TIME COURSE OF RELEASED ATRIAL NATRIURETIC PEPTIDE
AFTER ACUTE MYOCARDIAL INFARCTION

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The plasma concentration of atrial natriuretic peptide (pANP) was investigated at fixed times during 48h following the onset of an initial attack of mild acute myocardial infarction (AMI) in 11 patients. Six hours after onset, the mean pANP was elevated, but 6h later pANP had returned to the baseline level. Forty-eight hours after onset the mean pANP increased again. Thus, the curve of the time course of pANP consisted of 2 peaks separated by a dip. Six hours after onset, systemic hemodynamics and humor factors were measured in 27 patients. At 48h they were measured in 14 patients. The late elevation of pANP correlated with mean pulmonary arterial wedge pressure (r=0.63, n=14, p<0.05), while the early elevation of pANP did not (r=0.31, n=27, n.s.). The early elevation of pANP correlated with plasma concentrations of both noradrenaline (r=0.55, n=27, p<0.01) and creatine phosphokinase (r=0.54, n=27, p<0.01). In addition, noradrenaline levels positively correlated with mean pulmonary arterial wedge pressure (r=0.38, n=27, p<0.05). The cause of the early elevation of pANP in AMI is unclear, but it is suggested that injury to myocardium and activated sympathetic nerve activity may be responsible in part.

THE plasma concentration of atrial natriuretic peptide (pANP) has been reported to be elevated in patients with acute myocardial infarction (AMI) \(^1\)–\(^7\). In some instances AMI is complicated by congestive heart failure and/or disturbances in cardiac rhythm which may accelerate the release of atrial natriuretic peptide (ANP) \(^1\)–\(^4\). However, some investigators have reported patients without such complications whose pANP was increased. Whether or not a link with complications exists, the time course of changes in pANP has been controversial. Observations by Svanegaard et al. \(^6\) seem to be reasonable; they showed that ANP was released soon after the onset of AMI and that the initial elevation of pANP was immediately followed by an early decrease. Later, pANP recovered or increased again. We tried to elucidate the time course of pANP in patients with uncomplicated AMI, and then to investigate the reasons behind but time course if one existed.

SUBJECTS AND METHODS

Twenty-seven patients with acute chest pain over 30 min were diagnosed as having an AMI attack on the basis of evolving ST changes on electrocardiograms, elevated creatinine phosphokinase concentrations (CPK) and elevation of the MB isozyme level. These patients, 24 men and 3 women, aged 34 to 84 years (60±12; mean±SD) were admitted to our hospital within 6h of

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Fig. 1. Time course of plasma atrial natriuretic peptide (ANP) levels after the onset of AMI. Values are mean ± ISD.

Fig. 2. Time course of mean pulmonary arterial wedge pressure (PAW), mean pulmonary arterial pressure (mPA) and central venous pressure (CVP) after the onset of AMI. Values are mean ± ISD.

the onset of symptoms. The attack of AMI in all cases was the initial one; 16 cases were of anterior AMI, 10 of inferior AMI, and 1 of subendocardial AMI. There were no severe complications of AMI, except for slightly elevated mean pulmonary arterial wedge pressure (Forrester subset I; 24 cases, subset II; 3 cases). All patients received conventional treatment with nitrates, calcium antagonists, or antiarrhythmic drugs, depending on the clinical signs. However, those who received diuretics, pressor substances or acute thrombolytic therapy were not included in the present study. At 6h after the onset of AMI, the number of evaluable patients was 27. At 48h the number was 14. Thirteen patients were excluded at 12h because they were given diuretics and/or pressor substances. In 3 patients samples at 12h and at 24h were missed, but at 48h the determination of hemodynamic studies and blood samples were possible.

* P < 0.05
** P < 0.01
n = 11
(mean ± ISD)
Hemodynamic studies using the Swan-Ganz cardiac catheter, such as measurement of cardiac index (CI) by the thermodilution method, were performed; mean pulmonary arterial pressure (mPA), mean pulmonary arterial wedge pressure (PAW), central venous pressure (CVP), and CI were monitored. Mean blood pressure (mBP) was measured by a fluid-filled catheter inserted into femoral artery. Heart rate (HR) was monitored by electrocardiography. Blood samples for determination of plasma concentrations of ANP, adrenaline (pAD), noradrenaline (pNA), aldosterone (pAlD), plasma renin activity (PRA) and creatinine phosphokinase (CPK) were drawn from the femoral artery. Hemodynamic observations and determinations of blood samples were performed 4 times after the onset of AMI (at 6h, 12h, 24h, 48h).

The value of pANP was measured by the radioimmunoassay (RIA) method according to Marumo et al. In short, the assay buffer was 0.01 M phosphate buffer, pH 7.4 containing 0.14 M NaCl, 0.11 M K₂EDTA, 0.02 M glycine, 0.01 M ε-aminocaproic acid, 0.01 M sodium azide, and 11 mg/ml inactivated human serum albumin. 0.01 ml of samples or authentic standard α-hANP were each mixed with 0.1 ml of rabbit anti-ANP serum (1:80,000 diluted so as to produce in combined form α-ANP (1–28)-thyroglobulin as an immunogen) and 0.1 ml of the assay buffer. After allowing the mixture to stand for 20h at 4°C, 0.05 ml of [¹²⁵I]-α-hANP (Amersham, specific activity of 74 TBq/mmol 120 pg/ml) was added to the mixture, which was followed further by incubation for 24h at 4°C. The bound and free ligands were separated by addition of 0.5 ml of the assay buffer containing 10 μl of goat anti-rabbit γ-globulin, 1 μl of normal rabbit serum and 5% polyethylene glycol (mean Mr, 7500). The amount of pANP in each sample was read from a standard curve drawn using the values obtained from the
assays or the α-hANP standard. Normal values in 124 (62 males and 62 females) subjects who were normotensive and clinically having no illness, ranged from 10 to 60 pg/ml (31.7 ± 12.0 pg/ml, mean ± SD)\(^6\).

The values of pAD and pNA were measured by the HPLC-THI method and pAld and PRA by the RIA method. The normal range of pAD was less than 120 pg/ml, and that of pNA was 40–350 pg/ml in our laboratory.

**Statistical Analysis:** Correlations were calculated by the least squares method. All values were expressed as mean ± SD, and the differences in means were assessed by repeated analysis of variance. Differences were considered statistically significant if a p value was less than 0.05.

**RESULTS**

*Time course of pANP levels after the onset of AMI*

Fig. 1 shows the time course of pANP levels. At 6h after the onset of AMI, the mean pANP concentration (103 ± 39 pg/ml) was considerably higher than the upper value of normal in our laboratory. Thereafter, pANP levels significantly decreased until 24h after the onset; pANP level at 12h was 67 ± 10 (p<0.05 vs at 6h) and that at 24h was 56 ± 13 pg/ml (p<0.01 vs at 6h). However, the mean pANP concentration at 48h was significantly increased again; the level (80 ± 30 pg/ml) was higher than that at 24h (p<0.05 vs at 48h). Therefore, the curve of the time course of pANP fundamentally consisted of 2 peaks with 1 dip between them.

*Changes in hemodynamics caused by AMI, CPK and their correlations with the increased levels of pANP*

The mean values of PAW (12 ± 6 mmHg), CVP (5 ± 3 mmHg), and mPA (18 ± 7 mmHg) were greatest at 6h after the onset, and decreased gradually with the time course (Fig. 2). All the pressure parameters were the lowest at 48h (p<0.05 vs at 6h). The relationship between pANP levels and the pressure parameters were investigated at 6h when the early elevation of pANP was shown, and at 48h when the late elevation of pANP was revealed. At 6h, no pressure parameter correlated with the levels of pANP. However at 48h all except CVP showed significant correlations (Fig. 3, 4); PAW correlated with pANP (r=0.63, p<0.05), and mPA correlated with pANP (r=0.61, p<0.05). Thus, increased left atrial pressure is responsible for the late elevation of pANP, but not for the early elevation of pANP. Therefore, the relationship between myocardial injury and the release of ANP was investigated. As shown in Fig. 5, peak CPK was correlated with pANP 6h after the onset (r=0.54, p<0.01), but not 24h after the onset.

*Changes in the other humoral factors and the elevation of pANP*

Fig. 6 shows the time course of pAD. The mean pAD 6h after the onset of AMI (203 ± 148 pg/ml) was higher than the upper value of the normal range in our laboratory. Thereafter, pAD levels were decreased, and
each mean value at 12, 24 and 48h was within normal limits. The mean value at 6h was significantly greater than each of the later values (p<0.01 vs at 12h, p<0.05 vs at 24h and at 48h). Fig. 7 shows the time course of pNA. The mean pNA at 6h after the onset (479±230 pg/ml) was higher than the upper value of the normal range in our laboratory. The elevation of mean values of pNA persisted until 48h after the onset of AMI. The relationship between pANP and the humoral factors such as pAD, pNA and pAld was investigated at the time of early elevation of pANP (6h). The values of pAD were not correlated with pANP (r=0.36, n.s.). The values of pNA were significantly correlated with pANP, as shown in Fig. 8 (r=0.55, p<.01). PRA and pAld were not correlated with pANP. Additionally, pAD and pNA also correlated with severities of AMI represented by peak CPK or hemodynamics. At the time of early elevation of pANP, pNA was correlated with peak CPK (r=0.50, p<0.01), with HR (r=0.52, p<0.01) and PAW (r=0.38, p<0.05), while pAD correlated with peak CPK (r=0.55, p<0.01), HR (r=0.66, p<0.01), and mBP (r=0.40, p<0.01).

DISCUSSION

There are several reports concerning the time course of pANP in AMI. Wencker et al² found that pANP increased in the early stage after the onset of AMI, decreased within 3—8h and increased again within 12—24h in 4 patients with AMI without heart failure. We have presented similar results in this study. Wencker et al² explained the early decrease and the late elevation of pANP as follows: immediately after the onset of AMI the release of a large quantity of ANP will cause depletio of atrial storage granules, consequently the release of ANP is decreased and a dip is made in the time course of changes in ANP. Subsequently, ANP synthesis is increased and ANP storage is replenished. pANP consequently released again and the late elevation occurs. Therefore, the ANP system seems to have limitations on release in order to protect the body immediately after the onset of AMI. This explanation was also supported by Tan et al§ who showed similar results to ours in 38 patients with AMI.

Some reports concern the mechanisms of the secretory stimulation of ANP, but the most important factor is considered to be atrial wall stretch associated with atrial pressure. However, the secretion of ANP is known to be accelerated by various other factors such as hypoxia³, atrial tachycardia or rapid atrial pacing¹⁰ sympathetic agents¹¹,¹² vasopressin¹¹,¹³ angiotensin II¹⁴. On the other hand, the onset of AMI is associated with myocardial ischemia or injury and changes in various humoral factors, including many factors accelerating the release of ANP other than the extension of atrium. In this study we found no correlation between pANP and PAW and between pANP and mPA 6h after the onset of AMI. However, significant correlations were observed between pANP and PAW and between pANP and mPA at 48h. Tan et al§ did not observe a significant correlation between pANP and left ventricular ejection fraction immediately after the admission but did observe a correlation at 48h, suggesting drawing a conclusion that factors other than atrial pressure took part in the release of ANP at the initial pANP increase. Accordingly, much interest has been given to other factors which induce elevated pANP immediately after the onset of AMI.

Firstly, myocardial ischemia or injury may be responsible for the early elevation of pANP. regarding myocardial ischemia and injury, secreted ANP granules have recently been discovered in myocardial cells¹⁵. Therefore pANP may increase due to injury to the ventricular muscle caused by AMI. Ngo et al⁷ made a comparison of pANP between patients with angina pectoris without myocardial infarction and these with AMI. These authors reported a positive correlation between peak CPK and peak ANP of patients with AMI and suggested that pANP increased along with the increase of CPK (r=0.475, p<0.05). On the other hand, they reported that in patients with angina pectoris, pANP was not increased at the time of chest pain. In this study we also found a significant correlation between peak CPK and pANP at 6h. From these results it is presumed that release in pANP due to injury of the myocardial cells may be a factor for initial increased pANP.
Secondly humoral factors, particularly stimulated catecholamine, may have some effect. Bretel et al.\textsuperscript{10} reported that pAD and pNA increased rapidly after the onset of AMI in patients without complications, that pAD decreased immediately after the increase and that pNA decreased gradually. We showed a similar time course of pAD and pNA after the onset of AMI, but in any event, increase of catecholamine was observed after the onset of AMI. However, it is not clear whether catecholamine itself causes an increase of pANP. Matsubara et al.\textsuperscript{11} applied ergometer loading to patients with myocardial infarction at chronic phase and studied the relation of pANP with atrial pressure and catecholamine. These authors concluded that pANP was correlated with atrial pressure but not with catecholamine. Uehlinger et al.\textsuperscript{12} observed changes in pANP during intravenous injection of noradrenaline and during intravenous injection of sodium nitroprusside in normal subjects. They reported that noradrenaline itself increased pANP but time increase was blunted by both injections. This finding suggests that noradrenaline may stimulate ANP secretion, but the action of noradrenaline to stimulate ANP secretion may not be strong compared with atrial pressure. In this study we obtained significant correlations between pNA and pANP and between pNA and peak CPK. Therefore we can not rule out the possibility of the catecholamine on elevated pANP soon after AMI.

The change of pANP immediately after the onset of AMI is of great interest. In particular, injury to myocardial cells and increased pNA suggested to be important in the initial increase of pANP became no correlation was observed between pANP and atrial pressure.

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