Greater Nocturnal Blood Pressure Is Associated With Natriuretic Peptide Level in Aortic Stenosis With Preserved Ejection Fraction

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**Background:** Although careful monitoring of asymptomatic severe aortic stenosis (AS) is recommended to prevent missing the optimal timing of surgical or transcatheter aortic valve replacement, prophylactic treatment that could extend the asymptomatic period remains unknown. In a hypertensive population, high blood pressure (BP) measured at the doctor's office is known to be associated with B-type natriuretic peptide (BNP) level, a surrogate marker for symptomatic deterioration in AS. Little is known regarding the association between nocturnal BP variables and BNP in severe AS with preserved ejection fraction (EF).

**Methods and Results:** The subjects consisted of 78 severe AS patients (mean age, 79 ± 6 years) with preserved EF. Nocturnal BP was measured hourly using a home BP monitoring device. On multiple regression analysis, nocturnal mean systolic BP (SBP) remained independently associated with BNP after adjustment for age, sex, body mass index, estimated glomerular filtration rate, antihypertensive medication class, early diastolic mitral annular velocity, and left ventricular mass index (P=0.03), whereas diastolic BP (DBP) and variables of BP variability were not.

**Conclusions:** Higher nocturnal SBP rather than DBP or indices of BP variability was independently associated with BNP in AS patients with preserved EF. Intervention for nocturnal SBP may therefore extend the asymptomatic period and improve prognosis.

**Key Words:** Aortic stenosis; Blood pressure; Blood pressure variability; B-type natriuretic peptide
level has not been addressed in patients with severe AS.

The aim of the present study was therefore to assess the relationship between plasma BNP level and nocturnal BP variables (mean and variability) in severe AS patients with preserved ejection fraction (EF).

**Methods**

**Subjects**
This cross-sectional study of prospectively collected data was conducted at Osaka City University Hospital. We initially included 127 severe AS patients with preserved EF (≥50%) who were admitted to hospital for assessment of AS between April 2013 and October 2017. We excluded hemodialysis patients (n=15), those with previous valve surgery (n=7), and those who had more than mild mitral valve disease (n=15) or aortic regurgitation (n=10). Thus, 80 patients were eligible for inclusion in this study. Of the 80 patients, 2 did not have nocturnal BP data because of an inability to complete the test. This left a final sample size of 78. The study protocol conforms to the ethics guidelines of the 1975 Declaration of Helsinki and was approved by the hospital ethics committee of Osaka City University Graduate School of Medicine. Written informed consent was obtained from all patients. Hypertension was defined as systolic BP (SBP) ≥140 mmHg, diastolic BP (DBP) ≥90 mmHg, and/or antihypertensive medication use. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dL and/or use of lipid-lowering agents. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, glycated hemoglobin A1c ≥6.5%, and/or current use of insulin or oral hypoglycemic agents. Patients were defined as non-smokers if they had never smoked.

**BP Assessment**
We defined casual BP as the value measured at the time of admission by trained nurses using an oscillometric device (ES-H55; Terumo, Tokyo, Japan) with the patient in a sitting position after a 5-min rest. Nocturnal BP was measured using a validated home BP monitoring device (HEM-5041; Omron Healthcare, Kyoto, Japan)

**Statistical Analysis**
Statistical analysis was performed using SPSS 24.0 (SPSS, Chicago, IL, USA). Data are expressed as mean±SD for continuous variables and as percentages for categorical variables. Linear regression analysis was performed to examine the correlation between BNP level and clinical, echocardiographic, and BP variables. Multiple regression analysis adjusted for age, male sex, body mass index (BMI), estimated glomerular filtration rate (eGFR), antihypertensive medication use and classes, left ventricular (LV) mass index (LVMI), and early diastolic mitral annular velocity (e′) was performed to identify BP variables associated with BNP level. P<0.05 was considered significant.

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**Table 1. Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79±6</td>
</tr>
<tr>
<td>Male</td>
<td>34 (44)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0±3.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65 (83)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>43 (55)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Smoking</td>
<td>31 (40)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>55.6±19.4</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>241.2±551.1</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>45 (58)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>22 (28)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>47 (60)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>12 (15)</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

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**Table 2. Blood Pressure and Echocardiography Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casual SBP (mmHg)</td>
<td>132±20</td>
</tr>
<tr>
<td>Casual DBP (mmHg)</td>
<td>67±12</td>
</tr>
<tr>
<td>Mean nocturnal SBP (mmHg)</td>
<td>136±21</td>
</tr>
<tr>
<td>Mean nocturnal DBP (mmHg)</td>
<td>65±9</td>
</tr>
<tr>
<td>Nocturnal SBP SD (mmHg)</td>
<td>12.1±4.3</td>
</tr>
<tr>
<td>Nocturnal SBP CV (%)</td>
<td>9.1±3.6</td>
</tr>
<tr>
<td>Nocturnal DBP SD (mmHg)</td>
<td>7.0±3.9</td>
</tr>
<tr>
<td>Nocturnal DBP CV (%)</td>
<td>10.8±5.5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61±5</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>106±24</td>
</tr>
<tr>
<td>e′ (cm/s)</td>
<td>4.0±1.2</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.70±0.13</td>
</tr>
<tr>
<td>Aortic mean PG (mmHg)</td>
<td>50±18</td>
</tr>
<tr>
<td>Aortic peak PG (mmHg)</td>
<td>88±30</td>
</tr>
</tbody>
</table>

Data given as mean±SD. CV, coefficient of variation; DBP, diastolic blood pressure; e′, early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PG, pressure gradient; SBP, systolic blood pressure.
Nocturnal BP and BNP in AS With Preserved EF

In the present study, we have shown that mean nocturnal SBP rather than DBP was significantly associated with BNP level, a surrogate marker for symptomatic deterioration that carries a poor prognosis, after adjustment for well-known risk factors in severe AS with preserved EF. Moreover, no indices of BP variability were associated with BNP level on univariate or multivariate analysis. To the best of our knowledge, this is the first study to demonstrate that nocturnal SBP rather than its variability, or DBP, is associated with BNP level in severe AS with preserved EF.

In the present study, a higher nocturnal SBP was significantly associated with BNP. This is consistent with previous studies showing the importance of BP level for predicting BNP level. Hu et al reported that office BP level was associated with a higher BNP concentration in patients with essential hypertension. Similarly, the Japan Morning Surge-Target Organ Protection study showed that night-time SBP correlated with circulating BNP level in hypertensive patients whose morning or evening home SBP was ≥135 mmHg. These studies, however, were based on only SBP assessment and did not provide detailed

### Subjects

Clinical characteristics are listed in Table 1. BP and echocardiographic variables are given in Table 2. The subjects consisted of elderly patients (mean age, 79±6 years; 44% male) with severe AS (aortic valve area, 0.72±0.14 cm²) and comorbid hypertension (83%) and elevated BNP (241.2±551.1 pg/mL).

### Nocturnal BP Variables and BNP

The correlations between BNP level and clinical, echocardiographic, and BP parameters are presented in Table 3. On univariate analysis, casual SBP (r=0.27, P=0.02) and mean nocturnal SBP (r=0.36, P=0.001) were positively correlated with BNP level, whereas DBP variables and BP variability parameters were not. Moreover, eGFR was negatively associated with BNP level (r=−0.29, P=0.01). Table 4 lists the BP variables associated with BNP after the adjustment for age, male sex, BMI, eGFR, LVMI, e’, and antihypertensive medication class. Model 1, multivariate regression analysis including age, male sex, BMI, eGFR, LVMI, e’, and antihypertensive medication class. Model 2, model 1 plus casual SBP. Model 3, model 1 plus mean nocturnal SBP. BP, blood pressure. Other abbreviations as in Tables 1,2.

### Discussion

In the present study, we have shown that mean nocturnal SBP rather than DBP was significantly associated with BNP level, a surrogate marker for symptomatic deterioration that carries a poor prognosis, after adjustment for well-known risk factors in severe AS with preserved EF. Moreover, no indices of BP variability were associated with BNP level on univariate or multivariate analysis. To the best of our knowledge, this is the first study to demonstrate that nocturnal SBP rather than its variability, or DBP, is associated with BNP level in severe AS with preserved EF.

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### Table 3. Univariate Correlation With Plasma BNP

<table>
<thead>
<tr>
<th>Variables</th>
<th>BNP</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>(n=78)</td>
<td>r</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.15</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.12</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>−0.13</td>
<td>0.27</td>
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<tr>
<td>Hypertension</td>
<td>0.01</td>
<td>0.91</td>
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<tr>
<td>Diabetes mellitus</td>
<td>−0.03</td>
<td>0.82</td>
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<tr>
<td>Dyslipidemia</td>
<td>0.06</td>
<td>0.60</td>
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<tr>
<td>Ischemic heart disease</td>
<td>0.19</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>−0.07</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>−0.29</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>−0.12</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>LVMI</td>
<td>0.15</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>e’</td>
<td>−0.12</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Aortic valve area</td>
<td>0.07</td>
<td>0.55</td>
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<tr>
<td>Aortic mean PG</td>
<td>−0.06</td>
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<tr>
<td>Aortic peak PG</td>
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<tr>
<td>Antihypertensive medication class</td>
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</tr>
<tr>
<td>Casual SBP</td>
<td>0.27</td>
<td>0.02</td>
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<tr>
<td>Casual DBP</td>
<td>0.03</td>
<td>0.80</td>
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<tr>
<td>Mean nocturnal SBP</td>
<td>0.36</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Mean nocturnal DBP</td>
<td>0.07</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Nocturnal SBP SD</td>
<td>−0.11</td>
<td>0.33</td>
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<tr>
<td>Nocturnal SBP CV</td>
<td>−0.18</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Nocturnal DBP SD</td>
<td>−0.10</td>
<td>0.38</td>
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<tr>
<td>Nocturnal DBP CV</td>
<td>−0.11</td>
<td>0.35</td>
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</tbody>
</table>

Abbreviations as in Tables 1,2.

### Table 4. Multivariate Regression Analysis of Plasma BNP (n=78)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tbody>
<tr>
<td>BP variables</td>
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</tr>
<tr>
<td>Casual SBP</td>
<td>β</td>
<td>0.22</td>
<td>0.27</td>
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<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>β</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.83</td>
<td>0.52</td>
</tr>
<tr>
<td>Male sex</td>
<td>β</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.27</td>
<td>0.39</td>
</tr>
<tr>
<td>BMI</td>
<td>β</td>
<td>−0.15</td>
<td>−0.12</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.20</td>
<td>0.33</td>
</tr>
<tr>
<td>eGFR</td>
<td>β</td>
<td>−0.23</td>
<td>−0.17</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.09</td>
<td>0.20</td>
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<tr>
<td>LVMI</td>
<td>β</td>
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<td>0.16</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.29</td>
<td>0.18</td>
</tr>
<tr>
<td>e’</td>
<td>β</td>
<td>−0.13</td>
<td>−0.11</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.29</td>
<td>0.39</td>
</tr>
<tr>
<td>Antihypertensive medication class</td>
<td>β</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.66</td>
<td>0.76</td>
</tr>
<tr>
<td>Model</td>
<td>R²</td>
<td>0.14</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean nocturnal SBP</td>
<td>P-value</td>
<td>0.13</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Model 1, multivariate regression analysis including age, male sex, BMI, eGFR, LVMI, e’, and antihypertensive medication class. Model 2, model 1 plus casual SBP. Model 3, model 1 plus mean nocturnal SBP. BP, blood pressure. Other abbreviations as in Tables 1,2.
BP information including DBP and BP variability. Moreover, few studies to date have evaluated the association between BP and BNP level in patients with AS.

In the present study, nocturnal DBP was not associated with BNP level. This is consistent with a previous study that showed the superiority of SBP compared with DBP for predicting BNP. Kario et al showed that mean nocturnal SBP was significantly correlated with N-terminal BNP fragment level independently of clinical, morning, and evening BP measurement in patients with coronary risk factors, while DBP was not associated with BNP. Moreover, no studies to date have explored the impact of DBP on BNP level in patients with AS.

Although there is growing evidence for the association between BP variability and cardiovascular events and mortality, the present study found no association between nocturnal BP variability and BNP level. Similarly, Masugata et al failed to show an association between visit-to-visit SBP variability and BNP level. Conversely, Welsh et al successfully demonstrated an association between visit-to-visit SBP variability and BNP level in patients with hypertension, with ≥3 other risk factors for cardiovascular disease without a history of prior myocardial infarction or currently treated angina. Thus, the association between BNP and BP variability remains controversial.

Considering the present results, we speculated that higher nocturnal SBP rather than DBP or its variability plays an important role in BNP secretion (i.e., symptomatic deterioration) in severe AS patients with preserved EF. The mechanisms underlying the present findings remain poorly understood. There are, however, 2 considerable mechanisms that could explain the impact of high SBP on BNP secretion. First, given that BNP rises in proportion to LV end-systolic wall stress due to the obstruction of its outflow in patients with AS, SBP may be more closely associated with BNP level than DBP. Second, the LV, the organ moving intensely to maintain stroke volume, might be less affected by fluctuations in pressure overload (i.e., BP variability) than by a consistent high-pressure overload (i.e., mean BP).

In the present study, mean nocturnal SBP was 136±21 mmHg, therefore aggressive BP-lowering therapy may be difficult. Given, however, that nocturnal SBP 120 mmHg or 140 mmHg corresponds to clinic BP 140 mmHg or 160 mmHg, respectively, mean nocturnal SBP 136±mmHg may be classified as high BP. Moreover, given that guidelines recommend standard guideline-directed medical therapy, especially angiotensin-converting enzyme inhibitors due to the potential beneficial effects on LV fibrosis in addition to control of hypertension, for severe AS, BP reduction, starting at a low dose with frequent clinical monitoring, is expected to avoid the risk of acute decline in cardiac output and be of benefit in patients with mean nocturnal SBP 136±mmHg.

In the present study, a model without any BP-related variable and a model with casual SBP did not reach independent significance. A model with mean nocturnal SBP, however, was statistically significant. Moreover, mean nocturnal SBP remained independently associated with plasma BNP in the model. This is consistent with previous studies showing the importance of nocturnal BP in predicting the progression of atherosclerosis, target organ damage, and cardiovascular outcome and may support the clinical utility of nocturnal BP assessment for better managing patients with severe AS.

LVMI or LV diastolic function, which can be evaluated on echocardiography, are associated with BNP. Adding LVMI and LV diastolic function to the model, however, did not significantly affect the multiple regression analysis results. This suggests that mean nocturnal SBP has a stronger association with BNP level than does LVMI or LV diastolic function in patients with severe AS.

**Study Limitations**

This study had several limitations. First, although nocturnal BP is better than other BP parameters, nocturnal BP assessment may not be generally available in the daily clinical setting. Second, given that only 4 of the present patients had hospitalization due to heart failure or eventual aortic valve replacement, we could not perform reliable analysis regarding prognosis. Therefore, prospective studies are needed to assess whether BP-lowering therapy focusing on nocturnal SBP indeed extends the asymptomatic period in AS patients with preserved EF. Third, although we focused only on nocturnal BP variables, 24-h ambulatory BP assessment may better assess BP variability. Fourth, although we adjusted for variables that may affect circulating BNP level, some confounding factors may have been incompletely adjusted for. Fifth, although good agreement has been demonstrated between in-hospital and at-home nocturnal BP measurement, no studies to date have explored the association between nocturnal BP on the first hospital admission night and at home.

**Conclusions**

Higher nocturnal SBP rather than DBP or indices of BP variability was independently associated with plasma BNP, a surrogate marker for symptomatic deterioration, in AS patients with preserved EF. This supports the hypothesis that interventions for nocturnal SBP may extend the asymptomatic period and consequently improve prognosis in AS with preserved EF.

**Acknowledgments**

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**Disclosures**

The authors declare no conflicts of interest.

**References**


