Plasma Atrial Natriuretic Factor in Patients with Acute Myocardial Infarction

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SUMMARY

To examine whether atrial natriuretic factor (ANF) is secreted adequately in the early phase of myocardial infarction, plasma ANF concentration and clinical parameters, including hemodynamic variables, were studied in 118 patients with acute myocardial infarction (AMI). The patients were divided into 2 subgroups according to the absence (group A, n=41) or presence (group B, n=77) of a history of valvular heart disease, previous myocardial infarction, hypertension, or renal failure. Although no significant difference in atrial pressure after the infarction was found between the 2 groups, the plasma ANF level was significantly lower in group A than in group B (76±6 vs. 185±26 pg/ml; mean±SEM, p<0.01). Plasma ANF was correlated with pulmonary capillary wedge pressure in group B (r=0.54, p<0.001), whereas no relationship with hemodynamic parameters was observed in group A. In 56 of the 118 patients (group A, n=18; group B, n=38), the pulmonary arterial plasma level was significantly higher in group A (p<0.05), whereas the difference was not significant in group B. Seven of the 8 expired cases among these 56 patients had peripheral plasma ANF levels of more than 150 pg/ml, which were higher than those in pulmonary arterial plasma.

These observations suggest firstly that the plasma level of ANF is lower in patients with a new onset of myocardial infarction compared to those with a history of cardiac or renal diseases, and secondly that stimulated ANF release originates not only from the right side of the heart, but also from additional site(s), particularly in patients with chronic ventricle overload and a poor prognosis.

Key Words:
Myocardial infarction Atrial natriuretic factor Atrial pressure
Atrial natriuretic factor (ANF) is stored in atrial myocardial cells as a precursor form and secreted from the right atrium via the coronary sinus. Several studies have demonstrated a close relationship between plasma ANF levels and atrial pressure in a wide variety of heart diseases, implying that ANF release from the heart is regulated by atrial pressure. Moreover, it has been demonstrated that ANF may play an important role in the regulation of renal water-sodium excretion in health and disease. An increase in ANF secretion therefore seems to be one of the compensatory mechanisms that serve to counteract volume overload due to cardiac dysfunction.

However, only a few reports are available so far concerning plasma ANF levels in patients with acute myocardial infarction (AMI). It is still a matter of controversy whether the plasma concentration fluctuates with changes in intracardiac pressure in this disease condition. Tomoda demonstrated that plasma levels were correlated positively with intracardiac pressure and negatively with cardiac index in a wide variety of patients with AMI. However, Ngo et al have recently shown that the relationship between plasma ANF levels and left ventricular dysfunction was not significant in patients with myocardial infarction who had no clinical evidence of congestive heart failure. Moreover, Tan et al have demonstrated recently, in patients who were treated successfully after AMI, that plasma ANF levels had decreased several hours after admission, but were subsequently restored to the levels observed at the time of admission.

Because an increase in ANF secretion with an elevation in atrial pressure seems to be an important compensatory mechanism for the maintenance of water-sodium excretion in cardiac dysfunction, it may be meaningful to examine whether the hormone system is functioning adequately during the early phase of myocardial infarction. In order to know whether ANF is secreted from the right side of the heart in response to changes in atrial pressure, we have examined the relationship between plasma levels and atrial pressure in a large number of patients with AMI, and have compared the plasma concentration in the pulmonary artery with that in a peripheral site.

**Patients and Methods**

**Patients:** The 118 patients who participated in this study were admitted to our University Hospital Coronary Care Unit between August, 1984 and July, 1989, and gave informed consent prior to participation. The diagnosis of AMI was based on a history of typical chest pain, typical electrocardiographic criteria, and increased serum levels of myocardial enzymes. All
patients were admitted to the Unit within a day of the onset of symptoms. Any who had been treated with streptokinase, were unconscious, or had hepatic disturbance (serum bilirubin level >2.0 mg/dl) and/or shock (systolic blood pressure <90 mmHg) were excluded from the study. Patients with right ventricular infarction were also excluded because volume expansion was usually needed for treatment of these cases, and this might have increased their plasma ANF levels. All patients underwent strict recording of fluid intake and output for at least the first 3 days after the infarction occurred.

The patients were divided into 2 subgroups. Forty-one patients were designated as group A (simple myocardial infarction); they were experiencing the first attack of myocardial infarction and had no history of valvular heart disease, previous myocardial infarction, hypertension, or chronic renal failure. All of these conditions have been known to exhibit elevated plasma ANF levels. Group B consisted of 77 patients with AMI who had at least one of the conditions mentioned above.

**Hemodynamic measurements and plasma samples:** A Swan-Ganz triple lumen catheter was inserted into the pulmonary artery of each patient immediately after admission. The myocardial infarction was treated with two or more of the following drugs: nitroglycerin (50–100 mg/day; intravenously), nifedipine (40–60 mg/day; orally), dobutamine (220–360 mg/day; intravenously), and furosemide (10–60 mg/day; intravenously). Dobutamine and furosemide were used for cases with congestive heart failure. All patients routinely received oxygen inhalation (2–4 L/min), and those with a premature ventricular beat were administered lidocaine (60–120 mg/min). Within 12 hours of admission, and after the initiation of treatment, a 7-ml blood sample for estimation of plasma ANF levels was taken from a forearm vein or a radial artery through a small catheter for blood pressure monitoring. This was done within 5 min of the following hemodynamic evaluations: pulmonary capillary wedge pressure, right atrial pressure, and pulmonary arterial pressure were measured using a transducer (Nihon Kohden P-50, Tokyo) with a pressure monitor (Nihon Kohden OMP-6200); the zero pressure standard was taken at the left chest mid-ventricular level; direct systolic and diastolic blood pressures were measured using the pressure monitor system; and cardiac output was measured using the thermodilution method. To avoid dilution with flushing fluid, 2 ml of the fluid was drawn from the Swan-Ganz catheter prior to each blood sample collection.

In addition, to investigate whether ANF is adequately secreted from the right side of the heart in AMI, we compared plasma levels in the pulmonary artery to those at a peripheral site in 56 patients (group A, n=18; group B, n=38).
Plasma ANF measurement: Plasma ANF levels were determined by extraction and radioimmunoassay as reported elsewhere. In brief, blood samples were collected into tubes containing proteolytic enzyme inhibitors (EDTA 10^-5 M, phenylmethylsulfonyl fluoride 10^-5 M, pepstatin 5 x 10^-6 M; final concentrations). After centrifugation, the plasma obtained was stored at -80°C until extraction was carried out using Sep-Pak C-18 cartridges (Waters Associates, Milford, MA). The extracts were measured in duplicate using an alpha-human ANF radioimmunoassay kit (Amersham International, Buckinghamshire, UK). The interval between the blood sampling and the radioimmunoassay was less than 3 months. Intra- and inter-assay variability were 7.9% and 13.0%, respectively.

Statistical analysis: The results are given as mean ± SEM. Paired or unpaired Student’s t-tests were used to test for statistical significance. Correlation analyses were performed by using the method of least squares. Differences in sex or site of infarction between the 2 groups were analyzed by the chi-square method. All p values quoted were two-tailed. P<0.05 was taken as the level of significance.

Table I. Clinical Characteristics and Hemodynamic Parameters in Patients with Acute Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=41)</th>
<th>Group B (n=77)</th>
<th>Difference between groups</th>
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</thead>
<tbody>
<tr>
<td>Previous history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>—</td>
<td>6</td>
<td></td>
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<tr>
<td>Old myocardial infarction</td>
<td>—</td>
<td>18</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>—</td>
<td>62</td>
<td></td>
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<tr>
<td>Chronic renal failure</td>
<td>—</td>
<td>14</td>
<td></td>
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<tr>
<td>Clinical characteristics</td>
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<td></td>
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<tr>
<td>Age (years)</td>
<td>60±2</td>
<td>63±1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Male/Female</td>
<td>30/11</td>
<td>58/19</td>
<td>N.S.</td>
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<tr>
<td>Site of infarction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>anterior</td>
<td>24</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>inferior</td>
<td>14</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>subendomyocardium</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase (IU/ml)</td>
<td>3184±270</td>
<td>3177±281</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hemodynamic parameters</td>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
<td>120±2</td>
<td>127±2</td>
<td>p&lt;0.05</td>
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<td></td>
<td>3.1±0.1</td>
<td>2.8±0.1</td>
<td>p&lt;0.05</td>
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</tbody>
</table>
Results

Clinical characteristics, hemodynamic parameters, and plasma ANF levels (Table I and Fig. 1): The mean age of group A was younger than that of group B, but the difference was not significant. The sex, site of infarction, and peak creatine kinase levels between the 2 groups were not significantly different. No significant difference in heart rate was observed between the 2 groups, but systolic systemic blood pressure was higher in group B than in group A (p<0.05). Although the cardiac index was lower in group B than in group A (p<0.05), atrial pressures were not significantly different. However, the mean plasma ANF level was significantly higher in group B than in group A (76±6 vs. 185±26 pg/ml; p<0.01; Fig. 1). No significant relationship was found between the plasma ANF level and the peak value for creatine kinase in either group. No significant differences in plasma levels were observed between anterior and inferior infarctions.

Relationship between plasma ANF level and hemodynamic parameters (Figs. 2 and 3): In group A, no significant relationship was ob-

![Graph showing comparison of heart rate (HR), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and plasma atrial natriuretic factor (ANF) between groups A and B. Patients with no history of valvular heart disease, previous myocardial infarction, hypertension, and/or renal failure were classified as group A (A), while those with a history of these conditions were classified as group B (B).](image-url)
served between measured hemodynamic parameters and plasma ANF levels (Figs. 2A, 3A). However, in group B, the plasma levels were correlated with left atrial pressure estimated from pulmonary capillary wedge pressure (r = 0.54, p < 0.001; Fig. 2B). Weaker relationships were also observed between plasma ANF levels and both right atrial pressure (r = 0.29, p < 0.05; Fig. 3B) and cardiac index (r = −0.28, p < 0.05; data not shown).

Comparison between pulmonary and peripheral plasma ANF levels (Fig. 4): In order to determine whether the hormone is secreted from the right side of the heart, plasma ANF in the pulmonary artery, which may be directly influenced by atrial secretion of the hormone via the coronary sinus, was compared to that from a peripheral site in 56 of the 118 patients.
Fig. 4. Comparison between plasma atrial natriuretic factor (ANF) concentration obtained from the pulmonary artery (PA) and that from the peripheral site (Peri) in patients with acute myocardial infarction. For a description of groups A (A) and B (B), see Fig. 1. Open circles with dotted lines denote cases with a paradoxical rise of more than 10 pg/ml at plasma ANF concentration in the peripheral site compared to that in the pulmonary artery. † denotes patients who succumbed.

(group A, n=18; group B, n=38). In group A, the mean level obtained from the pulmonary artery was significantly higher than that from the peripheral site (111 ± 17 vs. 85 ± 11 pg/ml; p<0.05), which suggests that ANF is secreted from the right side of the heart. However, the difference between the two sampling sites was not significant in group B (197 ± 45 vs. 168 ± 33 pg/ml; N.S.). Eight cases among the 56 patients died in this admission. The causes of death were free wall rupture in 1 patient, and low-output heart failure with progressive renal impairment in the remaining 7. Seven of the 8 expired cases (87%) showed a rise in peripheral plasma levels of more than 150 pg/ml.
DISCUSSION

We have demonstrated a significant but weak relationship between plasma ANF and pulmonary capillary wedge pressure in myocardial patients with a history of chronic heart disease or renal disease (group B). This observation may be consistent with previous reports of a significant relationship between plasma ANF and atrial pressure in patients with a wide variety of chronic heart diseases.6)-10) However, we found no such correlation in patients with simple myocardial infarction (group A). Moreover, although no significant difference in atrial pressure after the infarction was found between the 2 groups, the plasma ANF level was significantly lower in group A than in group B. These findings are valid regardless of the administration of diuretics or calcium channel blockers which may decrease the release of the hormone from the heart, because such drugs were given to both groups. It is also unlikely that streptokinase acts as a venodilator, reducing atrial pressure and hence plasma ANF secretion,18) because no patients who had been treated with streptokinase were included in this study. Our results suggest that pressure-dependent release of the hormone may not function properly in patients with fresh myocardial infarction who have no history of chronic heart disease or renal disease.

Although the reason for this poor correlation between ANF release and atrial pressure in AMI is not yet clear, Tan et al have demonstrated a transient decrease in plasma level of the hormone 6 hours after admission in patients who were treated successfully after AMI.15) These investigators suggested that there may be a very early increase in secretion of the hormone after the onset of myocardial infarction and a subsequent depletion of ANF storage during the early phase of this condition.15) The hemodynamic results of the present study support this hypothesis, and indicate that this phenomenon might be observed particularly in patients with no preceding hypervolemia. This possible ANF exhaustion may, in part, contribute to the lack of correlation between ANF release and atrial pressure in cases with sudden cardiac dysfunction whose previous basal atrial secretion and storage of the hormone might have been normal.20),21) Conversely, since the atrial content of the hormone during hypervolemic states such as chronic heart failure or renal disease has been reported to be augmented in humans,20),21) atrial secretion in patients with myocardial infarction who had a history characterized by elevated atrial pressure or hypervolemia (group B) may possibly be preserved in the face of a sudden release of the peptide.

Although the clinical relevance of this finding has yet to be clarified, the relative impairment of ANF secretion may be one of the causes of water and
sodium retention in cases of myocardial infarction even in the absence of pulmonary congestion. Moreover, in view of the finding that elevated plasma ANF increases the coronary collateral blood flow in experimental animals and humans, the attenuation of ANF secretion could be one of the harmful factors in patients with coronary insufficiency.

We have also demonstrated that the ANF concentration in pulmonary arterial plasma was higher than that in peripheral plasma in group A. This observation suggests indirectly that for these patients the hormone may be secreted mainly from the right side of the heart, despite the attenuation of pressure-dependent ANF secretion. However, we found no significant difference in the plasma levels between these two sampling sites in group B patients, all of whom had a long history of cardiovascular and/or renal disease. In 10 of the 38 group B patients, plasma ANF levels at the peripheral site were apparently higher than those in the pulmonary artery. Although this phenomenon seems paradoxical, an examination of the literature indicates that similar results have been found in patients with myocardial infarction or congenital cardiac malformation.

This phenomenon may be explained by the possibility that in patients with myocardial infarction, especially those with histories characterized by elevated atrial pressure or chronic volume overload, the hormone is secreted not only from the right side of the heart via the coronary sinus but also from one or more additional unknown sites. Since cardiac ventricles have been reported as being capable of producing ANF as much or the same as the atrium in patients with congestive heart failure, it seems possible that release of ANF from the left ventricle muscle, including the necrotic tissue, directly into the left ventricle cavity may occur in this disease condition. Thus, the release of the hormone from the left ventricle may indicate massive necrosis caused by myocardial infarction. It is therefore likely that the paradoxical rise would tend to be observed in patients with a poor prognosis.

In conclusion, we have found that secretion of ANF is lower in patients with a new onset of myocardial infarction, and particularly those with no history of cardiac or renal disease. In the expired patients in this study, plasma ANF levels at the peripheral site were more than 150 pg/ml, and were higher than levels in the pulmonary artery. Although further studies are needed, the measurement of peripheral plasma ANF, as well as comparison of plasma levels between the two sampling sites, might be valuable predictors for prognosis in patients with myocardial infarction.
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