

Raised plasma concentrations of atrial natriuretic peptide are independent of left atrial dimensions in patients with chronic atrial fibrillation

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Abstract

The aim of the present study was to determine whether left atrial size—a likely indicator of atrial stretching—correlates with the plasma concentration of atrial natriuretic peptide and whether this relation is different in patients in sinus rhythm and in those with atrial fibrillation. Arterial plasma concentrations of immunoreactive atrial natriuretic peptide (ir-ANP), adrenaline, noradrenaline, aldosterone, and vasopressin were measured in 13 patients in sinus rhythm without apparent heart failure and in 13 patients in atrial fibrillation. The two groups were matched for left atrial diameter and the ratio of the left atrial diameter to the diameter of the aortic root (assessed by echocardiography). There were no significant differences in age, heart rate, blood pressure, or left ventricular end diastolic diameter between the two groups. Left atrial diameters varied from 33 to 60 mm. The mean (SD) plasma concentration of ir-ANP was significantly higher (35 (21) pmol/l) in the patients with atrial fibrillation than in those in sinus rhythm (12 (11) pmol/l). The concentration of plasma aldosterone was also higher in patients with atrial fibrillation (831 (366) v 523 (211) pmol/l). Concentrations of adrenaline, noradrenaline, and vasopressin were similar in both groups. None of the hormone concentrations correlated with left atrial dimensions.

These results indicate that plasma concentrations of ir-ANP and aldosterone are highly sensitive indicators of changes in haemodynamic function during atrial fibrillation. They also underscore the difficulties of correlating echocardiographic assessment of patients with plasma concentrations of a vasoactive hormone.

The discovery of the atrial natriuretic peptide (ANP)—a hormonal link between the heart and the kidney—evoked new interest in the mechanisms of heart-kidney interactions.¹ Atrial stretch is held to be the major stimulus for release of ANP.² This peptide has potent natriuretic, vaso-relaxant, and aldosterone-inhibiting properties.³⁻⁵ Plasma concentrations of immunoreactive (ir)-ANP increased during paroxysmal atrial fibrillation and decreased after successful electric cardioversion.⁶⁻⁸ The left atrial diameter was reported to increase

with the duration of atrial fibrillation.⁹ This increase might be attributable to long-standing stretching of the left atrial wall caused by a continuously raised atrial pressure leading to dilatation. The aim of the present study was to determine whether left atrial size—a likely indicator of such stretching—corresponds to the plasma concentration of ANP and whether this relation is different in patients in sinus rhythm and in those with atrial fibrillation.

Patients and methods

PATIENTS

The study group was selected from 52 patients admitted during 1982 and 1983 to our cardiac department with atrial fibrillation of short duration. All patients were successfully cardioverted and were subsequently followed up in the outpatient clinic. Thirteen patients with a mean (SD) age of 63 (7) years were still in sinus rhythm in 1988. From the group of patients who had relapsed into atrial fibrillation we selected 13 patients to form matching pairs with the 13 patients still in sinus rhythm (table 1). All were in New York Heart Association functional class I. Two patients in each group had an old myocardial infarction and four patients in the atrial fibrillation group and two patients in sinus rhythm had type II diabetes mellitus. Radiological signs of decompensation—that is redistribution of blood in the lung, widened or poorly outlined pulmonary vessels, Kerley B lines, or interstitial oedema—were not found on chest x ray.¹⁰ Table 1 gives the relative heart volume.¹¹ All patients were maintained on their regular medication, including digoxin, diuretics, β blockers, calcium antagonists, and class I antiarrhythmic agents. The drug intake was similar in the two groups except that seven of the patients in sinus rhythm and two in atrial fibrillation were taking class I antiarrhythmic agents. Only

Table 1 Patient characteristics (mean (SD))

Variable	Sinus rhythm	Atrial fibrillation
No	13	13
Age (years)	63 (7)	64 (5)
LAD/AO ratio	1.24 (0.14)	1.24 (0.16)
LAD (mm)	44 (6)	45 (6)
LVEDD (mm)	54 (10)	49 (6)
HR (beats/min)	64 (12)	66 (14)
BPs (mm Hg)	148 (14)	147 (17)
BPd (mm Hg)	86 (9)	88 (7)
Heart volume (ml/m ²)*	525 (79)	551 (125)

No statistically significant differences were found (paired *t* test). LAD, left atrial diameter; AO, aortic root diameter; LVEDD, left ventricular end diastolic diameter; HR, heart rate; BPs, systolic blood pressure; BPd, diastolic blood pressure.

* Assessed by chest x ray.¹¹

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patients in the atrial fibrillation group ($n = 4$) were taking calcium antagonists. Informed consent was obtained from each patient and the study was approved by the local ethics committee.

PROTOCOL

We used an Interspec Cardioscan echocardiograph. The heart was visualised from the left sternal border with the patient in the left lateral position. All examinations were undertaken by the same echocardiographer. The leading edge method was used for measurements.^{12,13} A left ventricular end diastolic dimension, left atrial end systolic dimension, and a diastolic aortic root dimension were measured in millimetres in a long axis view obtained from the left sternal border.

Immediately after the echocardiographic investigation and with the patient remaining in the supine position, an arterial blood sample was drawn to measure the concentrations of ir-ANP, vasopressin, aldosterone, adrenaline and noradrenaline in plasma. These samples were taken after 45–60 minutes of rest.

RADIOIMMUNOASSAY

Blood samples were drawn into chilled heparinised tubes and centrifuged within 10 minutes. Plasma samples were stored at -20°C until they were processed. ANP was measured by a competitive radioimmunoassay based on antiserum RAS 8798 (Peninsula, CA, USA) raised in a rabbit against alpha human ANP. The radioligand, ^{125}I ANP, was purchased from Amersham (England) and the standard was synthetic human ANP (Peninsula). The IC_{50} value concentration of unlabelled peptide in the assay tube inhibiting the maximal binding by 50% of the antiserum was 8.9 pmol/l. The antiserum cross reacts 100% with ANP (8–33), 60% with ANP (8–28), and 10% with auricularin A, but does not cross react with oxytocin or Arg 8 vasopressin. Plasma samples of 1.0 ml were extracted with Sep Pak (Waters, USA) as described by Theodorsson-Norheim *et al.*¹⁴ The recovery of synthetic human ANP added to human plasma was 83% at 25 pmol/l and 85% at 100 pmol/l ($n = 5$ in each group). The standards and samples were incubated with the antiserum at 4°C and the radioligand was then added; this was followed by a further 24 hour incubation. Bound radioligand was separated from free radioligand by a donkey-antirabbit IgG solid face second antibody coated cellulose suspension (Sac-Cel, Wellcome). The inter-assay coefficient of variation was 11%. In 23 healthy individuals (mean age 63 (4) years) the mean plasma concentration of ir-ANP was 18 (9) pmol/l.

Plasma concentrations of arginine vasopressin were measured by a commercial radioimmunoassay (Bühlman, Basel).¹⁵ The normal reference value for the plasma concentration of immunoreactive arginine vasopressin (AVP) at rest was <5.5 pmol/l.¹⁶ Aldosterone was analysed by a commercial radioimmunoassay (CIS, Biomedica, Saluggia, Italy) and the normal reference value was <860 pmol/l.^{17,18} Adrenaline and noradrenaline were measured

by high performance liquid chromatography with electrochemical detection.^{19,20} The reference value for adrenaline was <0.48 nmol/l and for noradrenaline it was <2.3 nmol/l.

STATISTICAL ANALYSIS

Values are expressed as mean and standard deviation. Linear regression analysis and Pearson's correlation coefficient were used to estimate the relation between the left atrial dimensions and the plasma concentrations of the hormones. Differences between the two patient groups were tested with the paired *t* test. *p* values of <0.05 were regarded as significant.

Results

Table 2 shows the results of the hormone analysis. The left atrial dimensions and the ratio of the left atrial diameter to the diameter of the aortic root varied considerably (33–60 mm and 1.03–1.48 respectively). No significant differences in heart rate, blood pressure, left ventricular end diastolic dimension, or concentrations of adrenaline and noradrenaline were found between the groups. The mean plasma concentration of ir-ANP was significantly higher in the group with atrial fibrillation than in the sinus rhythm group (35 (21) and 12 (11) pmol/l respectively; $p = 0.003$) (fig 1A). The mean plasma concentration of aldosterone (fig 1B) was also higher in patients with atrial fibrillation than in the group in sinus rhythm (831 (336) *v* 523 (211) pmol/l; $p = 0.003$). The mean noradrenaline, adrenaline, and vasopressin concentrations were all close to the upper normal limit but no statistically significant differences were found between the two groups. Figure 2 shows the relations between the left atrial dimensions and the measured hormones. We found no correlation in either group between left atrial diameter or left atrial diameter/aortic root diameter ratio and the plasma concentration of any of the hormones that we measured (table 3).

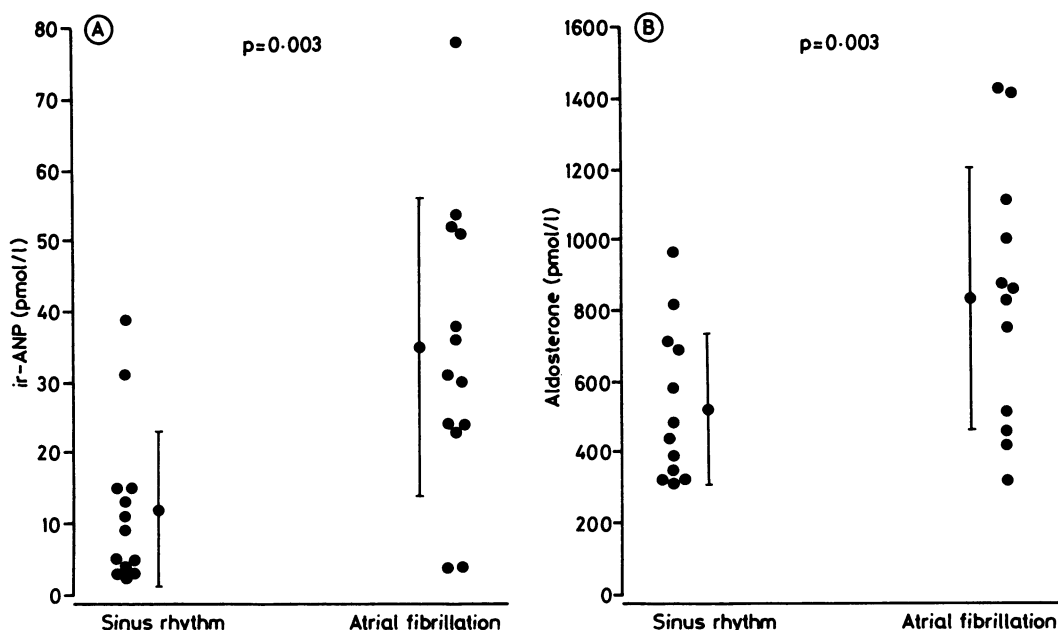
Discussion

Awareness that the heart secretes a peptide with natriuretic, vasodilating, and aldosterone-inhibiting properties has revitalised interest in the physiological and pathophysiological link between the atria and the control of fluid and electrolyte balance. Concentrations of this peptide were increased in conditions associated with raised atrial filling pressures.²¹ Furthermore, paroxysmal atrial fibrillation has been shown to increase plasma concentrations of ANP, and successful treatment with electrical

Table 2 Hormone concentrations (mean (1 SD))

	Sinus rhythm	Atrial fibrillation	<i>p</i> Value
ir-ANP (pmol/l)	12 (11)	35 (21)	0.003
Aldosterone (pmol/l)	523 (211)	831 (366)	0.003
Adrenaline (nmol/l)	0.31 (0.14)	0.44 (0.31)	NS
Noradrenaline (nmol/l)	2.33 (0.9)	2.34 (0.76)	NS
Arginine vasopressin (pmol/l)	6.5 (7.2)	5.4 (3.9)	NS

Figure 1 (A) Plasma concentrations of ir-ANP (mean (1 SD)) in 13 patients in sinus rhythm and in 13 with atrial fibrillation. (B) Plasma aldosterone concentrations (mean (1 SD)) in 12 patients in sinus rhythm and in 12 with atrial fibrillation.



cardioversion is followed by a decrease in plasma ANP.^{7,8} Whether these findings are fully explained by haemodynamic alterations in the atrium during atrial fibrillation or whether the reduced frequency of the atrial contractions in itself is an important factor is at present unknown; though it has been suggested that raised atrial pressure during atrial fibrillation may be the main cause of the increased concentration of ANP.²² An increase in left atrial dimensions with the duration of atrial fibrillation was reported, a finding that may be interpreted as a result of long-standing unfavourable distension of the left atrium.⁹ If we assume that ANP release is mediated by atrial stretch, it is not unreasonable to expect some correlation with atrial diameters, especially in patients with chronic atrial fibrillation.

In the present study we also investigated the relative importance of cardiac rhythm itself—that is sinus rhythm versus atrial fibrillation—

to the release of ir-ANP. The two groups investigated, with 13 patients in each, were almost identical in terms of several important echocardiographic cardiac variables. But the significantly higher concentration of ir-ANP in the atrial fibrillation group could not be explained by more pronounced dilatation of the left atrium because this variable was similar in both groups. Furthermore, no relation was found between left atrial dimensions and plasma concentration of ir-ANP in either of the two groups. Because the left atrial size varied considerably, significant correlations with plasma ir-ANP concentration should have been detected. This observation provides further evidence for the view that left atrial size, in clinically stable patients, is not a major determinant of the plasma concentration of ANP. The lack of a significant correlation between left atrial dimension and plasma ir-ANP accords with the findings in a previous study of 30 patients in sinus rhythm.²³ In

Figure 2 Relations between left atrial diameter and plasma concentrations of analysed hormones. No significant correlations were found. Table 3 shows the correlation data. Missing values: aldosterone (one); arginine vasopressin (two); ir-ANP (two patients had values of 43 mm and 24 pmol/l).

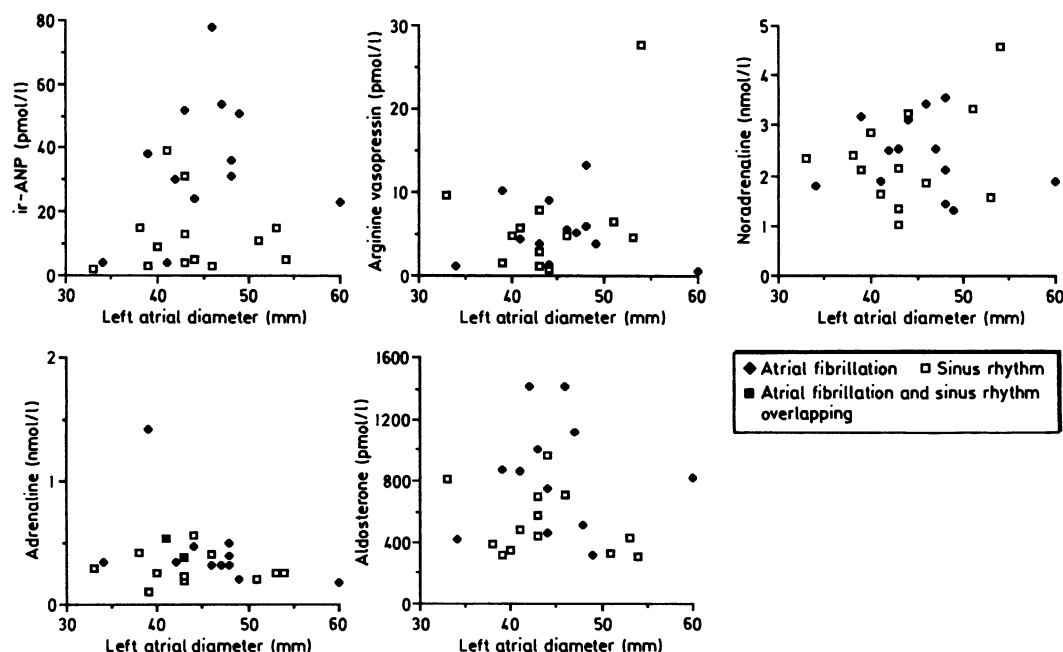


Table 3 Correlation between echocardiographic measurements and hormone concentrations

Variable	Sinus rhythm				Atrial fibrillation			
	LAD		LAD/AO		LAD		LAD/AO	
	r ²	p	r ²	p	r ²	p	r ²	p
ir-ANP (pmol/l)	2 × 10 ⁻⁴	0.96	0.01	0.70	0.07	0.38	0.18	0.15
Aldosterone (pmol/l)	0.09	0.31	0.01	0.83	2 × 10 ⁻⁴	0.96	0.11	0.28
Adrenaline (nmol/l)	0.02	0.64	0.01	0.80	0.20	0.13	0.17	0.16
Noradrenaline (nmol/l)	0.13	0.23	0.13	0.23	0.01	0.79	3 × 10 ⁻⁴	0.96
AVP (pmol/l)	0.17	0.19	0.18	0.17	0.01	0.74	0.02	0.69

AO, aortic root diameter; AVP, arginine vasopressin; LAD, left atrial diameter.

another study an unchanged left atrial diameter, measured by means of echocardiography, before, one, and 30 days after successful cardioversion treatment for short term atrial fibrillation was associated with a considerable and significant decrease in the plasma concentration of ir-ANP.⁸

Absence of a correlation between the left atrial diameter and the plasma concentration of ir-ANP is not a surprising finding in view of the complexity of the neurohormonal changes caused by a hypokinetic circulation and atrial stretch.²⁴ Probable modulating factors such as atrial compliance and transmural pressure might also reduce the value of echocardiographic measurements of the left atrium as an indication of actual dynamic distension of the atria. The possibility of resetting of at least some atrial receptors or a fall in sensitivity with chronic dilatation might also have influenced our results.²⁵

In contrast with our findings, in a study on children with congenital heart disease an index calculated as the right atrial area in relation to body area was found to correlate well with plasma concentrations of ANP.²⁶ It is reasonable to expect that factors modulating ANP release and atrial stretch will be less pronounced in this younger patient group with well-defined cardiac disease, making the postulated relation between atrial pressure and atrial size more easily detectable.

Plasma concentrations of adrenaline, noradrenaline, and arginine vasopressin were similar in both the groups and these hormone concentrations did not correlate with the left atrial measurements. Raised plasma concentrations of noradrenaline, adrenaline, and arginine vasopressin were reported during hypokinetic circulation.^{24, 27} The lack of difference in these variables emphasises the similarity between the two patient groups. Furthermore, the concentrations of these vasoactive hormones were close to the normal ranges, indicating that there was no major degree of derangement of the peripheral and renal circulations. Hence, an increased plasma ir-ANP concentration seems to be a very sensitive marker of atrial stretch, which is probably associated with atrial fibrillation.

Some studies suggest that the heart rate per se influences the release of ANP but other studies of atrial pacing and of patients with congestive heart failure showed no clear correlation between plasma ir-ANP and heart rate. A higher heart rate in the atrial fibrillation group is not a likely cause of the raised ir-ANP

because the heart rates were almost equal in both groups. The possibility that the dynamic pressure changes within the cardiac cycle and variability of pressure changes from beat to beat influenced the release of ANP cannot be ruled out. Furthermore, a difference in the relation between atrial pressure and atrial wall stretch between patients in atrial fibrillation and those in sinus rhythm, which might be attributable to the presence or absence of atrial contraction, is likely. A study comparing the influence of DDD and VVI pacing on plasma concentrations of ir-ANP in patients with type III atrioventricular block supports the view that irregularities in ventricular rhythm, with loss of the synchronous atrial contractions, may lead to disadvantageous atrial stretching.²⁸ VVI pacing was associated with raised concentrations of ir-ANP, whereas the plasma concentrations were normal in the group with DDD pacing. The importance of trying to find the most physiological pacing mode was shown in a study in which a lower cardiovascular morbidity and mortality was found among patients with sick sinus syndrome treated with AAI pacing than in those treated with VVI pacing.²⁹ Since the plasma concentrations of ir-ANP seem to be a sensitive marker of atrial distension, with a rapid responsiveness to changes in such distension, they might be of some use as a guide in optimising pacemaker treatment.

Information is limited on the effects of calcium entry blocking agents on renal haemodynamic function and plasma concentrations of aldosterone in patients with atrial fibrillation and mild compensated congestive heart failure. In some patients with congestive heart failure nifedipine can cause deterioration of renal function.³⁰ However, in the present study only four patients in the atrial fibrillation group were treated with calcium blockers and data on individual differences between these pairs of patients do not account for the observed statistically significant difference between the groups. Normal electrolytes and similar diuretic treatment in the examined groups make these factors less plausible as causes of the difference. Hence, it is possible that the difference in the plasma aldosterone concentration reflects unfavourable changes in haemodynamic function during atrial fibrillation.

We conclude that atrial fibrillation is associated with an increase in the plasma concentrations of ir-ANP and aldosterone that is independent of left atrial dimensions, age, and heart rate. These findings do not deviate from

the previous observation that atrial stretch, as reflected by atrial mean pressures, is the major stimulus for release of ANP, but they underscore the difficulties in correlating echocardiographic assessments of patients with plasma concentrations of cardiovascular hormones. We do not know whether our findings can be fully explained by unfavourable haemodynamic conditions in the atria (as reflected by raised mean atrial pressures) or are influenced by irregularities in atrial stretch caused by irregular ventricular contractions, or are attributable to a yet unknown link between atrial fibrillation and plasma ANP. To clarify this issue further, we need studies focusing on the atrial contraction pattern in relation to haemodynamic changes and hormone release. In addition, the present findings indicate that aldosterone is a highly sensitive indicator of alterations in haemodynamic function during atrial fibrillation.

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