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Plasma Brain Natriuretic Peptide Concentrations Predict Survival After Acute Myocardial Infarction

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Objectives. **This study sought to examine whether plasma brain natriuretic peptide levels can predict prognosis after myocardial infarction.**

Background. **It has been suggested that concentrations of plasma brain natriuretic peptide reflect left ventricular function. Although the prognosis after myocardial infarction depends on residual left ventricular function, it is not known whether plasma levels of brain natriuretic peptide after the onset of myocardial infarction can be used to predict long-term outcome.**

Methods. **Plasma brain natriuretic peptide and atrial natriuretic peptide levels as well as invasive hemodynamic variables were measured in 70 patients with acute myocardial infarction (53 men, 17 women; mean age 65 years). Measurements were obtained on admission (mean 6 h after onset) and on day 2 after onset. Mean follow-up period was 18 months.**

Results. **Plasma brain natriuretic peptide levels measured on admission and day 2 correlated significantly with hemodynamic variables, which are influenced by left ventricular function. However, plasma atrial natriuretic peptide levels correlated with none of the hemodynamic variables measured on admission; and of those measured on day 2, plasma atrial natriuretic peptide levels correlated only with left atrial filling pressure. During the follow-up period (mean 18 ± 7 months), 11 patients died of cardiac causes. By Kaplan-Meier analysis, it was found that patients with plasma brain natriuretic peptide levels higher than the median level, both on admission and on day 2, had significantly higher mortality rates than those with the submedian level (on admission, $p < 0.01$; on day 2, $p < 0.05$). However, only the plasma atrial natriuretic peptide level obtained immediately after admission was significantly related to survival ($p < 0.01$). By Cox proportional hazards model analysis of the noninvasive variables, it was found that plasma brain natriuretic peptide concentration was more closely related to survival after myocardial infarction ($p = 0.0001$).**

Conclusions. **Increased plasma brain natriuretic peptide concentrations in the early or subacute phase of myocardial infarction are a powerful noninvasive indicator of poor prognosis, possibly reflecting residual left ventricular function after myocardial infarction.**

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Brain natriuretic peptide and atrial natriuretic peptide have similar biologic activities. They induce diuresis, natriuresis, vasorelaxation and inhibition of the renin-angiotensin-aldosterone system in both the healthy (1–4) and diseased conditions (5–10). However, the principal sites where these natriuretic peptides are synthesized may be different, that of brain natriuretic peptide being in the ventricular cardiomyocyte (11–13) and that of atrial natriuretic peptide in the atrium (14–16). Plasma concentrations of both brain natriuretic peptide and atrial natriuretic peptide are reported to be increased according to the severity of chronic congestive heart failure (12,17–20). Plasma brain natriuretic peptide concentration may reflect left ventricular function in various cardiac diseases (21–24). In acute myocardial infarction, plasma brain natriuretic peptide level is thought to increase as left ventricular dysfunction progresses (25,26). Because prognosis after myocardial infarction is known to depend on residual left ventricular function (27,28), plasma brain natriuretic peptide concentration may be useful in predicting a prognosis after myocardial infarction.

Plasma atrial natriuretic peptide level has been used in predicting a prognosis after myocardial infarction (29–32). However, the sampling time-points for measuring plasma atrial natriuretic peptide varied: within 12 h (29), from 12 to 24 h (31), or 3 days (30,32) after onset. We demonstrated previously that plasma brain natriuretic peptide level is significantly increased from 12 h through 48 h after the onset of myocardial infarction, whereas plasma atrial natriuretic peptide level did not change significantly (33). Thus, in the present study, we used two different sampling time-points: on admission and on day 2 after onset. We compared the prognostic value of plasma brain natriuretic peptide measurements with those of atrial natriuretic peptide in patients with acute myocardial infarction.

Methods

Subjects. From January 1992 to March 1993, 70 consecutive patients (53 men, 17 women; mean age 65 ± 12 years)

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admitted to our hospital coronary care unit within 12 h of onset were subjects of the present study. Patients with cardiogenic shock or renal failure (serum creatinine >1.5 mg/dl), or both, were excluded from this study. The diagnosis of myocardial infarction was based on a history of typical chest pain, typical electrocardiographic changes and an increase in serum creatine kinase level. Based on electrocardiographic criteria, the site of infarction was anterior in 32 patients, inferior in 27 patients and at other locations in 11 patients. Fifty-two patients were admitted to the hospital within 6 h of onset, and these patients received coronary reperfusion therapy. Coronary intervention was chosen randomly according to the separate treatment protocols in our coronary care unit (infusion of tissue plasminogen activator, n = 30; emergency percutaneous transluminal coronary angioplasty, n = 22). Eighteen patients were admitted from 6 to 12 h after onset and received only conventional treatment (that is, nitrate and lidocaine). The study was approved by the ethics committee of our hospital, and informed consent was obtained from all patients.

Blood sampling and assays. Immediately after admission (mean, 6 ± 5 h after onset) and on day 2 after onset, blood was withdrawn from a forearm vein for measurement of plasma brain natriuretic peptide and atrial natriuretic peptide concentrations. Blood samples were collected into tubes containing 10 mg of EDTA-2Na and 2,500 U of aprotinin, centrifuged immediately (3,000 rpm at 4°C), and then stored at −80°C until they were analyzed. Plasma levels of brain natriuretic peptide and atrial natriuretic peptide were determined using a commercial radioimmunoassay kit (brain natriuretic peptide, Peninsula Laboratories; atrial natriuretic peptide, Amersham) after extraction using a Sep-Pak C-18 column (Waters Chromatography Division, Millipore) as described in our previous reports (10,34). These assays were performed in duplicate. The minimum detectable level of brain natriuretic peptide was less than 1.7 pg per tube, and cross-reactivity with human atrial natriuretic peptide was less than 0.01%. The intraassay and interassay coefficients of variation for brain natriuretic peptide assays were 12% and 19%, respectively. In our laboratory, mean plasma levels of atrial natriuretic peptide and brain natriuretic peptide in age-matched healthy subjects with no evidence of myocardial ischemia were 29 ± 15 pg/ml (n = 17) and 18 ± 6 pg/ml (n = 13), respectively.

Hemodynamic variables. Pulmonary capillary wedge pressure and cardiac output were measured using a Swan-Ganz catheter (Baxter Corp., Edwards Division) immediately after admission and on day 2 after onset in all patients. Left ventricular ejection fraction and left ventricular end-diastolic pressure were determined during ventricular catheterization in patients treated with reperfusion therapy at the time of admission. The clinical characteristics of the patients grouped according to the median plasma level of brain natriuretic peptide on admission are summarized in Table 1. Coronary reperfusion for acute phase of myocardial infarction was successful in all patients who had received the therapy.

Statistical analysis. Patient survival was assessed either to the day of death or to March 31, 1994. To assess the relation between brain natriuretic peptide and atrial natriuretic peptide and mortality rate, median values were used as a cutoff point; and the Kaplan-Meier method was used to examine the survival rate in each group. The significance of the difference between survival curves was tested by the log-rank test. The chi-square test was used to evaluate the differences in baseline characteristics between groups. Unpaired *t* tests were used to compare mean values between groups. Linear regression analysis was used to assess the relation between plasma levels of natriuretic peptides and hemodynamic variables. The prognostic value of the variables was tested in a Cox proportional hazards regression analysis using the program in the PHREG Procedure (SAS/STAT software). Predictors of survival were obtained by forward stepwise selection model. Data are expressed as mean ± SD. A level of $p < 0.05$ was accepted as statistically significant.

Table 1. Comparison of Clinical, Hemodynamic and Biochemical Variables Grouped According to Median Plasma Level of Brain Natriuretic Peptide on Admission

Variable	BNP ≤59 pg/ml (n = 32)	BNP >59 pg/ml (n = 38)	p Value
No. of deaths	0	11	
Clinical			
Age (yr)	59 ± 10	70 ± 11	< 0.001
M/F	26/6	27/11	NS
Previous MI	1	11	< 0.01
Hypertension	19	24	NS
Angina pectoris	17	25	NS
Anterior MI	10	22	< 0.05
Pulmonary congestion	3	15	< 0.01
Reperfusion therapy	24	28	NS
Medication	9	7	NS
Hemodynamic			
HR (beats/min)	76 ± 10	80 ± 19	NS
SBP (mm Hg)	132 ± 20	111 ± 25	< 0.001
PCWP (mm Hg)	11 ± 5	16 ± 6	< 0.001
CI (liters/min per m²)	3.3 ± 0.6	2.7 ± 0.8	< 0.001
LVEF (%) (n = 55)	55 ± 10 (n = 28)	47 ± 12 (n = 27)	< 0.05
LVEDP (mm Hg) (n = 55)	16 ± 5 (n = 28)	19 ± 9 (n = 27)	NS
Biochemical			
Max CK (IU/liter)	3,032 ± 4,300	3,325 ± 2,887	NS
Plasma ANP (pg/ml)	98 ± 113	125 ± 79	NS

Data presented are mean value ± SD or number of patients. ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CI = cardiac index; CK = creatine kinase; F = female; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; M = male; Medication = beta-blockers, angiotensin-converting enzyme inhibitors; MI = myocardial infarction; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

Results

The mean follow-up period was 18 months (range 2 days to 27 months), and the follow-up rate was 100%. Eleven patients died due to cardiac causes during the follow-up period, 7

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Table 2. Correlation Coefficients for Hemodynamic Variables and Plasma Natriuretic Peptide Levels in Acute Phase of Myocardial Infarction

	PCWP	CI	SV	LVEF	LVEDP
On Admission					
BNP	0.44*	0.46*	0.44*	−0.42*	0.31*
ANP	0.22	0.24	0.07	0.12	0.01
On day 2					
BNP	0.34*	0.42*	0.47*		
ANP	0.35*	−0.18	−0.16		

*$p < 0.05$. SV = stroke volume; other abbreviations as in Table 1.

patients died due to refractory heart failure, 2 patients died due to cardiac free-wall rupture during hospitalization, and 2 patients died suddenly after discharge from our hospital.

Plasma natriuretic peptide levels and hemodynamic data. Table 2 shows the correlation coefficients for hemodynamic variables and plasma natriuretic peptides levels on admission and on day 2 after onset. On admission and on day 2, plasma brain natriuretic peptide concentrations correlated significantly with the hemodynamic variables measured at the corresponding time point (pulmonary capillary wedge pressure: on admission, $r = 0.44$, on day 2, $r = 0.34$; cardiac index: on admission, $r = -0.46$, on day 2, $r = -0.42$; stroke volume: on admission, $r = -0.44$, on day 2, $r = -0.47$; left ventricular ejection fraction: on admission, $r = -0.42$; left ventricular end diastolic pressure: on admission, $r = 0.31$, all $p < 0.05$). Plasma atrial natriuretic peptide concentration, in contrast, showed a correlation only with pulmonary capillary wedge pressure and only on day 2 ($r = 0.35$, $p < 0.05$).

Plasma natriuretic peptide levels and clinical outcome. Plasma brain natriuretic peptide concentrations in the patients who died were significantly higher than in those who survived at both sampling time points (on admission: 176 ± 98 vs. 70 ± 58 pg/ml $p < 0.0001$; on day 2: 125 ± 78 vs. 52 ± 45 pg/ml, $p < 0.0001$). Plasma atrial natriuretic peptide concentrations were also significantly higher in the patients who died than in those who survived (on admission: 170 ± 54 vs. 102 ± 99 pg/ml, $p < 0.05$; on day 2: 138 ± 72 vs. 82 ± 90 pg/ml, $p < 0.05$). The correlation between plasma brain natriuretic peptide and atrial natriuretic peptide levels at corresponding time-points was weak (on admission: $r = 0.30$, $p < 0.05$; on day 2: $r = 0.24$, $p < 0.05$).

Plasma natriuretic peptide levels and survival curve. Figures 1 and 2 depict the Kaplan-Meier survival curves. The patients are divided into two groups according to the median plasma concentrations of brain natriuretic peptide and atrial natriuretic peptide. Figure 1 shows the results for brain natriuretic peptide: the groups with elevated plasma brain natriuretic peptide level on admission (>59 pg/ml) and on day 2 (>43 pg/ml) showed significantly higher mortality rates ($p < 0.01$, $p < 0.05$, respectively). Figure 2 shows the results for atrial natriuretic peptide: the group with higher plasma atrial natriuretic peptide level on admission (>80 pg/ml) showed a significantly higher mortality rate ($p < 0.01$), but the survival curves for day 2 plasma atrial natriuretic peptide levels did not differ significantly.

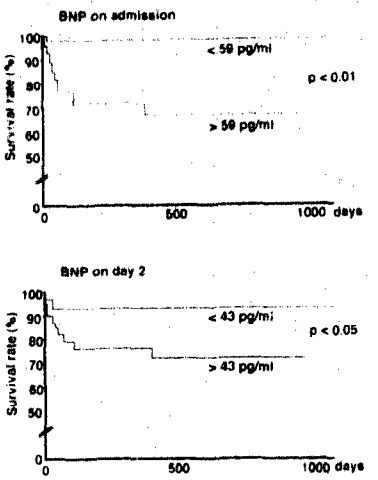

Figure 1. Kaplan-Meier analysis of cumulative survival rate in patients with acute myocardial infarction classified into two groups according to the median value of brain natriuretic peptide (BNP) concentrations on admission **(top)** and on day 2 **(bottom)**.

To determine if plasma brain natriuretic peptide level was associated with cardiac death caused by congestive heart failure, we examined the survival rate of all subjects excluding patients with sudden cardiac death (n = 2) and cardiac rupture (n = 2). We found that plasma brain natriuretic peptide level had a similar prognostic value for predicting cardiac death due to refractory congestive heart failure.

Using a univariate Cox proportional hazards model, we found that plasma brain natriuretic peptide concentrations on

Figure 2. Kaplan-Meier analysis of cumulative survival rate in patients with acute myocardial infarction classified into two groups according to the median value of atrial natriuretic peptide (ANP) concentrations on admission **(top)** and on day 2 **(bottom)**.

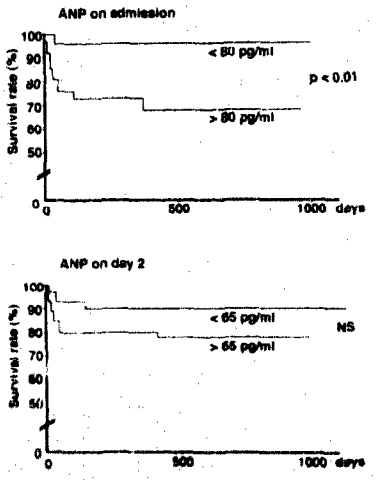

Table 3. Univariate Relations Between Selected Variables and Survival After Myocardial Infarction According to a Cox Proportional Hazards Model

Variable	Chi-Square	p Value
ANP on admission	3.93177	0.0474
BNP on admission	16.18948	0.0001
ANP on day 2	3.33955	0.0676
BNP on day 2	15.44217	0.0001
Maximal CK	0.22802	0.6330
Age	12.71720	0.0004
Gender	0.11084	0.7392
HR	1.14117	0.2854
PCWP	8.24654	0.0041
CI	16.30285	0.0001
SBP	8.63696	0.0033
Pulmonary congestion	10.54013	0.0012
MI site	0.07437	0.7851
Reperfusion therapy	0.40968	0.5221
Angina pectoris	1.49864	0.2209
Hypertension	3.51846	0.0607
Previous MI	3.31261	0.0688

Abbreviations as in Table 1.

admission and on day 2 were also significantly related to survival. Table 3 summarizes the relations between biochemical, hemodynamic and clinical variables and survival after myocardial infarction. Furthermore, according to a multivariate Cox proportional-hazards model, of the noninvasive variables, plasma brain natriuretic peptide concentration on admission was the significant and the most important noninvasive predictor of outcome ($p = 0.0001$, Table 4).

Receiver operating characteristic curve. We examined the sensitivity and specificity of various cutoff values of plasma brain natriuretic peptide and atrial natriuretic peptide levels on admission for predicting survival. A receiver operating characteristic curve was constructed. The curve plotted by the plasma brain natriuretic peptide level on admission was a better predictor than the model based on the plasma atrial natriuretic peptide level on admission (Fig. 3).

Discussion

Several recent reports have demonstrated that plasma atrial natriuretic peptide levels in the acute and subacute phases of myocardial infarction are a good predictor of survival (29–32). However, to our knowledge, our study is the first to report a relation between plasma brain natriuretic peptide level and prognosis after myocardial infarction. We have demonstrated that plasma brain natriuretic peptide concentration in the acute and subacute phases of myocardial infarction is a powerful predictor of long-term outcome and a useful noninvasive marker for identifying the risk of cardiac death. Moreover, plasma brain natriuretic peptide level is more useful as a predictor of survival after myocardial infarction than plasma atrial natriuretic peptide level.

Table 4. Multivariate Relations Between Selected Variables and Survival After Myocardial Infarction According to a Cox Proportional Hazards Model

Variable	Chi-Square	p Value
BNP on admission	21.0347	0.0001
Age	5.4428	0.0196
SBP	2.5948	0.1072
ANP on admission	0.1707	0.6794
Pulmonary congestion	0.8848	0.3757

Abbreviations as in Table 1.

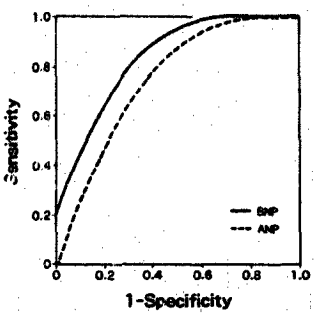

Figure 3. Receiver operating characteristic curves for brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) predicting cardiac death. The true-positive rates (sensitivity) and false-positive rates (1 − specificity) are plotted for various natriuretic peptide cutoff values predicting cardiac death during the follow-up period.

Brain natriuretic peptide and hemodynamic variables. In the present study, plasma brain natriuretic peptide concentrations in the acute and subacute phases of myocardial infarction correlated significantly with pulmonary capillary wedge pressure, cardiac index, stroke volume, left ventricular ejection fraction and left ventricular end-diastolic pressure. These findings are consistent with reports by Mukoyama and coworkers that showed that plasma brain natriuretic peptide concentration correlated significantly with left ventricular function values (25,26). Moreover, Motwani et al. (35) demonstrated that increases in plasma brain natriuretic peptide levels at both early and late stages of myocardial infarction were good indicators of alteration in left ventricular function after treatment with angiotensin-converting enzyme inhibitor. These data suggest that plasma brain natriuretic peptide level is influenced by left ventricular function.

Previous studies. We have found that in the acute and subacute phases of myocardial infarction, the relation between plasma atrial natriuretic peptide concentration and hemodynamic variables was not as strong as that of plasma brain natriuretic peptide. In patients with chronic heart failure, plasma atrial natriuretic peptide level appears to be a good indicator of atrial pressure or pulmonary capillary wedge pressure (cardiac filling pressure) (19,23,36). However, in the acute phase of myocardial infarction, the relation between plasma atrial natriuretic peptide level and intracardiac pres-

sure is not clear. It has been demonstrated that plasma atrial natriuretic peptide concentration after myocardial infarction correlates significantly with cardiac index and intracardiac filling pressure (37–39). Other reports have indicated that there is no significant relation between plasma atrial natriuretic peptide concentration and hemodynamic variables in the acute phase of myocardial infarction (40,41). The reason for this discrepancy is not clear, but there are several possible explanations.

First, massive release of atrial natriuretic peptide from atrial tissue into the circulation immediately after myocardial infarction could lead to depletion of atrial natriuretic peptide stores. Thus, plasma atrial natriuretic peptide concentration would decrease transiently without significant hemodynamic changes occurring (40,42). Second, myocardial infarction complicated by tachyarrhythmia may cause an increase in plasma atrial natriuretic peptide concentration (43). Third, there are reports that thrombolytic therapy in the acute phase of myocardial infarction decreases plasma atrial natriuretic peptide concentration (41,44). Last, in the isolated perfused rat heart, a decrease in coronary flow reduces cardiac atrial natriuretic peptide release (45). These possibilities suggest that plasma atrial natriuretic peptide level may not correlate directly with changes in the hemodynamic values associated with left ventricular dysfunction in patients with acute myocardial infarction.

Mechanisms of brain natriuretic peptide release. In isolated perfused rat hearts, stretching by intraventricular balloon inflation is an independent factor to stimulate brain natriuretic peptide release (46). In patients with chronic heart failure caused by dilated cardiomyopathy, plasma brain natriuretic peptide concentration correlated significantly with left ventricular end-diastolic pressure (21,23). In patients with hypertrophic cardiomyopathy characterized by left ventricular pressure overload, plasma brain natriuretic peptide level increased more than plasma atrial natriuretic peptide level (47). We have previously reported that plasma brain natriuretic peptide concentration correlated significantly with left ventricular end-diastolic pressure but not with left atrial pressure in patients with mitral stenosis (34). These findings indicate that, after myocardial infarction, the increase in ventricular wall stress/tension may be an important factor in stimulating brain natriuretic peptide synthesis and release from ventricular cardiomyocytes.

Two additional mechanisms may stimulate brain natriuretic peptide release in patients with acute myocardial infarction: 1) it has been shown that hypoxia is an independent stimulus for brain natriuretic peptide release (48), suggesting that myocardial ischemia stimulates the release of brain natriuretic peptide; 2) because the increase in plasma brain natriuretic peptide concentration after myocardial infarction is closely related to infarct size (33), brain natriuretic peptide, like cardiac enzymes or macromolecules, may be released from the infarcted or border area between the infarcted and noninfarcted areas. The observation that brain natriuretic peptide mRNA is expressed in ventricular tissue more rapidly than atrial natriuretic peptide mRNA in the rat myocardial infarction model (49) suggests that brain natriuretic peptide production may be immediately increased by the changes in ventricular function that occur after myocardial damage or myocardial ischemia. Thus, after myocardial infarction, cardiac production and release of brain natriuretic peptide may be immediately accelerated, in contrast to atrial natriuretic peptide, and plasma brain natriuretic peptide level may indicate the severity of left ventricular dysfunction and myocardial damage.

Study limitations. Various coronary interventions were used in the acute stage of myocardial infarction in this study. These differences in treatment may have affected prognosis. However, there was no difference in coronary interventions between the two groups classified by plasma brain natriuretic peptide level on admission (Table 1). No significant differences in the subsequent survival rate were found among the variations of coronary interventions in the acute phase of myocardial infarction in the present study group. Moreover, presence of angina pectoris before onset, history of previous myocardial infarction and difference in infarction site did not affect survival rate in the small number of our subjects. The effect of drug treatment (that is, angiotensin-converting enzyme inhibitors, beta-receptor blockers) after myocardial infarction was not assessed in the present study. However, because few patients were given angiotensin-converting enzyme inhibitors (n = 5) or beta-blockers (n = 11), there was no difference between the two groups. These medications, therefore, may not have significantly biased the results of the present study.

Conclusions. In this study, we found that plasma brain natriuretic peptide level reflects left ventricular function more directly than plasma atrial natriuretic peptide level does. Increased plasma brain natriuretic peptide concentration was significantly related to mortality. We suggest that measurement of plasma brain natriuretic peptide level in the early phase of myocardial infarction may be a useful noninvasive method for identifying individuals at high risk of cardiac death after myocardial infarction.

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