial fibrillation, age, and hemoglobin levels, but not AVA index.

**Conclusions**: There may be differences in the factors that influence plasma BNP levels between elderly and younger patients with severe AS. In elderly patients, plasma BNP levels may be influenced more by factors than AS severity compared with younger patients.

## Introduction

With the aging of society, the number of patients with aortic stenosis (AS) is increasing, and AS has become a common valvular disease [1]. Surgical intervention is critical to improve prognosis in patients with AS, and the importance of risk stratification and deciding optimal timing for surgery has been emphasized.

Previous reports have shown that B-type natriuretic peptide (BNP) is a predictor of outcome and helpful for risk stratification of AS [2-4], and BNP might be useful to help determine the optimal timing of non-pharmacological interventions such as aortic valve replacement (AVR) in patients with severe AS without symptoms or cardiac dysfunction. BNP is predominantly released from the left ventricular (LV) myocardium in response to elevated LV end-systole wall stress and hypertrophy, which may gradually progress in AS and lead to LV systolic and diastolic dysfunction [5-8]. In the modern era, the prevalence of a degenerative calcified valve has increased with aging and the prevalence of atherosclerosis, and is the most common etiology of AS [1]. However, LV diastolic dysfunction also progresses with aging [9, 10] and may influence plasma BNP levels in elderly patients with AS [11]. In addition, plasma BNP level is multifactorial and could be increased with aging even in a healthy population [11]. We hypothesized that age-related physical changes may influence plasma BNP levels in patients with severe AS and plasma BNP levels may not be useful for assessing LV dysfunction caused by AS in elderly patients. We aimed to investigate 1) whether plasma BNP levels are influenced by age in patients with severe AS, and if so, 2) whether there are differences in the clinical and echocardiographic factors associated with elevated plasma BNP levels between elderly and younger patients with severe AS.

## Methods

### Subjects

We enrolled 341 patients with isolated severe AS (aortic valve area (AVA) < 1.0 $cm^2$) referred to our echocardiographic laboratories in the present study. They were divided into two groups by age, with patients ≥ 75 years old included in the elderly group. We compared the clinical and echocardiographic factors associated with elevated plasma BNP levels between two groups using multivariate stepwise linear regression analysis. Exclusion criteria were: pulmonary disease, more than mild aortic or mitral regurgitation or mitral stenosis, and renal insufficiency (creatinine clearance < 30

ml/min). Ethical approval for this study was granted by the Sakakibara Heart Institute and Juntendo University School of Medicine ethics committees, and patients gave informed consent prior to participation in the study. We collected clinical data and information on symptoms in the study patients from medical records that were reviewed by experienced cardiologists. The presence of symptoms was defined as exertional dyspnea (NYHA ≥2), angina, presyncope, syncope and heart failure. First, we explored the independent determinant of plasma BNP levels in all study patients using multivariate stepwise linear regression analysis.

**Plasma BNP Measurements**

Plasma BNP levels were determined at the time of diagnosis of severe AS. Venous blood (4 ml) was obtained from each patient and transferred to tubes containing aprotinin and EDTA, and stored at -20˚C until analysis. The plasma concentration of BNP was measured using a chemiluminescent enzyme immunoassay kit (MI02 Shionogi BNP; Shionogi Co. Ltd., Osaka, Japan) and an immunoassay system (MI02; A&T Co. Ltd., Yokohama, Japan). The minimum quantity of a human BNP detectable using this system is 4 pg/ml.

**Echocardiographic Study**

Doppler echocardiography was performed using commercially-available echocardiographic machines. All patients underwent a comprehensive examination that included 2-dimensional and Doppler echocardiography by an experienced sonographer or cardiologist. The peak aortic valve (AV) velocity and mean AV pressure gradient were derived from transaortic flow recorded with continuous–wave Doppler using a multi-window approach. The AVA was calculated using the continuity equation [12]. The severity of AS was assessed by the AVA index in this study. The LV end-diastolic volume (EDV) and end-systolic volume (ESV) were measured by the method of disks using 2D images obtained from both the apical 4- and 2-chamber views. LV ejection fraction was calculated by the following equation: 100 x (EDV-ESV)/EDV [13]. LV mass was calculated using diastolic measurements of LV internal diameter and wall thickness on 2D echocardiography according to the formula recommended by the American Society of Echocardiography: LV mass (g) = 0.8 × $\{1.04[(IVST+LVID+PWT)^3 - (LVID)^3]\}$ + 6 g (IVST, interventricular septal wall

thickness; LVID, LV internal diameter; PWT, posterior wall thickness) [13]. Then, left ventricular mass index was calculated as LV mass / body surface area.

For assessing diastolic function, pulsed-wave Doppler examination of mitral inflow and tissue Doppler imaging of mitral annular motion at the septum were also performed, according to a previous study [14]. Peak velocities of early (E), late (A) diastolic flow and E/A ratio were measured from pulsed-wave Doppler examination of mitral inflow. Early (e') diastolic annular velocities were measured from tissue Doppler imaging. The ratio of mitral E to e' (E/e') was also calculated as an index of LV filling pressure.

Estimated systolic pulmonary artery pressure (eSPAP) was calculated using the peak pressure gradient of tricuspid regurgitation and right atrial pressure that was estimated on the basis of inferior vena cava size and collapse [15]. Furthermore, according to previous reports [14, 16], we classified diastolic function in all subjects into one of four categories (grade 0 (normal), grade 1, grade 2 or grade 3).

**Statistical Analysis**

Continuous data are expressed as mean ± SD or median (inter-quartile range (IQR)), as appropriate. Categorical data are presented as the number (percentage) of patients. Continuous variables were compared using Student's t test or Mann-Whitney U test, as appropriate. Categorical variables were compared using Fisher's exact test or a chi-square test, whenever appropriate. Pearson's linear correlation analysis was used to determine the correlations between $\log_{10}$ BNP and the echocardiographic and clinical variables. Multivariate linear regression analysis was also performed to determine the independent determinants of $\log_{10}$ BNP. Variables with $p<0.05$ in univariate analysis were incorporated into the linear regression model. Comparing independent determinants of $\log_{10}$ BNP between two groups, all variables with $p<0.05$ in univariate analysis either in younger or elderly group were incorporated into the linear regression model. AVA index was used as a variable in the linear regression model for assessing AS severity, because high prevalence of severe AS with low flow and low pressure gradient despite normal LV ejection fraction has been reported [17]. Pairs with missing values were excluded from the analysis. SPSS version 17.0 (SPSS Inc, Chicago, IL) was used for statistical analyses. Statistical significance was defined as $p<0.05$.

## Results

The median of plasma BNP levels was 115.7 (IQR; 55.7-247.5). A logarithmic transformation of plasma BNP was performed for assessing correlations with variables because plasma BNP levels did not follow a normal distribution. All clinical characteristics and echocardiographic parameters that showed significant correlations with plasma BNP levels in univariate regression analysis in a whole population are shown in **Table 1**. Other clinical characteristics including gender ($r=0.057$, $p=0.297$) did not have significant correlations with plasma BNP levels. When we explored the determinant factors of plasma BNP levels, age was found to be one of the independent determinants of plasma BNP levels in a whole population with severe AS (**Table 1**). The clinical and echocardiographic characteristics of patients in each age group are presented in **Tables 2 and 3**. Body mass index, body surface area, hemoglobin and creatinine clearance were significantly smaller in elderly patients, whereas the plasma BNP levels and the prevalence of coronary artery disease were significantly higher in elderly patients. Both elderly and younger patients had similar AVA index, peak AV velocity and mean AV pressure gradient, despite higher plasma BNP levels in elderly patients. Elderly patients had decreased e' and increased E/e' ($p<0.01$ for both) compared with younger patients, probably because of age-related LV diastolic dysfunction.

**Table 4** shows the comparison of factors that had significant correlations with $\log_{10}$ BNP among the demographic, clinical and echocardiographic variables between two groups. Other variables that were not listed in **Table 4** did not have significant correlations with $\log_{10}$ BNP. Although $\log_{10}$ BNP and AVA index were correlated in both younger and elderly patients (**Figure 1**), the association between plasma BNP levels and other variables was the not the same in the two patient groups (**Table 4**). In multivariate stepwise linear regression analysis, AVA index, atrial fibrillation, beta blocker use, LV ejection fraction, LV mass index, E/e' and eSPAP were found to be independent determinants of plasma BNP levels in younger patients. On the other hand, the severity of AS, as measured by the AVA index, was not an independent determinant of plasma BNP levels in elderly patients. In elderly patients, age and hemoglobin levels were also independent determinants of plasma BNP levels. Other factors including age were assumed to contribute to elevated plasma BNP levels in elderly patients with severe AS.

## Discussion

Our study indicates that plasma BNP levels were influenced by a complex interaction of clinical and echocardiographic parameters in patients with severe AS. In patients with severe AS, plasma BNP levels were influenced by age and higher in elderly patients than in younger patients, despite the similar severity of AS in this study. Furthermore, plasma BNP levels were influenced by other variables in addition to AS severity in elderly patients, including LV systolic and diastolic function, and anemia. In particular, elderly patients have been shown to have decreased e' and increased E/e', probably due to aged-related progression of LV diastolic dysfunction [9, 10], and this may contribute to elevated plasma BNP levels in elderly patients with AS. These additional associations need to be considered in interpreting plasma BNP levels and deciding the therapeutic strategy in patients with severe AS.

As previously reported [2, 18-20], AS severity was significantly correlated with plasma BNP levels in this study. On the other hand, AS severity did not emerge as an independent determinant of BNP in elderly patients. E/e' has been found to be a reliable estimate of LV filling pressure, and was shown to be an independent predictor of prognosis in patients with severe AS [21, 22]. Since systolic pressure overload leads to LV wall hypertrophy and decreased LV compliance, LV end-diastolic pressure increases before LV dilation, resulting in diastolic rather than systolic dysfunction in AS [23-26]. In elderly patients, but not younger patients, E/A and e' (parameters of diastolic dysfunction) were correlated with plasma BNP levels in univariate analysis. Age-related LV diastolic dysfunction might play a more important role in the elevation of plasma BNP levels in elderly than younger patients with AS. Hemoglobin levels also can decrease with age. Age and anemia were independently associated with plasma BNP level in our study, as previously reported in a population without AS [11, 27].

Several reports demonstrated a relationship between plasma BNP levels and the presence of symptoms [28-30]. However, symptoms did not emerge as an independent correlate of plasma BNP levels in our series. This might be because we included chest pain and syncope as well as exertional dyspnea as symptoms in our study, and chest pain and syncope have not been shown to be associated with natriuretic peptide levels [28]. In addition, approximately 30% patients had coronary artery disease in our study, which could have caused their symptoms, especially chest pain.

Independent clinical correlates of plasma BNP levels were atrial fibrillation

and beta blocker use in both groups. It has been reported that plasma BNP levels increase in patients with atrial fibrillation since BNP is produced in the atrium [31, 32]. On the other hand, since beta blockers may improve long-term systolic function in patients with reduced ejection fraction or reduce afterload in patients with hypertension, these changes might have influenced plasma BNP levels [6, 33]. In our echocardiographic evaluation, LV ejection fraction, LV mass index and eSPAP were also independent correlates of plasma BNP levels in both groups, as previously reported [6, 33-36]. On the other hand, creatinine clearance was not selected as an independent determinant of plasma BNP levels in this study, although it had a significant correlation with plasma BNP levels in younger group. Namely, plasma BNP levels were more influenced by cardiac dysfunction than renal dysfunction. This finding was assumed to be consistent with a previous report that plasma BNP levels are useful biomarker for mortality and cardiovascular events in patients with chronic kidney disease [37].

In regard to AS severity, AVA, peak AV velocity and mean AV pressure gradient have very close relationship and these cannot be incorporated together into the logistic regression models for multicollinearity. We used AVA index to assess the AS severity in our study. Because it was reported that elderly patients with severe AS often had low flow and low pressure gradient despite preserved ejection fraction [17]. In such patients, the assessment of AS severity using pressure gradient or peak velocity could result in underestimation of the AS severity and AVA index was assumed to reflect the hemodynamic AS severity most among them.

## Limitations

There were some limitations of our study. Our data were retrospectively derived from a modest number of patients. The role of plasma BNP levels for risk stratification and clinical decision making in patients with severe AS could not be assessed in the present study. Plasma BNP level measurements were not serially followed and the prognostic value of plasma BNP levels could not be assessed. In addition, plasma BNP levels has been reported to be markedly elevated in low-flow, low-gradient AS and was significantly higher in truly severe AS compared with pseudo-severe AS [4]. Since we evaluated the severity of AS only from AVA in this study, we might have included patients with pseudo-severe AS.

## Clinical implication

Currently, recognition of symptoms is critical to the selection of a therapeutic strategy, since the indication for surgery is largely based on the presence or absence of symptoms [38]. However, symptoms are often unclear particularly in elderly patients and might not reflect AS severity [39]. Furthermore, LV dysfunction caused by AS could progress without evident symptoms and be associated with poor outcome [38]. Plasma BNP level is a predictor of outcome and helpful for risk stratification of AS [2-4] reflecting myocardial damage, and BNP might be useful to help determine the optimal timing of surgical interventions in such patients with severe AS. In this study, AVA index was one of strongest determinant of plasma BNP levels in younger patients. Namely, elevated LV wall stress and hypertrophy were mainly caused by AS and surgical AVR might be effective in improving myocardial damage and dysfunction in these patients. On the other hand, AVA index was not an independent determinant of elevated plasma BNP levels and other factors, rather than AS, were more associated with elevated plasma BNP levels in elderly patients even with severe AS. Thus, surgical AVR might not be effective in improving myocardial damage and dysfunction in elderly AS patients with elevated plasma BNP levels, and plasma BNP levels might not be useful to help determine the timing of surgical interventions in these patients. Otherwise, our results can be interpreted in a different way. Age-related LV diastolic dysfunction might not be the sole reason why elderly patients had decreased e' and increased E/e' compared with younger patients. Namely, elderly patients have a longer disease period than younger patients, and could have more severe myocardial damage due to longer LV pressure overload caused by AS. If so, higher BNP might indicate severe myocardial damage caused by AS, irrespective of the current AVA index, and rather could be "useful to help determine the timing of surgical interventions" in elderly patients. However, we need further investigations to reach definitive conclusions. Anyway, we need to remember that plasma BNP levels may be influenced more by factors than AS severity in elderly patients.

## Conclusion

Clinical and echocardiographic determinants of plasma BNP levels were different between elderly and younger patients with severe AS. Plasma BNP levels were higher in elderly patients than in younger patients despite the similar severity of AS in this

study. Furthermore, plasma BNP levels may be influenced more by other factors such as LV diastolic dysfunction rather than AS severity in elderly patients. We may need to take these factors into consideration in interpreting plasma BNP levels and deciding the therapeutic strategy in severe AS.

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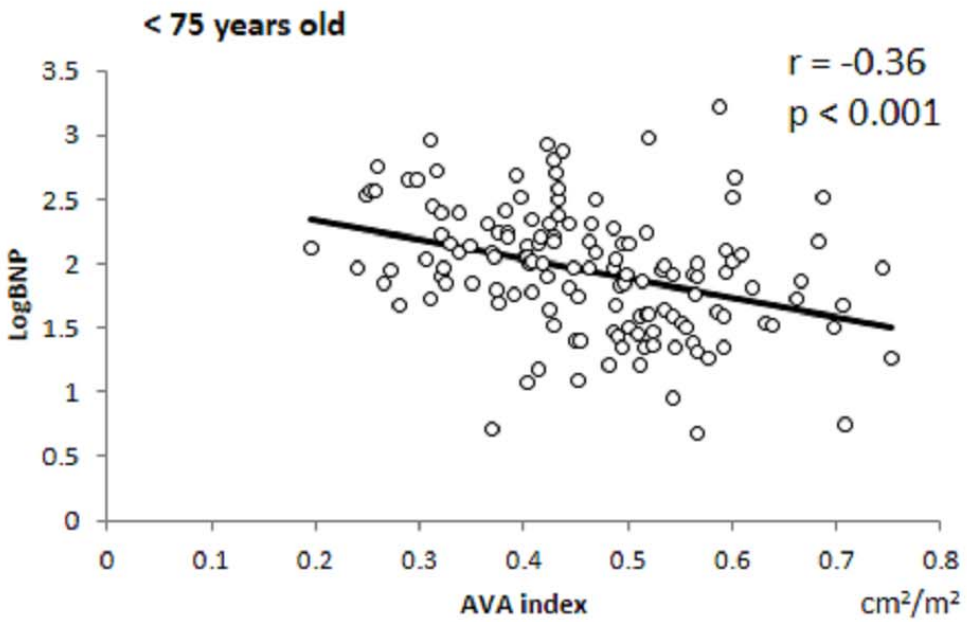
## Figure legends

**Figure 1**. The relations between Log $_{10}$ BNP and AVA index in patients aged <75 years old (left) and ≥75 years old (right).
Both groups had significant relationships between Log $_{10}$ BNP and AVA index.


< 75 years old
r = -0.36
p < 0.001
LogBNP
3.5
3
2.5
2
1.5
1
0.5
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
AVA index
cm²/m²

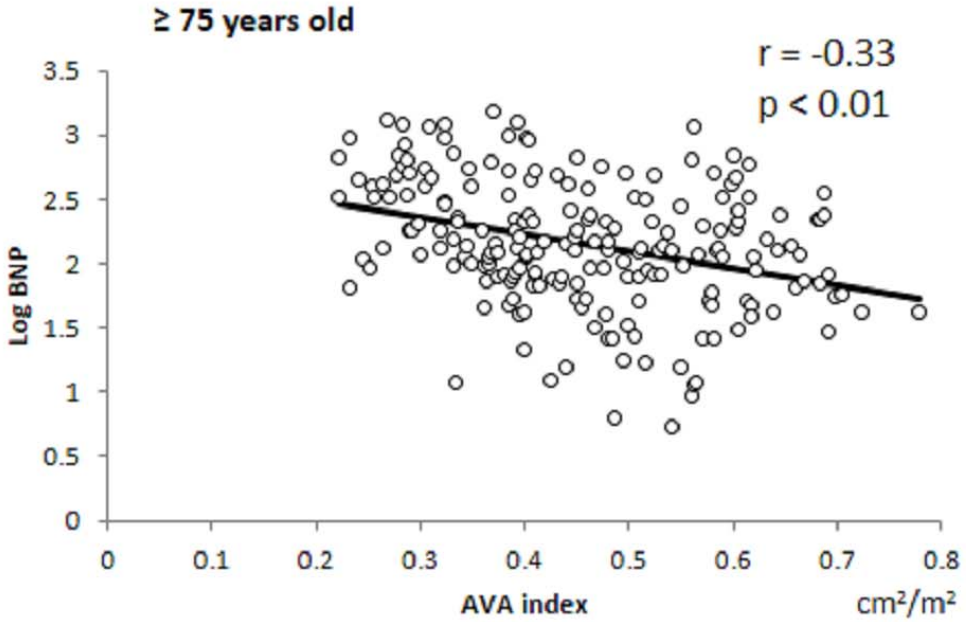

≥ 75 years old
r = -0.33
p < 0.01
Log BNP
3.5
3
2.5
2
1.5
1
0.5
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
AVA index
cm²/m²

Table 1. Factors associated with log BNP in univariate and multivariate linear regression analyses

| Variable | All patients | | | |
|---|---|---|---|---|
| | univariate | | multivariate | |
| | r | p value | ß | p value |
| Age | 0.328 | < 0.001 | 0.135 | 0.005 |
| Atrial fibrillation | 0.208 | < 0.001 | 0.157 | < 0.001 |
| Beta blocker use | 0.158 | 0.004 | 0.163 | < 0.001 |
| Hemoglobin | - 0.229 | < 0.001 | -0.130 | 0.006 |
| Creatinine clearance | - 0.184 | 0.001 | - | - |
| EDV index | 0.228 | < 0.001 | - | - |
| ESV index | 0.367 | < 0.001 | - | - |
| Ejection fraction | - 0.396 | < 0.001 | - 0.208 | < 0.001 |
| LV mass index | 0.462 | < 0.001 | 0.251 | < 0.001 |
| AVA index | - 0.342 | < 0.001 | - 0.161 | < 0.001 |
| E/A | 0.198 | < 0.001 | - | - |
| E/e' | 0.438 | < 0.001 | 0.206 | < 0.001 |
| eSPAP | 0.298 | < 0.001 | 0.130 | 0.006 |

EDV, end-diastolic volume; ESV, end-systolic volume index; AVA, aortic valve area; E, peak velocity of early diastolic flow of mitral inflow; A, peak velocity of late diastolic flow of mitral inflow; eSPAP, estimated systolic pulmonary artery pressure.

Table 2. Patient clinical characteristics

| Variable | < 75 years old (N=140) | ≥ 75 years old (N=201) | p value |
|---|---|---|---|
| Male | 64 (46%) | 81 (40%) | 0.42 |
| Age, years old | 67 ± 7 | 81 ± 4 | < 0.01 |
| Body mass index, kg/m$^2$ | 23.8 ± 3.8 | 22.9 ± 3.3 | 0.02 |
| Body surface area, m$^2$ | 1.6 ± 0.2 | 1.5 ± 0.2 | < 0.01 |
| Symptomatic | 91 (65%) | 135 (67%) | 0.76 |
| Comorbidity | | | |
| Hypertension | 84 (60%) | 137 (68%) | 0.14 |
| Diabetes mellitus | 32 (23%) | 45 (22%) | 0.91 |
| Hyperlipidemia | 72 (51%) | 99 (49%) | 0.78 |
| Coronary artery disease | 36 (26%) | 75 (37%) | 0.03 |
| Cerebrovascular disease | 10 (7%) | 20 (10%) | 0.48 |
| Atrial fibrillation | 10 (7%) | 19 (10%) | 0.58 |
| Medications | | | |
| RAS-I | 70 (50%) | 108 (54%) | 0.57 |
| Beta blocker | 43 (31%) | 45 (22%) | 0.11 |
| Calcium channel blocker | 54 (39%) | 87 (43%) | 0.45 |
| Statin | 65 (46%) | 93 (46%) | 0.98 |
| Laboratory data | | | |
| Hemoglobin, g/dl | 13.4 ± 1.4 | 12.2 ± 1.6 | < 0.01 |
| Creatinine clearance, ml/min | 70 ± 15 | 61 ± 17 | < 0.01 |
| BNP, pg/dl | 162 ± 218 | 253 ± 287 | < 0.01 |

RAS-I, renin-angiotensin system inhibitor.

Table 3. Echocardiographic data

| Variable | < 75 years old (N=140) | ≥ 75 years old (N=201) | p value |
|---|---|---|---|
| AS severity | | | |
| AVA index, $cm^2/m^2$ | 0.46 ± 0.12 | 0.46 ± 0.13 | 0.60 |
| Peak AV velocity, m/sec | 4.8 ± 1.0 | 4.8 ± 0.9 | 0.38 |
| Mean AV PG, mmHg | 55 ± 22 | 53 ± 22 | 0.44 |
| Left atrial diameter, cm | 4.0 ± 0.7 | 4.0± 0.6 | 0.84 |
| Left ventricle | | | |
| EDV index, $ml/m^2$ | 58 ± 22 | 54 ± 23 | 0.06 |
| ESV index, $ml/m^2$ | 21 ± 13 | 21 ± 15 | 0.79 |
| Ejection fraction, % | 65 ± 9 | 63 ± 10 | 0.16 |
| Mass index, $g/m^2$ | 132 ± 35 | 129 ± 35 | 0.37 |
| E/A | 0.8 ± 0.4 | 0.8 ± 0.3 | 0.06 |
| E/e' | 16 ± 6 | 20 ± 8 | < 0.01 |
| e' | 4.8 ± 1.4 | 4.1 ± 1.3 | < 0.01 |
| Diastolic dysfunction class | | | |
| Grade 0 | 1 (1%) | 0 (0%) | 0.86 |
| Grade 1 | 67 (48%) | 115 (57%) | 0.11 |
| Grade 2 | 59 (42%) | 63 (31%) | 0.05 |
| Grade 3 | 3 (2%) | 4 (2%) | 0.92 |
| eSPAP, mmHg | 31 ± 7 | 32 ± 8 | 0.48 |

AVA, aortic valve area; PG, pressure gradient; EDV, end-diastolic volume; ESV, end-systolic volume index; E, peak velocity of early diastolic flow of mitral inflow; A, peak velocity of late diastolic flow of mitral inflow; e', early diastolic annular velocity; eSPAP, estimated systolic pulmonary artery pressure.

Table 4. Factors associated with log BNP in univariate and multivariate linear regression analyses

| Variable | < 75 years old | | | | ≥ 75 years old | | | |
|---|---|---|---|---|---|---|---|---|
| | univariate | | multivariate | | univariate | | multivariate | |
| | r | p value | ß | p value | r | p value | ß | p value |
| Age | 0.255 | 0.002 | - | - | 0.330 | < 0.001 | 0.130 | 0.033 |
| Atrial fibrillation | 0.214 | 0.012 | 0.170 | 0.018 | 0.199 | 0.005 | 0.150 | 0.011 |
| Beta blocker use | 0.220 | 0.009 | 0.204 | 0.004 | 0.149 | 0.036 | 0.126 | 0.026 |
| Hemoglobin | - 0.065 | 0.442 | - | - | - 0.231 | 0.001 | - 0.180 | 0.002 |
| Creatinine clearance | - 0.221 | 0.009 | - | - | - 0.089 | 0.210 | - | - |
| EDV index | 0.255 | 0.002 | - | - | 0.256 | < 0.001 | - | - |
| ESV index | 0.349 | < 0.001 | - | - | 0.396 | < 0.001 | - | - |
| Ejection fraction | - 0.328 | < 0.001 | - 0.180 | 0.015 | - 0.430 | < 0.001 | - 0.277 | < 0.001 |
| LV mass index | 0.483 | < 0.001 | 0.254 | 0.002 | 0.482 | < 0.001 | 0.270 | < 0.001 |
| AVA index | - 0.360 | < 0.001 | - 0.253 | 0.001 | - 0.334 | < 0.001 | - | - |
| E/A | 0.168 | 0.054 | - | - | 0.267 | < 0.001 | - | - |
| E/e' | 0.434 | < 0.001 | 0.200 | 0.010 | 0.401 | < 0.001 | 0.212 | < 0.001 |
| e' | 0.101 | 0.248 | - | - | 0.140 | 0.049 | - | - |
| eSPAP | 0.322 | < 0.001 | 0.150 | 0.046 | 0.281 | < 0.001 | 0.147 | 0.018 |

EDV, end-diastolic volume; ESV, end-systolic volume index; AVA, aortic valve area; E, peak velocity of early diastolic flow of mitral inflow; A, peak velocity of late diastolic flow of mitral inflow; e', early diastolic annular velocity; eSPAP, estimated systolic pulmonary artery pressure.