Increased Plasma Levels of Brain Natriuretic Peptide in Patients With Acute Myocardial Infarction

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Background. Brain natriuretic peptide is a novel natriuretic peptide that is secreted predominantly from the ventricles, and its plasma levels have been shown to be markedly increased in patients with chronic congestive heart failure. This study was designed to examine the plasma levels of brain natriuretic peptide as well as atrial natriuretic peptide in patients with acute myocardial infarction.

Methods and Results. We examined the plasma levels of brain natriuretic peptide as well as atrial natriuretic peptide in 50 consecutive patients (36 men and 14 women; mean age, 66 years) with acute myocardial infarction over the time course of 4 weeks. The plasma level of brain natriuretic peptide was significantly increased on admission in patients with acute myocardial infarction compared with controls (92±28 versus 5.2±0.5 pg/mL, P<.01) and reached the peak level of 319±58 pg/mL at 16.4±0.7 hours after admission. Therefore, the level decreased and then again increased, forming the second peak of 277±66 pg/mL on day 5. The level then decreased gradually but was still much higher in the fourth week than that of controls (149±47 versus 5.2±0.5 pg/mL, P<.001). On the other hand, the plasma atrial natriuretic peptide level already had been increased at the time of admission compared with controls (116±14 versus 39.5±2.6 pg/mL, P<.01) and decreased thereafter, again increasing and making a small peak on day 2 to 3. The time course of the plasma brain natriuretic peptide level could be divided into two patterns: a monophasic pattern with one peak at about 16 hours after admission and a biphasic pattern with two peaks at about 16 hours and 5 days after admission. There were significantly more patients with anterior infarction, congestive heart failure, higher level of maximal creatine kinase-MB isoenzyme, and lower left ventricular ejection fraction in the biphasic group than in the monophasic group.

Conclusions. We conclude that the plasma level of brain natriuretic peptide is increased markedly in patients with acute myocardial infarction and may reflect the degree of left ventricular dysfunction in these patients. (Circulation 1993;88:82-91)

Key Words: • natriuretic peptides • plasma • myocardial infarction • heart failure, congestive

Atrial natriuretic peptide is a circulating hormone with a wide range of potent biological effects, including natriuresis, diuresis, vasodilation, and inhibition of the renin-angiotensin-aldosterone system1-5 and sympathetic nervous system.6 There is increasing evidence that it plays an important role in the regulation of fluid volume and blood pressure.2-5 Several studies have shown that plasma atrial natriuretic peptide levels are increased in patients with chronic congestive heart failure and that there is a linear relation between plasma atrial natriuretic peptide level and atrial pressure,7-13 implying that atrial pressure or stretch plays an important role in the regulation of secretion of atrial natriuretic peptide. Recently, we and others14-16 have shown that atrial natriuretic peptide is synthesized and secreted in increased amounts not only from atria but also from ventricles in patients with heart failure. We also have shown that the infusion of atrial natriuretic peptide improves left ventricular function by reducing both preload and afterload in patients with heart failure.17 Atrial natriuretic peptide thus appears to play an important role in the compensatory mechanisms of heart failure.

Several have reported on the plasma level of atrial natriuretic peptide in patients with acute myocardial infarction.18-22 However, there remain controversies regarding the level of atrial natriuretic peptide in patients with acute myocardial infarction, with some studies reporting increased plasma level of atrial natriuretic peptide in close relation to atrial pressure18,19 and others even in the absence of heart failure.20-22 and the time course of plasma level of atrial natriuretic peptide in patients with acute myocardial infarction is unknown.

Brain natriuretic peptide is another novel natriuretic peptide, which first was isolated from the porcine...
brain and subsequently from the hearts of pigs and rats. Recently, we isolated human brain natriuretic peptide from human heart, determined its amino acid sequence, and established a specific radioimmunoassay for human brain natriuretic peptide by developing a monoclonal antibody against it. With this assay system, we have shown that brain natriuretic peptide is a cardiac hormone secreted predominantly from the ventricle and that the synthesis, secretion, and clearance of brain natriuretic peptide differ from those of atrial natriuretic peptide and suggested discrete physiological and pathophysiological roles of brain natriuretic peptide in a dual-natriuretic peptide system.

We also have demonstrated that plasma levels of brain natriuretic peptide are increased more markedly than those of atrial natriuretic peptide in patients with chronic congestive heart failure in proportion to the severity of the disease. However, it is not known whether plasma levels of brain natriuretic peptide are increased in patients with acute myocardial infarction or how the levels change over time from the early to the late phase of the disease in these patients.

The present study was designed to examine the plasma levels of brain natriuretic peptide as well as those of atrial natriuretic peptide in relation to the hemodynamic and other parameters and over the time course from the early to the late phase of acute myocardial infarction using specific radioimmunoassays for both atrial natriuretic peptide and brain natriuretic peptide.

Methods

Study Patients

Fifty consecutive patients with acute myocardial infarction who were admitted within 8 hours after onset of symptom were included in this study. The study patients consisted of 36 men and 14 women, ranging in age from 44 to 85, with a mean age of 66.2±1.5 years. The diagnosis of acute myocardial infarction was made on the basis of chest pain persisting for at least 30 minutes, ST-segment elevation of at least 0.1 mV in at least two contiguous leads, and elevation of serum creatine kinase–MB isoenzyme (CK-MB) to more than twice the upper limit of the normal range. Twenty-five patients were diagnosed as having anterior infarction, 19 patients as having inferior infarction, and 6 patients as having posteriorateral infarction.

Seventeen patients had a history of angina pectoris, 10 patients had previous myocardial infarction, and 22 patients had hypertension. The average time from onset of symptom to admission was 3.6±0.4 hours, ranging from 1 to 8 hours. All patients were treated with nitrates and calcium antagonists after admission. β-Blocker was used in one patient, and angiotensin converting enzyme inhibitors were used in eight patients. Diuretics were used in four patients with congestive heart failure. Neither glucocorticosteroids nor nonsteroidal anti-inflammatory agents, which are known to retard healing of infarct, were used during the study protocol in any of the patients. Seven patients were treated by intra-aortic balloon pumping immediately after admission. Of all the 50 patients, 2 patients died during the study protocol: 1 patient died on the second day because of a complication of cerebral hemorrhage after a thrombotic therapy, and the other patient died in the fourth week because of a complication of renal failure following heart failure.

We included 30 age- and sex-matched healthy control subjects (21 men and 9 women; age range, 48 to 77 years; mean age, 64.9±1.9 years). None of them had hypertension, renal failure, or any kind of heart disease such as ischemic heart disease, cardiomyopathy, and valvular heart disease.

Written informed consent was obtained from each patient and/or his or her family in the early phase of acute myocardial infarction and after that from each patient. This study protocol was in agreement with the guidelines of the ethical committee of our institution.

Study Protocol

Coronary angiography on admission. In all of the 50 patients, coronary angiography was performed immediately after admission. Among these, 10 patients were treated with percutaneous transluminal coronary recanalization via intracoronary infusion of urokinase, 26 patients by direct percutaneous transluminal coronary angioplasty, and 11 patients by the infusion of tissue-type plasminogen activator or urokinase into a peripheral vein; the remaining 3 patients were treated conservatively because the infarct-related coronary arteries were patent at the time of coronary angiography.

The occluded coronary arteries were recanalized successfully by these treatments in 44 patients. Recanalization of the occluded coronary artery failed at the time of admission in three patients: one patient by percutaneous transluminal coronary recanalization, and two patients by direct percutaneous transluminal coronary angioplasty.

Hemodynamic study. The study protocol is shown in Fig 1. A Swan-Ganz catheter was inserted into the femoral or subclavian vein immediately after admission and before coronary angiography and was kept inserted during the first 2 days in all patients. Hemodynamic parameters, including heart rate, arterial pressure, right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, and cardiac index, were measured with a Swan-Ganz catheter during the first 2 days. Cardiac index was measured by thermodilution technique in triplicate. Heart rate was monitored continuously with the ECG on lead II. Arterial pressure was measured with a brachial cuff technique.

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FIG 1. Schematic of study protocol. Pressure measurements included heart rate, blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure. LV EF, left ventricular ejection fraction.
Cardiac catheterization 4 weeks after admission. Cardiac catheterization, including hemodynamic study, coronary arteriography, and left ventriculography, was performed in 32 patients in the morning after fasting overnight 4 weeks after admission. The patients had been receiving no drugs since the previous night. The infarct-related coronary artery was patent in 30 patients. The artery was occluded in two patients whose infarct-related coronary artery had remained occluded despite reperfusion therapy at the time of admission. In two patients, a left ventricular aneurysm was detected with left ventriculography. Left ventricular ejection fraction was calculated from the left ventriculogram.

Blood sampling. Blood samples were obtained immediately after admission; every 4 hours during the first 24 hours; thereafter once a day within the first week; and in the second, third, and fourth weeks when cardiac catheterization was done as shown in Fig 1. Blood sampling from the second day through the fourth week was done at 7:00 AM with the patient in the supine position after fasting overnight. Blood samples were taken from the ante-cubital or femoral vein and placed into EDTA-coated tubes containing 500 IU/mL aprotinin. Thereafter, the plasma immediately was centrifuged at 4°C and then stored at −80°C until analysis.

Measurement of Plasma Atrial Natriuretic Peptide Concentration

Plasma concentration of atrial natriuretic peptide was measured with a specific radioimmunoassay for α-human atrial natriuretic peptide as reported previously. In brief, this radioimmunoassay recognizes a carboxyterminal sequence of atrial natriuretic peptide, and the minimal detectable quantity is 1 pg per tube. The intra-assay and interassay coefficients of variation were 7.2% and 7.8%, respectively. The cross-reactivity with human brain natriuretic peptide and C-type natriuretic peptide was less than 0.01% each on a molar basis.

Measurement of Plasma Brain Natriuretic Peptide Concentration

Plasma concentration of brain natriuretic peptide was measured with a specific radioimmunoassay by using a monoclonal antibody that recognized the ring structure of human brain natriuretic peptide, and the minimal detectable quantity was 1 pg per tube. The intra-assay and interassay coefficients of variation were 8.4% and 6.4%, respectively. The cross-reactivity with α-human atrial natriuretic peptide and C-type natriuretic peptide was less than 0.01% and less than 1% on a molar basis, respectively.

The plasma brain natriuretic peptide levels in the control subjects were measured with an extracted method. In the assay with extraction, peptides were extracted from 5 to 10 mL of plasma using a Sep-Pak C18 cartridge (Waters Associates, Milford, Mass). The mean recovery of 3 to 15 fmol/mL brain natriuretic peptide added to plasma was 70%. In the patients with acute myocardial infarction, the measurement of the plasma brain natriuretic peptide concentration was performed uniformly without extraction because a large amount of blood for the extracted assay could not necessarily be obtained in all patients. In the assay without extraction, 25 μL of plasma was added to the incubation mixture.

Hormone-free plasma, prepared by passing normal plasma through a Sep-Pak C18 cartridge, was used for constructing the standard curve and diluted plasma samples. To examine the validity of the extracted method in measuring plasma brain natriuretic peptide levels in patients with acute myocardial infarction, 30 samples from eight patients were chosen randomly and measured with both extracted and nonextracted methods.

If the plasma brain natriuretic peptide levels were less than the assay sensitivity of 1 pg per tube (40 pg/mL) in the nonextracted method, we calculated them as the normal value of 5 pg/mL in the present study to avoid overestimating the plasma brain natriuretic peptide levels.

Measurement of CK-MB

CK-MB was measured in the clinical laboratory by using a standardized automated enzyme analyzer.

High-Performance Gel Permeation Chromatography for Analysis of Plasma Brain Natriuretic Peptide

High-performance gel permeation chromatography was performed on a TSK-GEL G2000 SW column (7.5x600 mm, Toyo Soda, Tokyo, Japan) and eluted with 10 mM trifluoroacetic acid containing 0.3 M sodium chloride and 30% acetonitrile as a solvent as reported previously.

Statistical Analysis

The plasma levels of atrial natriuretic peptide and brain natriuretic peptide were compared over the time course using ANOVA for repeated measures. Where the F value was found to be significant, the data were compared with Dunnett's multiple comparison tests. Comparison of parameters between two groups was performed with the χ² test or the unpaired Student's t test. All values were expressed as mean±SEM unless otherwise indicated. Statistical significance was defined as P<.05.

Results

Comparison Between Extracted and Nonextracted Plasma Assays

The plasma brain natriuretic peptide levels were measured in 30 samples obtained from eight patients with acute myocardial infarction using both extracted and nonextracted methods. A significant correlation was found between the two methods in the range of 40 to 1.5 ng/mL (r=0.983, r<.001) as shown in Fig 2.

Time Course of Plasma Levels of Atrial Natriuretic Peptide and Brain Natriuretic Peptide

The plasma levels of atrial natriuretic peptide in the age- and sex-matched control subjects were 39.5±2.6 pg/mL. The plasma levels of brain natriuretic peptide in the age- and sex-matched control subjects measured with the extracted method were 5.2±0.5 pg/mL.

Fig 3 shows the time course of the plasma levels of atrial natriuretic peptide and brain natriuretic peptide from admission to the fourth week. The plasma atrial natriuretic peptide level had already been augmented with a peak level of 116±14 pg/mL at the time of admission (3.7±0.4 hours after onset of symptom),
which was significantly higher than the normal range ($P<.01$). Thereafter, the plasma atrial natriuretic peptide level decreased gradually to the normal range within 8 hours after admission and reached a small second peak of 78±14 pg/mL on the second day.

The plasma brain natriuretic peptide level, which had already been elevated to 92±28 pg/mL at the time of admission, further increased, reaching a peak level of 319±58 pg/mL at 16.4±0.7 hours after admission (20.6±1.1 hours after onset of symptom). Thereafter, the level decreased and then again increased, forming the second peak of 277±66 pg/mL on the fifth day. Thereafter, the level decreased gradually but was still much higher in the fourth week than that of control subjects (149±47 versus 5.2±0.5 pg/mL, $P<.001$).

**Classification of the Time Course of Plasma Brain Natriuretic Peptide Levels Into Monophasic and Biphasic Patterns**

The time course of the plasma brain natriuretic peptide levels in all study patients except one patient, who died on the second day after admission, could be classified into two patterns: a monophasic pattern and a biphasic pattern, as shown in Fig 4. In the monophasic group, which included 22 patients, the plasma brain natriuretic peptide level decreased gradually after the first peak of 244±45 pg/mL at 17.0±1.0 hours after admission (20.3±1.5 hours after onset of symptoms). In the biphasic group, which included 27 patients, the first peak level was 382±43 pg/mL at 15.7±0.9 hours after admission (19.5±1.4 hours after onset of symptoms), and the second peak level was 416±68 pg/mL at 5±1 days after onset of acute myocardial infarction. There were significant differences in the plasma brain natriuretic peptide levels between the two groups from the second day to the fourth week, although there was no significant difference in the level within 24 hours after admission except at hour 20 ($P<.05$).

Comparison of clinical characteristics between the patients with the monophasic pattern and those with the biphasic pattern are shown in Table 1. There were more patients with higher classes of Forrester’s subset of II, III, or IV on admission (13 patients versus 5 patients, $P<.05$) and more patients with Killip’s classification of II, III, or IV (11 patients versus 2 patients, $P<.05$) in the biphasic group than in the monophasic group. There were more patients with anterior infarction in the biphasic group than in the monophasic group (18 patients versus 7 patients, $P<.05$). The maximal level of serum CK-MB was significantly higher in the biphasic group than in the monophasic group (340±50 versus 170±22 IU/L, $P<.01$).

The plasma atrial natriuretic peptide time course also could be divided into a monophasic pattern and a biphasic pattern, similar to the classification of the plasma brain natriuretic peptide time course. There were more patients with the biphasic pattern of the plasma atrial natriuretic peptide level in the biphasic group than in the monophasic group ($P<.05$). Left ventricular ejection fraction measured in the fourth week was significantly lower in the biphasic group than in the monophasic group (54.2±2.9% versus 65.7±1.8%, $P<.01$).
The time course of the plasma brain natriuretic peptide level was biphasic in the two patients whose infarct-related coronary arteries remained occluded in the fourth week and in the one patient who died in the fourth week. The time course of the plasma brain natriuretic peptide level also was biphasic in the two patients with ventricular aneurysm detected by left ventriculography in the fourth week, even though the infarct-related coronary artery was patent in both patients.

**Correlation of Plasma Levels of Atrial Natriuretic Peptide and Brain Natriuretic Peptide With Hemodynamic Parameters Within the First 2 Days After Onset of Acute Myocardial Infarction**

There were two peaks in the level of plasma atrial natriuretic peptide: at the time of admission and on the second day, as shown in Fig 3. We examined the relation between the plasma atrial natriuretic peptide levels and the time-matched hemodynamic parameters measured by a Swan-Ganz catheter at these two peak times and those obtained within the first 2 days. No significant relation between the plasma atrial natriuretic peptide level and pulmonary capillary wedge pressure was found by using all data obtained within the first 2 days, as shown in Fig 5A (n=302, r=.170, P=NS). There also was no significant correlation between the plasma atrial natriuretic peptide level and pulmonary capillary wedge pressure (n=49, r=.115, P=NS) at the time of admission, as shown in Fig 5B. However, there was a significant correlation between the plasma atrial natriuretic peptide level and pulmonary capillary wedge pressure (n=48, r=.518, P<.01) on the second day (Fig 5C). There was no significant correlation between the plasma atrial natriuretic peptide level and cardiac index as indicated by all data obtained within the first 2 days, at the time of admission, and on the second day, as shown in Fig 5D (n=302, r=-.114, P=NS), Fig 5E (n=49, r=-.306, P=NS), and Fig 5F (n=48, r=.183, P=NS), respectively.

We also examined the relation between the plasma brain natriuretic peptide levels and time-matched hemodynamic parameters at the first time peak of the plasma brain natriuretic peptide level and those ob-
Fig 5. Scatterplots of correlations between plasma level of atrial natriuretic peptide (ANP) and hemodynamic parameters. Upper panels show correlations between plasma ANP level and pulmonary capillary wedge pressure (PCWP) by using all data obtained within the first 2 days (panel A), at time of admission (panel B), and on the second day (panel C). Lower panels show correlations between plasma ANP level and cardiac index by using all data obtained within the first 2 days (panel D), at time of admission (panel E), and on the second day (panel F).

Correlation of Plasma Levels of Atrial Natriuretic Peptide and Brain Natriuretic Peptide With Hemodynamic Parameters in the Fourth Week

Fig 7 shows the correlation of the plasma levels of atrial natriuretic peptide and brain natriuretic peptide with time-matched hemodynamic parameters measured in the fourth week. There was a significant correlation of the plasma atrial natriuretic peptide level with pulmonary capillary wedge pressure (Fig 7A; n = 32, r = .496, P < .01) and left ventricular ejection fraction (Fig 7C; n = 32, r = -.433, P < .05), respectively. There also was a significant correlation of the plasma brain natriuretic peptide level with pulmonary capillary wedge pressure (Fig 7D; n = 32, r = .658, P < .01) and left ventricular ejection fraction (Fig 7F; n = 32, r = -.660, P < .01), respectively. The plasma levels of atrial natriuretic peptide and brain natriuretic peptide had no significant correlation with cardiac index (Fig 7B; n = 32, r = -.162, P = NS; Fig 7E; n = 32, r = -.306, P = NS, respectively).

Results of High-Performance Gel Permeation Chromatography Profiles

Fig 8 shows typical high-performance gel permeation chromatography profiles of plasma obtained from four patients with acute myocardial infarction included in this study. Plasma brain natriuretic peptide was composed of two components with approximate molecular masses of 12 and 3 kD in all four cases. The elution position of 3 kD was identical to that of synthetic human brain natriuretic peptide, and the 12-kD component corresponded to the precursor of brain natriuretic peptide.

Discussion

Brain natriuretic peptide, first isolated from the brains of pigs23 and subsequently from the hearts of pigs24 and rats,25 shares a highly homologous 17-amino acid ring structure with atrial natriuretic peptide and forms a natriuretic peptide family with atrial natriuretic peptide, although they are derived from distinct genes.23 We have demonstrated that brain natriuretic peptide is a novel cardiac hormone secreted predominantly from the ventricle27-29 and that plasma levels of brain natriuretic peptide are increased markedly in patients with congestive heart failure in proportion to its severity and
surpass those of atrial natriuretic peptide in severe cases.27

The present study shows that the plasma levels of brain natriuretic peptide are increased markedly in the early phase of acute myocardial infarction. The mean peak level of plasma brain natriuretic peptide was more than 60-fold the mean level of the age- and sex-matched control subjects. Although we measured plasma brain natriuretic peptide levels using the nonextracted method in the patients with acute myocardial infarction in the present study, we demonstrated the validity of this method compared with the extracted method in the present study. The plasma level of atrial natriuretic peptide also was increased in the early phase of acute myocardial infarction; however, the mean peak level was only approximately threefold the mean level of the age- and sex-matched control subjects.

In the present study, 22 of the 50 patients with acute myocardial infarction had a history of hypertension. We have reported previously that plasma levels of brain natriuretic peptide were higher in patients with hypertension than in the control subjects.35 However, because the mean plasma level of brain natriuretic peptide in patients with hypertension was approximately 30 pg/mL,35 the presence of hypertension cannot explain the marked increase of plasma brain natriuretic peptide levels in patients with acute myocardial infarction in the present study.

The plasma level of brain natriuretic peptide increased rapidly and reached a peak approximately 20 hours after onset of symptoms. In contrast, the plasma level of atrial natriuretic peptide was already the highest at the time of admission and decreased thereafter to within the normal range, remaining at almost the same levels within the 24 hours after admission. These facts strongly suggest that the regulations of synthesis and secretion of brain natriuretic peptide may be different from those of atrial natriuretic peptide and that brain natriuretic peptide is one of the acute-phase reactants that are released in response to acute tissue injuries.36 Brain natriuretic peptide thus may play a role as an emergency aid for atrial natriuretic peptide. The fact that DNA of brain natriuretic peptide has an AT-rich sequence in the 3'-untranslated region that is known to destabilize mRNA and is not found in DNA of atrial natriuretic peptide also supports this line of thinking.37 The levels of plasma brain natriuretic peptide in the early phase of acute myocardial infarction did not correlate significantly with the hemodynamic parameters. This suggests that the synthesis and secretion of brain natriuretic peptide may be stimulated by myocardial necrosis, local mechanical stress, or both on ventricular myocytes even when global hemodynamic pa-
rameters are within normal ranges. Other unknown mechanisms also may be involved in the regulation of brain natriuretic peptide synthesis and secretion in the early phase of acute myocardial infarction.

There also was no significant correlation between plasma atrial natriuretic peptide levels and hemodynamic parameters in the early phase of acute myocardial infarction. It is possible that rapidly progressive dysfunction of the infarct area during the first hours of onset provides sufficient stimulus for a total depletion of atrial natriuretic peptide granules and thus plasma atrial natriuretic peptide levels already were the highest on admission and decreased thereafter in the early phase of acute myocardial infarction. These results are in agreement with those of other reports.21,22 The plasma half-life of brain natriuretic peptide is longer than that of atrial natriuretic peptide,23 and this also may contribute to the higher plasma levels of brain natriuretic peptide than those of atrial natriuretic peptide.

The time course of plasma level of brain natriuretic peptide in patients with acute myocardial infarction could be divided into two patterns: monophasic and biphasic patterns. The monophasic pattern had only one peak occurring in the early phase of acute myocardial infarction, whereas the biphasic pattern also had a second peak occurring 4 to 7 days after onset of symptoms.

The patients with the biphasic pattern were associated more frequently with anterior transmural infarction, with signs and symptoms of heart failure as indicated by Killip or Forrester classification, with lower left ventricular ejection fraction, and with higher peak plasma levels of CK-MB than those with the monophasic pattern. Moreover, plasma levels of brain natriuretic peptide were significantly higher in patients with the biphasic pattern than in those with the monophasic pattern over the course of disease, at least by the fourth week (except during the early phase). Thus, the plasma levels and the presence or absence of the second peak of plasma brain natriuretic peptide level in the subacute phase appear to reflect the degree of left ventricular dysfunction, infarct size, or both in patients with acute myocardial infarction. The significant correlations of the plasma level of brain natriuretic peptide with the global hemodynamic parameters and left ventricular ejection fraction in the fourth week also support this line of thinking.

The mechanism(s) by which the second peak and elevated levels of plasma brain natriuretic peptide occur in the subacute phase of acute myocardial infarction is not clear at the present time. The results of the present study, however, suggest that this peak and elevated levels of plasma brain natriuretic peptide are related to infarct expansion and subsequent ventricular remodeling. Infarct expansion is defined as acute dilatation and thinning of the area of infarction not explained by the additional myocardial necrosis that occurs in the subacute phase of acute myocardial infarction38 and is observed most frequently in large anterior transmural
infarction, often associated with heart failure. Infarct expansion causes a significant increase in left ventricular cavity size, which in turn can increase the wall stress of noninfarcted as well as infarcted regions, resulting in ventricular remodeling and leading to ventricular aneurysm and ventricular rupture in some cases. All the patients who developed ventricular aneurysm and the patient who died from heart failure had a second peak and markedly elevated levels of plasma brain natriuretic peptide in the subacute phase in this study.

It is probable that increased ventricular wall stress caused by infarct expansion stimulated the synthesis and secretion of brain natriuretic peptide from ventricular myocytes. Thus, plasma levels of brain natriuretic peptide may be a sensitive marker of the degree of left ventricular dysfunction. We have shown that infusion of brain natriuretic peptide reduces both preload and afterload and improves left ventricular function in patients with heart failure. The increased plasma levels of brain natriuretic peptide therefore may play a compensatory role for ventricular dysfunction caused by acute myocardial infarction and thereby reduce progressive ventricular enlargement, attenuating ventricular remodeling after acute myocardial infarction.

The time course of plasma level of atrial natriuretic peptide also could be divided into the monophasic pattern and the biphasic pattern in patients with acute myocardial infarction, with the first and highest peak occurring at the time of admission and the second and modest peak occurring in the subacute phase of acute myocardial infarction. It is probable that atrial natriuretic peptide, which was rapidly released in large amounts and subsequently depleted by damage of myocardial infarction, was synthesized and secreted in increased amounts not only from atria but also from ventricles in the subacute phase in patients with a biphasic pattern. Atrial natriuretic peptide is synthesized and secreted from ventricles as well as from atria in the failing heart, as we and others have reported.  

In fact, there was a significant correlation between the plasma atrial natriuretic peptide level and pulmonary capillary wedge pressure on the second day of acute myocardial infarction, although this was not observed in the early phase of acute myocardial infarction. Most patients with a biphasic pattern of plasma level of brain natriuretic peptide also had a biphasic pattern of plasma level of atrial natriuretic peptide. Thus, atrial natriuretic peptide may play a role similar to that of brain natriuretic peptide for the compensation of left ventricular dysfunction in patients with acute myocardial infarction, although the contribution of atrial natriuretic peptide may be much smaller than that of brain natriuretic peptide.

We also demonstrated in the present study that not only authentic brain natriuretic peptide (molecular mass of 3 kD) but also its precursor (molecular mass of 12 kD) were increased in plasma from the patients with acute myocardial infarction. The observation is consistent with our previous report on two molecular forms of brain natriuretic peptide in plasma from patients with congestive heart failure. The precise secretion pattern and mechanism(s) of these two forms of brain natriuretic peptide are unknown at present.

In conclusion, the plasma level of brain natriuretic peptide was increased markedly in the early phase of acute myocardial infarction. Although the precise mechanisms by which brain natriuretic peptide is synthesized and released remain to be elucidated, the plasma level of brain natriuretic peptide appears to reflect the degree of ventricular dysfunction in the subacute phase and be a predictor of prognosis in patients with myocardial infarction.

Acknowledgments

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