Influence of Low-Grade Inflammation on Plasma B-type Natriuretic Peptide Levels

Terumasa Inoue, Makoto Kawai, Tokiko Nakane, Ayumi Nojiri, Kosuke Minai, Kimiaki Komukai, Takayuki Ogawa, Kenichi Hongo, Masato Matsushima and Michihiro Yoshimura

Abstract

Objective B-type natriuretic peptide (BNP) is a cardiac hormone. The results of previous in vitro studies suggest that neurohumoral factors, and not only hemodynamic factors, may cause BNP secretion. In this study, we examined the impact of serum C-reactive protein (CRP) levels on the relationship between echocardiographic parameters and plasma BNP levels in patients with cardiovascular diseases.

Methods and Patients The study population comprised 417 patients who visited our cardiovascular unit with a problem. Both blood sampling and echocardiography were performed within one month.

Results Multiple regression analysis showed that plasma BNP levels were negatively correlated with male gender, body mass index, and estimated glomerular filtration rate, and positively correlated with serum CRP levels and left ventricular end-systolic dimension (LVDs). The study population was divided into two groups based on the 75th percentile of the serum CRP levels. Single regression analysis showed that a regression line between LVDs and plasma BNP levels was steeper in the group of patients with CRP levels above the 75th percentile. Multiple regression analysis revealed that the interaction term (LVDs × CRP) was significant, which means LVDs had more impact on plasma BNP levels at higher CRP levels.

Conclusion Plasma BNP levels increased with respect to the severity of cardiac dysfunction and serum CRP levels, and should therefore be considered a collective or total marker for life-threatening conditions including systemic inflammation, and not simply as a marker of cardiac dysfunction in patients with cardiovascular diseases.

Key words: heart failure, left ventricular end-systolic dimension, serum C-reactive protein and prognosis

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Introduction

A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), also known as atrial and brain natriuretic peptides, respectively, are cardiac hormones with a wide range of potent biological effects, including vasodilation, natriuresis, and inhibition of the renin-angiotensin-aldosterone (RAA) and sympathetic nervous systems (1-4). We found that ANP is mainly secreted from the atria, and its secretion from the ventricles increases with increasing severity of heart failure (5, 6). In contrast, BNP is selectively secreted from the ventricles, and the magnitude of secretion also varies as a function of the severity of heart failure (7-9). Moreover, BNP is rapidly secreted from infarcted ventricles and from ventricles subjected to acute overload (10, 11). Therefore, the plasma levels of BNP may be clinically useful biochemical markers of heart failure (12-14). Stretch is an important stimulating factor for ANP and BNP secretion (5-9). In addition, we reported that the secretion of ANP and BNP from the ventricles is mainly regulated by ventricular cavity size and would dovetail with Laplace’s law (15).
In vitro studies conducted by us and others have shown that not only hemodynamic factors but also neurohumoral factors activated during heart failure, such as angiotensin II, endothelin, and cytokines, cause BNP secretion (11, 16-18). We have previously shown that among the cytokines, interleukin-1beta (IL-1β) is a strong stimulator of BNP secretion in neonatal rat cardiocytes (16).

In intensive or coronary care units, generalized inflammation often occurs in cardiovascular disease patients together with diverse disorders such as infectious diseases, hemorrhagic diseases, infarction, cancer, burn, trauma, post-operation shock, and others. The host response to these infections and other forms of tissue injury has been termed systemic inflammatory response syndrome, and cytokines play a major role in its process (19). Thus, together with cardiac dysfunction, plasma BNP levels may be augmented by cytokines and other factors in patients with systemic inflammation.

C-reactive protein (CRP) is a plasma protein that is called acute phase reactants because of a pronounced rise in concentration after tissue injury or inflammation. Interleukin-6 and tumor necrosis factor-alpha are inflammatory cytokines and main inducers of CRP secretion in the liver. Furthermore, minor elevations of CRP are predictive of cardiovascular events in patients with coronary heart disease (20-23). Therefore, CRP is not only a marker of acute or chronic systemic inflammation but also a marker of atherosclerosis (24-27). It can amplify the anti-inflammatory response through complement and endothelial cell activation as well as tissue damage (28).

Plasma BNP measurement is used for early assessment of heart failure. Many previous reports revealed that plasma BNP level was significantly associated with poor prognosis in patients with heart failure (10, 12, 29-36). However, the precise reasons for the high sensitivity of BNP with regard to prognosis have not been clarified. If there is a close correlation between plasma BNP and serum CRP levels, the close correlation between high plasma BNP levels and prognosis can be partly explained by the fact that the serum CRP level is a sensitive prognostic marker, as mentioned above (20-23).

To investigate whether plasma BNP levels are affected by systemic inflammation, we examined the relationship between plasma BNP and serum CRP levels in patients who visited our cardiovascular units.

**Methods**

**Study population**

The study population comprised 420 consecutive patients who visited our cardiovascular unit at The Jikei University Hospital between January 1st, 2006 and December 31st, 2008 for any reason. However, we excluded 3 patients who visited due to pneumonia as a main diagnosis from the statistical analysis in order to avoid overestimation of inflammation on plasma BNP levels. Both blood sampling and echocardiography were performed within one month. The study protocol (21-285 [6163]) was approved by the ethics committee of The Jikei University.

**Plasma BNP and serum CRP measurements**

A central laboratory examination for biological analyses was used in our hospital. Whole blood (5 mL) was collected in tubes containing potassium EDTA (1 mg/mL blood). Plasma BNP was determined within 24 hour before and after admission by a rapid enzyme-linked immunosorbent assay (ELISA) (non-extracted) using an antibody to human BNP (Shionogi Co., Ltd., Tokyo, Japan). Serum CRP was measured by a latex agglutination immunossay method (Mitsubishi Chemical Medience Corporation, Tokyo, Japan).

**Echocardiographic examination**

As an outpatient procedure or on admission, cardiologists performed echocardiography for all patients. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVDD), left ventricular end-systolic dimension (LVDs), fractional shortening (FS), left atrial dimension (LAD), interventricular septum (IVS) dimension, and posterior wall (PW) dimension were measured on M-mode images. Left ventricular mass index (LVMI) and body surface area (BSA) were calculated using the following Devereux equation (37) and Du Bois equation (38), respectively.

\[
\text{LVMI} = \frac{1.04 \times (\text{LVDd} + \text{PW} + \text{IVS})^3 - \text{LVDd}^3 - 13.6)}{\text{BSA}^3 (g/m^2)}
\]

\[
\text{BSA} = \frac{\text{height}^{0.725} \times \text{body weight}^{0.425} \times 0.007184}{m^2}
\]

**Definition of diseases**

The underlying disease was determined for each patient. Patients with hypertension, diabetes, and those on dialysis were diagnosed previously and were undergoing treatment before admission. Renal dysfunction was defined as estimated GFR (eGFR), which was calculated according to the Modification of Diet in Renal Disease equation (39) with coefficients modified for Japanese patients (40): eGFR (mL/min/1.73 m^2) = 194 × age^{0.26} × (Serum creatinine)^{-1.094} × (0.739 for females). The underlying diseases were categorized as ischemic heart, valvular, aortic, and infectious heart diseases as well as arrhythmia, cardiomyopathy, thrombosis, and others. Ischemic heart diseases included acute coronary syndrome or patients undergoing coronary angiography or percutaneous coronary intervention. Valvular disease included heart failure caused by moderate valvular disease and patients scheduled for surgery. Arrhythmia included a need for catheter ablation, an implantable cardioverter-defibrillator, cardiac resynchronization therapy, and patients with a pacemaker or syncope. Cardiomyopathy was defined as being diagnosed before admission and undergoing treatment or diagnosed after admission, excluding ischemic cardiomyopathy. Infectious heart disease included pericarditis, myocarditis, and infectious endocarditis. Thrombosis included pulmonary thromboembolism and deep vein throm-
Table 1. Clinical Characteristics and Main Diagnosis of Study Patients

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Number/Mean±SD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>417</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.4±15.1</td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>313 / 104</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>192.1 ± 536.9</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.556±1.844</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>72.1 ± 22.0</td>
<td></td>
</tr>
<tr>
<td>Main Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>29</td>
<td>7.0</td>
</tr>
<tr>
<td>Arrhythmias⁴</td>
<td>215</td>
<td>51.6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>44</td>
<td>10.6</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>5</td>
<td>1.2</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>5</td>
<td>1.2</td>
</tr>
<tr>
<td>Others*</td>
<td>119</td>
<td>28.5</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; BMI, body mass index; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate

⁴ Arrhythmias included 89 patients (21.3% for over all) with pulmonary vein isolation (ablation) therapy for atrial fibrillation

*Others included the patients with chest pain syndrome, pre-operating check and others.

bosis. Aortic disease included acute aortic dissection. Others included basal heart disease and conditions not stated above. Based on height and weight on admission, body mass index (BMI) was calculated as weight divided by the square of the height.

### Statistical analysis

Continuous variables were expressed as mean ± SD. Correlation analysis between plasma BNP levels and other various measurements was expressed as Pearson’s correlation coefficient and to adjust for other confounding variables, multiple linear regression analysis was performed. The comparison of four groups was performed by using analysis of variance test (ANOVA) and two groups or conditions were compared using Mann-Whitney U test or Pearson’s chi-square test where necessary.

To examine whether the serum CRP levels had a statistically significant impact on the relationship between plasma BNP levels and LVDs, multiple linear regression analysis was employed in which the dependent variable was plasma BNP levels and the explanatory variables were LVDs, serum CRP levels, and the interaction term between LVDs and serum CRP levels (LVDs × CRP). We present the scatter plots by serum CRP levels to illustrate the modification of the relationship between plasma BNP levels and LVDs.

For the purpose of accuracy, multiple regression analyses were additionally performed to examine the relationship of plasma BNP levels with other echocardiographic data such as LVDd, FS and LVMI. Furthermore, the sub-group analyses were subsequently performed; first, we recruited the non-arrhythmia group consisting of 202 patients to avoid possible influences of arrhythmia its self; secondly, we recruited the heart failure group consisting of 102 patients to examine whether our conclusion was adequate in the heart failure only population. The heart failure population was tentatively set by the criteria of plasma BNP levels over 100 pg/mL or LVEF less than 50% in this study.

All tests were two-tailed, and p<0.05 was considered statistically significant.

### Results

#### Study population

The baseline characteristics of the study population in the present study (n=417) are shown in Table 1. Plasma BNP levels ranged widely, with a mean level of 192.1 ± 536.9 pg/mL.

#### Single regression analysis and multiple regression analysis for plasma BNP level determination

Table 2 shows the results of single regression analysis and multiple regression analysis for determining plasma BNP levels. In the analysis, all parameters except for BMI were significantly associated with the plasma BNP levels. The plasma BNP levels were negatively correlated with male gender, BMI, and eGFR, and positively correlated with serum CRP level and LVDs. Among echocardiographic parameters, LVDs was the only significant parameter. Figure 1 shows a significant linear correlation between LVDs and plasma BNP levels as explained with the correlation coefficient at 0.588 (r) in the entire study population (p<0.001, n=417).
**Table 2. Single Regression Analysis and Multiple Linear Regression Analysis for Determination of the Plasma BNP Levels**

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Single regression analysis</th>
<th>Multiple linear regression analysis (R², 0.567)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person’s correlation</td>
<td>β-Coefficient</td>
</tr>
<tr>
<td></td>
<td>Coefficients (r)</td>
<td></td>
</tr>
<tr>
<td>n = 417</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.332</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>N/A</td>
<td>-110.551</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.067</td>
<td>0.172</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.414</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.529</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>-0.504</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (/mL)</td>
<td>0.199</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>0.329</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>0.446</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>0.588</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI (mm)</td>
<td>0.603</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (mm)</td>
<td>-0.606</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; BMI, body mass index; CRP, C-reacting protein; Cr, creatinine; eGFR, estimated glomerular filtration rate; WBC, white blood cells; LAD, left atrial dimensions; LVDd, left ventricular end-diastolic dimensions; LVDs, left ventricular end-systolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; N/A, not applicable

Multiple linear regression analysis: Objective variable was: BNP (R², 0.567), explanatory variables used in the equation: Age, BMI, CRP, Gender (male), eGFR, WBC, LAD, LVDd and LVDs.

**Figure 1. Correlation between LVDs and plasma BNP levels in the study population.** LVDs, left ventricular end-systolic dimension; BNP, B-type natriuretic peptide. The figure shows a significant linear correlation between LVDs and plasma BNP levels in the entire study population.

**Quartile analysis assessing the relationship between LVDs and plasma BNP levels**

The study population was split into four groups according to quartiles of serum CRP levels. The groups were defined as follows: group 1, CRP <0.04; group 2, 0.07> CRP ≥ 0.04; group 3, 0.24> CRP ≥ 0.07; and group 4, CRP ≥ 0.24. The clinical characteristics of each group are shown in Table 3.

Figure 2 shows the linear regression lines between LVDs and plasma BNP levels for each group. The regression was statistically significant for groups 2, 3, and 4. The regression lines became steeper, with the regression line for group 3 being steeper than that for group 2 and the regression line for group 4 being particularly precipitous compared to that for the other groups.

**Comparison of clinical characteristics between patients in group 4 and all other patients**

Table 3 shows the clinical characteristics of the study population when divided into two groups, i.e., group 4 comprising patients with serum CRP levels above the 75th percentile and groups 1-3 including all other patients. The results of the analysis show that plasma BNP levels and LVDs were much higher in group 4 than in the combined groups 1-3 (BNP, 65.6 ± 155.6 pg/mL vs. 578.0 ± 949.6 pg/mL; LVDs, 30.4 ± 5.5 vs. 35.4 ± 11.8 mm; p<0.001, p=0.001 respectively).

Figure 3 shows the linear regression lines between LVDs and plasma BNP levels in the combined groups 1-3 and group 4. At a glance, the regression line appeared much steeper for group 4 than for the combined groups 1-3.

**Multiple linear regression analysis for determining a possible impact of serum CRP levels on the relationship between LVDs and plasma BNP levels**

Multiple linear regression analysis was performed to determine whether serum CRP levels have a statistically significant impact on the relationship between LVDs and plasma BNP levels (Table 4). The statistical analysis in-
only hemodynamic parameters, in patients visiting cardio-
heart failure patients in conjunction with inflammation due
these results, the secretion of BNP may be augmented in
are related to the secretion of BNP (11, 16-18). In line with
heart failure and that BNP secretion from the heart is regu-
cluded LVDs, CRP, and its interaction term (LVDs x CRP)
as independent predictors of the dependent variable for
BNP level. As a result, each independent parameter
was statistically significant (p<0.001), suggesting that the re-
performed to examine the relationship of plasma BNP levels
It is well known that plasma BNP level is a marker for
Discussion

It is well known that plasma BNP level is a marker for
heart failure and that BNP secretion from the heart is regu-
lated by cardiac dysfunction (7-9). However, several in vitro
analyses have also shown that many neurohumoral factors are related to the secretion of BNP (11, 16-18). In line with
these results, the secretion of BNP may be augmented in
heart failure patients in conjunction with inflammation due
to any cause. However, such clinical investigations have not been conducted. In this study, we examined whether plasma
BNP levels change in relation to serum CRP levels, and not only hemodynamic parameters, in patients visiting cardio-
vascular units. The results of the present study confirmed
that plasma BNP levels are significantly associated with ag-
gravation of hemodynamic parameters in patients with heart
failure.

In this study, LVDs tended to be strongly associated with
plasma BNP levels rather than other echocardiographic pa-
rameters, which is similar to the results of a previous study (9). Although we used LVDs as a marker of cardiac
function in this main analysis, it is quite natural that the
plasma BNP levels would be significantly associated with
other parameters such as LVDd, LVMI, and LVEF (FS).

Before beginning this study, we postulated that inflamma-
tion affects plasma BNP levels only in patients with high se-
erum CRP levels. However, dividing the population into four
groups, we found that low grade inflammation affected the
relationship between LVDs and plasma BNP levels in pa-
patients with CRP levels above the 75th percentile. Further-
more, among all other groups, there was a tendency for se-
rum CRP levels to affect the relationship between LVDs and
plasma BNP levels, although this was not statistically sig-
ificant for group 1. If we increase the size of the study
population, the statistical analysis may change. However, the
population size of the present study population may be large enough to
confirm we added supplementary data (Table 5); a
similar result was obtained when using each parameter of
LVDs, LVMI or LVEF (FS).

Table 3. Clinical Characteristics in the Groups Quarters by Serum CRP Levels and in the Groups Divided by Top Quarter Serum CRP Levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1 (CRP&lt;0.04)</th>
<th>Group 2 (0.04&lt;CRP&lt;0.07)</th>
<th>Group 3 (0.07&lt;CRP&lt;0.24)</th>
<th>Group 4 (CRP&gt;0.24)</th>
<th>Overall</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>107</td>
<td>99</td>
<td>108</td>
<td>103</td>
<td>417</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.010±0.010</td>
<td>0.046±0.049</td>
<td>0.125±0.050</td>
<td>2.064±3.878</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.010±0.010</td>
<td>0.046±0.049</td>
<td>0.125±0.050</td>
<td>2.046±3.878</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.7±14.2</td>
<td>56.8±15.5</td>
<td>56.4±14.5</td>
<td>63.8±14.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male / female)</td>
<td>80 / 27</td>
<td>74 / 25</td>
<td>84 / 24</td>
<td>75 / 28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8±3.3</td>
<td>23.4±2.8</td>
<td>24.7±3.9</td>
<td>24.2±3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.82±0.16</td>
<td>0.83±0.33</td>
<td>0.94±0.89</td>
<td>1.31±1.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>75.5±15.5</td>
<td>77.0±19.7</td>
<td>76.1±21.7</td>
<td>59.6±25.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>34.9±5.3</td>
<td>36.3±6.9</td>
<td>37.2±6.6</td>
<td>39.3±8.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>66.6±5.8</td>
<td>65.0±10.4</td>
<td>65.1±8.5</td>
<td>56.9±17.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRP, C-reacting protein; BMI, body mass index; BNP, B-type natriuretic peptide; Cr, creatinine; eGFR, estimated glomerular filtration rate; WBC, white blood cells; LAD, left atrial dimensions; LVDD, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction

Statistical analysis between each groups (Group 1-4) was performed using ANOVA (analysis of variance) and analysis of Group 1-3 versus Group 4 was performed using Mann-Whitney U test (*) or Pearson’s chi-square test (†).
tem, sympathetic nervous system, and cytokines, may contribute to the mechanism. For instance, IL-1β is a pro-inflammatory cytokine with a wide range of effects on many different cell types (41, 42). In addition, IL-1β has been reported to partially regulate the BNP promoter through p38 kinase, a member of the MAP kinase family in myocytes (43). In an experimental study using neonatal rat ventricles, we showed that IL-1β strongly augments the secretion of BNP (18). It is well known that cardiothrophin-1, leukemia inhibitory factor, and others are important activators of BNP through gp130 and its transcription pathway (44). Furthermore, oxidative stress induces the secretion of BNP through re-expression of fatal gene programs and the apoptosis process in cardiomyocytes (45).

DNA of BNP has an AT-rich sequence in the 3'-untranslated region, which destabilizes mRNA (11, 28). For this reason, BNP is considered to be an acute-phase reactant in response to acute tissue injuries, which is reflected by the serum CRP levels (10, 11, 46-48). On the other hand, ANP does not have similar DNA sequences. Indeed, we preliminarily analyzed the influences of inflammation on the plasma ANP levels, and the results of the analysis showed that serum CRP level was significantly associated with plasma levels of BNP but not with those of ANP, although LVDs was significantly correlated with plasma levels of

Figure 2. Correlation between LVDs and plasma BNP levels in groups 1, 2, 3, and 4. LVDs, left ventricular end-systolic dimension; BNP, B-type natriuretic peptide. The figure shows the linear regression lines between LVDs and plasma BNP levels for groups 1, 2, 3, and 4. The regression was statistically significant for groups 2, 3, and 4 and became steeper, with the regression line for group 3 being steeper than that for group 2 and the regression line for group 4 being particularly precipitous compared to that for the other groups.

Figure 3. Correlation between LVDs and plasma BNP levels in group 4 versus patients from all other groups. LVDs, left ventricular end-systolic dimension; BNP, B-type natriuretic peptide. The figure shows the linear regression lines between LVDs and plasma BNP levels in the combined groups 1-3 (square symbols) and group 4 (circle symbols). The regression line was steeper in group 4 than in the combined groups 1-3. Many inflammatory molecules, including the RAA system, sympathetic nervous system, and cytokines, may contribute to the mechanism. For instance, IL-1β is a pro-inflammatory cytokine with a wide range of effects on many different cell types (41, 42). In addition, IL-1β has been reported to partially regulate the BNP promoter through p38 kinase, a member of the MAP kinase family in myocytes (43). In an experimental study using neonatal rat ventricles, we showed that IL-1β strongly augments the secretion of BNP (18). It is well known that cardiothrophin-1, leukemia inhibitory factor, and others are important activators of BNP through gp130 and its transcription pathway (44). Furthermore, oxidative stress induces the secretion of BNP through re-expression of fatal gene programs and the apoptosis process in cardiomyocytes (45).
A close correlation between plasma BNP levels and the prognosis of patients with heart failure has been demonstrated in many previous reports (10, 12, 29-36). In our long-term follow-up study of patients with acute myocardial infarction (AMI), plasma BNP levels measured at an early stage were significantly associated with the prognosis in patients with AMI (10). Although the statistical significance of hemodynamic parameters, such as LVEF, with regard to prognosis disappeared after a long follow-up period, only plasma BNP was a significant indicator of prognosis. In a series of studies including patients with non-ischemic heart failure, plasma BNP level was a significant indicator of prognosis compared to other factors (49). Furthermore, Wang et al reported a relationship between the prognosis of persons without heart failure and plasma BNP levels (30). Plasma BNP levels above the 80th percentile (20.0 pg/mL for men and 23.3 pg/mL for women) were associated with death, a first major cardiovascular event, atrial fibrillation, stroke or transient ischemic attack, and heart failure. Excess risk was apparent at low plasma BNP levels. Therefore, plasma BNP is universally accepted to be useful for assessing prognosis in patients with heart failure and possibly in the general population.

Compared to that of other hemodynamic parameters, the sensitivity of plasma BNP levels to prognosis is noteworthy (29). This result may be observed because BNP is a hormone that is complementarily secreted after hemodynamic deterioration in heart failure in order to improve the condition after heart failure by natriuretic action as well as vaso-

### Table 4. Multiple Linear Regression Analysis for Influence of Serum CRP Levels on a Relationship between Plasma BNP Levels and LVDs

<table>
<thead>
<tr>
<th>Explanatory variable (n = 417)</th>
<th>β-Coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVDs</td>
<td>25.543</td>
<td>20.399, 30.687</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>-205.112</td>
<td>-273.441, -136.782</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVDs × CRP</td>
<td>9.406</td>
<td>7.367, 11.445</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>-687.016</td>
<td>-850.726, -523.306</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Objective variable: BNP (R²: 0.546)
Explanatory variables used in the equation: LVDs, CRP, LVDs×CRP

BNP, B-type natriuretic peptide; CRP, C-reacting protein; LVDs, left ventricular end-systolic dimension

### Table 5. Multiple Linear Regression Analysis for Influence of Serum CRP Levels on Relationships of Plasma BNP Levels with LVDd, FS and LVMI

<table>
<thead>
<tr>
<th>Explanatory variable (n = 417)</th>
<th>β-Coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. (R²: 0.438)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDd</td>
<td>20.007</td>
<td>13.315, 26.699</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>-660.546</td>
<td>-836.791, -484.302</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVDd × CRP</td>
<td>15.568</td>
<td>12.027, 19.109</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>-844.507</td>
<td>-1168.510, -520.503</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B. (R²: 0.502)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FS</td>
<td>-37.326</td>
<td>-42.061, -32.590</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>87.997</td>
<td>67.754, 108.239</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FS × CRP</td>
<td>6.565</td>
<td>4.881, 8.249</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>1243.413</td>
<td>1069.306, 1417.520</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C. (R²: 0.595)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI</td>
<td>10.545</td>
<td>9.546, 11.545</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>74.193</td>
<td>55.726, 92.659</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI × CRP</td>
<td>-0.081</td>
<td>-0.095, -0.068</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>-348.162</td>
<td>-454.193, -242.131</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Objective variable: BNP
Explanatory variables used in the equation: (A; LVDd, CRP, LVDd×CRP) or (B; FS, CRP, FS×CRP) or (C; LVMI, CRP, LVMI×CRP)

BNP, B-type natriuretic peptide; CRP, C-reacting protein; LVDd, left ventricular end-diastolic dimension; FS, fractional shortening; LVMI, left ventricular mass index

both ANP and BNP (data not shown).
Table 6. Multiple Linear Regression Analysis for Influence of Serum CRP Levels on Relationships of Plasma BNP Levels on LVDs in the Non-arrhythmia Group and Heart Failure Group

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>β-Coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. (non-arrhythmia group, n=202)</td>
<td>(R²: 0.566)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDs</td>
<td>30.510</td>
<td>22.599, 38.420</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>-171.671</td>
<td>-267.347, -75.995</td>
<td>0.001</td>
</tr>
<tr>
<td>LVDs × CRP</td>
<td>8.315</td>
<td>5.463, 11.168</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>-802.439</td>
<td>-1064.384, -540.494</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B. (heart failure group, n=102)</td>
<td>(R²: 0.497)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDs</td>
<td>22.808</td>
<td>11.152, 34.465</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>-149.321</td>
<td>-283.821, -14.822</td>
<td>0.030</td>
</tr>
<tr>
<td>LVDs × CRP</td>
<td>8.148</td>
<td>4.276, 12.019</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>-390.686</td>
<td>-839.577, 58.205</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Objective variable: BNP
Explanatory variables used in the equation: LVDs, CRP, LVDs × CRP
Non-arrhythmia group (A) was eliminated patients with arrhythmias and heart failure group (B) was tentatively selected by the criteria of plasma BNP levels over 100 pg/mL or LVEF less than 50% in this study, respectively.

BNP, B-type natriuretic peptide; CRP, C-reacting protein; LVDs, left ventricular end-systolic dimension

dilating and inhibitory actions of RAA and sympathetic nervous systems (50, 51). However, the present study showed that plasma BNP levels were substantially affected by low-grade inflammation. Since it is accepted that serum CRP levels are significantly associated with the prognosis of patients with cardiovascular diseases (20-23), it should also be accepted that plasma BNP levels are sensitive to prognosis.

At present, the assessment of plasma BNP levels is applied to early detection, differential diagnosis, and assessment of heart failure severity as well as assessments of the effects of therapy and the prognosis of patients with heart failure (5-17). The scope of its clinical application should further expand, but the perception of discrepancies between plasma BNP level and the actual severity of heart failure according to inflammation has compromised the clinical significance of BNP and contributed to the prevailing perception that BNP is a rather unreliable marker of heart failure. However, we suggest that plasma BNP level be considered as a marker of collective conditions of hemodynamic dysfunction, inflammation, and prognosis. Thus, we highly recommend measurement of plasma BNP in clinical practice.

In this study, we preliminarily excluded 3 patients admitted with severe pneumonia in order to avoid overestimation of inflammation on plasma BNP levels; however, when using the whole study population of 420 consecutive patients, the conclusion was almost the same (data not shown).

Finally, in order to confirm our conclusion, sub-group analyses were additionally performed. We recruited the non-arrhythmia group (n=202) to exclude possible influences of arrhythmia itself; also, we recruited the heart failure group (n=102) to examine whether our conclusion was adequate in the heart failure only population. As shown in Table 6, the results were nearly similar to the main results using all of the study population (n=417).

In conclusion, plasma BNP levels were increased in relation to the severity of heart failure and were also affected by low-grade inflammation. The prognosis of heart failure would generally be regulated by not only the degree of cardiac dysfunction but also other factors including systemic inflammation. Thus, plasma BNP level may be considered a collective or total marker of life-threatening conditions in patients with heart failure.

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Disclosures
All authors have no conflict of interests to disclose.

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