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**First International Symposium
and Swiss Hypertension Workshop
on Atrial Natriuretic Peptides**

18-19 November 1985 Berne, Switzerland

Editors: Peter Weidmann
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**Journal of Hypertension
Supplement**

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Atrial Natriuretic Factor in Plasma of Patients with Arterial Hypertension, Heart Failure or Cirrhosis of the Liver

Rainer M. Arendt, Alexander L. Gerbes*, Detlef Ritter, Elisabeth Stangl, Peter Bach and Josef Zähringer

Since the discovery of the atrial natriuretic factor (ANF) an endocrine function has been attributed to the mammalian heart. This function may include definition of optimal conditions for efficient performance of the heart, e.g. by reduction of afterload in hypertension or of preload and afterload in heart failure. Plasma ANF levels were measured in various cardiovascular disease states and compared with those of controls and of patients with liver cirrhosis. Plasma ANF levels in hypertensive patients were sevenfold higher than in controls, and in patients with heart failure 40-fold higher than normal values. Small differences were detected between controls and patients with cirrhosis of the liver, in spite of the impaired renal sodium handling seen in cirrhotics. Plasma ANF levels were significantly correlated with haemodynamic parameters and were inversely related to the cardiac index. Treatment with an angiotensin converting enzyme inhibitor led to a significant decrease in plasma ANF levels in parallel with the haemodynamic improvement. Preliminary chromatographic analysis suggested differences in the structure of plasma ANF between normotensive and hypertensive subjects.

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Introduction

It has long been recognized that volume expansion increases the concentration of natriuretic agents in the plasma, enhances the $\text{Na}^+\text{K}^+\text{ATPase}$ inhibitory activity of plasma and causes vasoconstriction [1,2]. These changes are thought to be the result of a change in the concentration of one or more substances in the plasma, provisionally termed 'natriuretic hormone'.

Atrial natriuretic factors have now emerged as the first convincing candidates for the 'natriuretic hormone'. They comprise a family of naturally occurring peptides [2] with natriuretic and diuretic properties [3]. However, ANF does not influence $\text{Na}^+\text{K}^+\text{ATPase}$ activity [4] and causes a vasodilation [5,6], suggesting that natriuresis and $\text{Na}^+\text{K}^+\text{ATPase}$ inhibitory activity may not be caused by the same substance.

Atrial natriuretic factors are synthesized by atrial myocytes, stored in specific granules [7] and released into the circulation upon volume or pressure loading [8]. Their effects may be mediated at specific peripheral

binding sites following release into the systemic circulation [9]. By conventional criteria these polypeptides may be regarded as hormones, which implies that an endocrine function can be attributed to the mammalian heart. This endocrine function may include the definition of optimal conditions for efficient cardiac performance, e.g. by reduction of preload and afterload in heart failure or of afterload in hypertension.

By the combined use of a sensitive radio-immunoassay and a series of chromatographic techniques, we have recently been able to demonstrate the occurrence in human plasma of authentic α -ANF, the 28-amino-acid C-terminal portion of the human precursor hormone pre-pro-ANF [10].

To assess the possible role of this novel hormone in cardiovascular physiology and volume homeostasis, plasma levels of immunoreactive (ir) ANF were measured in patients with cardiovascular disease, before and after pharmacological intervention, and in patients with abnormal renal sodium handling due to cirrhosis of the liver.

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Methods

Radio-immunoassay

A radio-immunoassay was developed by conventional techniques, as described previously [10]. Briefly, a polyclonal antibody was raised against α -human (α -h) ANF (Nova Biochem, Switzerland), the 28-amino-acid residue portion of the human precursor-ANF. 125 I- α -human ANF was prepared by the chloramine T method. The final antibody dilution in the radio-immunoassay was 1:35 000. Separation of bound and free hormone following overnight incubation at 5°C was achieved by activated charcoal suspension.

Sample collection and plasma extraction

Peripheral blood was drawn into pre-cooled 20-ml syringes and immediately transferred to pre-cooled polystyrene tubes containing 500 KIU/ml aprotinin and 1 mg/ml sodium ethylenediaminetetracetic acid. Plasma was separated and stored at -70°C until extraction. Extraction was performed by adsorption to Amberlite XAD-2 adsorbent resin (particle size 0.3-1.0 mm; Serva, Heidelberg, Federal Republic of Germany) and adsorbed ANF was eluted with 55% acetonitrile in 0.1 mol/l acetic acid. The extraction recovery was 68% and was independent of the concentration in the range 6-200 fmol/ml; plasma values were not corrected for recovery. Eluates were lyophilized and either redissolved in buffer for radio-immunoassay or subjected to chromatographic analysis.

Chromatography

High performance gel permeation chromatography of plasma extracts was performed on a TSK-125 Bio Sil column (7.5 \times 600 mm; Bio Rad, Munich, Federal Republic of Germany) eluted with 0.09% trifluoroacetic acid containing 0.005 mol/l Na_2SO_4 plus 0.002 mol/l NaH_2PO_4 and 30% acetonitrile, as a solvent. The flow rate was 0.4 ml/min, and aliquots from column fractions were analysed for immunoreactive α -hANF. Thereafter immunoreactive peaks were re-chromatographed on a Waters C18 μ -Bondapak reverse-phase column (3.9 \times 300 mm) and fractions assayed for α -hANF immunoreactivity.

Patient characteristics

Blood was drawn from 41 normotensive control subjects who showed no evidence of cardiovascular, renal, pulmonary or gastrointestinal disease. Twenty-seven patients with essential hypertension were examined also; at the time of examination their mean blood pressure was 176 ± 4.1 (systolic) and 101 ± 3.5 (diastolic) mmHg. Thirteen hypertensive patients were either newly diagnosed or had discontinued their therapies. In addition, 14 patients with congestive heart failure [New York Heart Association (NYHA) stages II-IV] were studied also. Patients were hospitalized 1 week before catheterization of the heart and all medication was discontinued except for diuretics and digitalis. Measurements were taken before, immediately following and 6 months after institution of therapy with an angiotensin converting enzyme inhibitor (enalapril,

usually 2 \times 5 mg orally a day). Twenty patients with cirrhosis of the liver, confirmed by biochemical and histological examination, were investigated. Ascites was not evident in nine patients, moderate in five and severe in five. Ascitic patients were receiving spironolactone (100-400 mg orally a day). In five patients ANF measurements were reported after diuretic treatment had been discontinued for 4 days. All patients were on a hospital diet containing 150 mmol NaCl daily.

Experimental protocols were approved by the institutional committee on the ethics of human investigation.

Results

Plasma levels of irANF for various clinical conditions are given in Table 1. Hypertensive patients on average displayed a sevenfold increase in plasma irANF compared with normotensive controls. A subgroup of untreated patients with essential hypertension had comparably high levels.

Table 1. Plasma immunoreactivity of atrial natriuretic factor in various clinical conditions.

	Mean \pm s.e.m. (fmol/ml)
Normotensive controls (n = 41)	8.8 \pm 1.1
Hypertensive patients (n = 27)	62.2 \pm 16.8**
- untreated hypertension (n = 13; BP 188 \pm 6/103 \pm 4 mmHg)	51.0 \pm 20.0**
- treated hypertension, patients still hypertensive (n = 14; BP 168 \pm 5/100 \pm 5 mmHg)	73.0 \pm 27.0**
Patients with congestive failure heart (n = 14)	365 \pm 133**
Patients with cirrhosis of the liver (n = 19)	13.5 \pm 1.3*
Patients with pericardial tamponade (n = 4)	
- before puncture	34.2 \pm 24.7
- following puncture	297 \pm 215
Water immersion (n = 15)	
- before immersion	6.5 \pm 0.8
- during immersion	12.0 \pm 2.6 [†]
- following immersion	6.1 \pm 0.8

* $P < 0.02$; ** $P < 0.001$ (Student's unpaired t-test); [†] $P < 0.01$ (Wilcoxon matched pairs test); BP, blood pressure.

Patients with congestive heart failure (NYHA II-IV) displayed a 40-fold increase in plasma irANF. The relationship between the level of circulating irANF and cardiac performance was examined in more detail. Figure 1 shows plasma irANF levels plotted against mean right atrial pressure, mean pulmonary capillary wedge pressure and the cardiac index. Elevated plasma levels of irANF in patients with heart failure corresponded to increased atrial pressure and pulmonary capillary wedge pressure and were inversely related to the cardiac index. Haemodynamic parameters for patients with heart failure before and during treatment with the angiotensin converting enzyme inhibitor are given in Table 2. In parallel with the improvement in haemodynamic parameters, a statistically significant ($P < 0.02$, Wilcoxon paired-sample test) fall in plasma irANF to 43.8% of

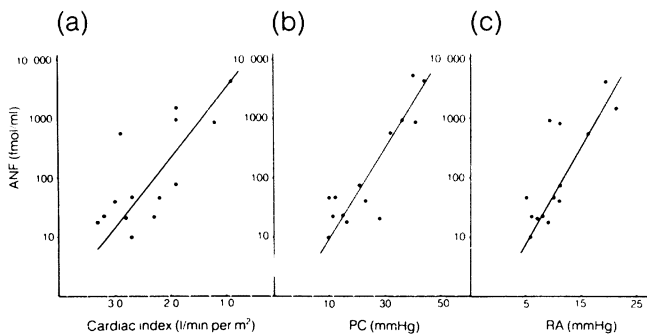


Fig. 1. Plasma levels of immunoreactive atrial natriuretic factor (ANF) are plotted versus (a) cardiac index ($r = -0.73$, $P < 0.01$), (b) mean pulmonary capillary wedge (PC) pressure ($r = 0.73$, $P < 0.01$) and (c) mean right atrial (RA) pressure ($r = 0.72$, $P < 0.01$) in patients with congestive heart failure.

Table 2. Haemodynamics and plasma levels of atrial natriuretic factor (ANF) in patients with heart failure before and during enalapril therapy ($n = 14$).

	Before enalapril	During enalapril
Haemodynamics		
PC (mmHg)	30 ± 3.9	15 ± 3.1
PAP (mmHg)	41 ± 4.1	29 ± 3.9
RA (mmHg)	12 ± 1.5	8 ± 1.3
MAP (mmHg)	104 ± 4.4	92 ± 3.6
CI (l/min per m ²)	2.0 ± 0.1	2.4 ± 0.2
HR (beats/min)	80 ± 3.9	77 ± 3.1
ANF level (fmol/ml) ($n = 7$)	237 ± 133	103 ± 64

PC, mean pulmonary capillary wedge pressure; PAP, mean pulmonary arterial pressure; RA, mean right atrial pressure; MAP, mean arterial pressure; CI, cardiac index; HR, heart rate. Values are given as means \pm s.e.m.

pretreatment values (from 237 ± 133 to 104 ± 64 fmol/ml) was seen in seven patients (remaining samples await analysis).

Plasma levels of irANF in the cirrhotic group were slightly but significantly higher than in the control group (Table 1). Immunoreactive-ANF concentrations in the five patients with tense ascites ranged from 7.4 to 16.5 fmol/ml and did not differ from those of the other cirrhotic patients. When spironolactone was discontinued in five of the patients with ascites, an average increase of 47% was observed in irANF concentrations.

The nature of the rise in ANF in hypertension was studied in more detail by characterization of the molecular-weight pattern of ANF in individual patients. By analysis of plasma extracts on high performance gel permeation chromatography (Fig. 2) and subsequent reverse-phase high performance liquid chromatography (Fig. 3), we had previously found that in normotensive individuals irANF consisted exclusively of authentic 28-amino-acid α -hANF, the C-terminal portion of the human precursor pre-pro-ANF [11]. Chromatographic analysis of the plasma extracts of a still limited number of hypertensive patients revealed that irANF comprised a peak co-eluting with synthetic α -hANF as in normotensive subjects (Fig. 4). In the hypertensive patient shown on Fig. 4, both total irANF and 3100-dalton ANF were increased compared with normotensive controls. In

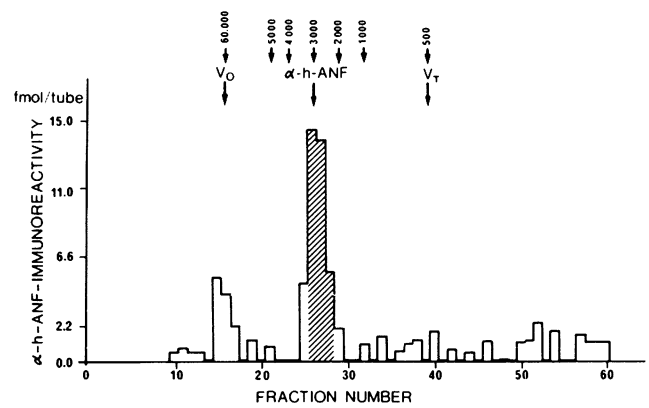


Fig. 2. Molecular weight pattern of immunoreactive atrial natriuretic factor (ANF) in plasma of a normotensive control subject on a 3.9×300 mm TSK-125 Bio Sil high performance gel permeation chromatography system. Fraction aliquots were assayed for alpha-human ANF (α -h-ANF) immunoreactivity (from [10]).

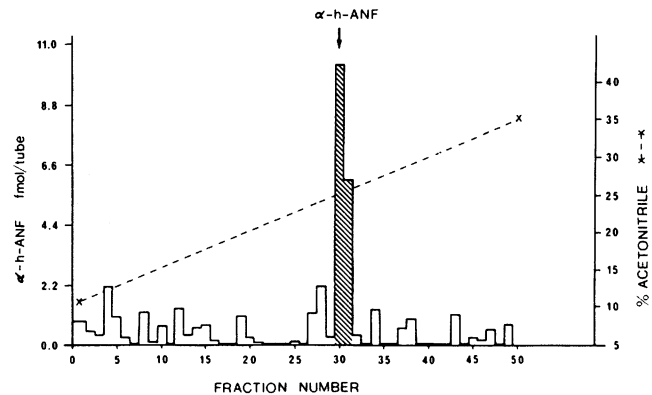


Fig. 3. Analysis by high performance liquid chromatography of α -human atrial natriuretic factor (α -h-ANF) from human plasma following high performance permeation chromatography (Fig. 2). The immunoreactive peak co-eluting with synthetic α -human atrial natriuretic factor on the high performance gel permeation chromatography system was re-chromatographed on a C18 reverse-phase system and re-assayed for α -human atrial natriuretic factor (from [10]).

contrast to normotensive controls, Fig. 4 shows the presence of a higher molecular weight ANF precursor of c. 13 000 dalton.

Discussion

In conjunction with a novel extraction and purification procedure employing adsorbent resins, our radio-immunoassay allows reliable detection of plasma irANF levels as low as 0.5 fmol/ml [10]. Plasma levels of irANF in healthy control subjects ranged from 1 to 23 fmol/ml.

It has been hypothesized that failure to elaborate a natriuretic hormone adequately contributes to sodium retention and ascites formation in cirrhotic patients [12]. However, we found that irANF was slightly increased in cirrhotics in comparison with normotensive controls. Moreover, the increase in plasma irANF that we found after discontinuation of diuretic treatment suggests that

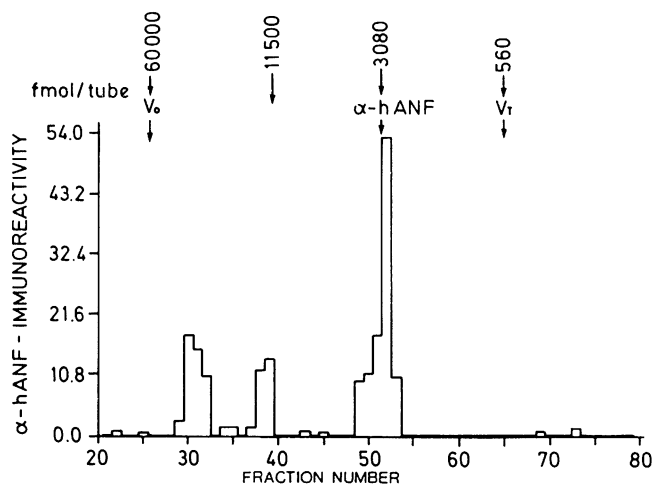


Fig. 4. Molecular weight pattern of immunoreactive atrial natriuretic factor (ANF) in the plasma of a hypertensive patient on a 3.9×600 mm TSK-125 Bio Sil high performance gel permeation chromatography system. The column was calibrated with bovine serum albumin (V_0), leu-enkephalin (V_7) and a series of opioid peptides. Fraction aliquots were assayed for α -human ANF (α -hANF) immunoreactivity. Compared with Fig. 2 the separation power has been increased by reducing the solvent flow rate from 0.8 to 0.4 ml/min.

release of ANF is unimpaired in cirrhosis. It is possible, therefore, that despite the expanded extracellular volume in cirrhotics, splanchnic sequestration of fluids may prevent an increase in central volume and atrial pressure, and thus release may not be adequate to combat the volume overload.

In contrast, patients with congestive heart failure have excessively elevated plasma levels of irANF. Elevations in plasma irANF concentrations in the present study were correlated with increases in right atrial and pulmonary capillary wedge pressure and were inversely related to cardiac index. While an accelerated release of ANF may be the physiological response to combat the volume overload in congestive heart failure, even a 40-fold increase in plasma irANF appears insufficient to reverse the clinical condition and may not improve symptomatology. The problem may be caused by receptor down-regulation [13] or by conformational changes resulting in a decreased response of ANF target organs even in the presence of elevated plasma levels. On the other hand, defective enzymatic processing or increased metabolism may lead to high levels of irANF without corresponding physiological activity. In this context, it is interesting that, in a preliminary study, patients suffering from heart failure and with elevated plasma levels of irANF benefited haemodynamically from the acute administration of synthetic α -hANF as a therapeutic agent; however, no data on chronic application are currently available [14].

Although volume load and atrial pressure stimulate ANF release [8], patients with pericardial effusion and developing tamponade have comparably low irANF (Table 1) in spite of elevated atrial and ventricular pressures. In the present study, plasma concentrations of irANF rose markedly following pericardial decompres-

sion (Table 1). This indicates that increased pressure alone may not be the only stimulus for ANF release.

Severe heart failure has of late been treated by angiotensin converting enzyme inhibitors. The beneficial effect of these inhibitors in congestive heart failure may be explained by a reduction in angiotensin II levels, but they are also associated with a reduction in circulating catecholamines, a decrease in antidiuretic hormone production and a reduction in aldosterone levels [15]. These factors may lead to the clinical improvement of patients and secondarily to a reduction in ANF release.

The greatest variability in plasma irANF levels was seen among hypertensive patients and ranged from normal to excessively elevated. The pathophysiological role of ANF in pressure regulation, and in 'pressure-diuresis', remains to be elucidated. Preliminary chromatographic data do not rule out the possibility that plasma ANF circulates in different molecular forms [16] and that differences in synthesis and enzymatic processing or metabolism may be involved in the pathophysiology of hypertension.

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