Clinical Studies

Relationship between Plasma Atrial Natriuretic Peptide Concentration and Atrial Pressure in Acute and Chronic Heart Failure

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SUMMARY

Several reports have demonstrated a close correlation between plasma atrial natriuretic peptide (ANP) concentration and atrial pressure in stable heart diseases. However, few studies have investigated whether plasma ANP concentration is a noninvasive indicator of hemodynamic parameters during the treatment of heart failure. Thus, we have studied the relationship between peripheral plasma ANP concentration and concurrent hemodynamic variables during the treatment of heart failure, and, in order to determine whether secretion of ANP is stimulated in this disease condition, we compared the plasma ANP concentration in the pulmonary artery with that in the peripheral veins.

Studies were performed in each of 9 patients with acute heart failure due to myocardial infarction (Group A) or chronic heart failure (Group B), who were matched as closely as possible for treatment, age, sex and cardiac output. In group A, no significant correlation was found between plasma ANP levels and any measured hemodynamic variables. In group B, peripheral plasma ANP concentrations were significantly correlated with left atrial pressure ($r=0.82$, $p<0.01$), but not with right atrial pressure ($r=0.56$, $p>0.05$). Furthermore, in group B ANP levels in pulmonary arterial plasma were consistently higher than those in peripheral venous plasma, whereas in group A the opposite was observed in expired cases.

These results suggest that measurement of peripheral plasma ANP is a useful noninvasive method for estimating left atrial pressure during the treatment of chronic heart failure. However, plasma ANP concentration may not be a valid means of estimating hemodynamic parameters in acute heart failure due to myocardial infarction. In such cases, the increased secretion of ANP was not obvious, and there may be other factors, in addition to atrial pressure, that regulate cardiac secretion of ANP.

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THE secretion of atrial natriuretic peptide (ANP) has been reported from animal studies to be stimulated by atrial wall stretch.[1),2)] In a wide variety of heart diseases, the plasma concentration of ANP is reported to rise in proportion to the severity of heart failure,[3),4)] and to be significantly correlated with the atrial pressures observed at the time of diagnostic cardiac catheterization.[5)-8)] These findings imply that the measurement of plasma ANP level would be a noninvasive indicator of atrial pressure in heart disease.[8)-10)] However, recent reports have shown that there is no significant correlation between plasma ANP levels and hemodynamic parameters in severe heart failure[11),12)] and in acute myocardial infarction.[13),14)]

In view of this, we considered it important to examine the relationship between plasma ANP levels and hemodynamic parameters during the treatment of heart failure in order to establish the hypothesis that measurement of plasma ANP is a noninvasive method for monitoring atrial pressure. However, because most recent studies confine themselves to the time the patient's condition is stable, with discontinuation of vasoactive drugs at the time of cardiac catheterization, we have studied the relationship between plasma ANP concentrations and hemodynamic parameters after the treatment of acute and chronic heart failure.

Furthermore, to determine whether the secretion of ANP from the heart is increased in these disease conditions, we examined the difference in ANP concentration between pulmonary arterial and peripheral venous plasma.

Patients and Methods

Patients: All patients were admitted to our University Hospital CCU and gave informed consent prior to participation in this study, which had been approved by our University's Hospital Ethical Committee. A clinical description of these patients is given in Table I. All patients showed moderate to severe pulmonary congestion on chest x ray which was taken immediately after admission.

Nine patients (age 52–83, mean 66.9) with acute myocardial infarction (MI), having been admitted 6 to 24 hours after the onset of symptoms, were designated group A. These patients had no previous history of heart failure and no peripheral edema. The diagnosis of acute MI was based on a history of typical chest pain, typical electrocardiographic criteria and an increased serum level of creatinine phosphokinase. Group B consisted of 9 patients

Table I. Clinical Details of Patients with Acute Heart Failure Due to Myocardial Infarction (Group A) and Patients with Chronic Heart Failure (Group B)

Case	Sex and age	Diagnosis	Clinical severity	Cardiac rhythm	Therapy
Croup A					
1	F 77	anterior MI	Killip's 2	sinus	c, d, e
2	M52	anterior MI	Killip's 2	sinus	a, c, e
3	M60	anterior MI	Killip's 4	sinus	a, b, c, d, e
4	M67	anterior MI	Killip's 2	sinus	b, c, e
5	M68	anterior MI	Killip's 2	sinus	a, b, c
6†	M76	anterior MI	Killip's 3	sinus	a, c, d, e
7†	F 83	inferior MI	Killip's 4	sinus	a, b, d, e
8	M84	inferior MI	Killip's 2	af	a, b, c, e
9	M62	inferior MI	Killip's 2	sinus	b, c, d
Mean±SEM	66.9±3.6				
Group B					
10	F 64	old MI	NYHA 4	sinus	b, c, e
11	F 84	old MI	NYHA 4	af	a, c, d, e
12	M64	old MI	NYHA 4	sinus	b, d, e
13	F 68	ASR	NYHA 4	af	a, b
14	M49	AR	NYHA 4	sinus	a, b, c
15	M59	ASR	NYHA 3	sinus	a, d, e
16	M59	MR	NYHA 4	sinus	a, b, d, e
17	M66	ASR	NYHA 4	sinus	a, b, c, d
18	M66	AR	NYHA 3	sinus	a, b, c, e
Mean±SEM	64.2±3.0				

MI=myocardial infarction; ASR=aortic stenosis and regurgitation; AR=aortic regurgitation; MR=mitral regurgitation; NYHA=New York Heart Association class; af=atrial fibrillation; Therapy a=digoxin; b=furosemide; c=nifedipine; d=dobutamine; e=nitroglycerin.
† denotes expired cases.

with heart failure due to chronic heart disease of at least one year's duration (age 49–84, mean 64.2). The etiology of the heart failure in 6 of these patients was valvular heart disease, and in the remaining 3 was old myocardial infarction. These patients had a long-standing history of cardiac impairment which included dyspnea, ankle swelling and effort-related fatigue. Patients were excluded from the study if any complications had occurred, and specifically if they had had renal failure, frequent premature beats, hepatic disturbance, or right ventricular infarction. Two patients with acute MI (patients 6 and 7) died 1 to 2 weeks after the study from refractory heart failure with frequent anginal attacks.

Hemodynamic evaluation and sampling: A Swan-Ganz triple lumen catheter was inserted into the pulmonary artery in all of the patients. Each received

treatment for heart failure with 2 or more of the following drugs (Table I): digoxin (0.125–0.25 mg/day; intravenously), furosemide (10–60 mg/day; intravenously), nifedipine (40–60 mg/day; orally), dobutamine (220–360 mg/day; intravenously) and nitroglycerin (50–95 mg/day; intravenously). All patients routinely received oxygen inhalation and lidocaine drip infusion (60–100 mg/min).

In group A, the interval between the last administration of sedative or analgesic and the commencement of the study was at least 2 hours. Within 10 hours after the initiation of therapy, hemodynamic evaluations were made under stable clinical conditions. On that occasion, heart rate, systemic blood pressure, right atrial pressure, pulmonary capillary wedge pressure, and cardiac output were measured. Within 5 min after the hemodynamic measurements, 7 ml blood samples were taken simultaneously from both the antecubital vein by venipuncture and the pulmonary artery through the catheter to determine the plasma ANP levels. Systolic and diastolic blood pressures were measured with a standard sphygmomanometer. Intracardiac pressures were recorded on a strip-chart as both phasic and electronically dampened mean pressure. The zero pressure reference level was taken at left chest mid-ventricular level. Cardiac output was determined in triplicate by the thermal dilution technique.

Plasma ANP concentration: Plasma ANP concentration was determined using radioimmunoassay (RIA) after extraction procedures.[15] In brief, blood samples were collected into tubes containing proteolytic enzyme inhibitors (in the final concentrations: EDTA 10^{-5} M, phenylmethylsulfonyl fluoride 10^{-5} M, pepstatin 5×10^{-6} M), and were immediately centrifuged at 4°C and stored at −80°C until assay. The peptide extraction was performed using a Sep-Pak C-18 cartridge (Waters Associates, Milfold, MA).

The extracts were reconstituted in assay buffer and subjected to RIA in duplicate, based on alpha-human ANP antiserum and I^{125} labeled alpha-human ANP (Amersham International, Buckinghamshire, UK), with alpha-human ANP standard (Peptide Institute, Osaka, Japan). Antibody-bound material was separated from the peptide by the dextran-charcoal technique.

Statistical analysis: 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. All p values quoted were two-tailed.

Results

Eighteen patients with congestive heart failure were examined during

Table II. Hemodynamic, Biochemical and Endocrine Data from Patients with Acute Heart Failure Due to Myocardial Infarction (Group A) and Patients with Chronic Heart Failure (Group B)

	Group A (n=9)	Group B (n=9)	Difference between groups
Hemodynamic data			
Systolic blood pressure (mmHg)	121.9±3.3	124.1±4.8	N.S.
Heart rate (beats/min)	89.8±6.3	84.2±6.5	N.S.
Cardiac index (l/min/m^2)	2.8±0.1	3.0±0.2	N.S.
Right atrial pressure (mmHg)	3.9±0.7	3.7±0.7	N.S.
Pulmonary capillary wedge pressure (mmHg)	10.0±1.6	15.2±2.4	N.S.
Biochemical data			
Serum sodium (mEq/l)	142.2±1.4	140.5±1.2	N.S.
Serum potassium (mEq/l)	3.9±0.1	3.9±0.1	N.S.
Serum creatinine (mg/dl)	0.9±0.1	1.0±0.1	N.S.
Plasma ANP concentration			
Pulmonary artery (pg/ml)	114.8±21.9	339.3±71.7	$p<0.05$
Peripheral vein (pg/ml)	109.9±22.1	284.3±75.4	$p<0.01$

ANP=atrial natriuretic peptide; N.S.=not significant.

treatment for heart failure (Table I). Sex and age were not significantly different between groups A and B. Atrial fibrillation was found in 1 case in group A, and in 2 cases in group B. There was no significant difference in the administration of digoxin, diuretics, nifedipine, dobutamine or nitroglycerin between the groups.

The corresponding values for hemodynamic variables are summarized in Table II. Mean systolic blood pressures were 121.9±3.3 mmHg in group A and 124.1±4.8 mmHg in group B, and were thus not significantly different. Heart rate was also not significantly different between the groups. Because several hours had elapsed since the initiation of therapy, the mean recorded atrial pressure and cardiac index values might have been subnormal. The difference in mean cardiac index between the 2 groups was not significant (2.8±0.1 versus 3.0±0.2 l/min/m^2). Right atrial pressure did not differ significantly between the groups (3.9±0.7 versus 3.7±0.7 mmHg). Left atrial pressure (estimated from pulmonary capillary wedge pressure) tended to be lower in group A than in group B, but the difference did not achieve statistical significance (10.0±1.6 versus 15.2±2.4 mmHg; N.S.). Serum sodium, potassium and creatinine levels were not significantly different between the 2 groups (Table II).

Plasma ANP concentration was significantly lower in group A than in group B (pulmonary arterial plasma ANP; 114.8±21.9 versus 339.3±71.7

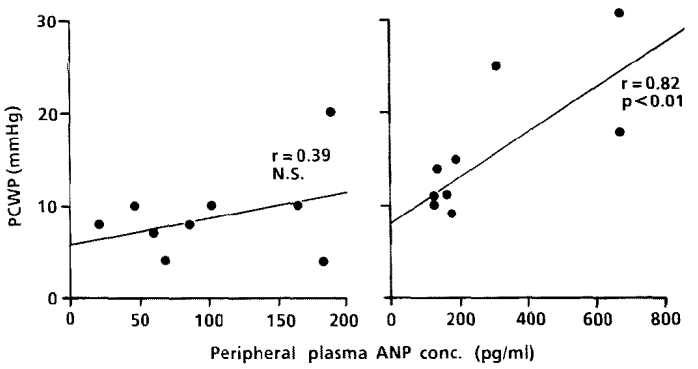

Fig. 1. Relationship between peripheral venous ANP concentration (Peripheral plasma ANP conc.) and pulmonary arterial wedge pressure (PCWP) in patients with acute heart failure due to myocardial infarction (left panel) and chronic heart failure (right panel).

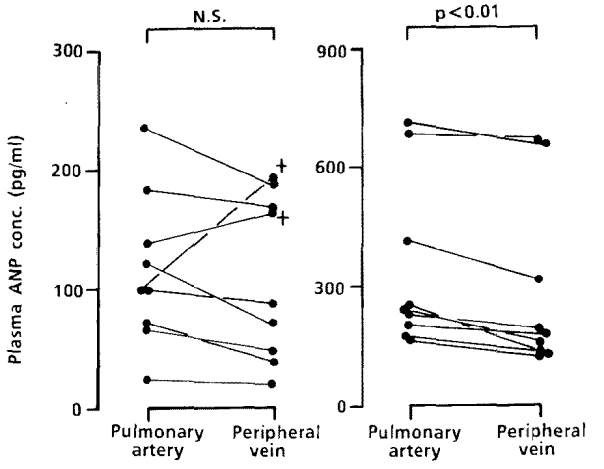

Fig. 2. Comparison of plasma concentration of ANP in samples from pulmonary artery and from peripheral vein in patients with acute heart failure due to myocardial infarction (left panel) and chronic heart failure (right panel). † denotes samples from expired cases (patients 6 and 7).

pg/ml: peripheral venous plasma ANP; 109.9±22.1 versus 284.3±75.4 pg/ml: Table II). The level of peripheral venous plasma ANP was significantly higher in both heart failure groups ($p<0.001$) than in normal supine subjects (28.8±3.9 pg/ml, $n=17$).

In group A, there was no significant correlation between peripheral venous plasma ANP level and either left atrial pressure ($r=0.39$, p=N.S.: Fig. 1 left) or right atrial pressure ($r=-0.07$, p=N.S.). In contrast, the peripheral venous ANP level in group B was significantly correlated with left

atrial pressure ($r=0.82$, $p<0.01$: Fig. 1 right), while a weaker correlation was found between plasma ANP level and right atrial pressure ($r=0.56$, N.S.). Heart rate, systemic blood pressure and cardiac index were not correlated with peripheral venous plasma ANP level in either group.

In group A, there was no significant difference between pulmonary arterial and venous plasma ANP concentrations (114.8 ± 21.9 versus 109.9 ± 22.1 pg/ml, p=N.S.: Fig. 2 left). Two patients from this group who died (patients 6 and 7) had a lower level of plasma ANP in the pulmonary artery than in the peripheral vein (patient 6; 100 versus 190 pg/ml: patient 7; 139 versus 165 pg/ml: Fig. 2 left). In group B, however, the plasma ANP concentration obtained from the pulmonary artery was consistently higher than that from the peripheral vein (339.3 ± 71.7 versus 284.3 ± 75.4 pg/ml, $p<0.01$: Fig. 2 right).

Discussion

We have demonstrated that plasma ANP levels in patients with chronic heart failure are correlated with left rather than right atrial pressure during treatment. Although several reports have indicated that peripheral venous plasma ANP levels are correlated more closely with right atrial pressure in stable heart diseases,[6)-8)] this is not a matter of complete agreement in severe heart failure[11),12),16)] and acute myocardial infarction.[13),14)]

Studies in normal rats and human beings have shown that there is a higher concentration of ANP in right atrial tissue than in left atrial tissue.[17),18)] However, no difference in concentration has been found in rats or in patients with congestive heart failure.[18),19)] Haass et al have indicated that there is an excellent correlation between plasma ANP concentration and left atrial dimension in valvular heart disease.[20)] Tsutamoto et al have recently reported that left ventricular end-diastolic pressure is closely correlated with plasma ANP levels in chronic left-sided heart failure.[10)] Furthermore, a significant decrease in plasma ANP concentration has been observed after a sudden fall in left atrial pressure without any decrease in right atrial pressure during percutaneous balloon mitral valvuloplasty.[21),22)] Our observations are consistent with the concept that changes in left atrial pressure are an important regulator of the release of the peptide from the heart, and suggest that plasma ANP levels may be a valid indicator of left atrial pressure during the treatment of chronic heart failure.

Heart failure due to MI is sometimes associated with hypovolemia as a consequence of vomiting, diaphoresis and anorexia. Furthermore, vasodilators and/or diuretics may be necessary to treat the impaired cardiac func-

tion. This type of heart failure showed lower atrial pressure than non-hypovolemic cases of chronic heart failure with the same cardiac output. We have demonstrated that plasma ANP levels were significantly lower under these conditions than in patients with chronic heart failure who were treated with the same kinds of vasoactive drugs and had equivalent cardiac outputs. These findings are valid despite the administration of calcium channel blockers which inhibit the release of ANP from the heart,[23] because such blockers were given to both groups.

Although this observation may be simply due to the lack of cases with elevated atrial pressures in group A, our study has shown that plasma ANP levels were not correlated with atrial pressures in patients with acute MI. Wencker et al have observed an unexplained decrease in plasma ANP levels several hours after the onset of MI, even though there were persistent signs of pulmonary congestion.[24] A similar observation was recently made by Tan et al,[14] and they indicated that the fall of plasma ANP level in MI may be due to the sudden elevation of intracardiac pressure rise causing an excessive release of the peptide up to depletion of atrial storage granules.[14] Furthermore, Naruse et al have reported that a decrease in coronary blood flow reduced ANP secretion in isolated animal hearts.[25] Therefore, our observations may indicate that the lower circulating level of ANP in group A is caused not only by a relative hypovolemia, but also by additional factors affecting the circulating level of ANP in acute MI.

We have observed that the ANP level in peripheral venous plasma was higher than that in pulmonary arterial plasma in the 2 patients who died. Although this phenomenon seems paradoxical, an examination of the literature on the relationships between peripheral venous plasma ANP levels and pulmonary or peripheral arterial plasma ANP levels indicates that similar results have been found in patients with heart disease.[26),27] The reasons for this could include the following possibilities: 1) acute events such as tachyarrhythmias might have occurred within the 5 min before the study, recognizing the half life of the peptide[28]; 2) ANP was secreted not only from the right side of the heart, but also from the lung[29] and the left ventricle[19),30] in heart failure. Although the present study cannot specify which of these is the cause, the first possibility is unlikely because hemodynamic changes and cardiac rhythm were monitored precisely in all subjects before and during the study.

In summary, ANP concentration in peripheral venous plasma was compared with measured hemodynamic variables, and with the concentration in pulmonary arterial plasma in patients with acute MI or chronic heart failure who were matched as closely as possible. These results suggest that the reli-

ability of peripheral venous plasma ANP as a indicator of atrial pressure is dependent on the causes of or states associated with heart failure, and that the secretion of ANP in acute MI may be lower than that in chronic heart failure.

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