Sustained elevation of plasma brain natriuretic peptide levels associated with progressive ventricular remodelling after acute myocardial infarction

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ABSTRACT

Previous studies have shown that levels of plasma brain natriuretic peptide (BNP) increase in an early phase of acute myocardial infarction. However, the relations between plasma BNP levels and left ventricular remodelling, which occurs long after acute myocardial infarction, are not fully understood. Venous plasma BNP levels were measured 2, 7, 14, 30, 90 and 180 days after the onset of acute myocardial infarction in 21 patients. Left ventricular end-diastolic volume index (EDVI, ml/m²) in acute (5 days) and chronic (6 months) phases were assessed by electron-beam computed tomography using Simpson’s method. The remodelling group (n = 9) was defined by an increase in EDVI ≥ 5 ml/m² relative to the baseline value. Plasma BNP levels on days 2, 7, 14, 30 and 90 were significantly higher in the remodelling group than in the non-remodelling group (n = 12, P < 0.05). Sustained elevation of plasma BNP levels was noted from day 2 (61 ± 12 pmol/l) to day 90 (55 ± 12 pmol/l) and significantly decreased on day 180 (24 ± 3 pmol/l) in the remodelling group. In contrast, plasma BNP levels significantly decreased from day 2 (25 ± 4 pmol/l) to day 90 (9 ± 1 pmol/l) and reached a steady level thereafter in the non-remodelling group. Plasma BNP levels on day 7 correlated positively with an increase in EDVI (r = 0.70, P < 0.001) from the acute to chronic phase. More importantly, the sustained elevation of plasma BNP (percentage decrease smaller than 25%) from day 30 to day 90 identified patients in the remodelling group with a sensitivity of 100% and a specificity of 83%. In conclusion, not only the high levels of plasma BNP in an acute phase, but also the sustained elevation of plasma BNP in a chronic phase, may be associated with progressive ventricular remodelling occurring long after acute myocardial infarction.

INTRODUCTION

Myocardial infarcts, particularly large transmural infarcts, cause complex alterations in ventricular architecture [1], resulting in disproportionate dilation and thinning of infarct myocardium [2,3], and dilation and hypertrophy of non-infarct myocardium, which continue long after healing of the infarct, over a period of 6 months [4,5]. The consequent ventricular enlargement, i.e. ventricular remodelling, has been shown to be

Key words: acute myocardial infarction, brain natriuretic peptide, ventricular remodelling.
Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CT, computed tomography; EDVI, left ventricular end-diastolic volume index; EF, left ventricular ejection fraction; NRG, non-remodelling group; RG, remodelling group.
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associated with increased morbidity and mortality in patients with myocardial infarction [6]. Thus, a simple, non-invasive, widely applicable method of predicting progressive ventricular remodelling would be desirable.

Earlier studies have shown that plasma brain natriuretic peptide (BNP), a cardiac hormone secreted mainly from cardiac ventricles [7,8], increases after acute myocardial infarction [9,10]. Recently, BNP has been used as a non-invasive marker for left ventricular dysfunction [11]. More recently, we have hypothesized that synthesis and secretion of BNP are regulated mainly by an increased mechanical force of the ventricular wall which will lead to ventricular remodelling, and have demonstrated that plasma BNP on day 7 is closely related to the ventricular remodelling that occurs within the first 30 days of acute myocardial infarction [12]. However, the relations between plasma BNP levels and ventricular remodelling, which occurs over a period of several months after the healing of the infarct, are not fully understood. Thus, the purposes of this study were to investigate (1) how plasma BNP levels may vary long after the onset of acute myocardial infarction in the presence or absence of progressive ventricular remodelling, and (2) whether the modes of plasma BNP elevation can predict the degree of ventricular remodelling 6 months after acute myocardial infarction.

In this study, electron-beam computed tomography (CT) was employed as a non-invasive technique to quantitatively assess ventricular remodelling because a high degree of accuracy in the measurements of ventricular volume and wall thickness with CT has been reported [13,14].

**Coronary angiography and reperfusion therapy**

Coronary angiography was performed in all patients using the Judkins technique as early as possible after admission. When occlusion [Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 to 2] of an infarct-related coronary artery was confirmed within 6 h of the onset of infarct, intracoronary thrombolysis or direct coronary angioplasty were performed. Some patients in whom occlusion of an infarct-related artery was confirmed more than 6 h after the onset also underwent reperfusion therapy. Patients with unsuccessful thrombolysis (TIMI grade 0 to 2) underwent rescue coronary angioplasty immediately. Successful reperfusion was defined as coronary blood flow improved to TIMI flow grade 3.

**Measurement of plasma BNP and atrial natriuretic peptide (ANP) levels**

Blood samples were taken from the ante-cubital vein in the supine position after an overnight fast on days 2, 7, 14, 30, 90 and 180 post infarction. Blood was immediately transferred into chilled glass tubes containing disodium EDTA (1 mg/ml) and aprotinin (500 units/ml), centrifuged immediately at 4 °C and the plasma frozen and stored at −80 °C until assayed. Plasma levels of ANP and BNP were measured directly with specific immunoradiometric assay kits (Shiono ANP assay kit and Shiono RIA BNP assay kit, Shionogi Co. Ltd, Osaka, Japan) [15].

**Electron-beam CT**

Ventricular volume and wall thickness were measured by electron-beam CT in acute (5 days) and chronic (6 months) phases of myocardial infarction. Electron-beam CT was performed with a C-150 scanner (Imatron) as reported previously [16]. Cine-mode scanning (scanning time, 50 ms for 256 matrix images) was performed after the administration of 40 to 50 ml of non-ionic contrast medium (Iopamidol 370, Nippon Schering). The scanner table was rotated 25° in a clockwise horizontal direction to obtain near short-axial views of the heart. Eight-level (10 contiguous images per level) or 10-level (8 contiguous images per level) cine-mode scans of the heart were obtained with ECG-gating. The end-diastolic (R wave on the ECG) and end-systolic (smallest ventricular chamber volume during the cardiac cycle) frames were identified at each tomographic level. An endocardial border of the left ventricle was determined using methods of edge detection for electron-beam CT described previously (Figure 1) [14]. We used a modified version of Simpson’s method to obtain multi-section cine-mode scans and then calculated left ventricular end-diastolic volume index (EDVI) and left ventricular ejection fraction (EF). End-diastolic wall thickness in the infarcted region (X) and

**METHODS**

**Study population**

Twenty-seven patients with first acute myocardial infarction who underwent emergent cardiac catheterization [19 men and 8 women, mean age 64 (range 46–80) years] were enrolled in this study. The diagnosis of myocardial infarction was based on a history of typical chest pain, typical electrocardiographic changes and an increase in the level of serum creatine kinase. Patients with non-transmural myocardial infarcts were excluded. All patients were in normal sinus rhythm (heart rate range 60 to 100 beats/min). No patients had echocardiographic or angiographic evidence of primary myocardial or significant valvular disease. Patients with chronic renal impairment (serum creatinine ≥ 1.5 mg/dl) were excluded from this study. The study included 16 age-matched control subjects [10 men and 6 women, mean age 62 (range 40–78) years]. All subjects gave their informed consent.
that in the non-infarcted region \( (Y) \) were obtained in the chronic phase of myocardial infarction. Thus, CT-derived remodelling parameters were defined as follows: (1) changes in EDVI \( (\Delta \text{EDVI}) \) equal EDVI in the chronic phase minus EDVI in the acute phase, and (2) infarct/non-infarct wall thickness ratio in the chronic phase \( (X/Y) \).

**Remodelling group versus non-remodelling group**

During the follow-up period, six patients were excluded from the study protocol: four patients because of death and two because of recurrent infarction. The remaining 21 patients were divided into two groups according to their \( \Delta \text{EDVI} \) values within 6 months of acute myocardial infarction. When median values were used as a cut-off point, the remodelling group (RG, \( n = 9 \)) was defined by \( \Delta \text{EDVI} \geq 5 \text{ ml/m}^2 \) relative to the baseline value. The remaining patients were defined as the non-remodelling group (NRG, \( n = 12 \)).

**Statistical analysis**

All data are expressed as means \( \pm \) S.E.M. unless otherwise indicated. Comparisons of variables between two groups were made by the Fisher’s exact test or the unpaired Student’s \( t \)-test. Changes in plasma levels of BNP or ANP were analysed by ANOVA for repeated measures with the Newman–Keuls test. Correlation coefficients between remodelling parameters and plasma ANP or BNP were calculated by linear regression analysis. A \( P \) value < 0.05 was considered statistically significant.

**RESULTS**

**Patient characteristics in the remodelling and non-remodelling groups**

There were no differences in age, sex, infarct site, haemodynamics on admission or medication use at discharge between the RG and NRG (Table 1). The NRG included more patients with successful early reperfusion (< 6 h of the onset) than the RG. Peak serum creatine phosphokinase levels were significantly higher in the RG. EDVI in the chronic phase was significantly greater and EF in the chronic phase was lower in the RG, although neither EDVI nor EF in the acute phase differed significantly between the two groups.

**Plasma BNP levels in the remodelling group**

Plasma BNP levels on days 2, 7, 14, 30, 90 and 180 were significantly elevated in the RG compared with normal subjects (3 \( \pm \) 1 pmol/l, Figure 2). Plasma BNP levels from day 2 to day 90 were significantly higher in the RG than in the NRG \( (P < 0.05) \). Plasma BNP levels in the RG
Table 1 Baseline clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>RG (n = 9)</th>
<th>NRG (n = 12)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62 ± 4</td>
<td>65 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/3</td>
<td>8/4</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior infarction (n)</td>
<td>8</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Early reperfusion (n)</td>
<td>2</td>
<td>8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Forrester’s subset H-2,3,4 (n)</td>
<td>3</td>
<td>3</td>
<td>NS</td>
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<td>Killip’s class</td>
<td></td>
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<tr>
<td>Peak creatine phosphokinase (units/l)</td>
<td>5947 ± 1505</td>
<td>2576 ± 504</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Haemodynamic data on admission</td>
<td></td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124 ± 6</td>
<td>129 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>11 ± 1</td>
<td>10 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (litres min⁻¹ m⁻²)</td>
<td>2.9 ± 0.2</td>
<td>3.2 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>EDP (mmHg)</td>
<td>17 ± 3</td>
<td>13 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Acute-phase EDVI (ml/m²)</td>
<td>73 ± 7</td>
<td>72 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic-phase EDVI (ml/m²)</td>
<td>85 ± 8</td>
<td>68 ± 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Acute-phase EF (%)</td>
<td>45 ± 4</td>
<td>53 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic-phase EF (%)</td>
<td>46 ± 4</td>
<td>59 ± 2</td>
<td>&lt;0.01</td>
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In-hospital medication therapy

|                         |            |              |     |
| Nitrates (n)           | 6          | 7            | NS  |
| Calcium-channel blockers (n) | 5     | 6            | NS  |
| Angiotensin-converting enzyme inhibitors (n) | 7 | 7 | NS |
| Diuretics (n)          | 4          | 4            | NS  |
| β-Blockers (n)         | 0          | 0            | NS  |

Figure 2 Time course of plasma BNP levels after acute myocardial infarction in the remodelling group (RG) and in the non-remodelling group (NRG).

In the RG, sustained elevation of plasma BNP levels was noted from day 2 to day 90 and plasma BNP levels significantly decreased on day 180. In the NRG, plasma BNP levels significantly decreased from day 2 to day 90 and reached a steady level thereafter. *P < 0.05 versus NRG; †P < 0.05 versus day 2.

remained elevated from day 2 (61 ± 12 pmol/l) to day 90 (55 ± 12 pmol/l) and subsequently decreased on day 180 (24 ± 3 pmol/l). The relative change in plasma BNP levels from day 30 to day 90 was significantly smaller in the RG than in the NRG (Figure 3).

Plasma ANP levels on days 2, 7, 14, 30, 90 and 180 were also significantly elevated in the RG compared with

Figure 3 Relative changes in plasma BNP levels from day 30 to day 90

The relative change was defined as 100 × (plasma BNP levels on day 90 – those on day 30)/those on day 30.
normal subjects (3 ± 1 pmol/l, Figure 4). Plasma ANP levels from day 2 to day 180 did not significantly differ between the RG and NRG except on day 14. Plasma ANP levels peaked on day 2, but were unaltered thereafter.

**Plasma BNP levels in the non-remodelling group**

Plasma BNP levels on days 2, 7, 14, 30, 90 and 180 were also significantly elevated in the NRG compared with normal subjects (3 ± 1 pmol/l, Figure 2). In contrast to the RG, plasma BNP levels in the NRG significantly decreased from day 2 (25 ± 4 pmol/l) to day 90 (9 ± 1 pmol/l) and reached a steady level thereafter.

**Plasma BNP levels in non-survivors**

Out of a total of 27 patients, four patients died during the 6-month follow-up period. Although we were not able to obtain CT data on day 180 in these patients, all four patients showed elevated plasma BNP levels on day 7 (Figure 5). In addition, three patients who survived until day 90 showed no decline in plasma BNP levels from day 30 to day 90.

**Plasma BNP levels as a predictor of ventricular remodelling**

Plasma BNP levels on day 2 correlated positively with ΔEDVI ($r = 0.64, P < 0.01$) and with the infarct/non-infarct wall thickness ratio ($r = -0.54, P < 0.05$). Plasma BNP levels on day 7 correlated more closely with ΔEDVI and the wall thickness ratio ($r = 0.70, -0.68, P < 0.001$ for both, Figure 6). On the other hand, plasma ANP levels on day 2 correlated weakly with ΔEDVI ($r = 0.47, P < 0.05$), but not significantly with the wall thickness ratio ($r = -0.26$). Plasma ANP levels on day 7 also showed weak correlation with ΔEDVI ($r = -0.55, P < 0.01$) and with the wall thickness ratio ($r = -0.59, P < 0.01$). When median values were used as a cut-off point, plasma BNP levels on day 7 $\geq 110$ pg/ml identified patients in the RG with a sensitivity of 89% and a specificity of 75%. It can also be said that day 7 plasma BNP levels $< 31$ pmol/l identified patients in the NRG with a sensitivity of 75% and a specificity of 89%.

Furthermore, we investigated whether continued elevation of plasma BNP levels in a chronic phase could identify progressive ventricular remodelling. When median values were used as a cut-off point, a percentage decrease smaller than 25% in plasma BNP from day 30 to day 90 identified patients in the RG with a higher sensitivity and specificity (100% and 83% respectively) than the plasma BNP levels on day 7. In contrast, peak creatine phosphokinase values (a measure of infarct size) higher than the median value (3068 units/l) identified patients in the RG with a lower sensitivity and specificity (78% and 67% respectively). Interestingly, all the three patients included in the NRG in spite of high plasma BNP levels on day 7 showed a percentage decrease greater than 55% in plasma BNP from day 30 to day 90. They all underwent successful reperfusion in an acute phase of myocardial infarction. In contrast, a patient included in the RG in spite of low plasma BNP levels on day 7 showed a relative change in plasma BNP of $> 19\%$ from day 30 to day 90.

**DISCUSSION**

In this study we demonstrated that (1) plasma BNP levels were significantly higher in the RG than in the NRG from day 2 to day 90 after myocardial infarction; (2) in the RG, plasma BNP levels remained elevated from day 2
to day 90 after acute myocardial infarction, whereas plasma BNP levels in the NRG significantly decreased from day 2 to day 90. We also demonstrated that (3) plasma BNP levels in an acute phase, particularly on day 7, predicted the magnitude of progressive ventricular remodelling 6 months after myocardial infarction, and that (4) sustained elevation of plasma BNP in a chronic phase complemented the early prediction by plasma BNP in the acute phase. Thus, this is the first report that has quantitatively characterized the long-term relationship between plasma BNP levels and the magnitude of ventricular remodelling.

**Ventricular remodelling and BNP secretion**

According to Laplace’s law, thinning and dilation of the infarcted region can augment systolic and diastolic wall stress, which would lead to ventricular remodelling. An experimental study has shown that both BNP secretion and BNP mRNA expression are increased mainly in the borderline region between the infarcted and non-infarcted regions [17], where mechanical wall stress may be maximal [18]. In human studies, we have demonstrated that plasma BNP on day 7 may be used as an early predictor of progressive ventricular remodelling within the first 30 days of acute myocardial infarction [12]. These findings suggest that in an acute phase of myocardial infarction, the elevation of plasma BNP may be related to short-term ventricular remodelling, possibly through the mechanism of increased myocardial stretch. However, long-term relationships between plasma BNP levels and left ventricular remodelling remained unclear. Thus, in the present study, we compared plasma BNP levels with changes in ventricular volume and wall thickness as long as 6 months after myocardial infarction. Electron-beam CT was employed because it enables the accurate and reproducible measurement of ventricular volume and wall thickness with an excellent spatial resolution [13,14].

In the present study, we have shown that plasma BNP levels were higher in the RG than in the NRG from day 2 to day 90 and that they remained elevated in the RG even at a chronic phase of myocardial infarction. The sustained elevation of BNP may be a result of the increased myocardial stretch starting in the early phase of acute myocardial infarction and continuing on to the late phase. In this study, plasma BNP levels in an acute phase, particularly on day 7, correlated with the magnitude of progressive ventricular remodelling 6 months after myocardial infarction. In addition, the sustained elevation of plasma BNP levels from day 30 to day 90 clearly distinguished patients in the RG from those in the NRG. These results are consistent with the hypothesis that a continued myocardial stretch in the chronic phase as well as infarct expansion in the acute phase are important factors for the progression of left ventricular remodelling.

A recent study by Omland et al. [19] demonstrated that plasma BNP in the acute phase is a powerful prognostic indicator of patients with acute myocardial infarction. It is interesting to speculate that the prognostic significance of plasma BNP in the acute phase may be attributed to the close relation between the plasma BNP levels and ventricular remodelling. In the present study, all of the four patients who died during the follow-up period demonstrated the sustained elevation of plasma BNP even in the chronic phase of myocardial infarction. Taken together, sustained elevation of plasma BNP may identify patients at high risk not only of progressive ventricular remodelling but also of fatal cardiac events.

It should be noted that plasma ANP is less useful as an indicator of ventricular remodelling than plasma BNP.
This may be consistent with the finding that, unlike BNP, ANP is secreted mainly from the atria in response to increased atrial stretch [20].

Clinical implications
Plasma BNP levels in an acute phase, particularly on day 7, may be an early predictor of progressive ventricular remodelling 6 months after acute myocardial infarction. In contrast, those patients with low BNP levels on day 7 after myocardial infarction are at low risk of progressive ventricular remodelling over a 6-month period. In addition, repeated measurements of plasma BNP levels in a chronic phase may be helpful for the follow-up of patients at high risk of complicating progressive ventricular remodelling. Patients showing decreased plasma BNP levels in the chronic phase in spite of high BNP levels on day 7 would probably have favourable results regarding the ventricular remodelling 6 months after myocardial infarction.

Study limitations
First, the use of pharmacological agents such as angiotensin-converting enzyme inhibitors may modify plasma BNP levels, which may reduce the significance of BNP as a predictor of ventricular remodelling. In this study, however, there was no difference regarding the medication used in the RG and NRG. Second, patients with renal dysfunction were excluded from this study because, in these patients, plasma BNP levels are probably elevated due to the renal dysfunction. Third, the presence of left ventricular hypertrophy would influence plasma BNP levels. The present study population included five patients with hypertension. However, none of them showed marked concentric hypertrophy, and therefore they are unlikely to demonstrate high plasma BNP levels [21]. Finally, the number of patients enrolled in this study might not be sufficient to draw a strong conclusion that plasma BNP is a clinically useful, independent predictor of progressive ventricular remodelling. Further study with a larger number of subjects would be required to address the usefulness of plasma BNP as an independent predictor of progressive ventricular remodelling.

Conclusions
The results of the present study suggest that not only a high level of plasma BNP in an acute phase (on day 7), but also the sustained elevation of plasma BNP in a chronic phase (from day 30 to day 90), may be used as predictors of progressive ventricular remodelling occurring long after acute myocardial infarction. In contrast, a low level of plasma BNP in an acute phase or a rapid decrease from the acute phase to the chronic phase may be a sign of favourable prognosis over the 6-month period.

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