Relationship Between Brain Natriuretic Peptide, Myocardial Wall Stress, and Ventricular Arrhythmia Severity

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SUMMARY

We previously demonstrated that the severity of arrhythmias is reflected by circulating brain natriuretic peptide (BNP) concentrations in patients without signs of congestive heart failure. In the present study, we evaluated the relationships between the severity of the arrhythmia, BNP concentration, and echocardiographic findings.

The subjects consisted of 52 patients with ventricular premature contractions (VPC) but no manifestations of heart failure and no digoxin or beta-blocker therapy. Patients underwent Holter monitoring, plasma sampling for BNP measurement, and transthoracic echocardiography (TTE). We scored the motion of 16 left ventricular segments, deriving a wall-motion score index (WMSI) by totaling the scores and dividing by the number of segments scored.

Twenty-three patients with Lown grade I to II arrhythmias constituted group A while group B consisted of 29 Lown III to IV patients. Group B had BNP concentrations triple those in group A (57.2 versus 18.1 pg/mL, \( P < 0.01 \)). Left ventricular ejection fraction (LVEF) was similar in groups A and B (65.2% versus 62.1%, NS). Although left ventricular end-diastolic dimension (LVEDD) was normal in both groups, group B exhibited a larger LVEDD than group A (50 versus 46 mm, \( P < 0.005 \)). The correlation (r) between BNP and interventricular septum thickness (IVST) was 0.27 (\( P = 0.013 \)) in group A and 0.37 (\( P < 0.0001 \)) in group B. Between BNP and posterior wall thickness (PWT), the correlation was 0.23 (\( P = 0.014 \)) in group A versus 0.33 (\( P < 0.0001 \)) in group B. The WMSI in group B was higher than in group A (1.34 versus 1.11, \( P < 0.05 \)).

We believe that besides the changes in echocardiographic parameters, the BNP elevation in group B could be a response to abnormal wall stress from the severe ventricular arrhythmias. (Jpn Heart J 2004; 45: 771-777)

Key words: Transthoracic echocardiography, Holter monitoring, Classification of arrhythmias, Cardiac hormones, Wall motion score index

CONGESTIVE heart failure (CHF) usually is associated with augmented secretion of brain natriuretic peptide (BNP). In our recent study, however, plasma BNP
concentrations also were increased in patients without a substantial reduction in left ventricular ejection fraction (LVEF), although these patients did have severe ventricular arrhythmias. The reasons for these BNP increases are still unknown. We conducted the present study to test a hypothesis that differences in BNP concentrations and ventricular arrhythmia severity might be linked by differences in spatial parameters measured by transthoracic echocardiography (TTE).

**METHODS**

**Study subjects:** We enrolled 52 patients (30 men, 22 women) who were referred to our outpatient clinic for evaluation of ventricular arrhythmias. No patient had symptoms of CHF or was receiving digoxin or beta-blocker treatment. Most patients had no underlying heart diseases, although some had stable coronary artery disease, valvular heart disease, or cardiomyopathy. Mean age was 61 ± 14 years, and the left ventricular ejection fraction (LVEF) was 63.5 ± 9.4%. Patients with an LVEF less than 55% were excluded from the study.

The most recent Holter recording was assessed to divide the patients into two groups according to the Lown classification of ventricular arrhythmias. Group A (n = 23) consisted of Lown grade I to II, with group B (n = 29) including Lown grade III to IV (Table I). No significant differences were seen in the distribution of underlying heart diseases between these two groups.

Blood samples were obtained to determine plasma BNP concentration at the time of study entry.

**Echocardiographic study:** M-mode and two-dimensional (2D) echocardiograms were obtained using Sonos 2500 (Hewlett-Packard, MA, USA) or Vivid Five (General Electric Medical Systems, WI, USA) instruments. Results were evaluated by a physician who specialized in TTE and was kept uninformed as to whether a given patient belonged to group A or B as well as the plasma BNP concentrations.

<table>
<thead>
<tr>
<th>Table I. Patient Characteristics</th>
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<tr>
<td>Age, years</td>
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<tr>
<td>Gender (female/male)</td>
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<tr>
<td>No. of VPC/24 hr</td>
</tr>
<tr>
<td>Underlying disease</td>
</tr>
<tr>
<td>Coronary artery disease (Old myocardial infarction)</td>
</tr>
<tr>
<td>Valvular disease</td>
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<td>Cardiomyopathy</td>
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<td>None</td>
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Except for gender, values are the mean ± SD. VPC = ventricular premature contractions.
M-mode echocardiographic measurements including left ventricular end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), diastolic thickness of the interventricular septum (IVST), and posterior LV wall thickness (PWT) were determined in accordance with the recommendations of the American Society of Echocardiography. LVEF was derived using the method of Teichholz, et al. Diastolic function of the left ventricle was evaluated by the ratio of peak early to peak late flow velocities (E/A index).

For ventricular motion analysis, a total of 16 segments of the left ventricle could be identified using three longitudinal views (long-axis, four-chamber and two-chamber) and three short-axis views (mitral valve level, the papillary muscle level and apical level). Kinetics of the segments were evaluated subjectively by an experienced echocardiographer. For scoring purposes, normal motion was given a value of 0, mild hypokinesis a value of 1, severe hypokinesis a value of 2, akinesis a value of 3, and dyskinesis a value of 4. Nonscored segments were eliminated from the calculation. We then computed a wall motion score index (WMSI) for the left ventricle by totaling the scores and dividing by the number of segments scored.

**Statistical analysis:** Data are presented as the mean ± standard deviation. Unpaired two-tailed Student’s t tests were used to compare continuous variables. P values less than 0.05 were considered to indicate statistical significance.

**RESULTS**

**Comparison of BNP concentration and LVEF:** Patients in group B had a mean plasma BNP concentration three times higher than patients in group A (57.2 versus 18.1 pg/mL, P < 0.01). In spite of this considerable difference in BNP concentration, the LVEF was comparable in the two groups (65.2 versus 62.1%, NS; Table II).

**Differences in ventricular dimensions:** Group B patients had a significantly larger LVEDD than group A patients (50 versus 46 mm, P < 0.005). Additionally, LVESD in group B was larger than in group A (33 versus 29 mm, P < 0.01; Table II).

<table>
<thead>
<tr>
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<th>Group A (Lown I and II)</th>
<th>Group B (Lown III and IV)</th>
<th>P value</th>
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<tbody>
<tr>
<td>BNP (pg/mL)</td>
<td>18.1 ± 13.8</td>
<td>57.2 ± 47.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.2 ± 7.4</td>
<td>62.1 ± 9.9</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>46 ± 4</td>
<td>50 ± 5</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>29 ± 3</td>
<td>33 ± 5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.11 ± 0.43</td>
<td>1.34 ± 0.52</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>E/A</td>
<td>0.96 ± 0.39</td>
<td>0.85 ± 0.28</td>
<td>NS</td>
</tr>
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Abbreviations as defined in the text.
**Correlations between myocardial thickness and BNP concentration:** Plasma BNP concentrations correlated more closely with IVST in group B ($r = 0.37, P < 0.0001$) than in group A ($r = 0.27, P = 0.013$; Figures 1 and 2). The correlation between BNP and PWT similarly was stronger in group B ($r = 0.33, P < 0.0001$ versus $r = 0.23, P = 0.014$ in group A; Figures 3 and 4).

**Figure 1.** Correlation between diastolic thickness of the interventricular septum (IVST) and brain natriuretic peptide (BNP) concentrations in plasma from patients with Lown I or II arrhythmias (group A).

**Figure 2.** Correlation between diastolic thickness of the interventricular septum (IVST) and brain natriuretic peptide (BNP) concentrations in plasma from patients with Lown III or IV arrhythmias (group B).
Difference in WMSI: WMSI was significantly greater in group B than in group A (1.34 ± 0.52 versus 1.11 ± 0.43, *P* < 0.05; Table II).

Left ventricular diastolic function: No significant difference was found in the E/A ratio between the groups (0.85 ± 0.28 in group B versus 0.96 ± 0.39 in group A, NS; Table II).
DISCUSSION

The plasma concentrations of natriuretic peptides have emerged as potential noninvasive markers for the detection of abnormal or reduced cardiac function. As BNP is produced primarily by ventricular myocytes, BNP elevations may closely reflect alterations in structure and function of the ventricle. 5)

However, in a recent study, we found that circulating BNP was much more abundant in patients with severe ventricular arrhythmias than in patients with less severe arrhythmias, even in the absence of any manifestation of heart failure. We therefore focused on mechanisms that could link increased BNP secretion with severe arrhythmias.

Ventricular ectopic beats of Lown grade III and IV could result in mechanical stress upon the myocardium because they are associated with different contraction patterns than those associated with normal sinus beats or Lown grade I or II ectopic beats. Our finding of a higher WMSI in Lown grade III and IV patients supports this view. Frequent contractions in highly abnormal patterns could induce dysfunction of the myocardium and may result in mechanical remodeling. 6) In the present study, LVEDD and LVESD were greater in patients with more severe arrhythmias than in patients with less severe arrhythmias, suggesting that Lown grade III and IV ventricular ectopic activity could modify ventricular geometry in the absence of CHF.

On the other hand, one may argue that an enlarged left ventricle could induce arrhythmias. A failing, chronically dilated left ventricle might be more susceptible to initiation of ventricular beats 7,8) triggered by stretch-induced depolarization. 9) Relatively high plasma BNP concentrations have been reported in patients with echocardiographic abnormalities. 10) The present study included only patients with no overt signs of CHF and no lowering of LVEF. However, diagnosis of mild, minimally symptomatic heart disease or latent impairment of cardiac function often is difficult. One limitation of this study is that we cannot exclude the possibility that mild or latent heart failure existed in some subjects and produced severe ventricular arrhythmias.

In CHF, the decrease in systolic function is sometimes preceded by diastolic dysfunction. However, our study did not detect any remarkable abnormalities in diastolic function, which could be explained by the presence of modifying underlying heart diseases. In the clinical setting, evaluation of diastolic ventricular function is complicated by the coexistence of more factors that affect diastolic filling. 11)

In the present study we also found that BNP concentrations correlated with IVST and PWT. Clinically, this finding could indicate myocardial hypertrophy. Since our previous study demonstrated a significant positive correlation between
the total number of VPC and BNP concentration, we believe that frequent VPC can stress the myocardium, resulting in more secretion of BNP and myocardial hypertrophy. In addition, the present correlation coefficients between BNP and wall thickness were greater in group B than in group A. Not only the total number of VPC but also the severity of VPC-induced contractile dysfunction may affect the degree and extent of myocardial hypertrophy. However, further evaluations including long-term follow-up study are needed to more fully examine this hypothesis.

**Conclusion:** Plasma BNP concentrations were elevated in patients with severe ventricular arrhythmias in the absence of manifest CHF or myocardial damage. In addition, larger left ventricular dimensions and a higher left ventricular wall motion score index were observed in these patients. However, these changes were not sufficient enough to explain the substantial BNP elevation, which could be a response to abnormal wall stress from severe ventricular arrhythmias. Accordingly, BNP might serve as an auxiliary early marker of mild myocardial dysfunction or latent myocardial damage underlying these arrhythmias.

**REFERENCES**